

**TOXICOLOGICAL PROFILE FOR  
PENTACHLOROPHENOL**

**U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Agency for Toxic Substances and Disease Registry**

September 2001

## **DISCLAIMER**

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## **UPDATE STATEMENT**

Toxicological profiles are revised and republished as necessary, but no less than once every three years. For information regarding the update status of previously released profiles, contact ATSDR at:

Agency for Toxic Substances and Disease Registry  
Division of Toxicology/Toxicology Information Branch  
1600 Clifton Road NE, E-29  
Atlanta, Georgia 30333



## FOREWORD

This toxicological profile is prepared in accordance with guidelines\* developed by the Agency for Toxic Substances and Disease Registry (ATSDR) and the Environmental Protection Agency (EPA). The original guidelines were published in the *Federal Register* on April 17, 1987. Each profile will be revised and republished as necessary.

The ATSDR toxicological profile succinctly characterizes the toxicologic and adverse health effects information for the hazardous substance described therein. Each peer-reviewed profile identifies and reviews the key literature that describes a hazardous substance's toxicologic properties. Other pertinent literature is also presented, but is described in less detail than the key studies. The profile is not intended to be an exhaustive document; however, more comprehensive sources of specialty information are referenced.

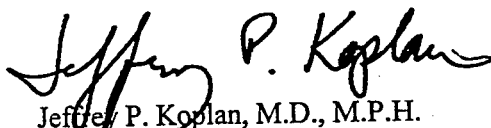
The focus of the profiles is on health and toxicologic information; therefore, each toxicological profile begins with a public health statement that describes, in nontechnical language, a substance's relevant toxicological properties. Following the public health statement is information concerning levels of significant human exposure and, where known, significant health effects. The adequacy of information to determine a substance's health effects is described in a health effects summary. Data needs that are of significance to protection of public health are identified by ATSDR and EPA.

Each profile includes the following:

- (A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;
- (B) A determination of whether adequate information on the health effects of each substance is available or in the process of development to determine levels of exposure that present a significant risk to human health of acute, subacute, and chronic health effects; and
- (C) Where appropriate, identification of toxicologic testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

This profile reflects ATSDR's assessment of all relevant toxicologic testing and information that has been peer-reviewed. Staff of the Centers for Disease Control and Prevention and other Federal scientists have also reviewed the profile. In addition, this profile has been peer-reviewed by a nongovernmental panel and was made available for public review. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



Jeffrey P. Koplan, M.D., M.P.H.  
Administrator

Agency for Toxic Substances and  
Disease Registry

### \*Legislative Background

The toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public law 99-499) which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed ATSDR to prepared toxicological profiles for hazardous substances most commonly found at facilities on the CERCLA National Priorities List and that pose the most significant potential threat to human health, as determined by ATSDR and the EPA. The availability of the revised priority list of 275 hazardous substances was announced in the *Federal Register* on November 17, 1997 (62 FR 61332). For prior versions of the list of substances, see *Federal Register* notices dated April 29, 1996 (61 FR 18744); April 17, 1987 (52 FR 12866); October 20, 1988 (53 FR 41280); October 26, 1989 (54 FR 43619); October 17, 1990 (55 FR 42067); October 17, 1991 (56 FR 52166); October 28, 1992 (57 FR 48801); and February 28, 1994 (59 FR 9486). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

## QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances will find the following information helpful for fast answers to often-asked questions.

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### *Primary Chapters/Sections of Interest*

**Chapter 1: Public Health Statement:** The Public Health Statement can be a useful tool for educating patients about possible exposure to a hazardous substance. It explains a substance's relevant toxicologic properties in a nontechnical, question-and-answer format, and it includes a review of the general health effects observed following exposure.

**Chapter 2: Relevance to Public Health:** The Relevance to Public Health Section evaluates, interprets, and assesses the significance of toxicity data to human health.

**Chapter 3: Health Effects:** Specific health effects of a given hazardous compound are reported by *type of health effect* (death, systemic, immunologic, reproductive), by *route of exposure*, and by *length of exposure* (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

**NOTE:** Not all health effects reported in this section are necessarily observed in the clinical setting. Please refer to the Public Health Statement to identify general health effects observed following exposure.

**Pediatrics:** Four new sections have been added to each Toxicological Profile to address child health issues:

Section 1.6	How Can (Chemical X) Affect Children?
Section 1.7	How Can Families Reduce the Risk of Exposure to (Chemical X)?
Section 3.7	Children's Susceptibility
Section 6.6	Exposures of Children

### **Other Sections of Interest:**

Section 3.8	Biomarkers of Exposure and Effect
Section 3.11	Methods for Reducing Toxic Effects

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### **ATSDR Information Center**

**Phone:** 1-888-42-ATSDR or 404-498-0110

**Fax:** 404-498-0057

**E-mail:** [atsdric@cdc.gov](mailto:atsdric@cdc.gov)

**Internet:** <http://www.atsdr.cdc.gov>

The following additional material can be ordered through the ATSDR Information Center:

*Case Studies in Environmental Medicine: Taking an Exposure History*—The importance of taking an exposure history and how to conduct one are described, and an example of a thorough exposure history is provided. Other case studies of interest include *Reproductive and Developmental Hazards*; *Skin Lesions and Environmental Exposures*; *Cholinesterase-Inhibiting Pesticide Toxicity*; and numerous chemical-specific case studies.

*Managing Hazardous Materials Incidents* is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident. Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

*Fact Sheets (ToxFAQs)* provide answers to frequently asked questions about toxic substances.

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### ***Other Agencies and Organizations***

*The National Center for Environmental Health* (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. *Contact:* NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015.

*The National Institute for Occupational Safety and Health* (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. *Contact:* NIOSH, 200 Independence Avenue, SW, Washington, DC 20201 • Phone: 800-356-4674 or NIOSH Technical Information Branch, Robert A. Taft Laboratory, Mailstop C-19, 4676 Columbia Parkway, Cincinnati, OH 45226-1998 • Phone: 800-35-NIOSH.

*The National Institute of Environmental Health Sciences* (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. *Contact:* NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212.

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### ***Referrals***

*The Association of Occupational and Environmental Clinics* (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: [AOEC@AOEC.ORG](mailto:AOEC@AOEC.ORG) • Web Page: <http://www.aoec.org/>.

*The American College of Occupational and Environmental Medicine* (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. *Contact:* ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-818-1800 • FAX: 847-818-9266.



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### THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.
2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific minimal risk levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.
3. Data Needs Review. The Research Implementation Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.



## PEER REVIEW

A peer review panel was assembled for pentachlorophenol. The panel consisted of the following members:

1. Dr. Donald Morgan, Professor Emeritus in Preventive Medicine, University of Iowa Medical School, 1650 Koehler Drive NW, #247, Cedar Rapids, IA 52405;
2. Dr. Norman Rawlings, Professor of Veterinary Physiological Sciences, Department of Veterinary Biomedical Sciences, University of Saskatchewan, 52 Campus Drive, Saskatoon, SK S7N 5B4 Canada;
3. Dr. Thomas Thompson, Manager of Environmental Sciences, Saskatchewan Health Provincial Laboratory, 3211 Albert Street, Regina, SK S4S 5W6 Canada;
4. Dr. Loren Koller, Professor, College of Veterinary Medicine, Oregon State University, 105 Magruder Hall, Corvallis, OR 97331-4802;
5. Dr. Philip Leber, Goodyear Tire & Rubber Company, 1485 East Archwood Avenue, Akron, OH 44306;
6. Dr. John Lech, Professor, Pharmacology and Toxicology, Medical College of Wisconsin, 8701 Watertown Park Road, Milwaukee, WI 53226; and
7. Dr. Frederick Oehme, Professor, Comparative Toxicology Laboratories, 1800 Denison Avenue, Kansas State University, Manhattan, KS 66506-5606.

These experts collectively have knowledge of pentachlorophenol's physical and chemical properties, toxicokinetics, key health end points, mechanisms of action, human and animal exposure, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.



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## 1. PUBLIC HEALTH STATEMENT

This public health statement tells you about pentachlorophenol and the effects of exposure.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites make up the National Priorities List (NPL) and are the sites targeted for long-term federal cleanup activities. Pentachlorophenol has been found in at least 313 of the 1,585 current or former NPL sites. However, the total number of NPL sites evaluated for this substance is not known. As more sites are evaluated, the sites at which pentachlorophenol is found may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

When a substance is released from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. This release does not always lead to exposure. You are exposed to a substance only when you come in contact with it. You may be exposed by breathing, eating, or drinking the substance, or by skin contact.

If you are exposed to pentachlorophenol, many factors determine whether you'll be harmed. These factors include the dose (how much), the duration (how long), and how you come in contact with it. You must also consider the other chemicals you're exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

### 1.1 WHAT IS PENTACHLOROPHENOL?

Pentachlorophenol is a synthetic substance, made from other chemicals, and does not occur naturally in the environment. It is made by only one company in the United States. At one time, it was one of the most widely used biocides in the United States. Since 1984, the purchase and use of pentachlorophenol has been restricted to certified applicators. It is no longer available to the general public. Application of pentachlorophenol in the home as an herbicide and pesticide accounted for only 3% of its consumption in the 1970s. Before use restrictions,

## 1. PUBLIC HEALTH STATEMENT

pentachlorophenol was widely used as a wood preservative. It is now used industrially as a wood preservative for power line poles, cross arms, fence posts, and the like.

Pure pentachlorophenol exists as colorless crystals. It has a very sharp characteristic phenolic smell when hot but very little odor at room temperature. Most people can begin to smell pentachlorophenol in water at less than 12 parts pentachlorophenol per million parts of water (ppm). Impure pentachlorophenol (the form usually found at hazardous waste sites) is dark gray to brown and exists as dust, beads, or flakes. Pentachlorophenol can be found in two forms: pentachlorophenol itself or as the sodium salt of pentachlorophenol. The sodium salt dissolves easily in water, but pentachlorophenol does not. These two forms have some different physical properties, but are expected to have similar toxic effects.

Humans are generally exposed to technical-grade pentachlorophenol, which usually contains such toxic impurities as polychlorinated dibenzo-*p*-dioxins and dibenzofurans. Table 3-2 lists the impurities found in three different grades of pentachlorophenol.

For more information on the physical and chemical properties of pentachlorophenol, see Chapter 4. For more information on its production, use, and disposal, see Chapter 5.

## 1.2 WHAT HAPPENS TO PENTACHLOROPHENOL WHEN IT ENTERS THE ENVIRONMENT?

Pentachlorophenol is released to the air by evaporation from treated wood surfaces and factory (chemical manufacturing plants and wood preservation plants) waste disposal. It enters surface water and groundwater from factories, wood-treatment facilities, and hazardous waste sites. It also enters the soil as a result of spills, disposal at hazardous waste sites, and its use as a pesticide. The physical and chemical properties of the compound suggest that not much will evaporate into the atmosphere and that most of it will move with water and generally stick to soil particles. Movement of pentachlorophenol in soils depends on the soil's acidity. The compound can be present in fish or other species used for food, as demonstrated by the ongoing food monitoring program of the Food and Drug Administration (FDA). In air, soil, and surface water,

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pentachlorophenol lasts for hours to days. The compound is broken down in soil and surface water by microorganisms, and in air and surface water by sunlight, to other compounds, some of which may be harmful to humans.

More information on the releases, occurrence, and movement of pentachlorophenol in the environment can be found in Chapters 5 and 6.

### 1.3 HOW MIGHT I BE EXPOSED TO PENTACHLOROPHENOL?

In addition to workplace exposures, humans can be exposed to very low levels of pentachlorophenol through indoor and outdoor air, food, soil, and drinking water. Exposure may also result from dermal contact with wood treated with preservatives that contain pentachlorophenol. Levels in the workplace, near certain hazardous waste sites, and near sites of accidental spills are usually higher than in the general environment.

Exposure to pentachlorophenol by eating contaminated food is limited. The average intake in food is estimated to be 0.0105 milligrams of pentachlorophenol for a 70 kg human. Daily intake by drinking contaminated water is also low and is estimated to be about 0.021 mg for a 70 kg human. In its survey of various population groups in 1986–1991, the ongoing food monitoring program of the FDA observed a substantial decrease in the daily intakes of pentachlorophenol. We do not have much information on the levels of pentachlorophenol in indoor and outdoor air, but the general population is estimated to breathe in about 0.063 mg/day. People who work or live near pentachlorophenol sources are exposed to higher levels. A 1984 report cites the measured concentration of pentachlorophenol in the indoor air of pressure-treated log homes brushed with pentachlorophenol in the range of 0.5–10 parts per trillion (ppt, 1 ppt is 1 million times less than 1 ppm) and in the air of industrially dipped, nonpressure-treated log homes at 34–104 ppt. Levels of pentachlorophenol in the air at wood-treatment facilities and lumber mills are much higher, and workers exposed at these places are estimated to breathe in 10.5–154.0 mg/day. Workers who handle treated lumber can take in about 35.0 mg/day through the skin.

## 1. PUBLIC HEALTH STATEMENT

For more information on exposure to pentachlorophenol, see Chapter 6.

**1.4 HOW CAN PENTACHLOROPHENOL ENTER AND LEAVE MY BODY?**

Pentachlorophenol easily enters your body through your lungs when you breathe it, through your digestive tract after you eat contaminated food or water, or through your skin. The most significant ways are through breathing and skin contact. After a short exposure period, pentachlorophenol quickly leaves your body (studies in humans show that half the amount taken in is usually gone within 33 hours). It does not seem to build up in the body very much. Most of the pentachlorophenol taken into your body does not break down, but instead leaves in your urine. Much smaller amounts leave in your feces. Only a small amount escapes through your exhaled air. Some of the pentachlorophenol taken into your body is joined with other natural chemicals that make the pentachlorophenol less harmful. The combined product can then leave your body more easily.

Chapter 3 contains more information on how pentachlorophenol enters and leaves your body.

**1.5 HOW CAN PENTACHLOROPHENOL AFFECT MY HEALTH?**

To protect the public from the harmful effects of toxic chemicals and to find ways to treat people who have been harmed, scientists use many tests.

One way to see if a chemical will hurt people is to learn how the chemical is absorbed, used, and released by the body; for some chemicals, animal testing may be necessary. Animal testing may also be used to identify health effects such as cancer or birth defects. Without laboratory animals, scientists would lose a basic method to get information needed to make wise decisions to protect public health. Scientists have the responsibility to treat research animals with care and compassion. Laws today protect the welfare of research animals, and scientists must comply with strict animal care guidelines.



## 1. PUBLIC HEALTH STATEMENT

Some, but not all, of the harmful effects associated with exposure to pentachlorophenol are due to impurities present in commercial pentachlorophenol. Short exposures to large amounts of pentachlorophenol in the workplace or through the misuse of products that contain it can cause harmful effects on the liver, kidneys, blood, lungs, nervous system, immune system, and gastrointestinal tract. Contact with pentachlorophenol (particularly in the form of a hot vapor) can irritate the skin, eyes, and mouth. If large enough amounts enter the body, heat is produced by the cells in the body, causing an increase in body temperature. The body temperature can increase to dangerous levels, causing injury to various organs and tissues and even death. This effect is the result of exposure to pentachlorophenol itself and not the impurities. The lengths of exposure and the levels that cause harmful effects have not been well defined. Long-term exposure to low levels such as those that occur in the workplace can cause damage to the liver, kidneys, blood, and nervous system. Studies in animals also suggest that the endocrine system and immune system can also be damaged following long-term exposure to low levels of pentachlorophenol. All of these effects get worse as the level of exposure increases.

Decreases in the number of newborn animals, harmful effects on reproductive organs of the mothers, decreases in the number of successful pregnancies, and increases in the length of pregnancy were observed in animals exposed to pentachlorophenol while they were pregnant. Harmful effects on reproductive organs of the females were also seen in animals exposed to pentachlorophenol while they were not pregnant. We do not know if pentachlorophenol produces all of the same effects in humans that it causes in animals.

An increased risk of cancer has been shown in some laboratory animals given large amounts of pentachlorophenol orally for a long time. There is weak evidence that pentachlorophenol causes cancer in humans. The International Agency for Research on Cancer (IARC) has determined that pentachlorophenol is possibly carcinogenic to humans, and the EPA has classified pentachlorophenol as a probable human carcinogen.

Chapters 2 and 3 contain more information on the health effects linked with exposure to pentachlorophenol.

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**1.6 HOW CAN PENTACHLOROPHENOL AFFECT CHILDREN?**

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans.

Children might be exposed to pentachlorophenol by eating fish and other foods contaminated with the substance, by accidentally or intentionally eating soil or drinking water contaminated with the substance, or by drinking breast milk contaminated with the substance. Tests have not been performed to measure pentachlorophenol in breast milk in the United States, although small amounts have been found in the milk of chemical workers in Eastern Europe. Children might also be exposed to pentachlorophenol by breathing air in homes that contain wood that has been treated with the substance or by skin contact with contaminated soils or with the exposed surface of wood that has been treated with the substance. For most people, food is the most important source of intake of pentachlorophenol, and most of this intake is from root vegetables. Based on analyses of foods representative of the diets of different age/gender population groups, daily intakes of pentachlorophenol from the diet, although low overall, are higher in infants and toddlers than in teenagers and adults. Daily intakes of pentachlorophenol from food have decreased over time.

Newborn children who were accidentally exposed to diapers and bedding that were contaminated with pentachlorophenol had high fevers, a large amount of sweating, a hard time with breathing, and harmful effects on their nervous system and liver, and some died. In the newborn animals of mothers that were given pentachlorophenol by mouth, slight changes were seen in the formation of bones and their weight was decreased at weaning. One study in animals showed that large amounts of pentachlorophenol taken by mouth can damage the testes, but it is unknown whether such large amounts affect the ability of animals to have babies. The immune system was suppressed in family members, including children as young as 8 years old, who were exposed to pentachlorophenol while living in log homes. Absorption of pentachlorophenol is expected by all routes of exposure, and the harmful effects of pentachlorophenol should be qualitatively similar over all routes of exposure; these effects might also occur in children exposed to low levels of pentachlorophenol by any route. There is not enough information to know whether

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children under 18 years of age differ from adults in their sensitivity to the health effects of pentachlorophenol. One study in animals found that small amounts of pentachlorophenol may cross the placenta, and it is possible that it can reach and cross the placenta in humans.

**1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO PENTACHLOROPHENOL?**

If your doctor finds that you have been exposed to significant amounts of pentachlorophenol, ask whether your children might also be exposed. Your doctor might need to ask your state health department to investigate.

Pentachlorophenol was a widely used pesticide and a wood preservative (utility poles) for a long time. It is no longer present in any product you can buy today. It can be applied only by certified applicators. Although it is no longer commonly used, traces of pentachlorophenol are still found in small amounts in air, water, and soil. It is also found at some hazardous waste sites.

Up until 1980, you could buy pentachlorophenol-containing pesticides. Since then, it has been regulated and can only be used in a restricted number of places. You may have old containers of pesticides in your attic, basement, or garage that contain pentachlorophenol. Removing these old containers will reduce your family's risk of exposure to pentachlorophenol. You should dispose of these old containers in an appropriate manner through your county's hazardous waste facility. Otherwise, place them out of reach of young children to prevent accidental exposures. You should never store pesticides or household chemicals in containers that children would find attractive to eat or drink from, such as soda bottles.

Your children may be exposed to pentachlorophenol if an unqualified person applies pesticides containing it around your home. In some cases, the improper use of pesticides banned for use in homes has turned homes into hazardous waste sites. Make sure that any person you hire is licensed and, if appropriate, certified to apply pesticides. Your state licenses each person who is qualified to apply pesticides according to EPA standards and further certifies each person who is

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qualified to apply “restricted use” pesticides. Ask to see the license and certification. Also ask for the brand name of the pesticide, a Material Safety Data Sheet (MSDS), the name of the product’s active ingredient, and the EPA registration number. Ask whether EPA has designated the pesticide “for restricted use” and what the approved uses are. This information is important if you or your family react to the product.

Though pentachlorophenol has been found in some foods, its levels are low. You can minimize the risk of your family’s exposure by peeling and thoroughly washing fruits and vegetables before cooking.

Small children have a tendency to eat soil, and to put their hands and foreign objects in their mouths. This could result in their exposure to pentachlorophenol that may be present in the soil and on objects. Children may be exposed to pentachlorophenol by absorption through the skin. Pentachlorophenol is known to be rapidly absorbed by the skin from the soil. You should prevent children from putting their hands and foreign objects in their mouths and you should discourage your children from eating dirt. Make sure they wash their hands frequently. Very low levels of pentachlorophenol have been detected in house and carpet dust. Keeping the house clean and free of dust will reduce your family’s exposure to pentachlorophenol.

Pentachlorophenol was used for treating wood. It is no longer used for treating wood used in and around homes. But it is still used for treating wood utility poles and railroad ties. If you live near a utility pole or railroad tracks, you should prevent your children from playing, climbing, or sitting on them especially in the hot summer months. Old playground equipment may contain pentachlorophenol, and children may be exposed dermally when playing on it. If you have old treated wood in or around your house, covering it with epoxy paint may reduce the risk of your family’s exposure to pentachlorophenol. Wood treated with pentachlorophenol (e.g., railway ties) should not be used for landscaping, especially near gardens or private wells

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**1.8 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO PENTACHLOROPHENOL?**

Pentachlorophenol and its products can be measured in the blood, urine, and tissues of exposed persons. Because urine and blood samples are easily collected, testing these fluids is the best way to find out whether a person has been exposed. Neither test is usually available at a doctor's office because both require the use of special equipment. Although these tests can prove that a person has been exposed, they cannot be used to tell how severe any health effects might be. Because pentachlorophenol leaves the body fairly quickly, these tests are best for finding exposures that occurred within the last several days. Exposure at hazardous waste sites usually includes exposure to other organic compounds, such as hexachlorobenzene, that could break down into pentachlorophenol. On the other hand, measurement of blood and urine levels for pentachlorophenol and its products in groups of exposed people and nonexposed people is a good way to tell whether exposure to pentachlorophenol or members of the same chemical family occurred.

Chapter 7 contains more information on tests for measuring pentachlorophenol in the body.

**1.9 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH?**

The federal government develops regulations and recommendations to protect public health. Regulations can be enforced by law. Federal agencies that develop regulations for toxic substances include the Environmental Protection Agency (EPA), the Occupational Safety and Health Administration (OSHA), and the Food and Drug Administration (FDA). Recommendations provide valuable guidelines to protect public health but cannot be enforced by law. Federal organizations that develop recommendations for toxic substances include the Agency for Toxic Substances and Disease Registry (ATSDR) and the National Institute for Occupational Safety and Health (NIOSH).

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Regulations and recommendations can be expressed in not-to-exceed levels in air, water, soil, or food that are usually based on levels that affect animals; then they are adjusted to help protect people. Sometimes these not-to-exceed levels differ among federal organizations because of different exposure times (an 8-hour workday or a 24-hour day), the use of different animal studies, or other factors.

Recommendations and regulations are also periodically updated as more information becomes available. For the most current information, check with the federal agency or organization that provides it. Some regulations and recommendations for pentachlorophenol include the following:

The federal government has set regulatory standards and guidelines to protect workers from the possible health effects of pentachlorophenol in air. OSHA has set a legally enforceable limit of 0.5 milligrams per cubic meter ( $\text{mg}/\text{m}^3$ ) in workroom air to protect workers during an 8-hour shift over a 40-hour work week.

The federal government has also set regulatory standards and guidelines to protect the public from the possible health effects of pentachlorophenol in drinking water. EPA decided that the amount in the drinking water should not be more than 0.022 milligram per liter ( $\text{mg}/\text{L}$ ) and that any release of more than 10 pounds to the environment should be reported. For short-term exposures, EPA decided that drinking water levels should not be more than 1.0  $\text{mg}/\text{L}$  for 1 day or 0.3  $\text{mg}/\text{L}$  for 10 days. EPA also estimates that for an average-weight adult, exposure to 0.03  $\text{mg}/\text{kg}/\text{day}$  will probably not cause any noncancer health effects. EPA is now working to measure the levels of pentachlorophenol found at abandoned waste sites.

For more information on criteria and standards for pentachlorophenol exposure, see Chapter 8.

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**1.10 WHERE CAN I GET MORE INFORMATION?**

If you have any more questions or concerns, please contact your community or state health or environmental quality department or

Agency for Toxic Substances and Disease Registry  
Division of Toxicology  
1600 Clifton Road NE, Mailstop E-29  
Atlanta, GA 30333

\* Information line and technical assistance

Phone: 1-888-42-ATSDR (1-888-422-8737)  
Fax: 1-404-498-0057

ATSDR can also tell you the location of occupational and environmental health clinics. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

\* To order toxicological profiles, contact

National Technical Information Service  
5285 Port Royal Road  
Springfield, VA 22161  
Phone: (800) 553-6847 or (703) 605-6000





## 2. RELEVANCE TO PUBLIC HEALTH

### 2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO PENTACHLOROPHENOL IN THE UNITED STATES

Pure pentachlorophenol exists as colorless crystals that are poorly soluble in water, but dissolve in organic solvents such as alcohol, ether, and benzene. Typically, commercial grade pentachlorophenol is 86% pure. Contaminants generally consist of other polychlorinated phenols, polychlorinated dibenzo-*p*-dioxins (CDDs), and polychlorinated dibenzofurans (CDFs), which are formed during the manufacturing process and can impart a darker color to the crystals. To increase its water solubility, pentachlorophenol has often been manufactured and marketed as a sodium salt. Pentachlorophenol was, in the past, one of the most heavily used pesticides in the United States, but is now regulated as a restricted-use pesticide and is no longer contained in wood preserving solutions or in insecticides or herbicides available for home and garden use. Its use is restricted to the treatment of utility poles, railroad ties, and wharf pilings. Pentachlorophenol is found in all environmental media as a result of its past widespread use; current releases to the environment are more limited as a result of changing use patterns. In addition, a number of other environmental contaminants, including hexachlorobenzene, pentachlorobenzene, pentachloronitrobenzene, and hexachlorocyclohexane isomers, are known to be metabolized to pentachlorophenol.

Humans may be exposed to pentachlorophenol in occupational settings through inhalation of contaminated workplace air and dermal contact with the compound or with wood products treated with the compound. General population exposure may occur through contact with contaminated environmental media, particularly in the vicinity of wood treatment facilities and hazardous waste sites. Important routes of exposure appear to be inhalation of contaminated air, inhalation exposure to pentachlorophenol that has volatilized from treated wood surfaces, ingestion of contaminated groundwater used as a source of drinking water, ingestion of contaminated food, and dermal contact with contaminated soils or wood products treated with the compound. Children are likely to be exposed to pentachlorophenol by the same routes as adults. In addition, small children are generally more likely than adults to have significant contact with soil and have less concern with hygiene than adults. ATSDR believes that the primary route of human exposure to pentachlorophenol at hazardous waste sites is ingestion of contaminated media, and to a lesser extent, inhalation and dermal contact with contaminated media. Pentachlorophenol has been identified in at least 313 of the 1,585 hazardous waste sites that have

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been proposed for inclusion on the EPA National Priorities List (NPL). However, the number of sites evaluated for pentachlorophenol is not known.

**2.2 SUMMARY OF HEALTH EFFECTS**

Adverse health effects have been observed in humans and experimental animals following short- and long-term exposure to pentachlorophenol by the inhalation, oral, and dermal exposure routes. Reports of inhalation and/or dermal exposure in humans and oral exposure studies in animals make up the bulk of the available toxicity data. The liver, thyroid, immune system, reproductive system, and the developing organism are the primary targets of pentachlorophenol toxicity. Case reports of individuals acutely exposed to pentachlorophenol via inhalation and dermal contact and longer-term occupational exposure via inhalation and/or dermal contact identify a number of adverse health effects. The observed effects include symptoms associated with uncoupling of oxidative phosphorylation (tachycardia, increased respiratory rate, labored breathing, profuse sweating, fever, metabolic acidosis), liver effects, and impaired immune function. The lack of information on exposure characterization and the possible concomitant exposure to other chemicals in the studies reporting these effects somewhat clouds their interpretation. However, acute and longer-term oral studies in experimental animals provide support for these health effects. Since humans are generally exposed to technical-grade pentachlorophenol, which usually contains such toxic impurities as polychlorinated dibenzo-*p*-dioxins and dibenzofurans, some of the effects observed in humans (or the severity and dose-response characteristics of the effects) may be related, at least in part, to the presence of the impurities. Animal studies with both technical-grade and purified pentachlorophenol have demonstrated that, within the ranges of doses tested, some of the toxic effects attributed to pentachlorophenol were actually due to the impurities. Because human exposure is generally to technical-grade pentachlorophenol, studies on technical-grade pentachlorophenol are considered relevant.

In addition to the liver, thyroid, immune, reproductive, and developmental effects, exposure to pentachlorophenol is also associated with carcinogenic, renal, and neurological effects. The results of several epidemiology studies suggest that pentachlorophenol may be a human carcinogen. This assessment is supported by the findings in chronic oral rodent studies of increased incidences of liver tumors (hemangiosarcomas, adenomas, and carcinomas) and adrenal gland pheochromocytomas in mice and mesotheliomas and nasal squamous cell carcinomas in rats. No increases in gene mutations have been observed in a variety of *in vivo* or *in vitro* studies. Clastogenic effects have been observed in a number of *in vitro* studies. The EPA classifies pentachlorophenol in group B2 (probable human

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carcinogen) and IARC classifies it in group 2B (possibly carcinogenic to humans). Several studies have reported adverse health effects in children accidentally exposed to pentachlorophenol. The observed effects were symptoms of oxidative phosphorylation uncoupling (high fever, profuse sweating, increased respiratory rate, labored breathing, tachycardia, hepatomegaly, and irritability) and death. Thus, the effects observed in children are similar to those seen in adults. However, the data are inadequate to assess whether children are more susceptible than adults to the toxicity of pentachlorophenol.

**Hepatic Effects.** A number of case reports describe liver effects in individuals exposed to technical-grade pentachlorophenol either occupationally or in the home via inhalation and/or dermal contact. The types of hepatic effects noted in the case reports include enlarged liver, jaundice, centrilobular degeneration, and elevated serum biliary acid concentrations. Liver enlargement was also observed in newborns exposed for a short time via contaminated diapers and bed linen in a hospital nursery. In addition, elevated urinary porphyrin and delta-amino levulinic acid concentrations and elevated levels of serum alanine aminotransferase and aspartate aminotransferase have been reported in epidemiological studies.

Animal studies have confirmed the identification of the liver as one of the primary targets of pentachlorophenol toxicity. Increased liver weights, increased serum enzymes, and histological alterations (centrilobular hepatocellular hypertrophy and vacuolization, necrosis, degeneration, and periportal fibrosis) have been observed in rats and mice exposed to pure and technical-grade pentachlorophenol.

**Thyroid Effects.** There are limited data on the effect of pentachlorophenol on thyroid function in humans. An inverse relationship between triiodothyronine levels and blood pentachlorophenol levels was found in women with gynecological and/or endocrinological disorders; who lived in homes with wood ceilings and wood panels treated with a wood preservative containing pentachlorophenol. However, the triiodothyronine levels were frequently within the normal range and it is likely that they were also exposed to other chemicals.

In animal studies, decreases in circulating and free concentrations of triiodothyronine and thyroxine have been observed in rats and sheep orally exposed to pure or technical-grade pentachlorophenol for an intermediate duration and first and second generation mink exposed to pentachlorophenol (purity not reported) in a multigeneration study. The chronic-duration oral MRL is based on alterations in thyroid hormone levels (see Section 2.3).

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**Developmental Effects.** Developmental effects (congenital eye cataracts) have been observed in the children of male sawmill workers exposed to a mixture of sodium salts of pentachlorophenol and tetrachlorophenol; however, other chemicals, in particular CDDs, may have contributed to the occurrence of these effects. However, animal studies provide strong evidence that pentachlorophenol is a developmental toxicant following oral exposure. Developmental effects are frequently observed at doses that cause decreases in maternal body weight gain. However, decreases in fetal or pup body weight have been observed at doses that do not result in maternal toxicity. Increases in fetal/neonatal mortality, and soft tissue and skeletal malformations/variation (subcutaneous edema, diaphragmatic hernia, dilation of kidneys, lumbar spurs, and delays in ossification), and decreases in offspring growth have been observed in rats and sheep. Pure pentachlorophenol appears to be slightly more developmentally toxic than technical-grade pentachlorophenol. The maternal dose of technical grade pentachlorophenol that would be lethal to 50% of embryos was over two times higher than for pure pentachlorophenol. The acute-duration oral MRL, see Section 2.3 for details, was based on the increased occurrence of delayed skull ossification in rats.

**Reproductive Effects.** No studies were found that adequately assessed the reproductive toxicity of pentachlorophenol in humans. A possible association between pentachlorophenol exposure and reproductive effects was found in women exposed to technical-grade pentachlorophenol from outgassing wood panels treated with a wood preservative containing pentachlorophenol; however, study limitations, particularly lack of exposure characterization and possible exposure to other chemicals, preclude using these study to establish a causal relationship. A number of animal studies provide evidence that the reproductive system is a sensitive target of pentachlorophenol toxicity. A decrease in fertility was observed in first generation rats administered pentachlorophenol by gavage in a two-generation study; no alterations in fertility were observed in the parental generation in this study. In contrast, no effects on fertility were observed in another multigeneration study in which mink were exposed to lower doses of pentachlorophenol. Several other studies have reported alterations in reproductive tissues. The observed effects include decreased testes weight and focal/multifocal mononuclear cell infiltrate in the epididymis in first generation rats, focal degeneration of the seminiferous tubules in sheep, and increased severity of uterine and oviduct cysts in sheep and mink. Histological alterations were not observed in rats orally exposed to pure or technical-grade pentachlorophenol for an intermediate or chronic duration.

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**Immunological Effects.** Immunological effects have been reported in humans exposed via inhalation and/or dermal contact with pentachlorophenol and in animals following oral exposure. A number of immunological effects (e.g., activated T-cells, autoimmunity, immunosuppression, B-cell dysregulation) have been reported in families living in pentachlorophenol-treated log homes and male factory workers involved in brushing technical-grade pentachlorophenol onto wood strips. A number of animal studies indicate that oral exposure to technical-grade pentachlorophenol affects a wide range of immune functions, such as humoral and cellular immunity, susceptibility to tumor induction, and complement activity. However, studies that tested both technical-grade and pure pentachlorophenol provide strong evidence that the immune effects are related to the level of impurities in the technical-grade product (e.g., CDDs and CDFs). There is some evidence that pure pentachlorophenol is an immunotoxicant in rats. Enhanced mitogen-induced T- and B-lymphocyte blastogenesis and suppression of the antibody response against sheep red blood cells has been observed in rats orally exposed to pure pentachlorophenol (>99% pure with no detectable dioxin impurities) for 28 days. However, studies in mice suggest that pure pentachlorophenol has relatively little immunotoxic activity.

### 2.3 MINIMAL RISK LEVELS

#### *Inhalation MRLs*

Inhalation MRLs for acute, intermediate, or chronic exposure have not been derived. While target organs have been identified in humans following inhalation exposure to technical-grade pentachlorophenol, the exposure levels at which these effects occur have not been quantified. No data exist on the toxicity of pentachlorophenol following inhalation exposure in animals from which MRLs could be developed.

#### *Oral MRLs*

For acute oral exposure, an MRL of 0.005 mg/kg/day has been derived for pentachlorophenol.

This MRL is based on a developmental toxicity study in which groups of pregnant rats were administered pure or technical-grade pentachlorophenol in corn oil by gavage on gestational days 6–15. At the lowest pure pentachlorophenol dose tested (5 mg/kg/day), a significant increase in the occurrence of delayed ossification of the skull was observed. At higher doses (15 mg/kg/day), significant increases in the occurrence of subcutaneous edema, lumbar spurs, and skeletal anomalies in the ribs, sternbrae, and vertebrae were observed. Increased fetal resorptions and decreased fetal body weight were observed at

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\$30 mg/kg/day. Decreases in maternal body weight gain were observed at \$30 mg/kg/day. Similar results were found in rats exposed to technical-grade pentachlorophenol. However, increased fetal resorptions and skeletal anomalies were observed at \$15 mg/kg/day. The MRL was derived by dividing the lowest-observed-adverse-effect level (LOAEL) of 5 mg/kg/day pure pentachlorophenol by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for interspecies extrapolation, and 10 for human variability). Similar developmental effects have been observed in another rat developmental toxicity study. In this study, significant increases in the occurrence of resorptions, and soft tissue and skeletal malformations and variations, and decreases in fetal body weight were observed in the offspring of rats that were administered by gavage 80 mg/kg/day technical-grade (89% pure) pentachlorophenol on gestational days 6–15. This study identified a no-observed-adverse-effect level (NOAEL) of 30 mg/kg/day. Intermediate-duration oral developmental toxicity studies in rats have also reported increased fetal/neonatal mortality, malformations and/or variations, and decreased growth.

C An intermediate-duration oral MRL of 0.001 mg/kg/day has been derived for pentachlorophenol.

This MRL is based on a LOAEL of 1 mg/kg/day for reproductive effects in mink exposed to pentachlorophenol (purity not reported) in the diet for 3 weeks prior to mating and throughout gestation and lactation. At the only dose tested, 1 mg/kg/day, decreases in the proportion of mated females accepting a second mating and mink that whelped were observed. No effect on the proportion of mink accepting the first mating or the proportion of mink with visible implantation sites were found. An increase in the severity cystic uterine glands was also observed in the pentachlorophenol-exposed mink. The MRL was derived by dividing a LOAEL of 1 by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for interspecies extrapolation, and 10 for human variability).

As discussed in the previous section, reproductive effects have also been observed in rats and sheep orally exposed to pentachlorophenol for intermediate or chronic durations, but the results have been inconsistent. Significant decreases in the number of rats mated and in the ratio of pregnant rats to number of rats in cohabitation were observed in a two-generation rat study. The effects were observed in the first generation of rats exposed to 60 mg/kg/day, but not in the parental generation. In contrast, no effects on fertility were observed in a multi-generation study in mink exposed to 1 mg/kg/day pentachlorophenol in the diet or in sheep or sheep offspring (only females were exposed) exposed to 1 mg/kg/day pentachlorophenol in the diet. Histological alterations in female reproductive tissues have also been observed in sheep; increased severity of oviductal intraepithelial cysts in sheep exposed to 2 mg/kg/day pentachlorophenol by gavage twice weekly for 43 days and lymphocyte infiltration into the endometrium

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were observed in sheep exposed to 1 mg/kg/day pentachlorophenol in the diet for 5 weeks prior to mating and during pregnancy and lactation. However, no histological alterations were observed in female mink exposed to 1 mg/kg/day pentachlorophenol in the diet in a multi-generation study.

Liver and developmental effects also appear to be sensitive end points of pentachlorophenol following intermediate-duration oral exposure; the lowest adverse effect levels for these effects are 10-fold higher than the reproductive effects reported in mink. Significant increases in relative liver weight and the occurrence of centrilobular hepatocellular hypertrophy have been reported in rats and mice exposed to <10 mg/kg/day pure or technical-grade pentachlorophenol. At higher doses, hepatocyte degeneration and necrosis have been observed. Developmental effects (decreased pup body weight) have also been observed in rat offspring at 10–15 mg/kg/day.

For chronic oral exposure, an MRL of 0.001 mg/kg/day has been derived for pentachlorophenol.

This MRL was based on a LOAEL of 1 mg/kg/day (only dose tested) for significantly decreased serum thyroxine concentrations first generation males and both males and females of the second generation, and decreased relative thyroid weight second generation females when mink were administered pentachlorophenol of unspecified purity continuously in the diet in a multigeneration reproduction study. Several studies support the identification of the thyroid gland as a sensitive target of pentachlorophenol toxicity. Oral gavage administration of pure pentachlorophenol to young adult female rats over a 28-day period at doses of 3 or 30 mg/kg produced decreases in circulating and free concentrations of the thyroid hormones triiodothyronine and thyroxine in serum, a decrease in serum thyroid stimulating hormone, decreases in intrathyroidal levels of triiodothyronine and thyroxine, a decrease in the thyroxine:triiodothyronine ratio in serum, and a reduction in thyroidal hormone stores. Technical-grade pentachlorophenol, tested only at a dose of 3 mg/kg, produced the same effects, except for the reduction in free triiodothyronine in serum (data for free serum thyroxine were not reported). A decrease in maternal serum thyroxine concentration throughout pregnancy and lactation and a significant increase in maternal thyroid gland follicle size were found in female sheep administered 1 mg/kg/day pentachlorophenol (purity not indicated) in the diet 5 weeks prior to mating and throughout pregnancy and lactation until 2 weeks after weaning of the lambs. Additionally, increased thyroxine levels were observed in their ewe and ram lambs that also received postnatal exposure to pentachlorophenol. The chronic-duration MRL was derived by dividing the LOAEL of 1 mg/kg/day by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for interspecies extrapolation, and 10 for human variability).

***Dermal MRLs***

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Appropriate methodology does not currently exist to develop MRLs for dermal exposure. This is most often because of the difficulty in identifying reliable, absorbed doses from most dermal studies. The paucity of dermal studies is in part due to the difficulty in constructing animal models which limit exposure exclusively to the dermal route. An approach to deriving dermal MRLs from oral or inhalation data through route-to-route extrapolation is currently being evaluated for potential use by the agency.



### **3. HEALTH EFFECTS**

#### **3.1 INTRODUCTION**

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of pentachlorophenol. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

#### **3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE**

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELs have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which

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major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of pentachlorophenol are indicated in Table 3-1 and Figure 3-1. Because cancer effects could occur at lower exposure levels, Figure 3-1 also shows a range for the upper bound of estimated excess risks, ranging from a risk of 1 in 10,000 to 1 in 10,000,000 ( $10^{-4}$  to  $10^{-7}$ ), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for pentachlorophenol. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

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A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

Since humans are generally exposed to technical-grade pentachlorophenol, which usually contains such toxic impurities as polychlorinated dibenzo-*p*-dioxins and dibenzofurans (see Table 3-2), some of the effects observed in humans (or the severity and dose-response characteristics of the effects) may be related, at least in part, to the presence of the impurities. Animal studies with both technical-grade and purified pentachlorophenol have demonstrated that, within the ranges of doses tested, some of the toxic effects attributed to pentachlorophenol were actually due to the impurities. Because human exposure is generally to technical-grade pentachlorophenol and because ATSDR's intent is to protect human health, studies on both technical-grade and purified pentachlorophenol preparations are reviewed, and special reference is made to those adverse effects seen in humans that are believed to be a result of the contaminants.

#### 3.2.1 Inhalation Exposure

Only limited data were available on the inhalation toxicity of pentachlorophenol in humans. Most of the information available for humans comes from cases of acute poisoning following home use of pentachlorophenol-containing products such as wood preservatives or herbicides in the garden (home and garden use of pentachlorophenol is no longer approved by EPA), and following occupational exposure in agricultural and wood-treatment industries. Many of these poisoning incidences involved inhalation and dermal exposure to pentachlorophenol. Below is a discussion of the case reports and studies in which inhalation is the primary route of exposure; the remaining studies are discussed in Section 3.2.3, Dermal Exposure. Exposure concentrations and duration, as well as information on other exposures and contaminants present in technical-grade pentachlorophenol, are often not available in these studies. Thus, no studies were considered suitable for presentation in a table describing significant levels of inhalation exposure to pentachlorophenol.

##### 3.2.1.1 Death

Data on the lethality of pentachlorophenol in humans is limited to a case report of a man who died following 3 weeks of daily occupational exposure to pentachlorophenol dust (purity not reported) (Gray et al. 1985).

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Death has been reported in experimental animals following acute inhalation of sodium pentachlorophenate aerosol. The reported  $LC_{50}$  (45 minutes) for rats is 14 mg/m<sup>3</sup> (11.7 mg/kg) (Hoben et al. 1976b).

#### 3.2.1.2 Systemic Effects

No studies were located regarding any systemic effects in animals after inhalation exposure to pentachlorophenol. No studies were located regarding cardiovascular, gastrointestinal, musculoskeletal, or renal effects in humans after inhalation exposure to pentachlorophenol. It should be noted that many of the systemic effects observed following occupational exposure which are discussed below resulted from uses of pentachlorophenol that are no longer accepted and that the pentachlorophenol used in these instances had a composition (e.g., presence of more impurities) different from the pentachlorophenol that is currently used.

**Respiratory Effects.** In humans, chronic high-dose occupational exposure to pentachlorophenol causes inflammation of the upper respiratory tract and bronchitis (Baader and Bauer 1951; Klemmer et al. 1980). The purity of pentachlorophenol in these cases was not specified, and inhalation of pentachlorophenol contaminants (chlorinated dibenzo-*p*-dioxins and dibenzofurans) and other compounds (such as dieldrin, chromium, fluorine, arsenic, copper, boron, and tin compounds) present in workplace air was likely and may have contributed to the respiratory response observed. Furthermore, the inflammation observed may have also been the result of physical irritation from the inhalation of particulate matter.

**Hematological Effects.** In a chronic occupational study, increased numbers of immature leukocytes and basophils were observed in workers exposed to technical-grade pentachlorophenol; however, these parameters were still within normal limits (Klemmer et al. 1980).

**Hepatic Effects.** In an epidemiology study of male and female pentachlorophenol-production workers, higher urinary excretion of coproporphyrins, compared with unexposed controls, was associated with workers with chloracne involved in the production of pentachlorophenol (Hryhoreczuk et al. 1998). In another epidemiology study, Cheng et al. (1993) found elevated urinary porphyrin and delta-amino levulinic acid concentrations among male workers who produced technical-grade pentachlorophenol, but there were no differences in these parameters between the workers with chloracne and those without.

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**Endocrine Effects.** In a brief report, Gerhard et al. (1991) noted that elevated blood levels of pentachlorophenol ( $>25\text{ }\mu\text{g/L}$ ) and/or lindane ( $>100\text{ ng/L}$ ) were found in 22 of 90 women with histories of habitual abortion, unexplained infertility, menstrual disorders, or the onset of menopause. Exposure duration was 4.6–10 years, and exposure occurred via offgassing (from wooden ceiling and wall panels and from carpets and leather upholstery treated with wood preservatives) as well as via dermal contact with these treated materials. Pentachlorophenol blood levels were highest in the women with infertility (mean= $73\text{ }\mu\text{g/L}$ ) and lower in those with menstrual dysfunction ( $42\text{ }\mu\text{g/L}$ ). Seventeen of the 22 women also exhibited adrenocortical insufficiency, and 6 of these women had thyroid dysfunction as assessed by measurement of thyroid stimulating hormone releasing hormone (no further details were provided). Conclusions cannot be drawn from these data because a control group was not used and statistical analyses were not performed. Gerhard et al. (1998) also examined several endocrine end points among 89 women with repeated miscarriages. An inverse correlation was found between triiodothyronine levels and pentachlorophenol levels. It should be noted that this is a preliminary study; study design limitations include lack of a matched control group, lack of control for other confounding factors, only 15% of the women had pentachlorophenol levels that were above the reference level of  $25\text{ }\mu\text{g/L}$ , no information was provided on possible sources of exposure to pentachlorophenol, and elevated levels of other chlorinated hydrocarbons (e.g., PCBs, DDT) were also present in some of the women. In a third study by Gerhard et al. (1999) of a group of women with gynecological and/or endocrinological disorders, a decrease in triiodothyronine levels were found in women with elevated pentachlorophenol serum levels (median level of  $3.59\text{ }\mu\text{g/L}$ ); although the levels were lower than levels found in age-, geographical region-, and condition-matched controls, the mean and median triiodothyronine levels were within the normal range. An euthyroid goiter was also observed in 50% of these subjects as compared to 30% in the controls. Other statistically significant alterations in endocrine hormones included an increase in adrenocorticotrophic hormone (ACTH)-stimulated cortisol levels and decreases in follicle stimulating hormone, testosterone, hydroepiandrosterone, hydroepiandrosterone sulfate, 17-hydroxypregnenolone, and 17-hydroxyprogesterone levels. As with the triiodothyronine levels, the hormone levels were within the normal range. The source of pentachlorophenol was wood ceilings that were treated with wood preservatives; it is likely that these women were also exposed to other chemicals in the wood preservative.

No studies were located regarding endocrine effects in animals after inhalation exposure to pentachlorophenol.

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**Dermal Effects.** Occupationally-exposed workers at a wood-treatment plant exhibited a statistically significant increase in low-grade inflammation of skin and subcutaneous tissue, and severe eruptions of the skin. However, it is possible these symptoms resulted from exposure to contaminants in pentachlorophenol (chlorinated dibenzo-*p*-dioxins, dibenzofurans) and other materials such as dieldrin, chromium, fluorine, arsenic, copper, boron, and tin compounds (Baader and Bauer 1951; Klemmer et al. 1980). Hosenfeld et al. (1986) reported the presence of skin abnormalities (type not specified) in some residents of log homes treated with pentachlorophenol (purity not indicated).

Numerous occupational exposure studies have reported chloracne, characterized by extensive cysts and pus forming abscesses on the face, chest, abdomen, and proximal part of the extremities in sodium pentachlorophenate (Seghal and Ghorpade 1983) and pentachlorophenol (Cheng et al. 1993; Hryhorczuk et al. 1998; O'Malley et al. 1990) production workers. It is likely that these workers were also exposed to chlorinated dibenzo-*p*-dioxins and dibenzofurans, which are known to induce chloracne in humans.

**Ocular Effects.** Inflammation of the conjunctival membrane of the eyes was observed in workers exposed to technical-grade pentachlorophenol at a wood treatment plant (Klemmer et al. 1980).

#### 3.2.1.3 Immunological and Lymphoreticular Effects

In an epidemiologic study, McConnachie and Zahalsky (1991) evaluated 18 lymphocyte phenotype frequencies, proliferative responses of peripheral lymphocytes to mitogens and allogenic stimulator lymphocytes, serum immunoglobulin levels, and autoantibody levels in 38 people ages 8–60 (21 males) and 9–60 (17 females) from 10 families who had been exposed to pentachlorophenol (purity not indicated) in their pentachlorophenol-treated log homes for periods of 1–13 years. Fifteen of the individuals were children ages 8–18. The mean serum concentration of pentachlorophenol in the individuals who still lived in log homes at the time of the study was 884 µg/L; this was higher than the mean of 420 µg/L found in another study of people living in log homes and a mean level of 40 µg/L reported for members of the general public with no known exposure to pentachlorophenol (Cline et al. 1989). Comparison of the pentachlorophenol-exposed individuals with controls indicated that the exposed individuals had activated T-cells, autoimmunity, immunosuppression, and B-cell dysregulation. T-cell activation was indicated by statistically-significant increases of more than 50% in the proportion of lymphocytes with T-cell activation markers, as detected by monoclonal antibodies, in pentachlorophenol-exposed individuals compared with controls. Autoantibodies were detected in 8 of 38 pentachlorophenol-exposed subjects, and there was increased expression of a monoclonal-antibody-detected marker

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associated with autoimmunity in the pentachlorophenol-exposed group. Functional immunosuppression was indicated by statistically-significant decreases of 24–41% in the proliferative response of peripheral lymphocytes of pentachlorophenol-exposed individuals, compared with controls, to three different mitogens and to allogeneic stimulation in mixed-lymphocyte culture. A statistically-significant increase in natural killer cell function was also reported in pentachlorophenol-exposed women compared with women of the control group. This study is limited by the absence of reported serum pentachlorophenol concentrations in members of the control group and the lack of control for potential confounders such as smoking, hypertension, and alcohol use. Gerhard et al. (1991) reported “immunological disorders” (no further details were given) in 15 of 22 women attending a clinic for reproductive and/or endocrinological disorders. The women were exposed to pentachlorophenol by the outgassing of wood products in the home.

No studies were located regarding immunological effects in animals after inhalation exposure to pentachlorophenol.

#### **3.2.1.4 Neurological Effects**

There are limited data on the neurotoxicity of inhaled pentachlorophenol in humans. Signs of central nervous system toxicity (lethargy and tachypnea) and cerebral edema with focal swelling of the myelin sheath was observed in a worker exposed to pentachlorophenol dust (Gray et al. 1985). It is likely that these effects were secondary to hyperthermia, which resulted from pentachlorophenol-induced uncoupling of oxidative phosphorylation.

A study by Peper et al. (1999) examined neurotoxicity in individuals exposed to wood preserving chemicals used to treat wood ceilings and wood paneling. An increase in subjective symptoms (increased fatigue, distractability, attenuated motivation, and depressed mood) and impaired performance on several objective tests of neurobehavioral performance (paired-associated learning with a distracting condition, verbal memory test with distraction, visual short term memory, and incidental learning of visual objects) were observed in 15 women with elevated pentachlorophenol (mean of 43.6 µg/L) and γ-hexachloro-cyclohexane (0.085 µg/L) blood levels, as compared to a sex-, age-, education-, and intelligence-matched control group. Additionally, the results of the reading speed, naming speed, paired associated learning, and visual short-term memory tests were significantly associated with pentachlorophenol blood levels. Although this study provides some suggestive evidence of the neurotoxic potential of pentachlorophenol,

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interpretation of the results is complicated by co-exposure to high levels of  $\gamma$ -hexachlorocyclohexane (lindane) and other solvents and the small number of subjects.

A reduction in median motor nerve conduction velocity was seen in male pentachlorophenol production workers, as compared to matched controls (Cheng et al. 1993). However, the reduction was only statistically significant in the subgroup of pentachlorophenol workers in the trichlorobenzene tank area where the highest levels of chlorinated dibenzo-*p*-dioxins (CDDs) were also found. In contrast, Triebeg et al. (1987) did not find significant alterations in motor or sensory nerve conduction velocities in the ulnar and/or median nerve in workers exposed to low levels (0.0003–0.18 mg/m<sup>3</sup>) of technical-grade pentachlorophenol.

In a case-control study of patients with Parkinson's disease, Seidler et al. (1996) found significant associations of Parkinson's disease with long-term (>15 years) exposure to wood paneling in the home, contact with wood preservatives in free time, and contact with wood preservatives at work. However, the association of Parkinson's disease with exposure to pentachlorophenol is uncertain because the patients were more likely than control subjects to have used organochlorines and alkylated phosphates/carbamates, and the patients reported more frequent exposure to heavy metals, solvents, exhaust fumes, and carbon monoxide than the control group.

No studies were located regarding neurological effects in animals following inhalation exposure to pentachlorophenol.

#### 3.2.1.5 Reproductive Effects

In a brief report, Gerhard et al. (1991) noted that elevated blood levels of pentachlorophenol (>25  $\mu$ g/L) and/or lindane (>100 ng/L) were found in 22 of 90 women with histories of habitual abortion, unexplained infertility, menstrual disorders, or the onset of menopause. However, a causal relationship between pentachlorophenol exposure and the effects is uncertain because of concurrent exposures to other chemicals, the absence of matched controls, and lack of control for other confounding factors. Gerhard et al. (1999) also examined a group of 65 women with gynecological and/or endocrinological alterations and elevated serum pentachlorophenol levels (median level was 35.9  $\mu$ g/L). Statistically significant decreases in follicle stimulating hormone and testosterone levels were found, as compared to age-, geographical-, region-, and condition-matched controls. Although the hormone levels were lower than in the control group, they were within the normal range of values. The women were exposed to pentachlorophenol via



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outgassing of wood ceilings treated with wood preservatives. It is likely that the women were also exposed to other components of the wood preservatives.

No studies were located regarding reproductive effects in animals following inhalation exposure to pentachlorophenol.

#### **3.2.1.6 Developmental Effects**

Information on the developmental toxicity of pentachlorophenol in humans is limited to a study of male sawmill workers exposed to CDD-contaminated chlorophenate (a mixture of the sodium salts of pentachlorophenol and tetrachlorophenol) (Dimich-Ward et al. 1996). A significant correlation between presumed exposure to chlorophenate and an increased incidence of congenital eye cataracts were observed in the workers' children. Because there were no data on exposure level, exposure to chlorophenate was estimated by 10 experienced workers based on each cohort member's job title.

No studies were located regarding developmental effects in animals after inhalation exposure to pentachlorophenol.

#### **3.2.1.7 Cancer**

Case reports suggest a possible association between cancer (Hodgkin's disease, soft tissue sarcoma, and acute leukemia) and occupational exposure to technical-grade pentachlorophenol (Fingerhut et al. 1984; Greene et al. 1978; Roberts 1983). These studies are limited by confounding factors such as concurrent exposure to other potentially carcinogenic chemicals, small sample size, follow-up periods too short to detect an excess cancer risk, mortality due to competing causes of death, and brief exposure periods.

Several epidemiological studies found no association between inhalation of pentachlorophenol (purity not stated) in any form and cancer in humans (Gilbert et al. 1990; Jäppinen et al. 1989; Johnson et al. 1990; Robinson et al. 1985). For example, workers exposed to wood treating chemicals between the years of 1960 and 1981 were evaluated for health-related problems. Eighty-eight wood treaters having exposures of 0.33–26.3 years, with a median of 6.5 years, were compared to 58 matched controls. No adverse health effects or increased incidence of mortality from exposure were detected even though the urinary pentachlorophenol excretion levels were clearly increased (174 ppb versus 35 ppb) (Gilbert et al. 1990). However, IRIS (1999) indicated that the study of Gilbert et al. (1990) cannot be used as evidence of no

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effect of the exposures based on their evaluation of various aspects of the experimental design and conduct.

Johnson et al. (1990) found no association between soft tissue sarcoma and exposure to chlorophenols in a meta-analysis of deaths due to cancer in 15 cohort studies published 1979–1987. However, each of the individual studies had a low power to detect elevated risk estimates (Johnson et al. 1990). Because of the nature of the analysis performed by Johnson et al. (1990) (deaths due to cancer), their study excluded analysis of two studies, which had only incidence data, that found an association between exposure to technical-grade pentachlorophenol and soft tissue sarcoma (Eriksson et al. 1981; Hardell and Sandstrom 1979). In a recent study, in which all data collection and coding were blinded as to cases or controls, Eriksson et al. (1990) found an association between soft tissue sarcoma and high-grade exposure (1 week or more continuously or at least 1 month totally over the years) to technical-grade pentachlorophenol. Compared with the high-grade pentachlorophenol association, a slightly stronger association was found for chlorophenols exposure and a weaker association was found for exposure to phenoxyacetic acids. In a meta-analysis of four of their previous case-control studies, Hardell et al. (1995) found a significant association between soft tissue sarcoma and exposure to pentachlorophenol (purity not specified). An increase in the occurrence of soft tissue sarcoma was also found in workers reporting exposure to phenoxyacetic acids or chlorophenols. Hoppin et al. (1998) found a significant association in men aged 30–60 years between soft tissue sarcoma risk and ever having high-intensity chlorophenol exposure. However, their findings were also consistent with an association to some other component of cutting oils. Seventeen percent of the jobs rated as high intensity involved wood preservation, whereas 82% involved cutting oils. Due to the limited nature of the exposure information in this study, potential for dioxin exposure could not be evaluated.

Hardell et al. (1994) also reported a significant association, in men of various professions, between non-Hodgkin's lymphoma and high-grade exposure (1 week or more continuously or at least 1 month in total over the years) to pentachlorophenol (purity not specified). Compared with the high-grade pentachlorophenol association, a slightly stronger association was found for high-grade exposure to chlorophenols. Hertzman et al. (1997) reported a borderline positive association between an increasing incidence of non-Hodgkin's lymphoma and increasing chlorophenolate exposure among sawmill workers. The trend approached statistical significance.

Ramlow et al. (1996) reported a significant association between death from kidney cancer and increasing exposure to technical-grade pentachlorophenol but indicated that the finding must be considered

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preliminary because of the small number of cases, lack of control for confounders, and absence of information concerning other occupational exposures.

No studies were located regarding cancer in animals after inhalation exposure to pentachlorophenol.

#### 3.2.2 Oral Exposure

Only two reports were found in the literature concerning adverse effects in humans of ingestion of pentachlorophenol (Cretney 1976; Haley 1977). However, pentachlorophenol (particularly the technical-grade) has been shown to affect several organ systems in experimental animals. Target organs or systems of oral pentachlorophenol-induced toxicity in experimental animals include liver, kidney, central nervous system, endocrine system, immune system, and reproductive system; the developing organism is also a sensitive target of pentachlorophenol toxicity. Hematologic, cardiovascular, and respiratory effects have also been noted following oral administration of pentachlorophenol in experimental animals. Oral administration of pentachlorophenol also produced developmental effects in animals and cancer in rats and mice.

Some of the effects of pentachlorophenol may be due, at least in part, to the uncoupling of oxidative phosphorylation by pentachlorophenol (see Section 3.5), which leads to hyperthermia and related effects. Some effects may also result from chlorinated dibenzo-*p*-dioxin and other impurities in technical-grade pentachlorophenol. The adverse effect of pure pentachlorophenol on thyroid homeostasis and the induction of oxidative deoxyribonucleic acid (DNA) damage by oral exposure to pentachlorophenol may also contribute to its spectrum of toxic effects.

##### 3.2.2.1 Death

One case report that described a suicide from pentachlorophenol ingestion was found in the reviewed literature, but the amount of pentachlorophenol ingested was not specified (Cretney 1976). The lowest human lethal dose for pentachlorophenol (purity not specified) is estimated to be 1 gram (approximately 17.0 mg/kg) (Driesbach 1980).

Pentachlorophenol may cause death in experimental animals following ingestion. Death usually is a result of hyperthermia. There does not appear to be much difference in doses that cause death across species. The LD<sub>50</sub> values were 80–120 mg/kg in rats (St. Omer and Gadusek 1987) and 117–177 mg/kg

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in mice (Borzelleca et al. 1985; Renner et al. 1986). Preweaned and adult rats have been reported to have lower oral LD<sub>50</sub> values for technical-grade pentachlorophenol than juvenile rats (25–50 days old) (St. Omer and Gadusek 1987). The ranges of LD<sub>50</sub> values in preweaned, juvenile, and adult rats were 50–180, 220–230, and 80–120 mg/kg, respectively. The lethality of pentachlorophenol was greatly enhanced when it was administered in a fuel oil or corn oil vehicle (Deichmann et al. 1942). Absorption of chemicals such as pentachlorophenol that have substantial lipid solubility across skin and mucous membranes is increased by the presence of hydrocarbon or corn oil solvents. The greater toxicity of pentachlorophenol when dissolved in these vehicles may be due partly or entirely to more efficient absorption of pure pentachlorophenol.

Deaths were also seen in a 30-day oral range-finding study in mice (NTP 1989), a 28-day oral range-finding study in rats with highly purified pentachlorophenol (Chhabra et al. 1999; NTP 1999), and a 6-month oral study in mice (NTP 1989). At the highest dietary concentration tested (12,500 ppm) in the 30-day study in mice (NTP 1989), incidences of deaths were higher in animals fed pure pentachlorophenol (98.6% pure with <0.0002% chlorinated dibenzo-*p*-dioxins and dibenzofurans) and the purified EC-7 pentachlorophenol preparation (90% pure with <0.0002% chlorinated dibenzo-*p*-dioxins and dibenzofurans) than in animals fed technical-grade pentachlorophenol (90% pure with 0.18% chlorinated dibenzo-*p*-dioxins and dibenzofurans).

All reliable LD<sub>50</sub> values from acute duration studies and NOAELs/LOAELs for death in longer-duration studies are recorded in Table 3-1 and plotted in Figure 3-1.

#### 3.2.2.2 Systemic Effects

No studies were located regarding gastrointestinal, musculoskeletal, dermal, or ocular effects in humans or animals after oral exposure to pentachlorophenol.

The highest NOAEL values and all reliable LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

**Respiratory Effects.** The National Toxicology Program (NTP) conducted a 6-month dietary range-finding study (NTP 1989) with 3 different preparations of pentachlorophenol (technical-grade, Dowicide EC-7, and pure) in B6C3F<sub>1</sub> mice (see analysis in Table 3-2). Increased incidences of nasal mucosal metaplasia/goblet cell hyperplasia, compared with controls, were seen in female mice that received

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral

Table 3-1. Levels of Significant Exposure to Pentachlorophenol							
Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
ACUTE EXPOSURE							
Death							
1	Rat	1x (GO, GW)				27 LD50-0.5% in fuel oil) 78 (LD50-olive oil) 211 (LD50-NaPCP in H2O)	Deichmann et al. 1942 tech NaPCP
2	Rat	1 x (G)				50 (LD50)	St. Omer and Gadusek 1987 tech
3	Mouse	1 x (G)				177 M (LD50) 117 <sup>b</sup> F (LD50)	Borzelleca et al. 1985 pure (approx. 99%)
4	Mouse	1 x (GO)				129 <sup>b</sup> M (LD50) 134 F (LD50)	Renner et al. 1986 pure (99%)
Systemic							
5	Mouse (B6C3F1)	up to 4 wk 7d/wk (F)	Hepatic		41 M (incr liver wt, severe hepatocyte swelling, incr hepatic DNA content and DNA adducts)		Umemura et al. 1996 pure (98.6%)
Immunological/Lymphoreticular							
6	Mouse	14 d 7 d/wk (G)			10 (decr IgM antibody response)		Holsapple et al. 1987 tech
7	Mouse	14 d 7 d/wk (G)		100			Holsapple et al. 1987 tech (90% pure)

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
8	Mouse	1 x (G)		15	30 (decr IgM antibody response)		Kerkvliet et al. 1985a tech (86% pure)
9	Mouse	1 x (G)		120			Kerkvliet et al. 1985a pure (>99%)
10	Mouse	14 d 7 d/wk (G)		100			White and Anderson 1985 tech (91% pure)
11	Mouse	14 d 7 d/wk (G)			100 (inhibition of complement activity)		White and Anderson 1985 tech (90.4% pure)
<b>Developmental</b>							
12	Rat (Sprague-Dawley)	GD6-15 (GO)		30		80 (incr resorptions, decr fetal body weight, and incr soft tissue and skeletal malformations and variations)	Argus 1993b tech (89% pure)
13	Rat	10 d Gd6-15 1 x/d (GO)		5		15 (fetal resorptions, subcutaneous edema, lumbar spurs)	Schwetz et al. 1974 tech (88.4% pure)
14	Rat	10 d Gd6-15 1 x/d (GO)			5 <sup>c</sup> (delayed ossification of skull bones)	30 (42% decr fetal weight; increased male:female ratio)	Schwetz et al. 1974 pure (97.5%)
15	Rabbit (New Zealand)	GD6-18 (GO)		30			Argus 1993a tech (88-89%)

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
INTERMEDIATE EXPOSURE							
Death							
16	Rat	1-3 mo 2x/wk (G)				300 (LD50)	Nishimura et al. 1980 tech NaPCP
17	Rat (Fischer- 344)	28d (F)				270 (death)	NTP 1999; Chhabra et al. 1999 pure (99%)
18	Mouse (B6C3F1)	30 d (F)				4428 M (death)	NTP 1989 tech (90.4% pure)
						3561 <sup>b</sup> F (death)	
19	Mouse (B6C3F1)	30 d (F)				1017 M (death)	NTP 1989 tech (90% pure)
						848 <sup>b</sup> F (death)	
20	Mouse (B6C3F1)	30 d (F)				650 M (death)	NTP 1989 pure (98.6%)

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Systemic							
21	Rat (Sprague- Dawley)	P0: 70 days premating, and through gestation and lactation F1: Bd Wt postnatal day 28 and through gestation and lactation (GO)	Hepatic		10 (incr absolute and relative liver weight and hepatocellular hypertrophy)	30 (hepatocellular necrosis)	Argus 1997 not reported
22	Rat (Fischer- 344)	28 d 2x/wk (GO)	Hepatic		2 M (incr relative wt)		Blakley et al. 1998 pure (>99%)
			Renal		2 M (incr relative wt)		
23	Rat	8 mo 7 d/wk (F)	Hepatic	6 M	36 M (centrilobular hepatocyte hypertrophy)		Kimbrough and Linder 1978 pure (>99%)
			Renal	45 F			
			Bd Wt	6 M	36 M (10% decr bw)		



Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
24	Rat	12 wk 7d/wk (F)	Hemato	2 M	4 M (incr and decr hemoglobin and decr RBC)		Knudsen et al. 1974 tech
			Hepatic	2 M	4 M (incr relative liver weight, centrilobular vacuolization)		
			Renal	4 F	8 F (decr calculi at corticomedullary junction)		
25	Rat	1-3 mo 2x/wk (G)	Hepatic		40 (incr liver weight; decr hepatic glycogen; incr serum lactate dehydrogenase, AST and ALT; hepatocellular swelling; vacuolization)		Nishimura et al. 1980 tech NaPCP
			Metab		40 (incr blood glucose)		
26	Rat (Fischer- 344)	28d (F)	Hepatic		20 F (incr absolute and relative liver wt )	40 (hepatocyte degeneration)	NTP 1999; Chhabra et al. 1999 pure (99%)
			Bd Wt		20 F (14% decr bw gain)	150 F (decr bw gain of 36% or more and wt loss)	
27	Rat	181 d 7d/wk (F)	Bd Wt	4	46 (15% decr maternal bw)		Welsh et al. 1987 pure (>99%)
28	Mouse	10-12 wk 7d/wk (F)	Hepatic		9 (hepatocellular swelling; nuclear swelling and vacuolization)	90 (multifocal necrosis)	Kerkvliet et al. 1982 pure (>99%)

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
29	Mouse	10-12 wk 7d/wk (F)	Hepatic		9 (hepatocyte swelling; nuclear swelling and vacuolization)	90 (multifocal necrosis)	Kerkvliet et al. 1982 tech (86% pure)
30	Mouse	6 wk 7d/wk (F)	Hepatic		47.1 (incr liver wt)		Kerkvliet et al. 1985a tech (86% pure)
			Other		47.1 (incr p-450 associated EROD activity)		
31	Mouse (B6C3F1)	6 mo (F)	Resp	209 F			NTP 1989 tech (90.4% pure)
			Hepatic			48 M (karyomegaly, cytomegaly, hepatocellular degen and necrosis, incr AHH activity and P450 levels, incr liver wt, incr liver porphyrins, incr serum ALT)	
			Bd Wt	376 M			
			Other		48 M (granular eosinophilic pigment in the urinary bladder, without inflammation)		

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
32	Mouse (B6C3F1)	6 mo (F)	Resp		64 F (nasal mucosal metaplasia/goblet cell hyperplasia)		NTP 1989 tech (90% pure)
			Hepatic			49 M (karyomegaly, cytomegaly, hepatocellular degen and necrosis)	
			Bd Wt	49 M	148 M (decr bw gain of 21%)		
			Other		49 M (granular eosinophilic pigment in the urinary bladder, without inflammation)		
33	Mouse (B6C3F1)	6 mo (F)	Resp		67 F (nasal mucosal metaplasia/goblet cell hyperplasia)		NTP 1989 pure (98.6%)
			Hepatic			67 F (karyomegaly, cytomegaly, and hepatocellular degen and necrosis, incr relative liver wt, incr serum ALT)	
			Bd Wt	168 F	544 F (decr bw gain of 18%)	381 M (decr bw gain of 30%)	
			Other		67 F (granular eosinophilic pigment in the urinary bladder, without inflammation)		
34	Mouse (B6C3F1)	30 d (F)	Hepatic	20 M		105 M (cytomegaly, karyomegaly, nuclear atypia, degen, or necrosis of the liver)	NTP 1989 tech (90.4%)
			Bd Wt	105 M		528 M (41% decr in bw gain)	

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Table 3-1. Levels of Significant Exposure to Pentachlorophenol							
Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference Chemical Form
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)	
35	Mouse (B6C3F1)	30 d (F)	Hepatic	21 M		104 M (cytomegaly, karyomegaly, nuclear atypia, degen, or necrosis of the liver)	NTP 1989 tech (90% pure)
			Bd Wt	104 M		1017 M (86% decr in bw gain)	
36	Mouse (B6C3F1)	30 d (F)	Hepatic	23 M		101 M (cytomegaly, karyomegaly, nuclear atypia, degen, or necrosis of the liver)	NTP 1989 pure (98.6%)
			Bd Wt	101 M		604 M (80% decr in bw gain)	
37	Mouse (B6C3F1)	up to 4 wk 7d/wk (F)	Hepatic		41 M (incr liver wt, severe hepatocyte swelling, incr hepatic DNA content and DNA adducts)		Umemura et al. 1996 pure (98.6%)
38	Pig	30 d 7d/wk (C)	Hemato	5	10 (decreased white blood cell count)		Greichus et al. 1979 pure
			Hepatic	5	10 (increased liver weight; diffuse cloudy hepatocellular swelling)		
			Renal	10			
Immunological/Lymphoreticular							
39	Rat (Fischer- 344)	28 d 2x/wk (GO)			2 M (enhanced lymphocyte blastogenesis, suppressed antibody response against sheep RBC)		Blakley et al. 1998 pure (>99%)

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
40	Mouse	10-12 wk 7d/wk (F)			9 (enhanced susceptibility to tumor growth)		Kerkvliet et al. 1982 tech (86% pure)
41	Mouse	10-12 wk 7d/wk (F)		9	90.3 (enhanced susceptibility to tumor growth)		Kerkvliet et al. 1982 pure (>99%)
42	Mouse	6 wk 7d/wk (F)			1.9 (decr antibody response)		Kerkvliet et al. 1985a tech (86% pure)
43	Mouse	8 wk 7d/wk (F)			50.1 (reduction in lymphoproliferative response in mixed lymphocyte culture)		Kerkvliet et al. 1985b tech (86% pure)
44	Mouse (B6C3F1)	6 mo (F)			48 M (decr immune response to sheep RBC injection)		NTP 1989 tech (90.4% pure)

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Key to <sup>a</sup> figure	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form	
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)		Serious (mg/kg/day)
Reproductive							
45	Rat (Sprague- Dawley)	P0: 70 days premating, and through gestation and lactation F1: postnatal day 28 and through gestation and lactation (GO)		10	30 (decr testicular spermatid count)	60 (decr fertility)	Argus Research Laboratories, 1997 not reported
46	Rat (Fischer- 344)	28d (F)		150 M		270 M (min to marked germinal epithelial degen & lack of spermatozoa in the seminiferous tubules of the testes, considered secondary to the generalized poor condition of the high-dose rats)	NTP 1999; Chhabra et al. 1999 pure (99%)
47	mink	3 wk pre-breeding thru weaning 1x/d (F)			1 <sup>d</sup> F (incr severity of cystic uteri, decr acceptance of 2nd mating, decr birth rate)		Beard et al. 1997  not reported

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Table 3-1. Levels of Significant Exposure to 1-Entandriophenol							
Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference Chemical Form	
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)		Serious (mg/kg/day)
Developmental							
48	Rat (Sprague- Dawley)	P0: 70 days premating, and through gestation and lactation F1: postnatal day 28 and through gestation and lactation (GO)		10	(decr pup body weight)	60 (decr pup survival)	Argus 1997 not reported
49	Rat	10 week premating throughout gestation and lactation (F)				48 (decr litter size)	Exon and Koller 1982 tech (85.5% pure)
50	Rat	181 d 7d/wk (F)		4	14 (10% decr fetal bw)	46 (embryo lethality)	Welsh et al. 1987 pure (>99%)

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
CHRONIC EXPOSURE							
Systemic							
51	Rat (Fischer- 344)	52 wk (F)	Bd Wt			60 (decr bw gain of 24-35% at wk 52)	NTP 1997; Chhabra et al. 1999 pure (99%)
			Hepatic		60 M (basophilic foci, hepatodiaphragmatic nodules, chronic inflammation, and hepatocyte cystic degeneration)		
52	Rat (Fischer- 344)	105 wk (F)	Hepatic		10 M (hepatocyte cystic degen and hepatodiaphragmatic nodules)		NTP 1999; Chhabra et al. 1999 pure (99%)
			Bd Wt	20	30 (decr bw gain of 10-17%)		
53	Rat	22-24mo 7d/wk (F)	Hepatic	3 F	10 F (accumulation of brown pigment; elevated ALT)		Schwetz et al. 1978 tech (90% pure)
			Renal	3 F	10 F (accumulation of brown pigment in kidney tubules; increase in urine specific gravity)		
			Bd Wt	10 F	30 F (12% decr bw as compared to controls)		
54	mink	3 gen (F)	Endocr		1 <sup>e</sup> (statistically significant decr serum thyroxine and decr relative thyroid wt)		Beard and Rawlings 1998 not reported



Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Table 3-1. Levels of Significant Exposure to Pentachlorophenol							
Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
Reproductive							
55	mink	3 gen (F)		1			Beard and Rawlings 1998 not reported
Cancer							
56	Rat (Fischer- 344)	52 wk at 60; 105 wk at lower doses (F)				60 M (CEL, malignant mesothelioma and nasal squamous cell carcinoma)	NTP 1999; Chhabra et al. 1999 pure (99%)
57	Mouse	103 wk 1x/d (F)				17.5 (pheocromocytomas; hepatocellular carcinoma-CEL)	NTP 1989 tech (90% pure)

Table 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (continued)

Key to figure <sup>a</sup>	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
58	Mouse	103 wk 1x/d (F)				18 (hemangiosarcomas of the liver and spleen-CEL)	NTP 1989 tech (90% pure)

<sup>a</sup>The number corresponds to entries in Figure 3-1.

<sup>b</sup>Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 3-1. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

<sup>c</sup>Used to derive an acute-duration oral Minimal Risk Level (MRL) of 0.005 mg/kg/day; dose divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

<sup>d</sup>Used to derive an intermediate-duration oral Minimal Risk Level (MRL) of 0.001 mg/kg/day; dose divided by an uncertainty factor of 1000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

<sup>e</sup>Used to derive a chronic-duration oral Minimal Risk Level (MRL) of 0.001 mg/kg/day; dose divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

Bd Wt = body weight; bw = body weight; CEL = cancer effect level; conc = concentration(s); d = day(s); decr = decrease; degen = degenerative;  
 EC-7 = a mixture containing 90% pure pentachlorophenol; Endocr = endocrine; (F) = feed; F = female(s); (G) = gavage; Gd = gestation day; gen = generation(s);  
 (GO) = gavage in oil; (GW) = gavage in water; IgM = immunoglobulin M; incr = increase; Ld = lactation day; LOAEL = lowest-observed-adverse-effect level;  
 LD50 = lethal dose, 50% kill; M = males; min = minimal; mo = month(s); NaPCP = sodium pentachlorophenol; NOAEL = no-observed-adverse-effect level;  
 RBC = red blood cell; Resp = respiratory; SGOT = serum glutamic oxaloacetic transferase; SGPT = serum glutamic pyruvic transaminase; tech = technical grade;  
 TG-penta = technical grade pentachlorophenol; (w) = water; wk = week(s); wt = weight; x = times(s)

Figure 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral  
Acute ( $\leq 14$  days)

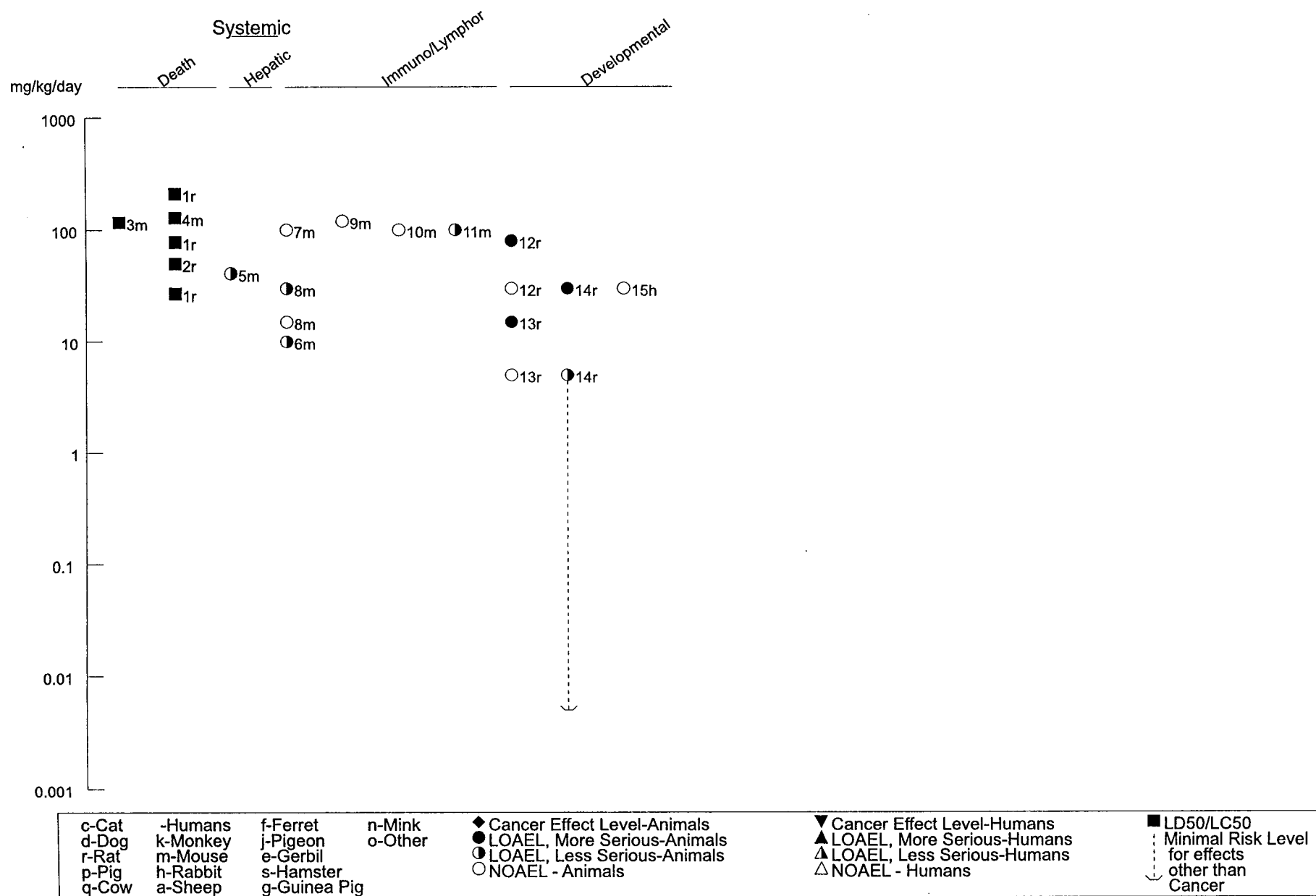
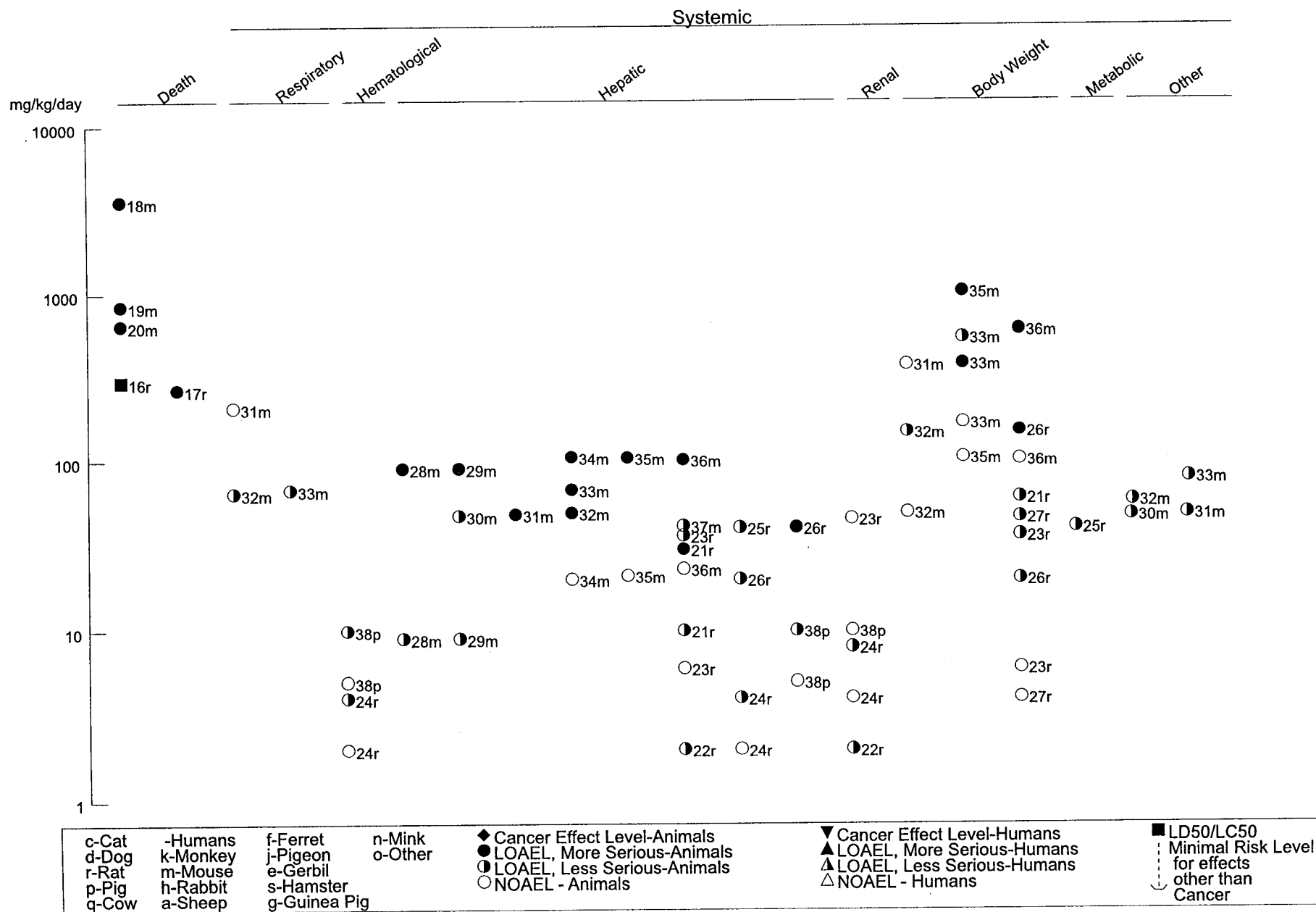


Figure 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (*continued*)

Intermediate (15-364 days)



Intermediate (15-364 days)

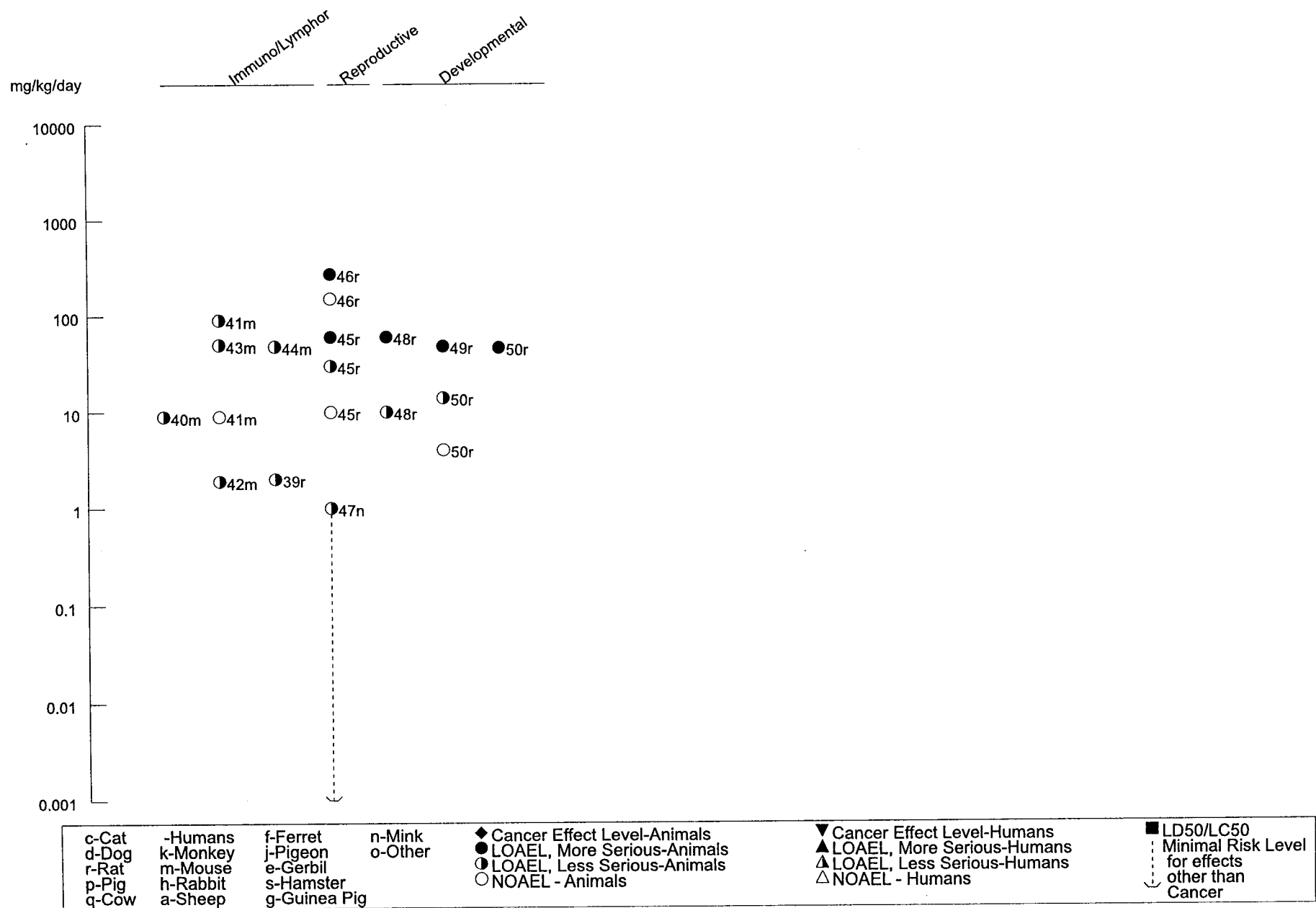
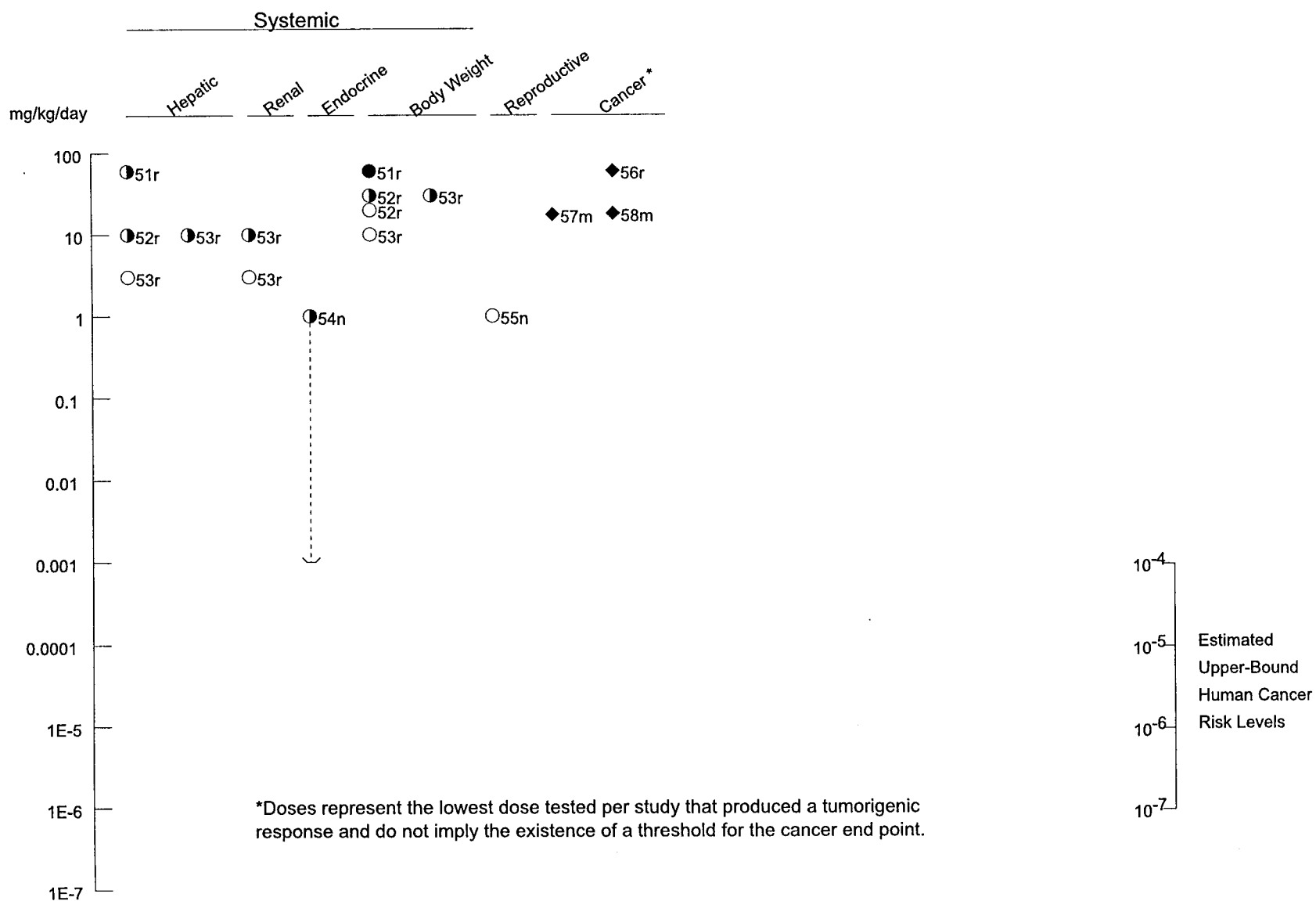


Figure 3-1. Levels of Significant Exposure to Pentachlorophenol - Oral (*continued*)Chronic ( $\geq 365$  days)

c-Cat	-Humans	f-Ferret	n-Mink	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	j-Pigeon	o-Other	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	Minimal Risk Level
r-Rat	m-Mouse	e-Gerbil		○ LOAEL, Less Serious-Animals	△ LOAEL, Less Serious-Humans	for effects
p-Pig	h-Rabbit	s-Hamster		○ NOAEL - Animals	△ NOAEL - Humans	other than
q-Cow	a-Sheep	g-Guinea Pig				Cancer

**Table 3-2. Results of Analyses of Impurities Present in the Pentachlorophenol Used in National Toxicology Program (NTP) Feeding Studies and the Types of Tumors They Induce<sup>a,b</sup>**

Impurity	Technical grade	Dowicide EC-7 <sup>c</sup>	Pure	Tumor type	Species
Dichlorophenol	–	–	–	No data	
Trichlorophenol <sup>d</sup>	100 ppm	70 ppm	100 ppm	Liver, leukemias <sup>e</sup> , lymphomas	Rat, mouse
Tetrachlorophenol	38,000 ppm	94,000 ppm	14,000 ppm	Not carcinogenic	Rat, mouse
Hexachlorobenzene	50 ppm	65 ppm	10 ppm	Liver	Rat, hamster, mouse
				Thyroid/ Parathyroid	Rat
				Adrenal	Rat
				Kidney	Rat
				Lymphosarcomas	Mouse
Tetrachlorodibenzodioxin	–	<0.04 ppm	<0.08 ppm	Liver, thyroid	Rat, mouse (both tumor types)
Hexachlorodibenzodioxin	10.1 ppm	0.19 ppm	<1 ppm	Liver	Rat, mouse
Heptachlorodibenzodioxin	296 ppm	0.53 ppm	–	No data	
Octachlorodibenzodioxin	1,386 ppm	0.69 ppm	<1 ppm	No data	
Pentachlorodibenzofuran	1.4 ppm	–	–	No data	
Hexachlorodibenzofuran	9.9 ppm	0.13 ppm	–	No data	
Heptachlorodibenzofuran	88 ppm	0.15 ppm	–	No data	
Octachlorodibenzofuran	43 ppm	–	–	No data	
Heptachlorohydroxydiphenyl ether	500 ppm <sup>f</sup>	–	100 ppm	No data	

**Table 3-2. Results of Analyses of Impurities Present in the Pentachlorophenol Used in National Toxicology Program (NTP) Feeding Studies and the Types of Tumors They Induce <sup>a,b</sup> (continued)**

Impurity	Technical grade	Dowicide EC-7 <sup>c</sup>	Pure	Tumor type	Species
Octachlorohydroxydiphenyl ether	19,100 ppm	–	900 ppm	No data	
Nanochlorohydroxydiphenyl ether	35,600 ppm	–	2,100 ppm	No data	
Hexachlorohydroxydibenzofuran	1,600 ppm	–	1,100 ppm	No data	
Heptachlorohydroxydibenzofuran	4,700 ppm	–	2,200 ppm	No data	

<sup>a</sup>Samples were dissolved in benzene, placed on a deactivated alumina column, and eluted with benzene. Further separation was carried out with a basic aluminum oxide column; elution was with methylene chloride in hexane. Identification was performed by gas chromatography with an SP2100 capillary column/mass spectrometry; quantitation was by comparison with spiked samples analyzed by gas chromatography with an SP1240 DA column.

<sup>b</sup>Derived from NTP 1989

<sup>c</sup>Four unidentified impurities with concentrations of 0.14, 0.057, 0.045, and 0.035 ppm were also detected.

<sup>d</sup>Identified as the 2,3,6-isomer; another isomer was believed to be present but was not identified.

<sup>e</sup>Data are for 2,4,6-isomer.

<sup>f</sup>Includes octachlorodiphenyl ether

– = not detected; EC-7 = Dow Company chemical name



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dietary doses of \$64 mg/kg/day EC-7 (90% pure) and \$67 mg/kg/day pure pentachlorophenol, but were not observed in the female mice exposed to 209 mg/kg/day technical-grade pentachlorophenol (which contains relatively high concentrations of chlorinated dibenzo-*p*-dioxins and dibenzofurans). The female mice appeared to be more sensitive to the nasal effects than the male mice. The LOAELs for nasal lesions were 148 and 381 mg/kg/day in the EC-7 and pure pentachlorophenol groups, respectively.

**Cardiovascular Effects.** One report describing effects of ingestion of pentachlorophenol in humans was found in the literature (Haley 1977). In this case, an adult male intentionally ingested an estimated 4–8 ounces of weed killer that contained 12% pentachlorophenol, 1.5% other chlorinated phenols, 82% aromatic hydrocarbons, and 4.5% inert ingredients. Clinical signs observed upon subsequent hospital admission included tachycardia. This effect is possibly the result of pentachlorophenol's ability to uncouple oxidative phosphorylation, leading to hyperthermia.

One early report described the occurrence of extensive vascular damage and heart failure in rats, rabbits, guinea pigs, and dogs following a single oral administration (dose not specified) of pentachlorophenol of unidentified purity (Deichmann et al. 1942).

**Hematological Effects.** No studies were located regarding hematological effects in humans after oral exposure to pentachlorophenol.

Various hematologic changes of questionable biological significance have been reported in animal studies. A depression in number of erythrocytes, a decrease in hemoglobin level, and a decrease in packed cell volume were observed in rats fed technical-grade pentachlorophenol for 90 days but not in those fed purified pentachlorophenol (Johnson et al. 1973). However, a decrease in white blood cell count was observed in pigs administered purified pentachlorophenol for 30 days (Greichus et al. 1979). Conflicting findings over time were reported in rats fed a purified pentachlorophenol preparation, which contained no tetrachlorodibenzo-*p*-dioxin (2,3,7,8-TCDD) and <0.03% of the other chlorinated dibenzo-*p*-dioxins, for 12 weeks (Knudsen et al. 1974). Increased hemoglobin and hematocrit were observed after 6 weeks of treatment, followed by a decrease in hemoglobin and erythrocytes at study termination.

**Hepatic Effects.** No studies were located regarding hepatic effects in humans after oral exposure to pentachlorophenol.

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The liver is a target organ for pentachlorophenol-induced toxicity in experimental animals. Evidence of biochemical (alterations in hepatic enzyme activities), and gross (increased liver weight), and histopathological (hypertrophy, vacuolization, hyperplasia, fibrosis, necrosis, and degeneration) effects is seen following acute, intermediate, and chronic oral exposure to pentachlorophenol in rodents. At low dosages, the observed liver effects are characteristic of enzyme induction. Increases in liver weight and hepatocellular hypertrophy and vacuolization have been observed in mice exposed to 41 mg/kg/day pure pentachlorophenol for 2 weeks (Umemura et al. 1996), in rats exposed to 1–40 mg/kg/day pure or technical-grade pentachlorophenol for an intermediate duration (Argus 1997/Bernard et al. 2001c; Blakley et al. 1998; Kimbrough and Linder 1978; Knudsen et al. 1974; Nishimura et al. 1982; NTP 1999), in mice exposed to 9 mg/kg/day pure or technical-grade pentachlorophenol for 4–12 weeks (Kerkvliet et al. 1982; Umemura et al. 1996), and in pigs exposed to 10 mg/kg/day pure pentachlorophenol for 30 days (Greichus et al. 1979).

The severity of the liver damage increased with increasing exposure concentrations. Intermediate-duration exposure to doses of 7–48 mg/kg/day pure or technical-grade pentachlorophenol resulted in necrosis, periportal fibrosis, and hepatocellular degeneration in rats (Argus 1997/Bernard et al. 2001c; Kimbrough and Linder 1978; NTP 1989) and multifocal necrosis and hepatocellular degeneration in mice exposed to 67–105 mg/kg/day pure or technical-grade pentachlorophenol (Kerkvliet et al. 1982; NTP 1989). Hepatocellular degeneration was observed in rats exposed to 10–60 mg/kg/day pure pentachlorophenol in the diet for 52 or 104 weeks (NTP 1999). The biochemical changes consisted of increases in the serum levels of alanine and aspartate aminotransferase at 40 and 67 mg/kg/day pure or technical-grade pentachlorophenol in rats (Nishimura et al. 1980) and mice (NTP 1989), respectively.

The results of the Kimbrough and Linder (1978) study suggests that the impurities found in technical-grade pentachlorophenol may influence its toxicity. The liver effects observed in this study included centrilobular hepatocyte hypertrophy at 1 mg/kg/day, periportal fibrosis at 7 mg/kg/day, and periportal fibrosis and bile duct proliferation at 48 mg/kg/day in rats exposed to technical-grade pentachlorophenol in the diet for 8 months. In contrast, minimal liver effects (centrilobular hepatocyte hypertrophy) were observed at the highest tested dose (32 mg/kg/day) of pure pentachlorophenol. It is possible that the tetrachlorophenol, hexachloro-*p*-dibenzodioxin, heptachloro-*p*-dibenzodioxin, octachloro-*p*-dibenzodioxin, hexachlorodibenzofuran, pentachlorodibenzofuran, and tetrachlorodibenzofuran present in the technical-grade pentachlorophenol influenced its hepatotoxicity. However, other studies that compared the hepatotoxicity of pure and technical-grade pentachlorophenol did not find differences in potency or the type of liver effects (Kerkvliet et al. 1982; NTP 1989).

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**Renal Effects.** No studies were located regarding renal effects in humans after oral exposure to pentachlorophenol.

There is evidence of mild-to-moderate renal toxicity in experimental animals as a result of long-term oral administration of pentachlorophenol. The most frequently reported toxic effects seen in kidneys of rodents include increased organ weight and altered enzyme levels. Histopathologic effects are rarely seen. The possibility that impurities in pentachlorophenol may be responsible for the adverse effects observed is likely. Furthermore, some of the data discussed below have many inconsistencies.

Purified pentachlorophenol (2 mg/kg/day, only dose tested, >99% pure with no detectable dioxin impurities) induced a small but significant increase in relative kidney weight in rats exposed twice weekly for 28 days (Blakley et al. 1998).

When similar doses of technical-grade and purified pentachlorophenol (>99% pure) were fed to rats for 8 months, the pure compound induced a slight, non-dose-related increase in kidney weight in males, whereas the technical-grade compound did not alter kidney weight in either sex (Kimbrough and Linder 1978). When similar doses of technical-grade and pure pentachlorophenol (no detectable chlorinated dibenzo-*p*-dioxins) were fed to rats for 3 months, increased kidney weight was reported at 10–30 mg/kg/day of the technical-grade preparation, but only at the 30 mg/kg/day dose of the pure pentachlorophenol (Johnson et al. 1973). In neither study were renal histopathological changes observed to accompany organ weight changes. Thus, the biological significance of these observations with regard to long-term toxicity is not known.

Increased kidney weight and urine specific gravity and a dose-related incidence of kidney discoloration were observed in rats fed 1–30 mg/kg/day of Dowicide EC-7 (a purified pentachlorophenol containing <0.0002% chlorinated dibenzo-*p*-dioxins and dibenzofurans) for 24 months (Schwetz et al. 1978). Pigmentation *per se* is not considered an adverse effect. Biochemical changes indicative of renal toxicity have also been reported in pentachlorophenol-treated animals. For example, after 15 days of oral exposure to purified pentachlorophenol at 10 or 15 mg/kg/day, young pigs exhibited statistically significant increased levels of blood urea nitrogen, but this effect was no longer significant after 30 days of treatment (Greichus et al. 1979). Proximal tubular alkaline phosphatase activity was decreased after 1 month of twice-weekly gavage doses (40–160 mg/kg/day) of 90% pure pentachlorophenol (sodium salt; impurities not identified) administered to rats, but this effect was no longer evident after 3 months of

## 3. HEALTH EFFECTS

treatment (Nishimura et al. 1980). The biological significance of these apparently transient renal effects with regard to long-term toxicity is not known.

**Endocrine Effects.** No studies were located regarding endocrine effects in humans after oral exposure to pentachlorophenol.

Significant alterations in thyroid hormone levels have been observed in several intermediate- and chronic-duration animal studies. Oral gavage administration of pure pentachlorophenol to young adult female rats over a 28-day period at a dose of 30 mg/kg produced decreases in circulating and free concentrations of the thyroid hormones triiodothyronine and thyroxine in serum, a decrease in serum thyroid stimulating hormone, decreases in intrathyroidal levels of triiodothyronine and thyroxine, a decrease in the ratio of serum thyroxine to triiodothyronine, and a reduction in thyroidal hormone stores. Decreases in circulating and free thyroxine were also observed at 3 mg/kg/day. Technical-grade pentachlorophenol, tested only at a dose of 3 mg/kg, produced the same effects as 30 mg/kg of pure pentachlorophenol except the reduction in free T3 in serum (data for free serum T4 were not reported). Technical-grade pentachlorophenol, in addition, produced an increase in thyroid epithelial-cell height (Jekat et al. 1994). In a multigeneration study in mink, significant decreases in serum thyroxine levels were observed in the F1 males and the F2 males and females exposed to 1 mg/kg/day pentachlorophenol (purity not reported) (Beard and Rawlings 1998). A decrease in relative thyroid weight was also observed in the F2 female mink. This LOAEL of 1 mg/kg/day was used to derive a chronic-duration oral MRL of 0.001 mg/kg/day, as described in the footnote in Table 3-1.

Alterations in thyroid hormone levels were also observed in a series of studies in sheep. A significant decrease in thyroxine levels was observed in female sheep administered 2 mg/kg/day pure pentachlorophenol by gavage twice weekly for 36 days (Rawlings et al. 1998). Exposure of female sheep to 1 mg/kg/day pentachlorophenol (purity not reported) for 5 weeks pre mating and throughout gestation and lactation, resulted in significant decreases in serum thyroxine levels in the mothers (Beard et al. 1999b), in the ram lambs that were also exposed for 20 weeks post weaning (Beard et al. 1999a), and in the ewe lambs also exposed for 67 weeks post weaning (Beard and Rawlings 1999). No alterations in thyroid stimulating hormone levels or the response to thyroid releasing hormone were observed in the female offspring. However, in response to thyroid stimulating hormone, there were reductions in the magnitude and duration of the thyroxine response and in the maximum triiodothyronine level and net triiodothyronine increase.

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There are limited data on the toxicity of pentachlorophenol to other endocrine tissues. A significant increase in mean serum insulin concentrations was seen in sheep receiving twice weekly gavage doses of 2 mg/kg/day (Rawlings et al. 1998). No alterations in cortisol levels were observed in ram lambs (Beard et al. 1999a).

**Body Weight Effects.** Significant (~10%) decreases in body weight gain were observed in several studies where both technical-grade and pure pentachlorophenol were administered orally for intermediate or chronic durations to rats or mice (Chhabra et al. 1999; Kimbrough and Linder 1978; Nishimura et al. 1980; NTP 1989, 1999; Welsh et al. 1987). Suppression of body weight gain by oral administration of pentachlorophenol was also reported in maternal animals, fetuses, and neonates.

**Metabolic Effects.** There are limited data on the metabolic toxicity of pentachlorophenol. Nishimura et al. (1980) reported significant increases in blood glucose levels and decreases in hepatic glycogen levels in rats administered 40 mg/kg/day technical-grade sodium pentachlorophenate by gavage twice weekly for 1 to 3 months.

**Other Systemic Effects.** In the intermediate-duration studies conducted by NTP (1989), granular eosinophilic pigment was observed in the epithelial cells of the urinary bladder of rats exposed to technical-grade pentachlorophenol, EC-7 (90% pure), and pure pentachlorophenol; the increase in pigment was not accompanied by inflammation.

#### 3.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans following oral exposure to pentachlorophenol.

Evidence for pentachlorophenol-induced alterations in immune function was obtained from studies conducted in experimental animals. The available data indicate that, at doses of 0.5–100 mg/kg/day, pentachlorophenol affects a wide range of immune functions, such as humoral and cellular immunity, susceptibility to tumor induction, and complement activity. Detailed studies in mice indicate that the majority of the immunotoxic effects of pentachlorophenol appear to be related to the level of impurities in the technical-grade product (e.g., polychlorinated dibenzo-*p*-dioxins and dibenzofurans) (Kerkvliet et al. 1982, 1985a; NTP 1989; White and Anderson 1985). However, a recent study in rats provides evidence that pure pentachlorophenol (>99% with no detectable dioxin impurities) can affect immune function

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(Blakley et al. 1998). Studies that compared effects of technical-grade to pure pentachlorophenol are reviewed below in an attempt to illustrate immunotoxic effects attributable to pentachlorophenol.

Female B6C3F<sub>1</sub> mice exposed daily to 10–100 mg/kg of technical-grade pentachlorophenol by gavage for 2 weeks exhibited a dose-related suppression of *in vivo* antibody response (IgM plaque-forming cells [PFC]) to sheep red blood cells (SRBC) when mice were immunized during exposure (Holsapple et al. 1987). This response was not seen following exposure to purified pentachlorophenol at a dose of 100 mg/kg. It was further observed that spleen cells from mice treated with technical-grade pentachlorophenol could still produce antibodies following *in vitro* immunization, indicating that the suppression seen following *in vivo* immunization was not due to a direct effect on antibody-forming cells.

Purified pentachlorophenol (>99% pure with no detectable dioxin impurities) administered to male F344 rats twice weekly for 28 days at a dose of 2 mg/kg/treatment significantly enhanced mitogen-induced T- and B-lymphocyte blastogenesis and significantly suppressed the antibody response against injected sheep red blood cells when the response was expressed per viable spleen cell (Blakley et al. 1998).

In 6-month dietary range-finding studies (NTP 1989) with 3 different preparations of pentachlorophenol (technical-grade, Dowicide EC-7, or pure) in B6C3F<sub>1</sub> mice (see Table 3-2), the antibody response to sheep red blood cell injection was decreased at doses of technical-grade pentachlorophenol \$48 mg/kg/day in males but was not affected in males by dosing with Dowicide EC-7 or pure pentachlorophenol. Antibody response data were not reported for females. In the same studies, significant increases in relative spleen weight were not seen in dosed females, but were seen in males at doses of 376 mg/kg/day technical-grade pentachlorophenol, \$49 mg/kg/day Dowicide EC-7, and \$225 mg/kg/day pure pentachlorophenol.

Effects of dietary administration of both technical-grade and purified pentachlorophenol for 10–12 weeks on the ability of male B6C3F<sub>1</sub> mice to resist syngeneic tumor growth, an indication of an organism's state of immunosurveillance, were studied (Kerkvliet et al. 1982). Technical-grade preparation induced a significant dose-independent enhancement of susceptibility to methylcholanthrene-induced sarcoma 1412 tumor growth, whereas the purified preparation had no effect on this parameter. In another test of immunocompetence, treated mice were studied for their ability to resist secondary tumor growth induced by Maloney sarcoma virus (MSV). After exposure to technical-grade pentachlorophenol, animals were inoculated with MSV, which resulted in transient subcutaneous injection-site tumors. Upon subsequent challenge with MSV-transformed tumor cells, a significant increase in mortality and secondary tumor

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susceptibility was seen in animals treated with technical-grade pentachlorophenol but not in animals administered purified pentachlorophenol. This result suggests a detrimental effect of components of the technical-grade pentachlorophenol on both primary and secondary T-cell-dependent cytotoxic immune response. An increase in secondary splenic tumors was seen in animals treated with both grades of pentachlorophenol at a dose of 25 mg/kg/day. This was interpreted as a more sensitive indicator of immunocompetence suppression by purified pentachlorophenol. In a third test designed to evaluate macrophage competence, resistance to encephalomyocarditis virus (EMCV) was also studied in mice treated with both grades of pentachlorophenol. No effect was seen on susceptibility of either group of animals to EMCV-induced mortality. The investigators concluded that immunomodulatory effects observed with pentachlorophenol were due primarily, but not exclusively, to contaminants present in the technical-grade preparation.

To further investigate the role of these impurities in immunotoxicity induced by technical-grade pentachlorophenol, the antibody (IgM) response to an SRBC challenge in C57BL/6 mice given single oral doses of both grades of pentachlorophenol was studied (Kerkvliet et al. 1985a). In agreement with results seen by Holsapple et al. (1987), technical-grade pentachlorophenol induced a dose-related suppression of this response at a dose of 30 mg/kg/day whereas purified pentachlorophenol did not. Co-administration of heptachloro-*p*-dibenzodioxin (HpCDD), one of the most prevalent chlorinated dibenzo-*p*-dioxin impurities in technical-grade pentachlorophenol, with pure pentachlorophenol resulted in an immunosuppressive response that was similar in magnitude to that seen with technical-grade pentachlorophenol or HpCDD alone. These results provide good evidence that impurities (particularly HpCDD) are responsible for some of the immunotoxic effects attributed to technical-grade pentachlorophenol. Results from the next series of experiments conducted by these investigators further supported this hypothesis. Technical-grade pentachlorophenol was fed to both C57BL/6 mice and DBA/2 mice for 6 weeks (Kerkvliet et al. 1985a). The former strain has a high-affinity aryl hydrocarbon (Ah) receptor and the latter a low-affinity Ah receptor. The ability of chlorinated dibenzo-*p*-dioxin and dibenzofuran congeners (that are present as impurities in pentachlorophenol) to bind to this receptor correlates with their toxicity and their ability to induce P<sub>1</sub>-450 monooxygenase activity. Antibody response to SRBC was suppressed by 28% (p#0.01) and 72% (p#0.01) in the 2 groups of C57BL/6 mice with different levels of technical-grade pentachlorophenol, as opposed to 0 and 45% (p>0.01) in corresponding groups of D2 mice. Based on these results, the authors concluded that the immunosuppressive effect of technical-grade pentachlorophenol was probably mediated by contaminant chlorinated dibenzo-*p*-dioxins and dibenzofurans via interaction with the Ah receptor.

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In a study designed to evaluate effects of dietary exposure to technical-grade pentachlorophenol on T-cell, macrophage, and natural killer cell activity, C57BL/6 mice were administered technical-grade pentachlorophenol for 8 weeks prior to conducting a number of *in vitro* immunofunction tests (Kerkvliet et al. 1985b). They found that T-cell and macrophage-mediated (cell-mediated) immunocompetence is relatively resistant to perturbation by technical-grade pentachlorophenol. The only statistically significant change seen was a reduction in lymphoproliferative response in mixed lymphocyte culture. This finding contrasts with marked effects that technical-grade pentachlorophenol has on antibody-mediated immunity.

The complement component of the immune system in mice has also been found to be affected by exposure to technical-grade pentachlorophenol, but not Dowicide EC-7, a preparation of 90% pentachlorophenol that contains reduced levels of chlorinated dibenzo-*p*-dioxins and dibenzofurans (see Table 3-2) (White and Anderson 1985). In this study, technical-grade pentachlorophenol inhibited functional activity of all aspects of complement in a dose-dependent manner. This suppression was still seen up to 30 days after termination of treatment.

The highest NOAEL values and all LOAEL values from each reliable study for immunological effects in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

#### 3.2.2.4 Neurological Effects

One report describing effects of ingestion of pentachlorophenol in humans was found in the literature (Haley 1977). In this case, an adult male intentionally ingested an estimated 4–8 ounces of weed killer that contained 12% pentachlorophenol, 1.5% other chlorinated phenols, 82% aromatic petroleums, and 4.5% inert ingredients. Clinical signs observed upon subsequent hospital admission included pyrexia, diaphoresis, hyperkinesis, muscle twitching, tremors, epigastric tenderness, leg pain, tachypnea, and tachycardia. These neurologic symptoms may be the result of pentachlorophenol's ability to uncouple oxidative phosphorylation (including the resultant increase in body temperature, tachycardia, and tachypnea) rather than a direct toxic effect of pentachlorophenol on the central or peripheral nervous systems.

Results from animal studies demonstrate that the central nervous system is adversely affected by pentachlorophenol, possibly as a result of hyperthermia induced by uncoupling of oxidative phosphorylation. At the neurochemical level, transient changes in activity of some brain enzymes and decreased glial



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glutathione levels were seen in rats administered technical-grade pentachlorophenol in drinking water for 14 weeks (Savolainen and Pekari 1979). These findings suggest another biochemical component to technical-grade pentachlorophenol neurotoxicity. The possibility and extent of the role of technical-grade contaminants in producing these effects are not known, although the study authors concluded that the neurochemical changes were most likely associated with the body burden of chlorophenols. Inhibition of the uptake of thyroxine into the cerebrospinal fluid, as demonstrated in rats following intraperitoneal injection of pentachlorophenol is another possible component of pentachlorophenol neurotoxicity.

Degenerative changes in 10% of the Types A and B fibers consisting of breaks in the myelin sheath of sciatic nerves and a variable loss of neurotubules, neurofilaments, and other axoplasmic components were observed in male rats administered 38 mg/kg/day pentachlorophenol (purity not reported) in drinking water for 90 days or 114 mg/kg/day for 120 days. Type C fibers were unaffected. These changes were more marked in the rats receiving the higher dose. No effects were observed in rats exposed to 11.4 mg/kg/day for 60 days or 38 mg/kg/day for 60 days. While these results suggest that pentachlorophenol can cause neurotoxic changes in the morphology of peripheral nerves, since the purity of the pentachlorophenol tested was not specified, it is not possible to determine whether these changes were due to pentachlorophenol itself or impurities present in technical-grade pentachlorophenol. Other limitations associated with this study include a lack of protocol details (e.g., number of animals per group) and a lack of quantitative incidence data (Villena et al. 1992).

The NTP (1989) conducted a 6-month dietary range-finding study with three different preparations of pentachlorophenol (technical-grade, Dowicide EC-7, or pure [see composition in Table 3-2]) in B6C3F<sub>1</sub> mice. Neurobehavioral studies were conducted during exposure weeks 5 and 26. No pentachlorophenol-related neurobehavioral effects were observed at 5 weeks except for animals administered technical-grade pentachlorophenol, which showed a dose-dependent decrease in motor activity and rotarod performance. In contrast, exposure to all 3 pentachlorophenol preparations caused dose-related increases in both motor activity and startle response in female mice at 26 weeks, whereas only technical-grade pentachlorophenol caused these effects in male mice. NTP (1989) did not provide actual dose-response data.

The LOAEL for neurological effects in rats following intermediate exposure is recorded in Table 3-1 and plotted in Figure 3-1.

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**3.2.2.5 Reproductive Effects**

No studies were located regarding reproductive effects in humans after oral exposure to pentachlorophenol.

A number of animal studies have examined the reproductive toxicity of pentachlorophenol. The available data suggest that long-term exposure to pentachlorophenol can decrease fertility, although the mechanism does not appear to be through histological damage to reproductive tissue. In a two-generation study, decreased fertility (significant decreases in the number of rats mated and in the ratio of pregnant rats to the number of rats in cohabitation) was observed in the first generation of rats exposed to 60 mg/kg/day pentachlorophenol (purity not reported) administered by gavage (Argus 1997/Bernard et al. 2001c). No alterations in fertility were observed in the F1 generation exposed to 10 or 30 mg/kg/day or in the parental generation. The only other reproductive effects observed in this study were a significant decrease in testicular spermatid count, decreases in absolute testes weight and the ratio of testes weight to brain weight, and focal/multifocal mononuclear cell infiltrate in the epididymis in the F1 rats administered 30 or 60 mg/kg/day. However, no alterations in the average number of motile or nonmotile sperm, epididymal or testicular sperm counts, or sperm morphology were observed in either generation. No alterations in reproductive tissues were observed in the female rats. Significant increases in the average day of preputial separation and vaginal patency were observed in the F1 generation, suggesting that *in utero* exposure to pentachlorophenol disrupted the normal development of the reproductive system. No adverse reproductive effects were observed in another multigeneration study in which mink were fed a diet containing 1 mg/kg/day pentachlorophenol (purity not reported) (Beard and Rawlings 1998). A single-generation mink study also conducted by this group reported significant decreases in the proportion of mated females accepting a second mating and the proportion of mink that whelped, although no effect on the proportion of mink that accepted the first mating or the proportion of mink with visible implantation sites were found (Beard et al. 1997). In both studies, the minks were exposed to 1 mg/kg/day pentachlorophenol (purity not reported) in the diet for 3 weeks prior to mating. Additionally, no significant alterations in mating response, ovulation rate, follicle and corpus luteum size, gestation length, pregnancy rate, lambing rate, and lamb birth rate were observed in sheep exposed to 1 mg/kg/day pentachlorophenol in the diet for 5 weeks pre-mating and throughout the gestation and lactation periods (Beard et al. 1999b). No effect on fertility was observed in the offspring of these sheep, later mated to unexposed males (Beard and Rawlings 1999).

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Several reproductive toxicity and nonreproductive toxicity studies have reported histological alterations in reproductive tissues. The observed effects include focal degeneration of the seminiferous tubules and decreased sperm density in the epididymis body (but not in caput or cauda epididymis) in sheep exposed to 1 mg/kg/day pentachlorophenol (purity not reported) in the diet during gestation, lactation, and for 20-weeks postnatally (Beard et al. 1999a), minimal to marked germinal epithelial degeneration and lack of spermatozoa in the seminiferous tubules of rats exposed to 270 mg/kg/day pure pentachlorophenol in the diet for 28 days (effects may have been secondary to poor condition of animals) (Chhabra et al. 1999; NTP 1999), increased severity of cystic uterine glands in mink exposed to 1 mg/kg/day pentachlorophenol (purity not reported) prior to mating and during gestation and lactation periods (Beard et al. 1997), increased severity of oviductal intraepithelial cysts in sheep administered 2 mg/kg/day pure pentachlorophenol by gavage twice weekly for 43 days (Rawlings et al. 1998), and lymphocyte infiltration into the endometrium in sheep exposed to 1 mg/kg/day pentachlorophenol (purity not reported) in the diet for 5 weeks pre-mating and during the gestation and lactation periods (Beard et al. 1999b). No histological alterations in reproductive tissues were observed in male or female rats chronically exposed to 30 mg/kg/day pure pentachlorophenol in the diet for 2 years (Chhabra et al. 1999; NTP 1999). Additionally, no alterations in reproductive hormones (estradiol, testosterone, progesterone, follicle stimulating hormone, and/or luteinizing hormone levels) have been observed in mink (Beard et al. 1997) or sheep (Beard et al. 1999a). The LOAEL of 1 mg/kg/day for decreases in the proportion of females accepting a second mating and the number of mink that whelped and the increased severity of cystic uterine glands identified in the single-generation mink study was used to derive an intermediate-duration oral MRL of 0.001 mg/kg/day, as described in the footnote in Table 3-1.

#### **3.2.2.6 Developmental Effects**

No studies were located regarding developmental effects in humans after oral exposure to pentachlorophenol.

A number of animal studies have examined the developmental toxicity of pentachlorophenol and provide evidence that gestational exposure can result in fetal/neonatal mortality, malformation/variations, decreased growth, and possibly functional deficits in rats and sheep. No developmental effects have been observed in rabbits administered up to 30 mg/kg/day 88–89% pure pentachlorophenol by gavage on gestational days 6–18 (Argus 1993a/Bernard et al. 2001c). Significant increases in postimplantation resorptions or embryo lethality were observed in rats administered 30 mg/kg/day pure pentachlorophenol or 15 mg/kg/day technical-grade (88.4% pure) pentachlorophenol by gavage on gestational days

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6–15 (Schwetz et al. 1974), in rats administered 80 mg/kg/day 89% pure pentachlorophenol by gavage on gestational days 6–15 (Argus 1993b/Bernard et al. 2001b), and in the offspring of rats exposed to 46 mg/kg/day pure pentachlorophenol in the diet during mating and gestation (Welsh et al. 1987). A decrease in litter size and decreases in neonatal survival were observed in offspring of rats exposed for 77 days prior to gestation and throughout the gestation and lactation periods to 30 mg/kg/day 90.4% pure pentachlorophenol in the diet (Schwetz et al. 1978), in rats exposed to 48 mg/kg/day 85.5% pure pentachlorophenol in the diet for 10 weeks prior to mating and throughout gestation and lactation (Exon and Koller 1982), and in F1 and F2 rat pups exposed to 60 mg/kg/day pentachlorophenol (purity not specified) (Argus 1997/Bernard et al. 2001c). Schwetz et al. (1974) reported marked changes in the sex ratio of rats exposed to pentachlorophenol; the majority of surviving rats were males. The ratios were 3.6 and 4.9 in the rats administered 50 mg/kg/day technical-grade pentachlorophenol and 30 mg/kg/day pure pentachlorophenol, respectively, as compared to respective control values of 1.0 and 1.1. Other developmental toxicity studies have not found alterations in sex ratio (Argus 1993b/Bernard et al. 2001b, Argus 1997/Bernard et al. 2001c).

The occurrence of malformations and variations has been reported in a small number of studies. Soft tissue (subcutaneous edema) and skeletal (lumbar spurs) anomalies were observed in the offsprings of rats exposed by gavage 15 mg/kg/day of technical-grade (88.4%) pentachlorophenol (Schwetz et al. 1974) and skeletal (variations in vertebral, sternal, and pelvic ossification, increased rib pairs, delays in sternal forelimb and hindlimb ossification) and soft tissue (diaphragmatic hernia, slight to moderate dilation of the kidneys) malformations and variations have been observed in rat offspring administered 80 mg/kg/day, but not 30 mg/kg/day, 89% pure pentachlorophenol on gestational days 6–15 (Argus 1993b/Bernard et al. 2001b).

Decreases in growth have been reported in a number of developmental toxicity studies. Statistically significant decreases in fetal body weights were observed in the offspring of rats administered pure or technical-grade pentachlorophenol by gavage at doses of 30 mg/kg/day (Argus 1993b/Bernard et al. 2001b; Courtney et al. 1976; Larsen et al. 1975; Schwetz et al. 1974). Decreases in pup weight have been observed in the offspring of rats administered 14 mg/kg/day 99% pure pentachlorophenol in the diet (Welsh et al. 1987), rats in a two-generation study administered 10 mg/kg/day pentachlorophenol (purity not specified) in the diet (Argus 1997/Bernard et al. 2001c), and in sheep fed 1 mg/kg/day pentachlorophenol (purity not reported) in the diet (Beard et al. 1999b).

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There is some limited evidence that gestational/lactational exposure to pentachlorophenol may impair the development of the reproductive system. Significant increases in the average day of vaginal patency in F1 females exposed to 60 mg/kg/day and preputial separation in F1 males exposed to 60 mg/kg/day (Argus 1997/Bernard et al. 2001c). Decreased fertility was also observed in the F1 generation.

Schwetz et al. (1974) examined the differences in the developmental toxicity between pure and technical-grade pentachlorophenol. The pure pentachlorophenol was slightly more toxic than the technical-grade pentachlorophenol in terms of maternal body weight gain, fetal resorptions, fetal body weight, and occurrence of fetal anomalies. The study authors estimated that the maternal dose that would be lethal to one half of the embryos was 16 mg/kg/day pure pentachlorophenol versus 44 mg/kg/day for technical-grade pentachlorophenol.

In many of the oral developmental toxicity studies, decreases in maternal body weight were observed at the same doses as the developmental effects in rats (Argus 1993b/Bernard et al. 2001b; Courtney et al. 1976; Schwetz et al. 1974). However, in other rat studies (Argus 1997/Bernard et al. 2001c; Welsh et al. 1987), the LOAEL for maternal toxicity was higher than the LOAEL for developmental effects (decreased fetal or pup body weight), suggesting that developmental toxicity can occur in the absence of maternal toxicity.

The highest NOAEL values and all LOAEL values from each reliable study for developmental toxicity in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

#### **3.2.2.7 Cancer**

Lampi et al. (1992) demonstrated significantly elevated risk ratios, compared to reference populations, for non-Hodgkin's lymphoma and soft tissue sarcoma among people who consumed fish from a lake contaminated with tri-, tetra-, and penta-chlorophenols and drank water from wells nearby. For non-Hodgkin's lymphoma, there was a significant association with fish consumption. The population was not exposed to chlorinated dibenzodioxins or dibenzofurans.

Carcinogenicity of orally administered pentachlorophenol has been tested in at least four studies using rats and mice (Inns et al. 1969; NCI 1968; NTP 1989, 1999 [data also reported by Chhabra et al. 1999]; Schwetz et al. 1978). The purity of pentachlorophenol in these studies varied; this is an important factor to consider because pentachlorophenol, during its production, is usually contaminated with chlorinated

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dibenzo-*p*-dioxins, some of which are animal carcinogens. NTP (1989) tested both technical-grade pentachlorophenol (TG-Penta), a 90% pure composite mixture of 3 technical-grades of pentachlorophenol, and Dowicide EC-7, a mixture containing 90% pure pentachlorophenol and fewer chlorinated dibenzo-*p*-dioxin impurities than TG-Penta (see Table 3-2). NCI (1968) tested Dowicide EC-7 as well. Schwetz et al. (1978) tested Dowicide EC-7. NTP (1999) tested pure pentachlorophenol (approximately 99% with one impurity, tetrachlorophenol).

NCI administered Dowicide EC-7 (0 or 17 mg/kg/day) in the diet of weanling B6C3F<sub>1</sub> mice for 78 weeks (NCI 1968), while NTP (1989) administered Dowicide EC-7 (0, 18, 37, or 118 mg/kg/day) in the diet of B6C3F<sub>1</sub> mice for 103 weeks. No significant elevation in incidence of cancer occurred in the NCI study; however, in the NTP study, significant increases in incidence of tumors were observed. Male mice displayed significant dose-related increases in the incidence of adrenal medulla pheochromocytomas (benign and malignant) and hepatocellular adenomas and carcinomas. Female mice in the high-dose group displayed significant increases in incidences of hepatocellular adenoma and carcinoma, in pheochromocytomas (benign and malignant), and in hemangiosarcomas (spleen and liver). The differences between the two studies were that NCI tested for a shorter period of time, used fewer animals per group, had higher mortality in the dose group leaving fewer animals to be at risk of developing tumors, and used only one dose that was one-sixth of the highest dose used in the NTP study, and, therefore, was probably not the maximum tolerated dose.

NTP (1989) also tested TG-Penta, a composite mixture of three technical-grades of pentachlorophenol. This mixture contained a higher percentage of chlorinated dibenzo-*p*-dioxin contaminants than did the Dowicide EC-7 mixture (see Table 3-2). Groups of male and female B6C3F<sub>1</sub> mice were given diets that contained 0, 100, or 200 ppm TG-Penta (equivalent to 0, 18, or 35 mg/kg/day, respectively) or Dowicide EC-7 (as described above for 103 weeks). Survival was reduced in all groups, including controls, when compared to historical controls. Male mice displayed a significant increase over the male control incidence in tumors of the adrenal medulla (benign and malignant pheochromocytomas combined) and liver (adenomas and carcinomas combined). Treated female mice displayed a significant increase over female controls with regard to incidence of hemangiosarcomas of the spleen and liver. Chlorinated dibenzo-*p*-dioxins were found in the TG-Penta mixture at a concentration of 0.17%, but the mixture contained no 2,3,7,8-TCDD. Chlorinated dibenzo-*p*-dioxin exposure has been associated with an increased incidence of liver tumors in treated mice but not with pheochromocytomas or hemangiosarcomas (NCI/NTP 1980). Although this study is limited because of unusually low survival in the male

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TG-Penta control group, the occurrence of rare hemangiosarcomas was considered a carcinogenic response due to pentachlorophenol exposure.

In the NTP (1999) study, groups of male and female F344 rats were given diets that contained 0, 200, 400, or 600 ppm pentachlorophenol (approximately 99% pure with one impurity, tetrachlorophenol) in the diet (equivalent to doses of 0, 10, 20, or 30 mg/kg/day) for 105 weeks. A stop-exposure group was given a diet that contained 1,000 ppm pentachlorophenol for 52 weeks (equivalent to a dose of 60 mg/kg/day) followed by a control diet through 105 weeks. At 2 years, a significantly increased incidence of malignant mesothelioma originating from the tunica vaginalis was present in 60 mg/kg/day stop exposure group males compared with controls, and the incidence exceeded the historical control range. Nasal squamous cell carcinomas were present in one control male, three 10 mg/kg/day males, one 20 mg/kg/day male, and five 60 mg/kg/day males at 2 years, and the incidence in 1,000-ppm males exceeded the historical control range.

In an earlier study, Dowicide EC-7 was administered to rats at dietary levels of 0, 1, 3, 10, or 30 mg/kg/day in males and females for 22 months and 24 months, respectively (Schwetz et al. 1978). No significant increases in incidence of tumors were observed during this study. The study was limited, however because a small number of animals was tested, no data on survival were provided to evaluate if enough animals survived for a long enough period of time to develop tumors, and it is not known if the maximum tolerated dose was attained.

The NTP (1999) study in F344 rats showed some evidence that purified pentachlorophenol (approximately 99% with one impurity, tetrachlorophenol) is carcinogenic, producing mesotheliomas and nasal squamous cell carcinomas. The most convincing evidence that 90% pure pentachlorophenol is carcinogenic to mice following ingestion comes from the NTP (1989) bioassay. This study was generally well conducted, taking into account the lifetime of the study animal, that gross necropsy and histopathology were completed on all suitable animals, and that percentages of the maximum tolerated dose were administered to determine carcinogenic response. It is limited because the unusually low survival of males in the TG-Penta control group left fewer control animals at long-term risk of developing tumors.

EPA has classified pentachlorophenol as a Group B2 substance (probable human carcinogen) (IRIS 2001). A cancer potency factor of  $0.12 \text{ (mg/kg/day)}^{-1}$  was calculated by IRIS (2001) based on the NTP (1989) data. This cancer potency factor translates to estimated upper-bound unit risk levels of  $9 \times 10^{-3}$ ,

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$9 \times 10^{-4}$ ,  $9 \times 10^{-5}$ ,  $9 \times 10^{-6}$ , and  $9 \times 10^{-7}$  mg/kg/day for cancer risks of 1 in 1,000, 1 in 10,000, 1 in 100,000, 1 in 1 million and 1 in 10 million respectively (see Figure 3-1).

The CELs for pentachlorophenol are recorded in Table 3-1 and plotted in Figure 3-1, and the estimated upper-bound human cancer risk levels are plotted in Figure 3-1.

#### 3.2.3 Dermal Exposure

Data on the toxicity of pentachlorophenol in humans exposed via dermal contact come from a number of case reports and studies in individuals applying wood preservative products containing pentachlorophenol, using pesticides containing sodium pentachlorophenate, or children exposed to pentachlorophenol used in the laundering of diapers and bedding. The primary route of exposure is believed to be dermal contact, although inhalation exposure also occurred. Studies in which inhalation exposure was the primary route and dermal contact the secondary route are discussed in Section 3.2.1 Inhalation Exposure. No studies considered suitable for presentation in a table describing significant levels of dermal exposure to pentachlorophenol were found.

##### 3.2.3.1 Death

In most instances, death in humans exposed to pentachlorophenol was a result of occupational exposure or use of pentachlorophenol-containing products in the home by individuals who did not employ proper precautionary measures. All of these reports are limited in that the possibility of concurrent exposure to other potentially toxic substances in technical-grade pentachlorophenol and concurrent exposure to other toxic substances (e.g., lindane, dieldrin) cannot be excluded, and because the pentachlorophenol exposure level and duration cannot be quantified because appropriate measurements were not taken at the time. Deaths were also seen in human infants exposed to pentachlorophenol used in the laundering of diapers and bedding. Though the primary route of exposure in all of these studies was believed to be dermal, the probability that inhalation exposure also occurred must be considered. It should be noted that occupational exposure to pentachlorophenol has been strictly limited not only by use patterns but by application procedures, and all household uses of pentachlorophenol have been banned. Therefore, exposure to pentachlorophenol resulting in death as described in this section is currently improbable, with the exception of hazardous waste workers involved in the clean up of pentachlorophenol-containing ponds or soils. It should also be noted that the deaths discussed below resulted from the use of



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formulations that likely had a different composition (e.g., presence of more impurities) than the pentachlorophenol that is currently used.

In a case report, nine infants in a small nursery for newborns exhibited an illness characterized by high fever, profuse sweating, increased respiratory rate, labored breathing, tachycardia, hepatomegaly, irritability followed by lethargy, metabolic acidosis, proteinuria, increased blood urea nitrogen, and pneumonia or bronchiolitis (Smith et al. 1996). Two of the infants died. At autopsy, both infants showed fatty metamorphosis of the liver and one showed fatty vacuolar changes in the renal tubules. The remaining infants recovered after exchange transfusions and transfer to another hospital. The clinical findings and deaths were attributed to the use of pentachlorophenol in a mixture of synthetic phenolic derivatives in the hospital laundry as an antimildew agent. Pentachlorophenol was found in freshly laundered diapers and in the serum and urine of the infants.

Five cases of fatal blood dyscrasias were reported. Reports followed exposures to technical-grade pentachlorophenol or pentachlorophenol of undefined purity for 1-month to 4-year periods—three as a result of industrial exposure and two from home use (Roberts 1963, 1981, 1990). The cause of death in all cases was reported to be either aplastic anemia or red blood cell aplasia. Clinical signs, chemistries, and postmortem findings revealed functional and degenerative changes in most organ systems. Deaths attributed to pentachlorophenol were also reported in a male working as a wood preserver for 1 week (Bergner et al. 1965), 5 herbicide sprayers exposed once (Gordon 1956), and nine sawmill workers exposed for 3–30 days (Menon 1958). Deaths reported by Gray et al. (1985), Bergner et al. (1965), and Menon (1958) were all due to hyperthermia that resulted from uncoupling of oxidative phosphorylation by pentachlorophenol. Manifestations of overexposure were chiefly those associated with hyperthermia: flushing, intense thirst, sweating, weakness, and occasionally, muscle spasms. Toxic effects seen in these fatalities will be discussed in sections dealing with specific organ toxicity. Hyperthermia is the major factor leading to death following fatal pentachlorophenol exposure in humans.

One report of death following dermal exposure in experimental animals was found in the reviewed literature (Deichmann et al. 1942). Eight out of 20 rabbits administered dermal applications of 4% pentachlorophenol (purity not indicated) in fuel oil for 6–61 weeks died of unspecified causes. The vehicle contained known toxic substances (e.g., polyaromatic hydrocarbons), which may have contributed to the lethal effects observed.

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**3.2.3.2 Systemic Effects**

Most of the literature reviewed concerning systemic effects of dermal exposure to pentachlorophenol in humans described case reports of individuals exposed either occupationally or in the home during misuse of pentachlorophenol-containing solutions as a result of failure to adhere to appropriate precautionary measures. The predominant route of exposure in such cases is dermal, but the possibility of some inhalation exposure cannot be ruled out. All of these reports are limited because the possibility of concurrent exposure to other potentially toxic substances in technical-grades of pentachlorophenol cannot be excluded, and because the pentachlorophenol exposure level and duration were not quantified. Some of the effects observed may be secondary to hyperthermia generated by uncoupling of oxidative phosphorylation (see Section 2.5).

No studies were located regarding cardiovascular, musculoskeletal, endocrine, or ocular effects in humans or respiratory, cardiovascular, gastrointestinal, musculoskeletal, hepatic, renal, endocrine, or ocular effects in animals after dermal exposure to pentachlorophenol.

**Respiratory Effects.** In a case report, nine infants in a small nursery for newborns exhibited increased respiratory rate and labored breathing from exposure to pentachlorophenol in a mixture of synthetic phenolic derivatives in diapers and linens from the hospital laundry (Smith et al. 1996). It is likely that these effects are secondary to hyperthermia rather than a direct effect on the respiratory tract.

**Gastrointestinal Effects.** Except for anecdotal reports of abdominal pain, nausea, and vomiting in humans occupationally exposed to pentachlorophenol of undefined purity (Gordon 1956; Menon 1958), no studies were located regarding gastrointestinal effects in humans or animals following dermal exposure to pentachlorophenol.

**Hematological Effects.** Incidents of fatal hematological disorders were found in case reports following exposure (level and duration not specified) to technical-grade pentachlorophenol or pentachlorophenol of undefined purity as a result of predominantly dermal exposure. Thirteen cases of aplastic anemia, pure red blood cell aplasia, or severe pancytopenia with abnormal marrow have been reported in individuals using pentachlorophenol-containing wood preservative products, eight of which resulted in death (Roberts 1981, 1990). Aplastic anemia was also diagnosed in an individual using pentachlorophenol in the renovation of an old home (Rugman and Cosstick 1990). A case of intravascular hemolysis was attributed to use of an insecticide containing pentachlorophenol (Hassan et al. 1985).

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**Hepatic Effects.** Most of the studies reviewed concerning hepatic effects of dermal exposure to pentachlorophenol in humans described case reports of individuals exposed either occupationally or in the home following the use of pentachlorophenol-containing solutions by individuals who did not employ appropriate precautionary measures. Information regarding pentachlorophenol-induced hepatic toxicity in humans following dermal exposure, discussed below, is subject to some doubt regarding the extent to which the adverse effects seen can be attributed to pure pentachlorophenol. Hepatic enlargement has been observed in herbicide sprayers (Gordon 1956), and in neonates exposed for a short time via contaminated diapers and bed linen in a hospital nursery (Armstrong et al. 1969; Robson et al. 1969; Smith et al. 1996). Autopsy findings in those affected individuals who died revealed fatty infiltration of the liver (in the neonates) and severe centrilobular congestion with hepatocellular fat accumulation (in the chemical worker). Centrilobular degeneration was also observed in a liver specimen from a worker who dipped wood in a preservative that contained 4.1% pentachlorophenol every day for 1 week (Bergner et al. 1965). In an epidemiologic study of male factory workers who brushed technical-grade pentachlorophenol onto wood strips, sometimes without gloves, serum biliary acid concentrations were elevated in the high-exposure group, but not the low-exposure group, compared with controls. Exposure was assessed by measurement of pentachlorophenol concentrations in plasma and urine (Colosio et al. 1993b). The presence of elevated concentrations of bile acids in serum is a sensitive indicator of liver dysfunction (Franco et al. 1986). Evidence of liver damage was seen in an epidemiologic study of adult males occupationally exposed to pentachlorophenol in wood-treatment plants or as farmers or pest control operators in Hawaii (Klemmer 1972). This evidence consisted of elevated levels of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) following chronic, predominantly dermal exposure to technical-grade pentachlorophenol or pentachlorophenol of undefined purity. Hyperthermia induced by pentachlorophenol may be a major factor leading to liver injury.

**Renal Effects.** Four reports were found that described renal toxic effects following dermal exposure to pentachlorophenol in humans. All involved either occupational exposure or accidental poisoning with the predominant route of exposure being dermal, but the possibility of inhalation exposure cannot be excluded. In one instance, a 3-year-old girl was exposed to pentachlorophenol of undefined composition via a pesticide-contaminated domestic water supply. Transient disruption of acid-base equilibrium and metabolic balance as evidenced by acidosis, aminoaciduria, and ketonuria suggested the occurrence of renal dysfunction in this child (Chapman and Robson 1965). In a case study of nine infants, metabolic acidosis, proteinuria, and increased blood urea nitrogen were found following exposure of the infants to pentachlorophenol of undefined composition in diapers and bedding at a hospital that used pentachlorophenol in the hospital laundry as an antimildew agent. Fatty vacuolar changes in the renal tubules were

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noted in one of the two infants that died (Smith et al. 1996). An autopsy conducted on a worker who dipped wood in a preservative that contained 4.1% pentachlorophenol every day for 1 week revealed mild renal tubular degeneration (Bergner et al. 1965). Finally, evidence for pentachlorophenol-induced impaired glomerular filtration and tubular function was reported in 18 workers employed at a wood-treatment facility (Begley et al. 1977). These findings consisted of depressed creatinine clearance and phosphorus reabsorption. Considerable improvement in these symptoms was seen following a 20-day absence from work. These data suggest that the renal toxicant effects of technical-grade pentachlorophenol are reversible. The extent to which contaminants of technical-grade pentachlorophenol are responsible for the effects discussed above is not known. Hyperthermia may also be a mechanism of renal injury in individuals that are acutely overexposed to pentachlorophenol.

**Dermal Effects.** Transient localized redness and pain subsequent to immersion of the hands in a 0.4% pentachlorophenol solution for 10 minutes were exhibited by an adult male (Bevenue et al. 1967). Two cases of pemphigus vulgaris and one of chronic urticaria (both examples of severe skin lesions) attributed to nonoccupational chronic pentachlorophenol exposure (i.e., via contact with wood treated with pentachlorophenol) have been described (Lambert et al. 1986). The dermal effects discussed above may have resulted from impurities present in the pentachlorophenol resulting from the manufacturing process.

Pentachlorophenol-induced toxic effects on the skin of experimental animals have also been reported. A single application of pentachlorophenol of unspecified purity (1,111 mg/kg in 95% ethyl alcohol or 150 mg/kg in pale paraffin oil) resulted in gross changes such as pronounced edema and inflammation leading to wrinkling, cracking, desquamation, and hair loss. Microscopic changes observed include widespread foci of atrophy and necrosis, thinning and disappearance of upper skin layers, and hyperkeratinization and hypertrophy of hair follicles (Deichmann et al. 1942). Single dermal applications of 250 mg/kg of a 10% aqueous solution of sodium pentachlorophenate of unspecified purity to rabbits did not result in dermal irritation. Repeated application of lower doses of pentachlorophenol (40 mg/kg in mineral oil) to rabbits for 21 days induced no irritation, whereas daily application of 10–50 mg/kg of a 4% solution of pentachlorophenol in fuel oil for 6–61 weeks resulted in pronounced dermal effects, and daily application of 63 mg/kg of an aqueous sodium pentachlorophenate solution for 32 days was without effect (Deichmann et al. 1942). No evidence of histologic changes in the epidermis or pilosebaceous unit were noted after application of 0.036 mg of sodium pentachlorophenate of unspecified purity to a 9 cm<sup>2</sup> area of the dorsal skin of hairless dogs once daily for 7 days. The toxic effects of dermal exposure to pentachlorophenol appear to be most severe following high-dose, acute exposure to pentachlorophenol in fuel oil.

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Acne was observed in rabbits following application of technical-grade pentachlorophenol to the ear, but was not observed following application of pure pentachlorophenol (Johnson et al. 1973), suggesting that the effects were due to contaminants rather than the pentachlorophenol.

#### **3.2.3.3 Immunological and Lymphoreticular Effects**

Two cases of pemphigus vulgaris and one of chronic urticaria (skin diseases with an immunologic etiology) have been attributed to nonoccupational exposure to pentachlorophenol (Lambert et al. 1986). Alterations in immune function were reported in patients who had been exposed for more than 6 months to pentachlorophenol-containing pesticides (composition not defined) (Daniel et al. 1995) and workers who brushed technical-grade pentachlorophenol onto wood strips (Colosio et al. 1993b).

No studies were located regarding immunological effects in animals following dermal exposure to pentachlorophenol.

#### **3.2.3.4 Neurological Effects**

Numerous signs of central nervous system toxicity have been reported in case reports of individuals exposed to high levels of pentachlorophenol via dermal contact and inhalation exposure. The observed effects include intermittent delirium and convulsions (Chapman and Robson 1965) and irritability (Robson et al. 1969; Smith et al. 1996). It is likely that these are effects secondary to hyperthermia due to pentachlorophenol-induced uncoupling of oxidative phosphorylation.

No studies were located regarding neurological effects in animals following dermal exposure to pentachlorophenol.

#### **3.2.3.5 Reproductive Effects**

No studies were located regarding reproductive effects in humans and animals following dermal exposure to pentachlorophenol.

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**3.2.3.6 Developmental Effects**

No studies were located regarding developmental effects in humans and animals following dermal exposure to pentachlorophenol.

**3.2.3.7 Cancer**

Epidemiological studies and case reports described in Section 3.2.1.7 (in which dermal exposure was also likely) provide evidence that exposure to pentachlorophenol may be associated with soft tissue sarcomas and non-Hodgkin's lymphoma in humans.

Only one study was located in which investigators topically administered pentachlorophenol to animals (Boutwell and Bosch 1959). These investigators applied a 20% solution of commercial grade pentachlorophenol in benzene to shaved dorsal skin of mice twice a week for 13 weeks. Mice were previously treated with a dose of 0.3% dimethylbenzanthracene (DMBA) in benzene to induce skin cancer. No increase in DMBA-induced skin tumors resulted from pentachlorophenol treatment. This study was designed to determine if pentachlorophenol was a tumor promoter and was therefore severely limited in its ability to detect a carcinogenic effect caused by pentachlorophenol because of administration of an insufficient dose over a short treatment period. However, based on results of this study, pentachlorophenol was inactive as a promotor of skin tumors in mice.

**3.2.4 Other Routes of Exposure**

**Endocrine Effects.** Studies in animals have shown that acute (single-dose, intraperitoneal injection) pentachlorophenol administration causes a marked, statistically significant decrease in serum total thyroxine levels in rats (van Raaij et al. 1991a). This decrease peaked 6–24 hours after administration, and thyroxine levels slowly returned to control values within 96 hours after administration. Further *in vitro* studies by these investigators revealed that the likely mechanism of action for this anti-thyroid effect was competition for serum protein thyroxine binding sites (van Raaij et al. 1991b).

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**3.3 GENOTOXIC EFFECTS**

Numerous *in vivo* and *in vitro* studies have assessed the genotoxic potential of pentachlorophenol, and the results of these studies are presented in Tables 3-3 and 3-4, respectively. Three studies examined the clastogenic activity of pentachlorophenol in workers primarily exposed via inhalation. A marginal increase in chromosomal aberrations was found in the lymphocytes of workers exposed to pentachlorophenol or its sodium salt (Bauchinger et al. 1982). In contrast, studies by Wyllie et al. (1982) and Ziemson et al. (1987) did not find significant increases in the occurrence of chromosomal aberrations in their studies of workers. The occurrence of sister chromatid exchange was not increased in the lymphocytes of workers (Bauchinger et al. 1982; Ziemson et al. 1987). No other human *in vivo* genotoxicity studies were located. An increase in DNA adduct formation was observed in the liver of mice orally exposed to pentachlorophenol (Sai-Kato et al. 1995; Umemura et al. 1996), but not in the kidney or spleen (Sai-Kato et al. 1995), and positive results were seen in a coat color spot test in mouse embryos treated transplacentally with pentachlorophenol (Fahrig et al. 1978). In other *in vivo* assays, no evidence of genotoxicity was observed; the assays included sex-linked recessive lethal mutations in *Drosophila melanogaster* (Fahrig 1974; Fahrig et al. 1978; Vogel and Chandler 1974), micronuclei formation in rats and mice (NTP 1999), and gene mutations and recombination in a mouse spot test (Fahrig and Steinkamp-Zucht 1996).

No alterations in the occurrence of gene mutations (Andersen et al. 1972; Donnelly et al. 1998; Lemma and Ames 1975; Markiewicz et al. 1996; Moriya et al. 1983; NTP 1999; Simmon et al. 1977; Waters et al. 1982) or DNA damage (Fahrig 1974; Waters et al. 1982) were observed in bacterial systems, with the exception of one study that reported positive activity in the rec assay using *Bacillus subtilis* (Waters et al. 1982). In yeast, pentachlorophenol induced gene mutations (Fahrig 1974; Fahrig et al. 1978) and genetic recombination (Fahrig et al. 1978; Waters et al. 1982). Weak clastogenic activity was observed in chromosomal aberration assays in human lymphocyte (Fahrig 1974) and in chromosomal aberration and sister chromatid exchange assays in Chinese hamster ovary cells (NTP 1999). No significant increases in the occurrence of DNA damage (adduct formation or single-strand breaks) were seen in mammalian cells (Dalhaus et al. 1996; Ehrlich 1990; Wang and Lin 1995).

A few studies were found regarding the genotoxic potential of pentachlorophenol metabolites. Tetrachloro-*p*-hydroquinone (TCHQ), (isomer not specified) but not tetrachlorocatechol, induced a dose-related and significant mutagenic response in Chinese hamster V-79 cells in the absence of exogenous metabolic activation (Jansson and Jansson 1991). The para isomer of TCHQ, but not the ortho isomer,

**Table 3-3. Genotoxicity of Pentachlorophenol *In Vivo***

Species (test system)	End point	Results	Reference
<i>Drosophila melanogaster</i> spermatocytes	Sex-linked recessive lethal mutation	–	Fahrig 1974; Fahrig et al. 1978; Vogel and Chandler 1974
Human lymphocytes (occupational exposure)	Chromosomal aberrations	(+)	Bauchinger et al. 1982
Human lymphocytes (occupational exposure)	Chromosomal aberrations	–	Wyllie et al. 1982
Human lymphocytes (occupational exposure)	Chromosomal aberrations	–	Ziensen et al. 1987
Human lymphocytes (occupational exposure)	Sister chromatid exchange	–	Bauchinger et al. 1982
Human lymphocytes (occupational exposure)	Sister chromatid exchange	–	Ziensen et al. 1987
B6C3F1 mouse (oral exposure)	DNA adduct formation	+	Sai-Kato et al. 1995; Umemura et al. 1996
Mouse bone marrow (intraperitoneal exposure)	Micronuclei	–	NTP 1999
Rat bone marrow (intraperitoneal exposure)	Micronuclei	–	NTP 1999
Mouse embryonic cells (transplacental exposure)	Gene mutation	(+)	Fahrig et al. 1978
Mouse/spot test	Gene mutation	–	Fahrig and Steinkamp-Zucht 1996
Mouse/spot test	Recombination	–	Fahrig and Steinkamp-Zucht 1996

– = negative results; + = positive results; (+) = weakly positive results



Table 3-4. Genotoxicity of Pentachlorophenol and its Metabolites *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
<b>Pentachlorophenol</b>				
Prokaryotic organisms:				
<i>Salmonella typhimurium</i>	Gene mutation	–	–	Donnelly et al. 1998; Markiewicz et al. 1996; Moriya et al. 1983; NTP 1999; Simmon et al. 1977; Waters et al. 1982
<i>S. typhimurium</i> /spot test	Gene mutation	NT	–	Andersen et al. 1972; Lemma and Ames 1975
<i>S. typhimurium</i> (mouse host-mediated assay)	Gene mutation	–	NT	Buselmaier et al. 1973
Invertebrate animal cells:				Moriya et al. 1983; Simmon et al. 1977; Waters et al. 1982
<i>E. coli</i> /spot test	Gene mutation	NT	–	Waters et al. 1982
<i>Serratia marcescens</i> /spot test	DNA damage	NT	–	Fahrig 1974
<i>Bacillus subtilis</i> /rec- assay	DNA damage	NT	+	Waters et al. 1982
<i>E. coli</i> pol A	DNA damage	NT	–	Waters et al. 1982
Eukaryotic organisms:				
Fungi:				
<i>Saccharomyces cerevisiae</i> MP-1	Gene mutation	NT	+	Fahrig et al. 1978
<i>S. cerevisiae</i> aAeZ	Recombination	NT	+	Fahrig 1974
<i>S. cerevisiae</i> MP-1/intergenic recombination	Recombination	NT	–	Fahrig et al. 1978
<i>S. cerevisiae</i> MP-1/intergenic recombination	Recombination	NT	+	Fahrig et al. 1978
<i>S. cerevisiae</i>	Recombination	+	+	Waters et al. 1982

**Table 3-4. Genotoxicity of Pentachlorophenol and its Metabolites *In Vitro* (continued)**

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Mammalian cells:				
Human lymphocytes	Chromosomal aberrations	NT	(+)	Fahrig 1974
Chinese hamster ovary cells	Chromosomal aberrations	(+)	–	NTP 1999
Chinese hamster ovary cells	DNA damage	NT	–	Ehrlich 1990
Chinese hamster ovary cells	Sister chromatid exchange	–	(+)	NTP 1999
Chinese hamster V79 cells	DNA damage (8-OH-dG adduct)	NT	–	Dahlhaus et al. 1996
Chinese hamster V79 cells	DNA damage (single-strand breaks)	NT	–	Dahlhaus et al. 1996
Mouse embryonic fibroblast cells	DNA damage (single-strand breaks)	(+)	–	Wang and Lin 1995
<b>Tetrachloro-o-benzoquinone</b>				
Mammalian cells:				
Chinese hamster V79 cells	DNA damage (8-OH-dG adduct)	NT	+	Dahlhaus et al. 1996
Chinese hamster V79 cells	DNA damage (single-strand breaks)	NT	–	Dahlhaus et al. 1996
<b>Tetrachloro-p-benzoquinone</b>				
Mammalian cells:				
Chinese hamster V79 cells	DNA damage (8-OH-dG adduct)	NT	+	Dahlhaus et al. 1996
Chinese hamster V79 cells	DNA damage (single-strand breaks)	NT	+	Dahlhaus et al. 1996

**Table 3-4. Genotoxicity of Pentachlorophenol and its Metabolites *In Vitro* (continued)**

Species (test system)	End point	Results		Reference
		With activation	Without activation	
<b>Tetrachloro-<i>o</i>-hydroquinone</b>				
Mammalian cells:				
Chinese hamster V79 cells	DNA damage (8-OH-dG adduct)	NT	–	Dahlhaus et al. 1996
Chinese hamster V79 cells	DNA damage (single-strand breaks)	NT	–	Dahlhaus et al. 1996
<b>Tetrachloro-<i>p</i>-hydroquinone</b>				
Mammalian cells:				
Chinese hamster ovary cells	DNA damage	NT	+	Ehrlich 1990
Chinese hamster V79 cells	DNA damage (8-OH-dG adduct)	NT	+	Dahlhaus et al. 1996
Chinese hamster V79 cells	DNA damage (single-strand breaks)	NT	+	Dahlhaus et al. 1996
<b>Tetrachlorohydroquinone</b>				
Mammalian cells:				
Chinese hamster V79 cells	Gene mutation	NT	+	Jansson and Jansson 1991

– = negative result; + = positive result; (+) = weakly positive result; DNA = deoxyribonucleic acid; 8-OH-dG = 8-hydroxydeoxyguanosine; NT = not tested

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induced DNA damage in Chinese hamster V79 cells as evidenced by DNA single-strand breaks and an increase in the amount of 8-hydroxydeoxyguanosine in DNA (Dahlhaus et al. 1996). In the same study, the para isomer of tetrachlorobenzoquinone produced DNA single-strand breaks and an increase in the amount of 8-hydroxydeoxyguanosine in DNA, whereas the ortho isomer of this compound produced an increase in the amount of 8-hydroxydeoxyguanosine in DNA but did not produce DNA single-strand breaks (Dahlhaus et al. 1996). TCHQ was also found to exert a severe cytotoxic effect and cause marked DNA damage (i.e., single-strand breaks and/or alkali-labile sites) in Chinese hamster ovary cells; the parent compound was weakly cytotoxic but not genotoxic at comparable levels (Ehrlich 1990).

**3.4 TOXICOKINETICS**

Pentachlorophenol is efficiently absorbed following inhalation, oral, and dermal exposure. Absorbed pentachlorophenol is distributed to the liver, lungs, kidneys, blood, fat tissues, and brain. The binding of pentachlorophenol to plasma proteins plays a significant role in the distribution of pentachlorophenol (Braun et al. 1977; Gómez-Catalán et al. 1991). Results from animal and human studies indicate that pentachlorophenol is not completely metabolized, as evidenced by a large portion of the administered dose being excreted in urine unchanged in all species studied. Pentachlorophenol binds extensively to plasma proteins as discussed in Section 3.4.2.2. Pentachlorophenol has a greater binding affinity for thyretin, a major thyroxine transport protein in the rat, than thyroxine itself (den Besten et al. 1991), and the binding of pentachlorophenol to thyretin is likely responsible for its adverse effect on thyroid homeostasis. The available human and animal data indicate that metabolism of pentachlorophenol does occur in the liver, and the major pathways are conjugation to form the glucuronide and oxidative dechlorination to form tetrachlorohydroquinone (TCHQ). However, recent studies in rats and mice following oral administration of pentachlorophenol (Lin et al. 1997; Waidyanatha et al. 1994, 1996) suggest that the metabolism of pentachlorophenol can also proceed through the quinols TCHQ and Cl<sub>4</sub>CAT via microsomal cytochrome P 450 enzymes and that these quinols can be oxidized via semiquinone intermediates (tetrachloro-1,2-semiquinone [Cl<sub>4</sub>-1,2-SQ] and tetrachloro-1,4-semiquinone [Cl<sub>4</sub>-1,4-SQ]) into the corresponding quinones (tetrachloro-1,2-benzoquinone [Cl<sub>4</sub>-1,2-BQ] and tetrachloro-1,4-benzoquinone [Cl<sub>4</sub>-1,4-BQ]). Both the quinones and semiquinones are electrophilic and can bind to cellular macromolecules (Lin et al. 1997). Horseradish peroxidase catalyzed the oxidation of pentachlorophenol to Cl<sub>4</sub>BQ *in vitro* via a phenoxyl radical intermediate (Samokyszyn et al. 1995). The study authors suggest that this is a potential *in vivo* metabolic step that could be catalyzed by mammalian peroxidases, including prostaglandin H synthase, myeloperoxidase, salivary peroxidase, lactoperoxidase, or uterine peroxidase.

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The primary route of pentachlorophenol elimination in all species studied, including humans, by all routes of exposure, is urine. Approximately 74 and 12% (total of 86%) of pentachlorophenol ingested by humans was eliminated as pentachlorophenol and its glucuronide conjugate, respectively (Braun et al. 1979). In rodents, from 60–83% of the administered oral dose is eliminated in the urine (Ahlborg et al. 1974; Braun et al. 1977; Larsen et al. 1972; Reigner et al. 1991); in monkeys, 45–75% of the administered oral dose is eliminated in the urine (Braun and Sauerhoff 1976) (see Section 3.4.4.2 for a discussion of the metabolites of pentachlorophenol excreted in each species). Fecal elimination of pentachlorophenol and its metabolites accounted for 4% of the administered oral dose in humans, 4–34% of the administered oral dose in rodents, and 4–17% in monkeys. Only trace amounts were eliminated in expired air. The pharmacokinetic profile of pentachlorophenol excretion following single doses is species- and possibly sex-dependent. Elimination was rapid and biphasic in rats (Braun et al. 1977; Reigner et al. 1991) and slow and first-order in monkeys and humans following oral exposure (Braun and Sauerhoff 1976; Braun et al. 1979). Enterohepatic circulation and plasma protein binding influence the elimination kinetics of pentachlorophenol, but no data are available to assess whether the elimination kinetics of pentachlorophenol are dependent on its concentration in blood.

#### 3.4.1 Absorption

##### 3.4.1.1 Inhalation Exposure

There are limited data on the absorption of inhaled pentachlorophenol in humans. In an attempt to measure inhalation absorption of pentachlorophenol in humans, 2 volunteers were exposed to pentachlorophenol in an enclosed area for 45 minutes while they applied pentachlorophenol to wood with a brush (Casarett et al. 1969). Ambient pentachlorophenol concentrations in air were 0.230 and 0.432 ng/m<sup>3</sup>. The extent of pentachlorophenol absorption in these 2 subjects was calculated to be 88 and 76% of the total potential inhaled dose, based on measurements of respiratory rates during exposure, total urinary pentachlorophenol recovered for up to 1 week postexposure, and tidal volume estimates. These data indicate that pentachlorophenol is readily absorbed through the lungs of humans. These data are supported by the finding of increased plasma and urine pentachlorophenol levels in exposed workers (Casarett et al. 1969; Jones et al. 1986; Pekari et al. 1991) and in residents of log homes treated with pentachlorophenol (Cline et al. 1989; Hosenfeld et al. 1986).

Pulmonary absorption of pentachlorophenol in rats has been demonstrated to occur readily; 70–75% of radioactivity from a single 20-minute inhalation exposure (at a concentration calculated by the authors to

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be equivalent to 5.7 mg [ $^{14}\text{C}$ ]-pentachlorophenol/kg) was recovered in urine, plasma, liver, and lung by 24 hours postexposure (Hoben et al. 1976c).

**3.4.1.2 Oral Exposure**

Results of studies in humans (Braun et al. 1979; Uhl et al. 1986) and animals (Ahlborg et al. 1974; Braun and Sauerhoff 1976; Braun et al. 1977; Meerman et al. 1983; Reigner et al. 1991) indicate that pentachlorophenol and its sodium salt are readily absorbed following oral administration. Oral absorption of pentachlorophenol (as the sodium salt in water) in humans was determined to be first order, with peak blood levels of 0.248  $\mu\text{g/mL}$  pentachlorophenol being achieved within 4 hours of ingestion of 0.1 mg sodium pentachlorophenate/kg by four healthy male volunteers (Braun et al. 1979). The average half-life of absorption was calculated to be approximately 1.3 hours, indicating that oral absorption of pentachlorophenol in humans is rapid.

Oral absorption of pentachlorophenol by rats and monkeys was compared following administration of single oral doses in corn oil of 10 mg [ $^{14}\text{C}$ ]-pentachlorophenol/kg (monkeys) (Braun and Sauerhoff 1976) and 10 or 100 mg [ $^{14}\text{C}$ ]-pentachlorophenol/kg (rats) (Braun et al. 1977). In both species, absorption through the gastrointestinal tract was rapid; females in both species exhibited faster absorption than males as evidenced by different rate constants of absorption. These rate constants were 1.95  $\text{hour}^{-1}$  and 1.52  $\text{hour}^{-1}$  for male and female rats, respectively, and 0.215  $\text{hour}^{-1}$  and 0.383  $\text{hour}^{-1}$  for male and female monkeys, respectively. The half-lives of absorption were 3.64 and 1.81 hours, for male and female monkeys, respectively. Peak blood levels of approximately 60  $\mu\text{g}$  pentachlorophenol/g plasma were achieved in both sexes of rat within 4–6 hours, and peak plasma levels of 10–30  $\mu\text{g}$  pentachlorophenol/g plasma were reached by 12–24 hours in both sexes of monkey. Absorption of pentachlorophenol through the gastrointestinal tract was extensive in both species following administration of a single dose of [ $^{14}\text{C}$ ]-pentachlorophenol as evidenced by more than 90% recovery of radioactivity in urine, feces, expired air, tissues, and carcass.

Similar results were obtained in another study in rats using a lower dose (2.5 mg/kg) of pentachlorophenol (Reigner et al. 1991). Peak plasma concentrations ( $7.3 \pm 2.8$   $\mu\text{g/mL}$ ) were achieved between 1.5 and 2 hours after administration. Absorption appeared to be first order and fit a one-compartment model in three of five animals tested. Half-life of absorption varied between 0.25 and 1.50 hours. Based on the results of this study, the authors concluded that pentachlorophenol is virtually completely absorbed after oral administration in rats. These same investigators studied the pharmacokinetics of pentachloro-

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phenol in B6C3F<sub>1</sub> mice following the administration of a single gavage dose of 15 mg/kg (Reigner et al. 1992b). Peak plasma concentrations ( $28 \pm 7$  µg/mL) were achieved between 1.5 and 2 hours after administration. Half-life of elimination from the blood averaged  $5.8 \pm 0.6$  hours. Based on the results of this study, the study authors concluded that pentachlorophenol is virtually completely absorbed after oral administration in mice.

Absorption of pentachlorophenol (>99%) from the gastrointestinal tract of F344 rats after gavage doses of 9.5 or 38 mg/kg in an aqueous methylcellosolve vehicle was first order, with an absorption half-life of about 1.3 hours. The absorption rate of pentachlorophenol, determined after administration of 302 or 1,010 ppm concentrations in the diet (approximately 21 or 64 mg/kg), was comparable to that obtained from aqueous methylcellosolve gavage formulations, but the bioavailability of pentachlorophenol administered in the diet (52% at 302 ppm and 30% at 1,010 ppm) was markedly lower than the bioavailability of pentachlorophenol administered by gavage (100% at 9.5 mg/kg and 86% at 38 mg/kg). Following gavage administration of a single dose of 9.5 or 38 mg/kg pentachlorophenol to the male rats, peak plasma concentrations of pentachlorophenol appeared in 2–4 hours and the concentration was dose-dependent. In males administered pentachlorophenol in the diet for 5 days, diurnal variation was seen in the serum concentration of pentachlorophenol, with increases during the 12-hour dark period and decreases during the 12-hour light period (Yuan et al. 1994).

The extent of absorption of pentachlorophenol or sodium pentachlorophenate from the gastrointestinal tract was studied in rats allowed free access to drinking water that contained a 1.4 millimolar (mM) solution of sodium pentachlorophenate (288 mg/L) or food that contained 350 ppm pentachlorophenol or sodium pentachlorophenate (Meerman et al. 1983). Based on analysis of pentachlorophenol plasma concentrations over a 24-hour period and comparison with parameters obtained after intravenous administration, the study authors concluded that absorption of pentachlorophenol and sodium pentachlorophenate under these conditions was essentially complete.

#### 3.4.1.3 Dermal Exposure

Using human abdominal skin (dermis and epidermis) obtained at autopsy, it has been demonstrated that 62% of pentachlorophenol in diesel oil solution penetrated skin *in vitro*, while only 16% of an aqueous solution of sodium pentachlorophenate penetrated skin (Hortsman et al. 1989). Thus, it appears that pentachlorophenol is absorbed to a much greater extent in an oily solution than in an aqueous solution following dermal exposure in humans. The only other available information on dermal absorption of

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pentachlorophenol and its salts by humans comes from occupational case studies in which elevated levels of pentachlorophenol have been detected in urine and plasma of workers who handle pentachlorophenol-treated wood and/or do not wear adequate personal protective gear when working in areas where pentachlorophenol is being sprayed (Jones et al. 1986). In addition, numerous case reports describe occurrence of severe toxicity and/or death in individuals whose exposure to pentachlorophenol is presumed to be predominantly via the dermal route (Gray et al. 1985; Robson et al. 1969; Smith et al. 1996; Wood et al. 1983).

Animal studies support the human findings that pentachlorophenol is absorbed across the skin. In a Rhesus monkey study, pentachlorophenol was well absorbed following percutaneous application in soil or in acetone (Wester et al. 1993). Under the conditions of this study ( $0.7 \mu\text{g}/\text{cm}^2$  in soil and  $0.8 \mu\text{g}/\text{cm}^2$  in acetone of  $^{14}\text{C}$ -pentachlorophenol applied for 24 hours to abdominal skin),  $24.4 \pm 6.4\%$  of the applied dose in soil and  $29.2 \pm 5.8\%$  of the applied dose in acetone were absorbed. In an *in vivo* swine model,  $40 \mu\text{g}/\text{cm}^2$  [ $^{14}\text{C}$ -UL]-pentachlorophenol was applied occlusively or nonocclusively in a soil-based mixture to a clipped abdominal site of 8–10-week-old female pigs (Qiao et al. 1997). By 408 hours after dosing, total radiolabel absorption was 29.08% under nonocclusive conditions and 100.72% under occlusive conditions. When antibiotics (neomycin sulfate, bacitracin, and polymyxin B) were codosed with occlusively applied [ $^{14}\text{C}$ -UL]-pentachlorophenol, total radiolabel absorption by 408 hours was 86.21%. The antibiotics were selected to provide a combined wide spectrum of antimicrobial and antifungal activity. If it assumed that the antibiotics had no direct effect on the dermal absorption of pentachlorophenol, then the inhibition of dermal absorption by the antibiotics suggests that degradation of pentachlorophenol by skin microorganisms may play a role in dermal absorption. The percentage of applied dose present in blood or plasma reached maxima at approximately 96 hours under occlusive conditions (with or without antibiotics) and 144 hours under nonocclusive conditions. These results indicate that pentachlorophenol is readily absorbed following dermal exposure and is bioavailable from soil.

#### 3.4.2 Distribution

There are limited data on the distribution of pentachlorophenol in humans. The distribution of background levels of pentachlorophenol were measured in the urine and tissues collected during the autopsy of 21 humans (Grimm et al. 1981). The highest concentrations of pentachlorophenol were found in the liver ( $0.067 \mu\text{g}/\text{g}$ ), kidneys ( $0.043 \mu\text{g}/\text{g}$ ), brain ( $0.047 \mu\text{g}/\text{g}$ ), spleen ( $0.019 \mu\text{g}/\text{g}$ ), and body fat ( $0.013 \mu\text{g}/\text{g}$ ). The median pentachlorophenol levels in the urine and blood were 0.0044 and  $0.033 \mu\text{g}/\text{mL}$ , respectively. Low levels of pentachlorophenol were found in human breast milk from West Germany



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(Gebefugi and Korte 1983) and Slovakia (Veningerova et al. 1996). The source of pentachlorophenol was not specified. It is possible that the pentachlorophenol in breast milk was not due to pentachlorophenol exposure, but rather to exposure to other industrial chemical (e.g., hexachlorobenzene, hexachlorocyclohexane), which are metabolized to pentachlorophenol. Since pentachlorophenol was detected in 64% of urine samples gathered from 1,000 human adults living in the United States (Hill et al. 1995), it is likely that pentachlorophenol is present in breast milk in U.S. citizens. Because pentachlorophenol is a metabolite of a number of environmental contaminants, it is not known if the pentachlorophenol present in the urine, breast milk, or tissues resulted from exposure to pentachlorophenol. The discussion of experimental animal studies follows.

#### 3.4.2.1 Inhalation Exposure

Information regarding distribution of pentachlorophenol following inhalation exposure in animals is limited. Distribution of pentachlorophenol was evaluated following single and multiple (five) 20-minute inhalation exposures to concentrations calculated by the authors to be equivalent to a dose of 5.7 mg pentachlorophenol/kg body weight by measuring concentrations of pentachlorophenol in liver, lungs, blood, and urine only (Hoben et al. 1976c). Rapid distribution away from the site of exposure was apparent after a single exposure since only 1.8% of the administered dose was present in lungs immediately after exposure. By 24 hours postexposure, approximately 55% of the administered dose was recovered in urine, 7% in plasma, 9% in liver, and 0.7% in lung. These data indicate that pentachlorophenol was cleared rapidly, and only small amounts accumulated in the tissue samples studied. Repeated-exposure experiments support the observation that pentachlorophenol does not accumulate in rats following inhalation exposure. By 24 hours after the last (fifth) exposure, 70% of the administered dose was recovered in urine, 5% in plasma, 4% in liver, and 0.3% in lung. It is not clear from these data where pentachlorophenol was distributed immediately following exposure, but high levels in urine suggest that pentachlorophenol was cleared rapidly and did not reach an appreciable body burden following repeated exposure. Binding of pentachlorophenol to plasma proteins influences its distribution (see Section 3.4.2.2). Binding of pentachlorophenol to plasma proteins varies linearly with increasing dose following inhalation exposure (Hoben et al. 1976d). No studies were located regarding distribution of pentachlorophenol in animals following long-term inhalation exposure.

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**3.4.2.2 Oral Exposure**

Distribution studies in rats conducted 9 days after oral administration of a single dose of 10 mg [ $^{14}\text{C}$ ]-pentachlorophenol/kg body weight in corn oil demonstrated that the highest levels of radioactivity are found in liver and kidneys and lower levels are found in brain and fat tissue. Radioactivity was also detected in lungs, testes, ovaries, heart, and adrenal glands. Levels of radioactivity were uniformly higher in plasma and tissues of females as compared to males, though the distribution pattern was qualitatively the same (Braun et al. 1977). A similar distribution pattern was observed by Larsen et al. (1972) in rats 40 hours after gavage administration of 37–41 mg [ $^{14}\text{C}$ ]-pentachlorophenol/kg body weight in corn oil.

Larsen et al. (1975) administered a single oral dose of 60 mg/kg pentachloro[U- $^{14}\text{C}$ ]phenol (99.54% radiochemical purity) to 14 rats on day 15 of gestation. Groups of 2 rats were sacrificed at 2, 4, 8, 12, 16, 24, and 32 hours after dosing, and the distribution of administered dose was determined in blood serum, placentas, and fetuses. Tissue distributions, expressed as the percentage of administered dose per gram tissue, were 0.88% in blood serum, 0.20% in placentas, and 0.05% in fetuses at 2 hours after dosing. Peak amounts occurred in serum at 8 hours (1.12%), in placentas at 12 hours (0.28%), and in fetuses at 12 hours (0.08%). By 32 hours after dosing, percentages of administered dose were 0.43% in serum, 0.08% in placentas, and 0.04% in fetuses. The chemical nature of the radioactivity present in serum, placentas, and fetuses was not investigated. Since the administered pentachlorophenol did not have 100% radiochemical purity, it is possible that some of the radioactive material distributed in the fetuses was due to radioactive impurities.

Following gavage administration of a single dose of 9.5 or 38 mg/kg pentachlorophenol (>99%) to male F344 rats, peak plasma concentrations of pentachlorophenol appeared in 2–4 hours and the concentration was dose dependent. In male F344 administered pentachlorophenol at 302 or 1,010 ppm concentrations in the diet (approximately 21 or 64 mg/kg) for 5 days, diurnal variation was seen in the serum concentration of pentachlorophenol, with increases during the 12-hour dark period and decreases during the 12-hour light period (Yuan et al. 1994).

At the end of the 2-year dietary bioassay of pentachlorophenol (approximately 99% with one impurity, tetrachlorophenol) in F-344 rats (NTP 1999), mean plasma concentrations of pentachlorophenol were approximately proportional to pentachlorophenol concentrations in the feed, and plasma concentrations in females were higher than those in males. Plasma concentration of pentachlorophenol were 24, 44, and

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67 µg/mL in females and 17, 36, and 53 µg/mL in males at dietary concentrations of 200, 400, and 600 ppm, respectively.

Distribution of [ $^{14}\text{C}$ ]-pentachlorophenol was measured in 2 monkeys 360 hours after oral administration of a single dose of 10 mg [ $^{14}\text{C}$ ]-pentachlorophenol/kg body weight. Approximately 11% of administered radiolabel was found in the body at the time of analysis; 80% of this activity was in the liver and in the large and small intestines. These data suggest that the monkey differs from the rat with regard to distribution of orally absorbed pentachlorophenol. There appears to be extensive biliary secretion and enterohepatic circulation of pentachlorophenol in the monkey as evidenced by the long half-life of pentachlorophenol in the body of monkeys and the fact that most of the radiolabel still present in the body 360 hours after administration was in the liver and large and small intestines (Braun and Sauerhoff 1976).

Binding of pentachlorophenol to plasma proteins plays a significant role in the distribution of pentachlorophenol. Tissue/plasma ratios and renal clearance rates following oral administration of pentachlorophenol were much lower than would be predicted, based on the octanol/water partition coefficient and glomerular filtration rate (Braun et al. 1977). This could be explained by extensive binding of pentachlorophenol to plasma proteins. The authors subsequently demonstrated using an *in vitro* diafiltration technique that 95% of pentachlorophenol in plasma is protein bound (Braun et al. 1977). In another experiment in rats,  $97.1 \pm 2.0\%$  of the administered dose of pentachlorophenol was found bound to plasma proteins as compared to plasma lipoproteins (Gómez-Catalán et al. 1991). Protein binding may result in lower levels being distributed to tissues (i.e., liver and kidney) for metabolism and excretion and increased retention in the body.

### 3.4.2.3 Dermal Exposure

The distribution of radiolabelled pentachlorophenol was examined in female pigs following occlusive application of 40 µg/cm<sup>2</sup> [ $^{14}\text{C}$ -UL]-pentachlorophenol (Qiao et al. 1997). The distribution of radiolabel 17 days after dosing was as follows (highest to lowest): liver, lung, ovary, gall bladder, kidney, spleen, uterus, urinary bladder, heart, diaphragm, and brain. A large amount of the label was retained in the body, approximately 50–67% of the absorbed label was present in the tissues 17 days after exposure.

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**3.4.2.4 Other Routes of Exposure**

Distribution of radioactivity in mice following intraperitoneal and subcutaneous administration of single doses of [ $^{14}\text{C}$ ]-pentachlorophenol has been reported (Jakobson and Yllner 1971). Only 0.4–6% of the administered dose was found in tissues 96 hours after intraperitoneal injection of 14.8–37.2 mg [ $^{14}\text{C}$ ]-pentachlorophenol/kg body weight. The highest concentrations of radiolabel were found in the gall bladder, liver, stomach wall, and gastrointestinal contents, indicating the occurrence of biliary secretion of pentachlorophenol. Lesser amounts of radiolabel were found in the kidneys, heart, and brain. A similar distribution pattern was observed after subcutaneous administration of 50 mg [ $^{14}\text{C}$ ]-pentachlorophenol/kg body weight. The concentration of radiolabel in the liver remained high 1 week after dosing. These data are similar to those obtained after oral administration of pentachlorophenol.

Dose- and time-dependent uptake of pentachlorophenol (purity not stated) into the cerebrospinal fluid of rats was demonstrated following single intraperitoneal injections of pentachlorophenol into rats at doses up to 17 mg/kg. Since similar doses of pentachlorophenol also significantly decreased the uptake of radiolabeled T4 into cerebrospinal fluid, the study authors suggested that pentachlorophenol may interact with the T4 binding site of transthyretin and compete with T4 for uptake into cerebrospinal fluid (van Raaij et al. 1994). This is a plausible explanation since the affinity of pentachlorophenol for the T4 binding site on transthyretin is 2.5-fold greater than that of T4 itself (den Besten et al. 1991).

Based on plasma concentrations and clearance rates, the volume of distribution of pentachlorophenol was estimated to be relatively small and approximately correspond to the volume of distribution of albumin and volume of extracellular fluid following intravenous injection of a single dose of 2.5 mg/kg to rats (Reigner et al. 1991). Similar results were obtained in mice (Reigner et al. 1992b). Following intravenous administration of 5 mg/kg pentachlorophenol (>99% purity) into rats, plasma concentrations tended to be slightly higher in males than in females during the first 12 hours. The volume of distribution was  $0.13 \pm 0.006$  L/kg in males and  $0.19 \pm 0.04$  L/kg in females, but the difference was not statistically significant (Yuan et al. 1994).

Reigner et al. (1993) investigated the binding of radiolabeled pentachlorophenol to serum proteins *in vitro* using ultrafiltration. The percent unbound pentachlorophenol in serum was 1.37 in mice, 0.85 in rats, 0.67 in monkeys, 0.53 in humans, and 0.43 in cows. These percentages correlated inversely with the total protein levels in the same serum samples. Percent unbound pentachlorophenol also correlated inversely with serum albumin concentrations with the exception of the cow, which had a lower albumin

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concentration than humans. These data suggest that the distribution of pentachlorophenol may be restricted due to extensive plasma protein binding.

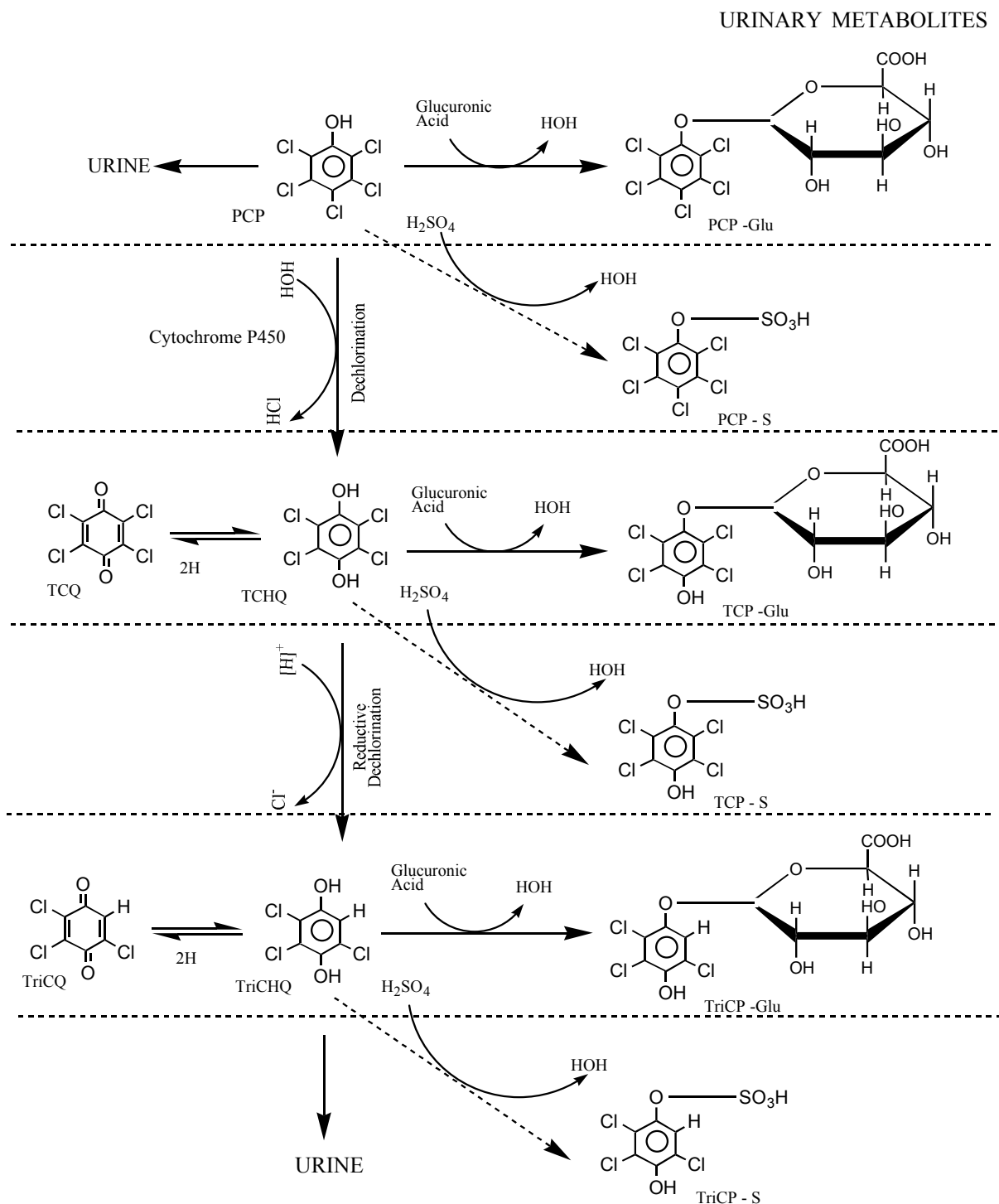
**3.4.3 Metabolism**

Results from animal and human studies indicate that pentachlorophenol is not extensively metabolized, as evidenced by a large portion of the administered dose being excreted in urine unchanged in all species studied. Extensive plasma protein binding of pentachlorophenol discussed in Section 3.3.2.2 may account for the low degree of metabolism because protein-bound material is not readily distributed to tissues. However, available human and animal data indicate that metabolism of pentachlorophenol does occur in the liver, and the major pathways are conjugation to form glucuronide and oxidative dechlorination to form TCHQ. A summary of possible metabolic pathways for pentachlorophenol is presented in Figure 3-2.

UDP-glucuronosyl transferase and sulfotransferases are involved in phase II metabolism of pentachlorophenol. Both of these enzymes are thought to be developmentally regulated (Leeder and Kearns 1997). Although the ontogeny of UDP-glucuronosyl transferase is isoform-specific, the adult level of activity seems to be achieved in humans by 6–18 months of age (Leeder and Kearns 1997). Ontogeny for the sulfotransferases seems to be more rapid than that for UDP-glucuronosyl transferase, and the activity for some isoforms of sulfotransferase may exceed adult levels during infancy and early childhood (Leeder and Kearns 1997).

Mehmood et al. (1996) has provided evidence that human cytochrome P450 3A4 may metabolize pentachlorophenol to TCHQ in phase I metabolism of pentachlorophenol; however, the initial purity of the pentachlorophenol used in this study was not indicated. In humans, this enzyme has low activity in the first month of life, with approach toward adult levels by 6–12 months of postnatal age; adult activity may be exceeded between 1–4 years of age and then activity progressively declines, reaching adult levels at the conclusion of puberty (Leeder and Kearns 1997). By Western immunoblotting using monoclonal antibodies to identify the different P 450 isozymes, pure pentachlorophenol (>99%) was identified as an inducer of cytochrome P450 3A7 in studies in cultured rat hepatocytes, quail hepatocytes, and human hepatoma (Hep G2) cells (Dubois et al. 1996). In humans, functional activity of cytochrome P450 3A7 in the fetus is approximately 30–75% of adult levels (Leeder and Kearns 1997).

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**Figure 3-2. Proposed Metabolic Scheme for Pentachlorophenol**

PCP = pentachlorophenol; PCP-Glu = pentachlorophenol- $\beta$ -glucuronide; PCP-S = pentachlorophenylsulfate;  
 TCHQ = tetrachloro-p-hydroquinone; TCP-Glu = tetrachlorophenol- $\beta$ -glucuronide; TCP-S = tetrachlorophenylsulfate;  
 TCQ = tetrachloroquinone; Tri CHQ = trichloro-p-hydroquinone; Tri CP-Glu = trichlorophenyl- $\beta$ -glucuronide;  
 Tri CP-S = trichlorophenylsulfate; Tri CQ = trichloro-p-quinone

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**3.4.3.1 Inhalation Exposure**

Ahlborg et al. (1974) analyzed urine from 2 workers employed as spraymen 24 hours after exposure to sodium pentachlorophenate that was presumably via the inhalation route. Both unchanged pentachlorophenol and TCHQ were identified (relative proportions were not specified), but no mention was made regarding the possible presence of glucuronide conjugates. Thus, at least oxidative dechlorination of pentachlorophenol occurs in humans exposed via inhalation. In rats, 70–75% of inhaled pentachlorophenol is excreted unchanged in urine following a single exposure (Hoben et al. 1976a).

**3.4.3.2 Oral Exposure**

Oral administration of small doses of pentachlorophenol (0.02–0.31 mg pentachlorophenol/kg) of 99% purity to volunteers resulted in excretion of unchanged pentachlorophenol (78% of administered dose) and pentachlorophenol glucuronide (12% of the administered dose) in urine and feces (Braun et al. 1979; Uhl et al. 1986). No TCHQ was identified.

Studies in rats indicate that both metabolic pathways described above were operative following oral administration of pentachlorophenol, but most of the administered dose was excreted unchanged (Ahlborg et al. 1974; Braun et al. 1977; Renner 1989; Renner and Hopfer 1990). The following urinary metabolites were recovered and identified by gas chromatography from female Sprague-Dawley rats dosed with pentachlorophenol (>99% pure) for 28 days: 2,3,4,5-tetrachlorophenol; 2,3,4,6-tetrachlorophenol; 2,3,5,6-tetrachlorophenol; tetrachlorocatechol ( $\text{Cl}_4\text{CAT}$ ); trichloro-1,4-benzenediol; tetrachloro-1,4-benzenediol; tetrachlororesorcinol; trichlorohydroquinone; TCHQ; and traces of trichloro-1,4-benzoquinone and tetrachloro-1,4-benzoquinone. The major metabolite was TCHQ, which was excreted mainly as a glucuronide conjugate (Renner and Hopfer 1990). Based on the urinary metabolites identified, the study authors concluded that the main metabolic pathway for pentachlorophenol in the rat was pentachlorophenol to 2,3,5,6-tetrachlorophenol to TCHQ, with a minor pathway being pentachlorophenol to 2,3,4,6- and 2,3,4,5-tetrachlorophenol to trichlorohydroquinone. Pentachlorophenol (conjugated with glucuronic acid and unconjugated) and TCHQ (conjugated with glucuronic acid and unconjugated) were recovered from urine and quantified by high-performance liquid chromatography and confirmed by using capillary gas chromatography from female Sprague-Dawley rats dosed with pentachlorophenol (>99% pure) for 28 days (Renner and Hopfer 1990). Unconjugated pentachlorophenol accounted for 36–58% of pentachlorophenol recovered, and 10–19% of the TCHQ excreted was unconjugated. Concentrations of both pentachlorophenol and TCHQ in urine fell to negligible amounts

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within one week after cessation of treatment. The study authors concluded that conjugation of pentachlorophenol with glucuronide and the metabolism of pentachlorophenol to TCHQ in rats results in more rapid excretion than in species that excrete unchanged pentachlorophenol (e.g., monkey) (see discussion below).

In other studies in rats, 48% of the 100 mg [ $^{14}\text{C}$ ]-pentachlorophenol/kg administered orally to rats was recovered as unchanged pentachlorophenol in urine, 10% was TCHQ, and 6% was pentachlorophenol-glucuronide. No TCHQ-glucuronide was detected (Braun et al. 1977). Similar results were obtained in rats and mice when a single dose of 25 mg [ $^{14}\text{C}$ ]-pentachlorophenol was administered by gavage, except that TCHQ conjugates (not positively identified as glucuronides) were identified in urine (Ahlborg et al. 1974). These investigators found that 41–43% of the administered radiolabel was recovered in the urine as unchanged pentachlorophenol in rats and mice, 5% as TCHQ in rats, and 24% as TCHQ in mice. An unspecified proportion of radioactivity was found in urine as conjugated pentachlorophenol and TCHQ, but it could not be determined whether these were glucuronide conjugates. Other investigators have reported results in rats that differ from those of Braun et al. (1977). Approximately 60% of a 2.5 mg/kg dose of pentachlorophenol was recovered in the urine of Sprague-Dawley rats after 72 hours, mostly as conjugated pentachlorophenol and TCHQ, with only  $5.3 \pm 0.2\%$  of the dose recovered as unchanged pentachlorophenol (Reigner et al. 1991). Treatment of urine with sulfuric acid indicated that sulfate conjugates of pentachlorophenol and TCHQ accounted for about 90% of conjugated pentachlorophenol and TCHQ (glucuronide conjugates reported by Braun et al. [1977]). Metabolites and unchanged pentachlorophenol in feces accounted for 10% of the administered dose.

It has been demonstrated that the monkey differs from the rat and mouse in that virtually all radioactivity recovered in urine following oral administration of 10 mg [ $^{14}\text{C}$ ]-pentachlorophenol/kg was associated with pentachlorophenol; no TCHQ or glucuronide conjugates were identified (Braun and Sauerhoff 1976). These data suggest that pentachlorophenol is not metabolized to any great degree by the monkey.

Binding of pentachlorophenol to specific components of liver cells or differential distribution of pentachlorophenol to different cellular organelles can affect its metabolic fate or that of other xenobiotics and ultimately regulate the manifestation of toxic effects. Arrhenius et al. (1977) administered a single dose of gas-chromatographically pure pentachlorophenol (40 mg/kg) by stomach tube to rats, killed them 16 hours later, separated subcellular fractions, and determined that the relative concentration of pentachlorophenol in microsomes was 6 times greater than in mitochondria. Since maximum effects on inhibition of microsomal detoxification processes (requiring electron transport from flavin to cytochrome)



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occur at a pentachlorophenol concentration (100  $\mu\text{M}$ ) that is 4 times greater than the concentration of pentachlorophenol required to cause maximum inhibition of oxidative phosphorylation in mitochondria (25  $\mu\text{M}$ ), Arrhenius et al. (1977) suggested that inhibition of mitochondrial oxidative phosphorylation and inhibition of microsomal detoxification by pentachlorophenol might be equally important. The possibility that the presence of pentachlorophenol in microsomes allows this substance to inhibit its own metabolism provides a possible explanation for the relative lack of pentachlorophenol metabolism seen in all species studied. Another possible explanation is that extensive plasma binding of pentachlorophenol limits distribution of pentachlorophenol to the liver for subsequent biotransformation. In either case, any perturbation that increases the level of free circulating pentachlorophenol may result in enhanced toxicity as well as an increased rate of biotransformation and elimination. For individuals living in close proximity to areas of potentially high pentachlorophenol exposure, concomitant exposure to chemicals or intentional ingestion of drugs that compete with pentachlorophenol for protein binding may enhance pentachlorophenol-induced toxicity.

**3.4.3.3 Dermal Exposure**

No studies were located regarding metabolism in humans or animals after dermal exposure to pentachlorophenol.

**3.4.3.4 Other Routes of Exposure**

Results of studies in rats and mice indicate that metabolism of pentachlorophenol following intraperitoneal injection is similar to that observed following oral exposure (Ahlborg et al. 1978; Jakobson and Yllner 1971). *In vitro* studies in both human and rat liver homogenates clearly demonstrate that pentachlorophenol is converted to TCHQ (Juhl et al. 1985). Using a genetic construct in which human cytochrome P450 3A4 is expressed in *Saccharomyces cerevisiae* strain AH22, Mehmood et al. (1996) demonstrated that human cytochrome P450 3A4 may metabolize pentachlorophenol to TCHQ; however, the initial purity of the pentachlorophenol used in this study was not indicated. By Western immunoblotting using monoclonal antibodies to identify the different P 450 isozymes, pure pentachlorophenol (>99%) was identified as an inducer of cytochrome P450 3A7 in studies in cultured rat hepatocytes, quail hepatocytes, and human hepatoma (Hep G2) cells (Dubois et al. 1996).

Since studies with rat liver microsomes using  $^{19}\text{F}$  nuclear magnetic resonance have demonstrated the cytochrome P450-dependent oxidation of pentafluorophenol to tetrafluorobenzoquinone (den Besten et al.

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1993), it can be speculated that cytochrome P450 may also catalyze the oxidation of pentachlorophenol to tetrachlorobenzoquinone.

Horseradish peroxidase catalyzed the oxidation of pentachlorophenol to Cl<sub>4</sub>BQ *in vitro* via a phenoxyl radical intermediate (Samokyszyn et al. 1995). The study authors suggest that this is a potential *in vivo* metabolic step that could be catalyzed by mammalian peroxidases, including prostaglandin H synthase, myeloperoxidase, salivary peroxidase, lactoperoxidase, or uterine peroxidase.

The rate of pentachlorophenol-glucuronide conjugation in human liver microsomes is reported to be one-third of that found in rat liver microsomes (Lilienblum 1985), although phenobarbital-enhanced dechlorination of pentachlorophenol, phenobarbital, and 3-methylcholanthrene (another microsomal enzyme inducer) had little effect on the conjugation reaction in rat liver microsomes (Ahlborg et al. 1978). This indicated that the extent of glucuronide conjugation was governed by factors other than phenobarbital- and 3-methylcholanthrene-inducible microsomal enzyme activity.

It has been proposed that accumulation of pentachlorophenol by lipid-containing tissues seen *in vitro* is due to conjugation with fatty acids (Leighty and Fentiman 1982). These investigators reported that pentachlorophenol conjugated with palmitic acid in an *in vitro* rat liver coenzyme A fortified microsomal system. This ester is also found in human fat (Ansari et al. 1985). The mechanism by which the palmitoyl-pentachlorophenol is formed in human fat has yet to be determined. The presence of this ester in human fat demonstrates that xenobiotics such as pentachlorophenol can be made more lipophilic and stored in the fat of humans rather than excreted by the kidneys, thereby providing a potential reservoir of toxin that could be released at a later time.

#### 3.4.4 Elimination and Excretion

##### 3.4.4.1 Inhalation Exposure

The available information regarding pentachlorophenol excretion following inhalation exposure in humans comes predominantly from occupational case studies. Data obtained by Bevenue et al. (1967) from measuring urinary levels of pentachlorophenol in residents of Honolulu (some with a history of occupational exposure to pentachlorophenol) indicated that elimination was biphasic, with urinary pentachlorophenol levels decreasing approximately 35% per day in the first 2 days. Urinary levels of pentachlorophenol measured in wood-treatment workers prior to, during, and after vacation implied a urinary

## 3. HEALTH EFFECTS

half-life of elimination of 19–20 days following inhalation exposure (Begley et al. 1977). A 10-day half-life of pentachlorophenol excretion in urine was estimated from urinary levels of pentachlorophenol measured in a tannery worker 1 day after the last day of work-related pentachlorophenol exposure and during a subsequent holiday period (Barbieri et al. 1995). The results of studies conducted by Casarett et al. (1969) in occupationally exposed humans suggest that pentachlorophenol excretion kinetics differ between single high-level and chronic low-level exposure. Urinary half-lives of approximately 10 hours were displayed by 2 subjects following a 45-minute inhalation exposure resulting from painting household materials in an enclosed area, whereas urine pentachlorophenol levels in exposed workers decreased only by 60–80% when the workers were absent from work for up to 18 days. The authors hypothesized that slower elimination of pentachlorophenol in the chronic situation may be the result of the establishment of an equilibrium between lung, plasma proteins, urine, and tissue depots.

A group of 7 sawmill workers (6 males and 1 female) exposed to a sodium chlorophenolate wood-preserving product containing 3% pentachlorophenol were monitored for serum and urinary concentrations of pentachlorophenol (as well as other chlorophenols) throughout a wood-treatment season of approximately 7 months and an additional 171 days after the termination of exposure for the season (Pekari et al. 1991). Maximal pentachlorophenol urine concentrations after the period of exposure were 0.2–0.9  $\mu\text{mol/L}$ . Approximately 76% of the pentachlorophenol in urine was conjugated. The elimination rate constant in these workers using a one-compartment model was  $0.044 \pm 0.018/\text{day}$  with a corresponding half-life of 16 days for pentachlorophenol. The minimal urinary clearance for pentachlorophenol was 0.2 mL/minute and varied with urine flow. The study authors noted that the relatively high concentrations of pentachlorophenol found in the serum (23%) as compared to the low percentage of pentachlorophenol in the technical product (3%) indicates that pentachlorophenol accumulates in the serum, in accordance with its relatively long half-time (16 days as compared to 18 hours and 4.2 days for tri- and tetrachlorophenol, respectively). Breathing zone measurements of concentration of airborne contamination compared to quantitative urine measurements would greatly improve the quality of the study.

Excretion of pentachlorophenol following inhalation exposure in animals has not been well documented. The elimination half-life of pentachlorophenol following a single 20-minute inhalation exposure to 5.7 mg [ $^{14}\text{C}$ ]-pentachlorophenol/kg was 24 hours (Hoben et al. 1976c). Pentachlorophenol does not undergo appreciable biotransformation as most of the inhaled dose was found to be eliminated unchanged in the urine. The authors of this study also reported that repeated (five) exposures increased urinary output of pentachlorophenol. These results are not inconsistent with those of Casarett et al. (1969).

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Elimination of many toxicants from high body burdens follows first-order kinetics initially, but the pattern of elimination becomes much more complex as lower body burdens are attained. Accumulation with repeated exposure will occur if rate of absorption exceeds rate of elimination, irrespective of excretion kinetics or tissue storage.

**3.4.4.2 Oral Exposure**

Studies investigating excretion of pentachlorophenol by humans following ingestion of 0.016–0.31 mg pentachlorophenol/kg have yielded conflicting results. Uhl et al. (1986) found that pentachlorophenol was excreted slowly, displaying an elimination half-life in both blood and urine of 14 days and a renal clearance of 0.07 mL/minute following ingestion of 0.016–0.31 mg pentachlorophenol/kg in ethanol by volunteers. The authors concluded that slow elimination could be attributed to extensive plasma protein binding and tubular reabsorption.

When Braun et al. (1979) studied excretion kinetics of pentachlorophenol (as the sodium salt) in volunteers who ingested 0.1 mg pentachlorophenol/kg, they found that the half-life of elimination was 30.2 hours from plasma and 33.1 hours from urine for pentachlorophenol, and 12.7 hours from urine for the glucuronide conjugate. Approximately 74% of the administered dose was eliminated in urine as pentachlorophenol and 12% as pentachlorophenol-glucuronide within 168 hours postingestion, and 4% was recovered as pentachlorophenol and pentachlorophenol-glucuronide in feces. These investigators concluded that pentachlorophenol elimination in humans followed first-order kinetics with enterohepatic recirculation following oral exposure. One possible explanation for the different half-lives observed in the Uhl et al. (1986) and the Braun et al. (1979) studies is the different dosing procedures employed. Subjects in the Uhl et al. (1986) study were reported to have ingested pentachlorophenol "without restriction of diet," while Braun et al. (1979) reported that "food was withheld 8 hours before and 1 hour after ingestion of the dose." Dispersion in gut contents may have slowed absorption in the Uhl et al. (1986) subjects, while absorption of the full dose occurred over a much shorter interval in the Braun et al. (1979) subjects, thus accounting for the different half-lives observed. Other explanations for the differences observed between the two studies include the fact that sodium pentachlorophenate was used for the Braun et al. (1979) study and pentachlorophenol in ethanol was used for the Uhl et al. (1986) study, and the vehicle used in the Uhl et al. (1986) study (ethanol) may have altered the solubility of pentachlorophenol.

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Elimination of pentachlorophenol in rats following oral exposure was shown to be rapid and biphasic, with urine being the major route of excretion (Braun et al. 1977). The authors of this study reported that within 8–9 days, 80% of the radioactivity from the single oral administration of 10 mg [ $^{14}\text{C}$ ]-pentachlorophenol/kg to rats was recovered in urine and 19% in feces; 64% was detected in urine and 34% in feces following single oral administration of 100 mg [ $^{14}\text{C}$ ]-pentachlorophenol/kg. Elimination half-lives were 17 and 13 hours for the first phase and 40 and 30 hours for the second phase in low-dose males and females, respectively. Ninety percent of the radioactivity was eliminated in the first phase. High-dose males exhibited elimination half-lives of 13 and 121 hours for the first and second phases, respectively. High-dose females exhibited first-order kinetics with a half-life of 27 hours. No explanation was offered for the difference in kinetics seen in high-dose females. These data indicate that: (1) the rate of elimination in the slow phase only and the relative distribution of radioactivity in feces varied linearly with increasing dose, (2) females eliminated pentachlorophenol faster than males, and (3) plasma binding and hepatic retention could account for the prolonged second phase of elimination.

Different results were reported in rats administered single doses of 37–41 mg [ $^{14}\text{C}$ ]-pentachlorophenol/kg (Larsen et al. 1972). While the half-lives of rapid phases of elimination were comparable, Larsen et al. (1972) reported a half-life of 102 days for the second phase. However, these data are questionable because Larsen et al. (1972) did not obtain 100% recovery in urine and assumed that fecal excretion was constant. Therefore, they only reported a total fecal excretion value after 10 days.

Results similar to those obtained by Braun et al. (1977) were reported by Reigner et al. (1991, 1992b) with respect to urinary and fecal elimination of pentachlorophenol following single-dose exposure in rats and mice. In the Reigner et al. studies, 8–10% of the administered dose (2.5 and 15 mg/kg, respectively, for rats and mice) of pentachlorophenol was recovered in the feces. Therefore, biliary excretion must play some role in elimination of pentachlorophenol.

Elimination of pentachlorophenol by monkeys was slow and followed first-order kinetics. Braun and Sauerhoff (1976) orally administered single doses of 10 mg [ $^{14}\text{C}$ ]-pentachlorophenol/kg to monkeys and monitored excretion of radioactivity for up to 360 hours after administration. They found that 10–20% of administered radioactivity was steadily excreted in the feces, attesting to a relatively high degree of biliary secretion. Urinary pentachlorophenol accounted for 70–80% of the administered radiolabel. The half-life of elimination was 40.8 hours in males and 92.4 hours in females. The long half-life was attributed to enterohepatic circulation with subsequent biliary secretion.

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The role of enterohepatic circulation and biliary secretion in pentachlorophenol elimination in monkeys was further investigated by measuring the relative extent of excretion of pentachlorophenol in urine, feces, and bile before and after administration of cholestyramine, a substance that binds phenols (Ballhorn et al. 1981; Rozman et al. 1982). The cholestyramine was administered in the diet 24 hours after pentachlorophenol exposure. At 30 mg/kg/day, control excretion was 92.3% in urine and 7.7% in feces. Following cholestyramine administration, excretion was 12.1% renal and 86.9% fecal. At 50 mg/kg/day, control excretion was 79.9% renal and 20.1% fecal. Following cholestyramine administration, excretion was 15.4% renal and 84.6% fecal. Total excretion was also increased by cholestyramine administration. Total recovery of administered dose over a 6-day period increased from 26 to 45% at the low dose and from 15 to 31% at the high dose (Ballhorn et al. 1981).

In a follow-up study, cholestyramine treatment reduced urinary excretion of pentachlorophenol from 35 to 5% of the administered dose and increased fecal excretion from 3 to 54% of the administered dose. The increase in fecal excretion induced by cholestyramine exceeded the decrease in urinary excretion. Total excretion increased by 40%. Seventy percent was excreted in bile during the control period, and 52% was excreted in bile after cholestyramine treatment (Rozman et al. 1982), suggesting that cholestyramine treatment also enhanced the excretion of pentachlorophenol across the intestinal wall.

The following conclusions can be drawn from these studies:

- In untreated monkeys, oral absorption of pentachlorophenol was followed by elimination via bile into the duodenum, reabsorption in the small intestine, and enterohepatic circulation and excretion, predominantly via the kidney.
- Cholestyramine, which binds phenols, interrupted enterohepatic circulation by binding pentachlorophenol and/or its metabolites, resulting in predominantly fecal excretion.
- Total excretion was increased after cholestyramine treatment, suggesting that it reduced the half-life of pentachlorophenol in the monkey by enhancing its elimination from the body.
- Cholestyramine increased elimination of pentachlorophenol by sequestering it from enterohepatic circulation and increasing its excretion across the intestinal wall.

#### 3.4.4.3 Dermal Exposure

No studies were located regarding excretion in humans after dermal exposure to pentachlorophenol.

In an *in vivo* swine model, 40 µg/cm<sup>2</sup> [<sup>14</sup>C-UL]-pentachlorophenol was applied occlusively or nonocclusively in a soil-based mixture to a clipped abdominal site of 8–10-week-old female pigs (Qiao et

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al. 1997). As an additional dosing protocol, antibiotics (neomycin sulfate, bacitracin, and polymyxin B, selected to provide a combined wide spectrum of antimicrobial and antifungal activity) were codosed with occlusively-applied [ $^{14}\text{C}$ -UL]-pentachlorophenol to determine if inhibition of dermal microbial activity would influence absorption and disposition. Only one-third to one-half of the absorbed dose was almost equally excreted through urinary and fecal routes at constant rates over the 408-hour study period. In general, both the urinary and fecal excretion rates were faster for occlusive than for nonocclusive conditions. At 408 hours, the excretion data indicated that occlusion significantly increased the urinary (4x) and fecal (2.5x) excretion. Codosing of antibiotics with occlusive pentachlorophenol application significantly decreased urinary and fecal excretion. Based on the excretion curves, the urinary excretion rates were 0.35, 1.29, and 0.65% dose/day for nonocclusive, occlusive, and occlusive-antibiotic conditions, respectively, and the fecal excretion rates were 0.47, 1.24, and 0.82% dose/day for nonocclusive, occlusive, and occlusive-antibiotic conditions, respectively.

**3.4.4.4 Other Routes of Exposure**

Kinetics of elimination of pentachlorophenol in rats following a single intravenous injection (Reigner et al. 1991) differ from those reported by Braun et al. (1977) following oral exposure. In the Reigner et al. (1991) study, the clearance rate of pentachlorophenol from plasma was  $0.026 \pm 0.003$  L/hour/kg. Elimination of pentachlorophenol from plasma was biphasic and fit a two-compartment model, with the half-life for the first phase being  $0.67 \pm 0.46$  hours and the half-life for the second phase being  $7.11 \pm 0.87$  hours. Most of the pentachlorophenol was eliminated during the second phase. However, routes of excretion and main metabolites recovered in urine and feces were similar to those seen by these same investigators after oral administration (Reigner et al. 1991). The study authors proposed that specificity of the analytical methodology is one possible explanation for the difference in elimination kinetics seen between their study and the study by Braun et al. (1977), who, instead of taking multiple blood samples from the same animal, killed two animals at different times to get the kinetic profile. Use of pooled data such as this may have provided inaccurate data for modeling.

Following intravenous administration of 5 mg/kg pentachlorophenol (>99% purity) into rats, the estimated mean terminal elimination half-life of pentachlorophenol was  $5.6 \pm 0.37$  hours in males and  $9.5 \pm 4.2$  hours in females, but the difference was not significant (Yuan et al. 1994).

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**3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models**

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for



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many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-3 shows a conceptualized representation of a PBPK model.

No PBPK modeling studies were located for pentachlorophenol.

## 3.5 MECHANISMS OF ACTION

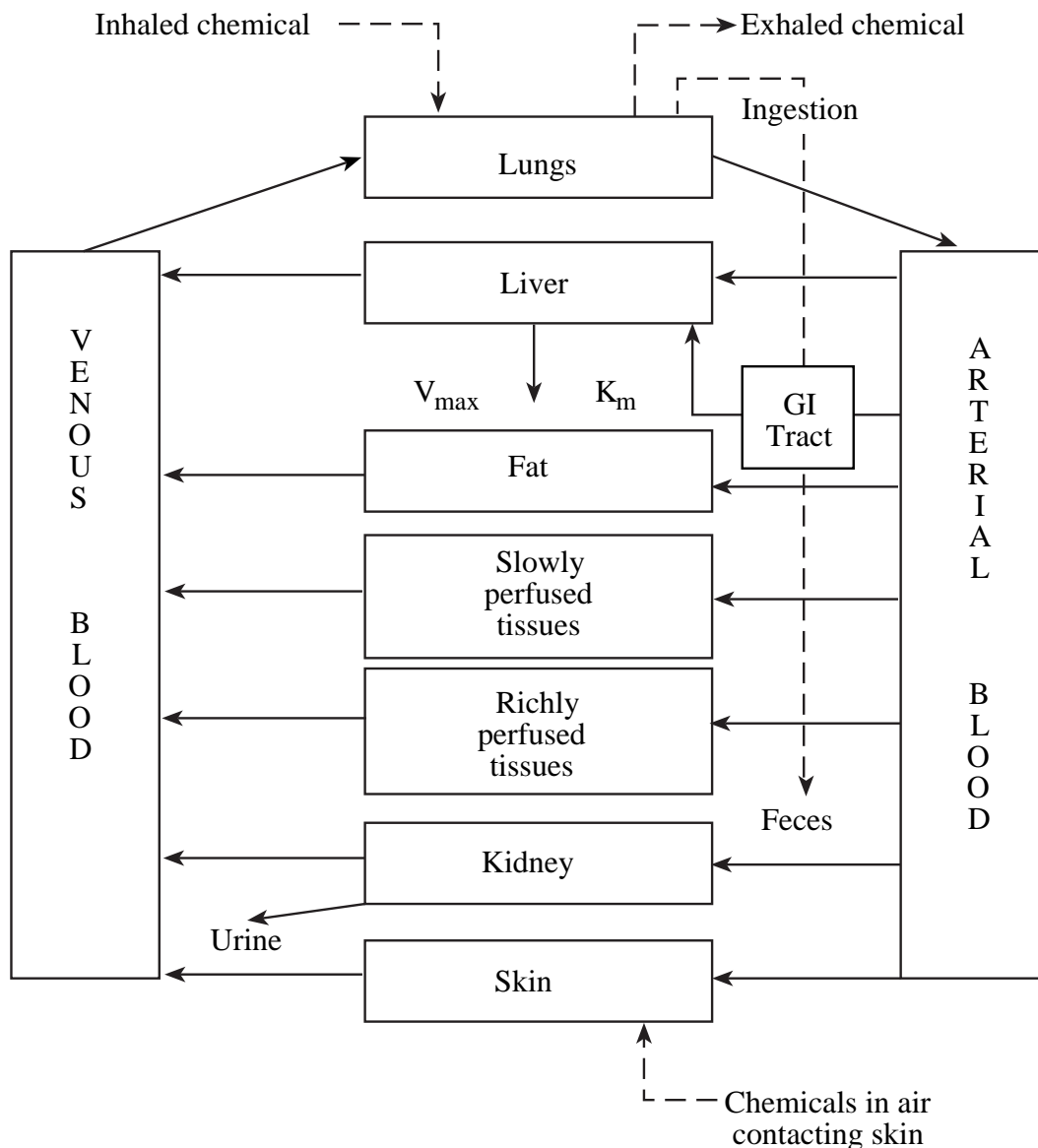
### 3.5.1 Pharmacokinetic Mechanisms

Pentachlorophenol is a nonpolar, lipophilic substance. While the exact mechanism of absorption is not known, it can be assumed that because of its lipophilicity it can easily cross cell membranes and be absorbed in lungs, gastrointestinal tract, and skin. Toxicokinetic studies in animals and humans demonstrate this to be the case (see Section 3.4.1).

Binding of pentachlorophenol to plasma proteins plays a role in the distribution of pentachlorophenol. It has been demonstrated, using an *in vitro* diafiltration technique (Braun et al. 1977), that 95% of the pentachlorophenol in plasma is protein bound. Extensive plasma protein binding of pentachlorophenol may account for the low degree of metabolism seen with this compound (most pentachlorophenol is excreted unchanged) because protein-bound material is not readily distributed to tissues where it can be metabolized. van Raaij et al. (1994) demonstrated a dose- and time-dependent uptake of pentachlorophenol into the cerebrospinal fluid of rats following single intraperitoneal injections. Since similar doses of pentachlorophenol also significantly decreased the uptake of radiolabeled T4 into cerebrospinal fluid, the study authors suggested that pentachlorophenol may interact with the T4 binding site of transthyretin and compete with T4 for uptake into cerebrospinal fluid (van Raaij et al. 1994). This is a plausible explanation since the affinity of pentachlorophenol for the T4 binding site on transthyretin is 2.5-fold greater than that of T4 itself (den Besten et al. 1991).

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**Figure 3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance**



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

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**3.5.2 Mechanisms of Toxicity**

It is widely believed that pentachlorophenol exerts its toxic effects, at least in part, by uncoupling mitochondrial oxidative phosphorylation, thereby causing accelerated aerobic metabolism and increased heat production. Pentachlorophenol has been found to bind to purified rat liver mitochondrial protein. This may induce conformational changes in enzymes involved in oxidative phosphorylation (Weinbach and Garbus 1965). The pattern of pentachlorophenol-induced toxicity often seen in humans and animals supports this proposed mechanism of action. A young worker who died following 3 weeks of exposure to pentachlorophenol dust in a chemical plant was found to have cerebral edema and fatty degeneration of liver and lungs at necropsy (Gray et al. 1985). The study authors concluded that these clinical findings are consistent with a hypermetabolic state resulting from a derangement of aerobic metabolism and characterized by hyperthermia, which can lead to tachycardia, tachypnea, hyperemia, diaphoresis, and metabolic acidosis. This is usually followed by death and rapid, profound rigor mortis. Toxicity resulting from uncoupling of oxidative phosphorylation was generally seen prior to death in animals acutely exposed to pentachlorophenol. These included accelerated respiration, hyperemia, cardiac and muscular collapse, asphyxial convulsions, death, and rapid rigor mortis (St. Omer and Gadusek 1987). The ultrastructural changes observed in mitochondria from liver cells of rats treated with technical-grade pentachlorophenol for 15 days are consistent with uncoupling of oxidative phosphorylation (Fleischer et al. 1980).

The cell membrane is apparently a possible site of action for pentachlorophenol. Lipid bilayers of purified and total cell membranes have been reported to destabilize following sublethal pentachlorophenol treatment (Duxbury and Thompson 1987). This was evidenced by a 50% decrease in bulk lipid fluidity attributable to disruption of the bilayer by pentachlorophenol. These authors also found that pentachlorophenol partitions into the hydrophobic interior of the bilayer. Other membrane changes observed by these investigators included a decrease in phospholipid phosphate levels that they believe was a result of a selective chemical effect on phospholipase C. However, the authors concluded that this was only a sublethal effect since the cells remained viable.

In another investigation of the physicochemical basis of pentachlorophenol membrane effects, membrane toxicity was associated with the pentachlorophenol-induced change in hydrogen ion permeability of the membrane lipid matrix (Smejtek 1987). The onset of toxic effects was correlated with the loss of membrane electrical resistance and a measurable amount of pentachlorophenol binding to the membrane.

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Studies described above indicate that pentachlorophenol can disrupt membrane structure and function. These effects could conceivably occur throughout the body and could therefore explain the wide range of toxic effects associated with pentachlorophenol, including the uncoupling of oxidative phosphorylation.

Oral and intraperitoneal administration of pentachlorophenol to animals causes adverse effects on thyroid homeostasis (e.g., decreased serum thyroxine) and on the thyroid gland (Beard and Rawlings 1998; Beard et al. 1999b; Jekat et al. 1994; van Raaij et al. 1991a). These effects may occur during gestation, pregnancy, and lactation (Beard and Rawlings 1998; Beard et al. 1999b). Further *in vitro* studies by van Raaij et al. (1991b) revealed that the likely mechanism of action for this anti-thyroid effect of pentachlorophenol was competition for serum protein thyroxine binding sites. van Raaij et al. (1994) subsequently demonstrated a dose- and time-dependent uptake of pentachlorophenol into the cerebrospinal fluid of rats following single intraperitoneal injections. Since similar doses of pentachlorophenol also significantly decreased the uptake of radiolabeled T4 into cerebrospinal fluid, the study authors suggested that pentachlorophenol may interact with the T4 binding site of transthyretin and compete with T4 for uptake into cerebrospinal fluid (van Raaij et al. 1994). This is a plausible explanation since the affinity of pentachlorophenol for the T4 binding site on transthyretin is 2.5-fold greater than that of T4 itself (den Besten et al. 1991).

Such effects on thyroid parameters, combined with the activity of pentachlorophenol as a potent inhibitor of oxidative phosphorylation (Weinbach 1954), may be expected to have general adverse effects on basal metabolic rate and many critical processes including development, reproduction, nervous system function, and the specific functioning of endocrine and other organs.

In addition, the effects of pentachlorophenol on thyroid homeostasis and the availability of T4 to the central nervous system may have adverse effects on development of the nervous system. Deficiencies in thyroxine during prenatal and postnatal life can cause decrements in intellectual function in children (Bargagna et al. 1997; Birrell et al. 1983; Kooistra et al. 1994), and hypothyroidism in animals leads to disorders in structural and functional development of the brain (Gould et al. 1990; Neveu and Arenas 1996; Stein et al. 1991; Vega-Nunez et al. 1995). However, testing has not been performed on animals exposed to pentachlorophenol, either prenatally or postnatally, to examine the potential for the anti-thyroid effects of pentachlorophenol to produce adverse effects on neurobehavior.

Recent studies in rats and mice involved the characterization of chlorinated protein adducts arising from pentachlorophenol metabolism following oral administration of pentachlorophenol (Lin et al. 1997;

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Waidyanatha et al. 1994, 1996). Results from these studies and previously summarized studies suggest that the metabolism of pentachlorophenol can proceed through the quinols TCHQ and Cl<sub>4</sub>CAT via microsomal cytochrome P 450 enzymes and that these quinols can be oxidized via semiquinone intermediates (tetrachloro-1,2-semiquinone [Cl<sub>4</sub>-1,2-SQ] and tetrachloro-1,4-semiquinone [Cl<sub>4</sub>-1,4-SQ]) into the corresponding quinones (tetrachloro-1,2-benzoquinone [Cl<sub>4</sub>-1,2-BQ] and tetrachloro-1,4-benzoquinone [Cl<sub>4</sub>-1,4-BQ]). Both the quinones and semiquinones are electrophilic and can bind to cellular macromolecules (Lin et al. 1997). The redox cycling associated with oxidation of TCHQ and reduction of Cl<sub>4</sub>-1,4-BQ generates oxygen radicals that caused an increase in 8-hydroxy-2-deoxyguanosine levels in liver DNA in mice that had been fed pentachlorophenol (Sai-Kato et al. 1995; Umemura et al. 1996) or TCHQ (Dahlhaus et al. 1994) in the diet for up to 4 weeks. It is possible that the formation of such adducts is involved in the induction of hepatic neoplasms in mice (NTP 1989). Lin et al. (1997) measured levels of chlorinated protein adducts arising from pentachlorophenol metabolism in the livers of mice and rats administered pentachlorophenol in the diet for up to 4 weeks. After aggregation of the estimated contributions of all quinone species derived from pentachlorophenol metabolism, mice had a four-fold greater dose to liver nuclei than rats, whereas rats had a three-fold greater dose to liver cytosol than mice. The increased nuclear dose to mouse liver compared to that of the rat suggests that the mouse is at greater risk to hepatic DNA damage from pentachlorophenol-derived quinones. Using a model to predict quinone and semiquinone production, Lin et al. (1999) estimated that at low doses of pentachlorophenol, the production of semiquinone adducts was proportionally greater in rats than mice; in mice, direct oxidation to quinones and the production of quinone adducts is favored in mice exposed to low doses of pentachlorophenol. These data suggest that both the types and amounts of adducts differ in rats and mice, which may account for the occurrence of liver tumors in mice but not in rats in bioassays conducted by NTP (1989, 1999).

In an epidemiologic study of male factory workers who brushed pentachlorophenol onto wood strips, sometimes without gloves, serum biliary acid concentrations were elevated in the high-exposure group, but not the low-exposure group, compared with controls (Colosio et al. 1993b). This effect may have been caused in part by the impurities in the pentachlorophenol. The presence of elevated concentrations of bile acids in serum is a sensitive indicator of liver dysfunction (Franco et al. 1986). Since bile acids are essential for lipid transport, are the major products of cholesterol metabolism, and regulate the transcription of genes that control cholesterol homeostasis (Makishima et al. 1999; Parks et al. 1999), the elevation of serum bile acids by exposure to high levels of pentachlorophenol may have some effect on biochemical pathways involved in cholesterol metabolism and homeostasis.

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**3.5.3 Animal-to-Human Extrapolations**

Reigner et al. (1993) investigated the binding of radiolabeled pentachlorophenol to serum proteins *in vitro*, found that the percentage of unbound pentachlorophenol in serum was 1.37 in mice, 0.85 in rats, 0.67 in monkeys, 0.53 in humans, and 0.43 in cows and found that these percentages correlated inversely with the total protein levels in the same serum samples. These investigators, assuming that pentachlorophenol itself is responsible for carcinogenicity in mice, developed a new method for interspecies extrapolation in which the interspecies differences in clearance and serum protein binding of pentachlorophenol were taken into account in interspecies scaling. Several pharmacokinetic parameters, including volume of distribution, unbound volume of distribution, clearance, unbound clearance, and unbound clearance time maximum life potential, were scaled to body weight. The method produced estimates of equivalent human doses of pentachlorophenol (derived from experimental doses in mice that caused increased tumor incidences in the NTP [1989] 2-year bioassay) that are up to four times smaller than those obtained using body surface area.

**3.6 ENDOCRINE DISRUPTION**

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones, or otherwise interfere with the normal function of the endocrine system. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. Some scientists believe that chemicals with the ability to disrupt the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. Others believe that endocrine disrupting chemicals do not pose a significant health risk, particularly in light of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavonoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These compounds are derived from plants and are similar in structure and action as endogenous estrogen. While there is some controversy over the public health significance of endocrine disrupting chemicals, it is agreed that the potential exists for these compounds to affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior (EPA 1997). As a result, endocrine disruptors may play a role in the disruption of sexual function, immune suppression, and neurobehavioral function. Endocrine disruption is also thought to be involved in the induction of breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

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Several studies have documented effects of pentachlorophenol on thyroid homeostasis (Beard and Rawlings 1998, 1999; Beard et al. 1999a, 1999b; Jekat et al. 1994; van Raaij et al. 1991a). These effects include decreased serum thyroxine concentration (Beard and Rawlings 1998, 1999; Beard et al. 1999a, 1999b; Jekat et al. 1994; van Raaij et al. 1991a), decreased thyroxine and triiodothyronine response to thyroid stimulating hormone (Beard and Rawling 1999), and decreased uptake of thyroxine into cerebrospinal fluid (van Raaij et al. 1994); these effects may be linked with a demonstrated competition of pentachlorophenol with the thyroxine binding site on transthyretin, a major thyroxine transport protein (den Besten et al. 1991).

Developmental toxicity studies provide some limited evidence that pentachlorophenol has the ability to disrupt endocrine function. A marked increase in the sex ratio (most female fetuses did not survive) was observed in the offspring of rats administered pure or technical-grade pentachlorophenol on gestational days 6–15 (Schwetz et al. 1974). However, the finding was not confirmed in other developmental toxicity studies (Argus 1993b/Bernard et al. 2001b, Argus 1997/Bernard et al. 2001c). In a multigeneration study in rats, significant increases in the average day of vaginal patency and preputial separation were observed in the F1 offspring exposed to an unspecified purity pentachlorophenol (Argus 1997/Bernard et al. 2001c).

In an *in vitro* test system, pure pentachlorophenol inhibited the activity of the human progesterone receptor. Tran et al. (1996) transformed a yeast strain with an expression plasmid for the human progesterone (hPR) receptor and a reporter containing two progesterone response elements. In the resulting yeast strain, hPR-PRE, beta-galactosidase activity was measured as an indicator of stimulation of the hPR signaling pathway. When the signaling pathway was stimulated by progesterone, 1  $\mu$ M pentachlorophenol (99% pure) significantly inhibited hPR activity. Competitive binding studies indicated that pentachlorophenol effectively competed with a radiolabeled synthetic progestin for binding to hPR. Investigation of the interaction of pentachlorophenol with the progesterone-signaling pathway in animals might be another avenue for future research.

In rainbow trout hepatocytes, pentachlorophenol inhibited the induction of the estrogen receptor by estradiol and inhibited the induction of vitellogenin messenger RNA by estradiol (Flouriot et al. 1995). In short-term, whole-embryo assays using *Xenopus laevis*, pentachlorophenol significantly decreased the rates of tail resorption in metamorphs studied from day 50 (stage 60) to day 64 (stage 66) of development (Fort and Stover 1997).

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**3.7 CHILDREN'S SUSCEPTIBILITY**

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient



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tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility while others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

There have been several reports of children accidentally exposed to pentachlorophenol; the children were predominantly exposed via dermal contact and, to a lesser extent, by the inhalation route. The observed health effects include symptoms of hyperthermia (high fever, profuse sweating, increased respiratory rate, labored breathing, tachycardia, hepatomegaly, and irritability) due to the uncoupling of oxidative phosphorylation and death in newborn infants following dermal contact with diapers and bedding washed in an antimildew agent containing pentachlorophenol (Robson et al. 1969; Smith et al. 1996) and in a child exposed to bath water contaminated with pentachlorophenol (Chapman and Robson 1965). The Chapman and Robson (1965) report provides suggestive evidence that young children may be more susceptible to the toxicity of pentachlorophenol than adults. All members of the child's family bathed in the contaminated bath water over a 13-day period; however, the only symptoms reported in the other family members were nasal stuffiness and swollen, painful eyes. A study by McConnachie and Zahalsky (1991) also reported health effects in children. Alterations in immunological parameters were observed in individuals living in log homes treated with a wood preservative containing pentachlorophenol. Fifteen of the 38 subjects were children aged 8–18. This study cannot be used to assess whether children would be more susceptible to the toxicity of pentachlorophenol because no comparisons across age groups were made. In addition to these health effects, hematological disorders (Cheng et al. 1993; Hryhorczuk et al. 1998; Klemmer et al. 1980; Roberts et al. 1981, 1990; Rugman and Cosstick 1991) and liver (Armstrong et al. 1969; Bergner et al. 1965; Colosio et al. 1993b; Gordon 1956; Robson et al. 1969; Smith et al. 1996) effects have been observed in adults exposed to pentachlorophenol, and these are likely targets in children. An animal study that compared LD<sub>50</sub> values provides evidence that infants may be more susceptible than children. Lower LD<sub>50</sub> values were found in preweaning animals, as compared to juvenile rats (25–50 days); however, the LD<sub>50</sub> value in adult rats was similar to the value for preweaning rats (St. Omer and Gadusek 1987).

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There is some limited evidence that the developmental process in humans is altered by paternal exposure to pentachlorophenol. An increased risk of congenital eye cataracts was observed in the children of men presumably exposed to CDD-contaminated chlorophenolate (Dimich-Ward et al. 1996); however, as discussed in Section 3.2.1.5, deficiencies in the study design limits interpretation of these results. Studies of potential developmental effects of pentachlorophenol in animals indicate that the developing organism is a sensitive target of toxicity. Fetal/neonatal mortality (Argus 1993b/Bernard et al. 2001b, Argus 1997/Bernard et al. 2001c; Schwetz et al. 1974; Welsh et al. 1987), malformations/anomalies (Argus 1993b/Bernard et al. 2001b; Schwetz et al. 1974), decreased growth (Argus 1993b/Bernard et al. 2001b; Beard et al. 1999b; Courtney et al. 1976; Larsen et al. 1975; Schwetz et al. 1974; Welsh et al. 1987), and possibly impaired development of the reproductive system (Argus 1997/Bernard et al. 2001c) have been observed in rats and sheep following gestational exposure. In most of these studies, the developmental effects occurred at maternally toxic doses; however, decreases in fetal body weight gain have been observed at doses that were not associated with maternal toxicity (Argus 1997/Bernard et al. 2001c; Welsh et al. 1987). A number of studies in rats (Jekat et al. 1994) and sheep (Beard and Rawlings 1998; Beard et al. 1999a, 1999b) have demonstrated that exposure to pentachlorophenol can result in decreased serum thyroxine and triiodothyronine levels. Deficiencies in thyroxine during prenatal and postnatal life can cause decrements in intellectual function in children (Bargagna et al. 1997; Birrell et al. 1983; Kooistra et al. 1994). It is not known if this will also occur following exposure to pentachlorophenol, and neuro-behavioral testing has not been performed on animals exposed to pentachlorophenol either prenatally or postnatally. Such testing might be an avenue for future research.

There is no information regarding pharmacokinetics of pentachlorophenol in children or regarding nutritional factors that may influence absorption of pentachlorophenol. There are no PBPK models for pentachlorophenol. Mehmood et al. (1996) has provided evidence that human cytochrome P450 3A4 may metabolize pentachlorophenol to TCHQ in phase I metabolism of pentachlorophenol; however, the purity of the pentachlorophenol used in this study was not indicated. In humans, this enzyme has low activity in the first month of life, with approach toward adult levels by 6–12 months of postnatal age; adult activity may be exceeded between 1–4 years of age and then activity progressively declines, reaching adult levels at the conclusion of puberty (Leeder and Kearns 1997). By Western immunoblotting using monoclonal antibodies to identify the different P 450 isozymes, pure pentachlorophenol (>99%) was identified as an inducer of cytochrome P450 3A7 in studies in cultured rat hepatocytes, quail hepatocytes, and human hepatoma (Hep G2) cells (Dubois et al. 1996). In humans, functional activity of cytochrome P450 3A7 in the fetus is approximately 30–75% of adult levels (Leeder and Kearns 1997). UDP-glucuronosyl transferase and sulfotransferases are involved in phase II

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metabolism of pentachlorophenol. Both of these enzymes are thought to be developmentally regulated (Leeder and Kearns 1997). Although the ontogeny of UDP-glucuronosyl transferase is isoform-specific, the adult level of activity seems to be achieved in humans by 6–18 months of age (Leeder and Kearns 1997). Ontogeny for the sulfotransferases seems to be more rapid than that for UDP-glucuronosyl transferase, and the activity for some isoforms of sulfotransferase may exceed adult levels during infancy and early childhood (Leeder and Kearns 1997). Larsen et al. (1975) provided evidence that pentachlorophenol (0.05–0.08% of an oral dose administered on day 15 of gestation) may cross the placenta; the chemical nature of the radioactive material present in the fetuses was not investigated.

Low levels of pentachlorophenol were found in human breast milk of women living in Germany or Slovakia (Gebefugi and Korte 1983; Veningerova et al. 1996). It is likely that pentachlorophenol will also be present in the breast milk of women living in the United States, particularly since pentachlorophenol has been detected in more than half of the urine samples of adults living in the United States (Hill et al. 1995). However, it is not known if the pentachlorophenol present in the breast milk or urine samples resulted from exposure to pentachlorophenol or to other industrial chemicals that are metabolized to pentachlorophenol.

There is no reason to suspect the mechanism of action of pentachlorophenol is different in children. There are no specific biomarkers of exposure or effect for pentachlorophenol that have been validated in children or adults exposed as children. No studies were located regarding interactions of pentachlorophenol with other chemicals in children.

There are no pediatric-specific methods for reducing peak absorption or reducing body burden following exposure to pentachlorophenol.

### 3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target

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molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to pentachlorophenol are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by pentachlorophenol are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10. "Populations That Are Unusually Susceptible".

#### **3.8.1 Biomarkers Used to Identify or Quantify Exposure to Pentachlorophenol**

Since pentachlorophenol is excreted in the urine largely unchanged (Ahlborg et al. 1974; Braun et al. 1979; Larsen et al. 1972; Reigner et al. 1991) and since it can be easily detected and quantified in the urine at concentrations as low as <1 ppb (Chou and Bailey 1986; Drummond et al. 1982; Edgerton et al. 1979; EPA 1980b; Holler et al. 1989; NIOSH 1984b; Pekari and Aitio 1982; Rick et al. 1982; Siqueina and Fernicola 1981), pentachlorophenol in the urine is a useful biomarker of exposure. In addition,

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pentachlorophenol can be easily detected and quantified in blood serum at concentrations as low as <1 ppb (Bevenue et al. 1968; EPA 1980b; Needham et al. 1981; NIOSH 1984b) and adipose tissue (Kuehl and Dougherty 1980; Needham et al. 1981; Ohe 1979; Shafik 1973). It has been demonstrated that pentachlorophenol is present in human adipose tissue as an ester of palmitic acid (Ansari et al. 1985). The detection limit for pentachlorophenol in adipose tissue is approximately 5 ppb (Kuehl and Dougherty 1980; Ohe 1979; Shafik 1973). However, measuring pentachlorophenol in body fluids and tissues is not a specific biomarker for pentachlorophenol exposure because other compounds to which exposure may occur (e.g., hexachlorobenzene and lindane) may be metabolized to pentachlorophenol in the body. In addition, the available data do not permit the establishment of a quantitative relationship between levels of pentachlorophenol in the environment and levels in human fluids or tissues. However, it has been reported that repeated workday exposure to pentachlorophenol at a concentration of 0.5 mg/m<sup>3</sup> has resulted in a maximum steady state level of pentachlorophenol in plasma of about 0.5 mg/L (Wood et al. 1983). Based on samples taken prior to 1989, background levels of up to 0.1 ppm pentachlorophenol could be found in blood and urine of members of the general population who had no recognized exposure to pentachlorophenol (Cranmer and Freal 1970; EPA 1989b; Hill et al. 1989; Kutz et al. 1978).

TCHQ, a major urinary metabolite of pentachlorophenol, has potential use as an indicator of exposure to pentachlorophenol. It has been demonstrated that pentachlorophenol is converted to TCHQ by human microsomal enzymes (Juhl et al. 1985). In human and animal studies, TCHQ has been identified as the major urinary metabolite of pentachlorophenol (Ahlborg et al. 1974; Braun et al. 1977; Reigner et al. 1991; Renner 1989). However, the presence of TCHQ in the urine is not specific to pentachlorophenol and would also be present following exposure to chemicals that are metabolized to pentachlorophenol.

The presence of elevated levels of 8-hydroxydeoxyguanosine in the liver may serve as a nonspecific marker of oxidative DNA damage by pentachlorophenol. Administration of pentachlorophenol (98.6% pure) to mice in the diet for up to 4 weeks produced oxidative damage to hepatic nuclear DNA as evidenced by an increase in the amount of 8-hydroxydeoxyguanosine in DNA (Sai Kato et al. 1995; Umemura et al. 1996). A single oral dose of pentachlorophenol (98.6% pure) produced an increase in the amount of 8-hydroxydeoxyguanosine in liver DNA but not in kidney or spleen DNA (Sai-Kato et al. 1995).

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**3.8.2 Biomarkers Used to Characterize Effects Caused by Pentachlorophenol**

Two of the major target organs for both humans and animals exposed to pentachlorophenol are liver and kidney. Clinical manifestations of hepatic and renal toxicity include elevated serum ALT and AST levels for toxicity to the liver (Armstrong et al. 1969; Bergner et al. 1965; Gordon 1956; Gray et al. 1985; Klemmer 1972; Robson et al. 1969) and increased enzyme levels, increased blood urea nitrogen, and loss of proximal tubular alkaline phosphatase activity for toxicity to the kidney (Greichus et al. 1979; Kimbrough and Linder 1978; Nishimura et al. 1980). Indices of changes in hepatic oxidative phosphorylation may also be useful as biomarkers for pentachlorophenol-induced liver changes (Ellinger et al. 1991). These effects are not specific for exposure to pentachlorophenol and have been associated with exposure to other compounds such as some chlorinated hydrocarbons. Therefore, the major use of these biomarkers is restricted to comparisons between work groups exposed to the chemical in the workplace and control subjects. Other data indicate that contaminants in the commercial grade product may play an important role in these observed hepatotoxic effects.

Human case reports of pentachlorophenol exposure suggest that the central nervous system appears to be a target of pentachlorophenol exposure (Chapman and Robson 1965; Gray et al. 1985; Haley 1977; Robson et al. 1969). As discussed in Section 3.2.2.4, the neurologic syndrome observed following exposure to pentachlorophenol is possibly the direct result of hyperthermia generated by uncoupling of mitochondrial oxidative phosphorylation rather than a direct effect on the nervous system. The neurological syndrome observed following exposure to pentachlorophenol can be manifested by lethargy, tachypnea, tachycardia, intermittent delirium, convulsions, cerebral edema, focal swelling of the myelin sheath, and respiratory distress (Chapman and Robson 1965; Gray et al. 1985). However, these symptoms are not specific for pentachlorophenol exposure.

In general, there is no simple relationship between nonfatal health effects and levels of pentachlorophenol detected in serum and urine. Serum levels of pentachlorophenol ranging from 23 to 162 mg/L (ppm) have been reported in cases of fatal overexposure to pentachlorophenol. Serum levels of pentachlorophenol below 1.3 mg/L have not been associated with any adverse health effects (Cline et al. 1989; Klemmer et al. 1980).

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**3.9 INTERACTIONS WITH OTHER CHEMICALS**

No studies were located regarding the direct toxic interactions of pentachlorophenol with other chemicals in humans, including children, or animals. No interactions between pentachlorophenol contaminants and the pure pentachlorophenol component of technical-grade pentachlorophenol have been demonstrated in some tests of immunotoxicity (Kerkvliet et al. 1985a).

Pentachlorophenol may alter the toxicities of other compounds through its inductive action on microsomal metabolic enzymes (Vizethum and Goerz 1979). While this inductive effect has not specifically been demonstrated to alter the toxicity of other compounds, these types of alterations in enzyme activity may influence metabolism and toxicity of many compounds. Pentachlorophenol inhibits cytosolic sulfotransferases (Mulder and Scholtens 1977). Compounds such as n-hydroxy-2-acetylaminofluorene, which are activated by the formation of a sulfate ester, are considerably less toxic in animals pretreated with pentachlorophenol (Meerman et al. 1980). Pentachlorophenol, an inhibitor of arylsulfotransferase, significantly decreased 2-acetylaminofluorene-induced DNA damage in rat hepatocytes *in vitro*. *In vivo*, pentachlorophenol alone induced a significant increase in unscheduled liver DNA synthesis, but also caused a significant decrease in 2-acetylaminofluorene-induced unscheduled liver DNA synthesis (Monteith 1992).

Male rats were given pentachlorophenol (91.6%) daily by gavage at a dose of 20 mg/kg. At 1, 2, 4, and 5 weeks, the animals were given a single gavage dose of 2,6-dinitrotoluene, and urine was collected for 24 hours and tested for mutagenicity in *Salmonella typhimurium* strain TA98. A statistically-significant increase in revertants at week 5 in pentachlorophenol-treated animals, compared with controls that did not receive pentachlorophenol, suggested that pentachlorophenol caused an increase in the excretion of mutagenic metabolites of 2,6-dinitrotoluene. A slight, but statistically-significant, decrease in nitroreductase activity in the small intestine was also reported in the pentachlorophenol-treated rats compared with controls (Chadwick et al. 1993).

Since pentachlorophenol is metabolized to a small extent by hepatic microsomal enzymes, chemicals that alter the activity of these enzymes can modify metabolism, and subsequently, the toxicity of pentachlorophenol (see discussion above). For example, phenobarbital, a microsomal enzyme inducer, increases biotransformation of pentachlorophenol to TCHQ thereby reducing the level of pentachlorophenol in the body (Ahlborg et al. 1978).

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A great deal of pentachlorophenol is bound to plasma proteins (Braun et al. 1977). Other agents that also have a high affinity for protein bonds (e.g., anticoagulants such as warfarin) could compete with and displace pentachlorophenol from proteins. This action could then result in a higher level of free-circulating pentachlorophenol that can be metabolized, or excreted, and/or induce toxic effects. However, this hypothesis has not been experimentally confirmed.

Various agents have been used in experimental animals to try to decrease the toxicity of pentachlorophenol. Cholestyramine is known to bind phenols (Reiman and Walton 1970) and to enhance fecal elimination of chlordecone (Kepone) in rats and humans (Boylan et al. 1977). Rozman et al. (1982) found that cholestyramine enhances excretion of pentachlorophenol in Rhesus monkeys and recommends that its use be considered in cases of human pentachlorophenol overexposure.

#### **3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE**

A susceptible population will exhibit a different or enhanced response to pentachlorophenol than will most persons exposed to the same level of pentachlorophenol in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of pentachlorophenol, or compromised function of organs affected by pentachlorophenol. Populations who are at greater risk due to their unusually high exposure to pentachlorophenol are discussed in Section 6.7, Populations With Potentially High Exposures.

Groups possibly at greater-than-average risk of suffering from the toxic effects of pentachlorophenol include persons laboring in hot environments, persons with an inability or decreased ability to disperse body heat, geriatric and pediatric subpopulations, pregnant women, and those that are malnourished or consume an unbalanced diet. People with impaired liver and kidney function are likely to be susceptible to the toxic effects of any chemical/product that is metabolized and/or excreted by these organs, and therefore, may be unusually susceptible to the toxic effects of pentachlorophenol.

Persons laboring in hot environments are unusually susceptible to the acute toxic effects of pentachlorophenol. One of the principal effects of pentachlorophenol is hyperthermia induced by the uncoupling of oxidative phosphorylation. The manifestations of overexposure to pentachlorophenol, particularly in persons laboring in a hot environment, are usually those associated with hyperthermia: flushing, intense thirst, sweating, weakness and, occasionally, muscle spasms. Persons working in hot environments are



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unable to disperse excess body heat, resulting in potentially life-threatening hyperthermia. For example, occupational deaths reported by Bergner et al. (1965), Gray et al. (1985), and Menon (1958) were all due to hyperthermia, and the symptoms of hyperthermia described above were exhibited by affected workers prior to death.

There is some evidence that young children are more susceptible than older children or adults to the toxic effects of pentachlorophenol often associated with the uncoupling of oxidative phosphorylation. In a study by Chapman and Robson (1965), signs of hyperthermia (resulting from the uncoupling of oxidative phosphorylation) were observed in a 3-year old child exposed to pentachlorophenol in contaminated bath water. However, no signs of hyperthermia were observed in older children or adults in the family. Prewaning and adult rats have been reported to have lower oral LD<sub>50</sub>s for technical-grade pentachlorophenol than juvenile rats (25–50 days old) (St. Omer and Gadusek 1987); similar differences in sensitivity are possible in humans.

Age-related differences in the frequency or severity of toxic effects from pentachlorophenol exposure may arise from developmental regulation of cytochrome P-450s, which are involved in phase I metabolism of pentachlorophenol, and sulfotransferases and UDP-glucuronosyl transferase, which are involved in phase II metabolism of pentachlorophenol (see Section 3.7).

Oral and intraperitoneal administration of pentachlorophenol to animals causes adverse effects on thyroid homeostasis (e.g., decreased serum thyroxine) and on the thyroid gland, and such effects may occur during gestation, pregnancy, and lactation. Pentachlorophenol also significantly decreased the uptake of radiolabeled thyroid hormone into cerebrospinal fluid (see Section 3.7). These effects of pentachlorophenol on the thyroid gland, thyroid homeostasis, and the availability of thyroid hormone to the central nervous system may have adverse effects on development of the nervous system. Deficiencies in thyroxine during prenatal and postnatal life can cause decrements in intellectual function in children (Bargagna et al. 1997; Birrell et al. 1983; Kooistra et al. 1994), and hypothyroidism in animals leads to disorders in structural and functional development of the brain (Gould et al. 1990; Neveu and Arenas 1996; Stein et al. 1991; Vega-Nunez et al. 1995).

Individuals with liver or kidney disease may be unusually susceptible to the toxic effects of pentachlorophenol. In certain fatal human cases, the victim was found to have renal insufficiency (Hayes 1982). Experiments have shown that rabbits made nephrotic experimentally were much more susceptible to the toxic effects of pentachlorophenol than were normal rabbits (Hayes 1982). Individuals exposed to other

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chemicals that bind to plasma proteins (e.g., anticoagulants such as warfarin) may be at greater risk of suffering from pentachlorophenol-induced toxicity as well.

#### 3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to pentachlorophenol. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to pentachlorophenol. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to pentachlorophenol:

Ballhorn L, Rozman T, Rozman K, et al. 1981. Cholestyramine enhances fecal elimination of pentachlorophenol in Rhesus monkeys. *Chemosphere* 10:877-888.

EPA. 1989b. Recognition and management of pesticide poisonings. 4th ed. Washington, DC: U.S. Environmental Protection Agency. EPA-540/9-88-001.

Goodman AG, Rall TW, Nies AS, et al. 1990. Goodman & Gilman's the pharmacological basis of therapeutics. 8th ed. New York, NY: Pergamon Press, 1635.

Rozman T, Ballhorn L, Rozman K, et al. 1982. Effect of cholestyramine on the disposition of pentachlorophenol in Rhesus monkeys. *J Toxicol Environ Health* 10:277-283.

##### 3.11.1 Reducing Peak Absorption Following Exposure

Means of limiting absorption of phenols include washing exposed skin and eyes and removing contaminated clothing in the case of dermal exposure, and inducing emesis, performing gastric lavage, and administering activated charcoal and a cathartic in the case of oral exposure (EPA 1989b). Emesis is induced only if the patient is fully alert and the pentachlorophenol has not been ingested in a solvent so that there is no chance that the stomach contents may be aspirated. If the patient is unconscious or vomiting cannot be induced, intubation, aspiration, and lavage of the stomach are suggested (EPA 1989b).

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#### 3.11.2 Reducing Body Burden

Various agents have been used in experimental animals to try to decrease the toxicity of pentachlorophenol by reducing body burden. Cholestyramine is known to bind phenols (Reiman and Walton 1970) and to enhance fecal elimination of chlordecone (Kepone) in rats and humans (Boylan et al. 1977). In studies performed on Rhesus monkeys, oral administration of cholestyramine enhanced fecal excretion of pentachlorophenol by interrupting enterohepatic circulation of pentachlorophenol and/or its metabolites (Ballhorn et al. 1981; Rozman et al. 1982). Thus cholestyramine administration may be an effective means of reducing the body burden of pentachlorophenol in humans (Goodman et al. 1990); it should be noted that testing would be required to determine whether or not cholestyramine treatment would be effective for humans. Hemodialysis and forced diuresis may not be effective means of reducing body burden of phenolic substances, and hemoperfusion has not been sufficiently tested as a means of accelerating elimination of phenols (EPA 1989b).

#### 3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The naturally occurring antioxidants ellagic acid, epigallocatechin gallate, and vitamin C provided partial protection from pentachlorophenol-induced oxidative damage to liver DNA during daily oral administration of pentachlorophenol at 60 mg/kg/day for 5 days to male B6C3F<sub>1</sub> mice (Sai-Kato et al. 1995). Since these antioxidants are protective of animals, they may reduce toxic effects in humans.

### 3.12 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of pentachlorophenol is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of pentachlorophenol.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean

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that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

**3.12.1 Existing Information on Health Effects of Pentachlorophenol**

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to pentachlorophenol are summarized in Figure 3-4. The purpose of this figure is to illustrate the existing information concerning the health effects of pentachlorophenol. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a “data need”. A data need, as defined in ATSDR’s *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (ATSDR 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Much of the literature reviewed concerning the health effects of pentachlorophenol in humans described case reports of individuals exposed occupationally, in log homes treated with pentachlorophenol as a preservative, or in the home following misuse of pentachlorophenol-containing solutions. The predominant route of exposure in such cases is often dermal, but the possibility of some degree of inhalation exposure cannot be ruled out. Therefore, Figure 3-4 reflects that information exists for both inhalation and dermal routes of exposure. However, all of these reports are limited because of the possibility of concurrent exposure to other potentially toxic substances, present as either contaminants in technical-grade pentachlorophenol (i.e., chlorinated dibenzo-*p*-dioxins and dibenzofurans), as other components in pentachlorophenol-containing mixtures (i.e., pesticides and herbicides), or simply other compounds also in the environment. Additionally, duration and level of exposure to pentachlorophenol generally cannot be quantified from information presented in these anecdotal reports.

The database for health effects of pentachlorophenol following ingestion in experimental animals is substantial. However, as can be seen in Figure 3-4, very little information is available on the effects of inhalation and dermal exposure to pentachlorophenol in animals. Furthermore, the health effects associated with acute and intermediate exposure durations are more fully characterized than those associated with chronic exposure. Genotoxicity data on pentachlorophenol are available from both *in vitro* and *in vivo* studies. Finally, when evaluating much of the data on health effects of pentachlorophenol, the toxicity of its impurities (which may themselves present a hazard at disposal sites) must be

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**Figure 3-4. Existing Information on Health Effects of Pentachlorophenol**

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	•	•		•	•	•	•	•	•	•
Oral	•	•								
Dermal	•	•		•	•	•	•	•	•	•

**Human**

	Systemic									
	Death	Acute	Intermediate	Chronic	Immunologic/Lymphoretic	Neurologic	Reproductive	Developmental	Genotoxic	Cancer
Inhalation	•									
Oral	•	•	•	•	•	•	•	•	•	•
Dermal	•	•								•

**Animal**

- Existing Studies

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taken into account. However, it is now clear that pure pentachlorophenol is toxic to several organs and systems in rats and mice and is oncogenic in mice.

**3.12.2 Identification of Data Needs**

**Acute-Duration Exposure.** Information on the acute toxicity of pentachlorophenol in humans comes from a number of case reports involving home use of pentachlorophenol-containing products, such as wood preservatives or herbicides in the garden (Gordon 1956; Hassan et al. 1985) and from a series of reports of newborn infants exposed to pentachlorophenol from diapers and linens treated with an antimildew agent (Armstrong et al. 1969; Robson et al. 1969; Smith et al. 1996). In many of the cases, it is likely that the individuals were primarily exposed to technical-grade pentachlorophenol via dermal contact, although there may have also been some inhalation exposure. There are also cases of individuals ingesting pentachlorophenol (Cretney 1976; Dreisbach 1980; Haley 1977). In general, no information on exposure concentration, duration of exposure, exposure to other chemicals, or the impurities present in the technical-grade pentachlorophenol is available. A number of health effects were consistently observed in these individuals, including death, symptoms of hyperthermia generated by uncoupling of oxidative phosphorylation (e.g., tachycardia, increased respiratory rate, labored breathing, profuse sweating, fever, metabolic acidosis), hemolytic anemia, hepatic enlargement, and dermal toxicity (irritation and chloracne).

The only available inhalation study in animals (Hoben et al. 1979b) reported death, but did not examine other end points. The lack of exposure information in the human studies and the inadequate animal study precluded deriving an acute-duration inhalation MRL. Additional inhalation studies are needed to characterize target organs and establish exposure-response relationships.

Most of the available information on the acute toxicity of pentachlorophenol in animals comes from oral exposure studies. A number of adverse effects were observed in oral exposure studies including death (Borzelleca et al. 1985; Deichmann et al. 1942; Renner et al. 1986; St. Omer and Gadusek 1987), cardiovascular effects (extensive vascular damage and heart failure) (Deichmann et al. 1942), hepatotoxicity (increased relative liver weight) (Nishimura et al. 1982), impaired immune function (Holsapple et al. 1987; Kerkvliet et al. 1985a; White and Anderson 1985), reproductive toxicity (Schwetz et al. 1974), and developmental toxicity (Schwetz et al. 1974). The developing fetus was identified as the most sensitive target in rats following acute gavage exposure to pure pentachlorophenol (Schwetz et al. 1974). The observed effects included delayed ossification at the lowest dose tested (5 mg/kg/day

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administered on gestational days 6–15) and skeletal anomalies, decreased fetal body weights, increased male:female sex ratio, and increased resorptions at higher doses. The Schwetz et al. (1974) study is the basis for an acute-duration oral MRL of 0.005 mg/kg/day.

Pentachlorophenol is well absorbed through the skin, and is expected to produce effects in the same tissues affected by exposure via other routes. Human reports describe numerous systemic effects in individuals predominantly exposed through dermal contact. Skin irritation was reported in a dermal study in rabbits (Deichmann et al. 1942). Additional studies via dermal exposure would be useful in determining target organs and dose-response relationships following acute-duration exposures.

**Intermediate-Duration Exposure.** There is limited information on the toxicity of pentachlorophenol in humans following intermediate-duration exposure. Case reports of individuals exposed either occupationally or in the home during misuse of pentachlorophenol-containing solutions as a result of failure to adhere to appropriate precautionary measures provide some information on the toxicity of pentachlorophenol in humans. The observed effects include hematological alterations (aplastic anemia), hyperthermia (due to uncoupling of oxidative phosphorylation), hepatic enlargement, and impaired immune function (Daniel et al. 1995; Gray et al. 1985; Roberts 1963, 1981, 1990; Rugman and Cosstick 1990). Dermal contact is probably the primary exposure route in these cases, although the possibility of inhalation exposure cannot be ruled out. The interpretation of the reports is limited by the small number of subjects and the lack of information on exposure concentration, route, and duration, concomitant exposure to other chemicals, and description of impurities present in the commercial- or technical-grade pentachlorophenol. No studies were located that examined the toxicity of pentachlorophenol in humans following intermediate-duration oral exposure.

No inhalation studies in animals were located. An intermediate-duration inhalation MRL was not derived due to the lack of human and/or animal data. A 90-day inhalation study is necessary to identify sensitive end points and dose-response relationships.

Information on the toxicity of pentachlorophenol in animals following intermediate-duration exposure primarily comes from oral exposure studies. The results of these studies suggest that the reproductive system is the most sensitive target of toxicity following intermediate-duration exposure. An increase in the severity of cystic uterine glands and decreases in the proportion of female mink accepting a second mating and the number of mink that whelped have been observed in a single-generation mink study (Beard et al. 1997). Other sensitive end points include the liver (increased liver weight, centrilobular

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hepatocyte hypertrophy and vacuolation, hepatocellular degeneration, and periportal fibrosis) (Blakley et al. 1998; Greichus et al. 1979; Johnson et al. 1973; Kerkvliet et al. 1982; Kimbrough and Linder 1978; Knudsen et al. 1974; Nishimura et al. 1980; Umemura et al. 1996), endocrine system (decreased thyroxine levels, increased thyroid gland follicle size) (Beard et al. 1999; Rawlings et al. 1998), immune system (Blakley et al. 1998; Kerkvliet et al. 1982, 1985a, 1985b; NTP 1989), and the developing fetus (decreased litter size, decreased fetal body weights, embryo lethality) (Argus 1997/Bernard et al. 2001c; Beard et al. 1999; Welsh et al. 1987). The studies in sheep suggest that the thyroid system is a sensitive target of pentachlorophenol toxicity. Additional studies are needed in conventional laboratory species to confirm the sensitivity of this organ and to evaluate the relevance of the effect to human health; other endocrine tissues should also be examined for potential effects. The LOAEL identified for reproductive effects in mink was used to derive an intermediate-duration oral MRL. Additional studies are needed to better define dose-response relationships and to identify no adverse effect levels.

Information on the dermal toxicity of pentachlorophenol in animals is limited to a study that reported death and dermal irritation in rabbits following application of pentachlorophenol in fuel oil; the vehicle may have contributed to the observed effects (Deichmann et al. 1942). Studies examining systemic endpoints following dermal exposure would be useful to establish thresholds.

**Chronic-Duration Exposure and Cancer.** Occupational exposure studies and reports of families living in log homes that were treated with pentachlorophenol provide information on the chronic toxicity of pentachlorophenol in humans. The reported effects include inflammation of the upper respiratory tract and bronchitis (Baader and Bauer 1951; Klemmer et al. 1980), reduced glomerular filtration rate and tubular function (Begley et al. 1977), hepatic effects (increased levels of biliary acid concentrations, urinary porphyrin, and serum alanine and aspartate transaminases) (Cheng et al. 1993; Colosio et al. 1993a; Hryhorczuk et al. 1998; Klemmer 1972), and impaired immune function (McConnachie and Zahalsky 1991). It is likely that the individuals were exposed via inhalation and dermal contact. In general, the epidemiology studies involved exposure to technical-grade or undefined purity pentachlorophenol; therefore, other chemicals may have contributed to these effects. Little information on exposure concentrations is available. No chronic oral human studies were located.

Chronic-duration animals studies are only available for the oral route. Liver effects (hepatocyte cystic degeneration, hepatodiaphragmatic nodules) (Chhabra et al. 1999; NTP 1999; Schwetz et al. 1978) and effects on the thyroid (decreased serum thyroxine and decreased relative thyroid weight) (Beard and Rawlings 1998, 1999; Beard et al. 1999a) were reported in these studies. A chronic-duration oral MRL of



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0.001 mg/kg/day was calculated based on a LOAEL of 1 mg/kg/day for significantly decreased serum thyroxine concentrations in males of the first generation and males and females of the second generation, and decreased relative thyroid weight in females of the second generation when mink were administered pentachlorophenol of unspecified purity continuously in the diet in a multigeneration reproduction study (Beard and Rawlings 1998). A chronic-duration inhalation MRL was not developed because concentrations that cause toxic effects in humans were not quantified and no animal studies were identified. Chronic inhalation studies are necessary for establishing exposure-response relationships and identifying sensitive targets of toxicity. No dermal animal studies were identified; chronic dermal exposure studies would be useful for identifying sensitive targets of the toxicity and establishing exposure-response relationships.

Epidemiology studies have not provided a firm association between pentachlorophenol exposure and an increased risk of cancer. Several occupational studies reported no association between inhalation of pentachlorophenol in any form and cancer in humans (Gilbert et al. 1990; Jappinen et al. 1989; Johnson et al. 1990; Robinson et al. 1985). However, each of the individual studies had a low power to detect elevated risk estimates. In contrast, other occupational studies reported an association between pentachlorophenol exposure and soft tissue sarcoma (Eriksson et al. 1990; Hardell et al. 1995; Hoppin et al. 1998; Lampi et al. 1992) or non-Hodgkin's lymphoma (Hardell et al. 1994; Hertzman et al. 1997; Lampi et al. 1992). Many of these studies also reported significant associations between increased cancer risk and exposure to other chemicals (e.g., other chlorophenols, phenoxyacetic acids, cutting oil components). Additional follow-up of pentachlorophenol-exposed cohorts using epidemiological methods and study designs of sufficient power and discrimination to distinguish effects of pentachlorophenol from effects attributable to other possible causes would be useful for assessing the carcinogenic potential of pentachlorophenol in humans. Sufficient information exists from animal studies to support the conclusion that pentachlorophenol may cause cancer in humans. Significant increases in the incidence of hemangiosarcomas, liver adenomas and carcinomas, and adrenal gland pheochromocytomas were observed in mice (NTP 1989), and mesotheliomas and nasal squamous cell carcinomas were observed in rats orally exposed to pure pentachlorophenol (Chhabra et al. 1999; NTP 1999). No information is available on the carcinogenic potential following inhalation or dermal exposure; chronic bioassays by these routes would be useful in determining whether pentachlorophenol induces cancer of the respiratory tract and skin, respectively.

The suggestive human data and the positive carcinogenicity results from animal bioassays (Chhabra et al. 1999; NTP 1989, 1999), along with genotoxicity data suggesting that pentachlorophenol is clastogenic,

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provide sufficient evidence to suggest that pentachlorophenol may be a human carcinogen. The International Agency for Research on Cancer (IARC 1999) has placed pentachlorophenol in group 2B (possibly carcinogenic to humans). EPA classified pentachlorophenol as a group B2 carcinogen (probable human carcinogen) (IRIS 2001).

**Genotoxicity.** The available genotoxicity data indicate that pentachlorophenol may have genotoxic potential. Two studies investigated the genotoxicity of pentachlorophenol in humans; both of these are inadequate because of the small number of subjects studied (Bauchinger et al. 1982; Wyllie et al. 1975). The observed effects included a small increase in the frequency of dicentrics and acentrics, but no increases in sister chromatid exchange, and an increase in chromosome aberrations. In general, *in vitro* and *in vivo* studies have not reported evidence of genotoxicity. Pentachlorophenol did not induce gene mutations in *Salmonella typhimurium* (Donnelly et al. 1998; Markiewicz et al. 1996; NTP 1999; Simmon et al. 1977; Waters et al. 1982) or *Escherichia coli* (Anderson et al. 1972; Lemma and Ames 1975; Moriya et al. 1983; Simmon et al. 1977; Waters et al. 1982); or DNA damage in *E. coli* (Fahrig 1974), *Bacillus subtilis* (Waters et al. 1982), Chinese hamster ovary cells (Ehrlich 1990), Chinese hamster V79 cells (Dahlhaus et al. 1996), or mouse embryonic fibroblast cells (Wang and Lin 1995). Several *in vitro* studies suggest that pentachlorophenol has clastogenic activity (Fahrig 1974; NTP 1999). Increases in the occurrence of chromosomal aberrations in human lymphocytes and Chinese hamster ovary cells and sister chromatid exchange in Chinese hamster ovary cells have occurred (NTP 1999). In *Saccharomyces cerevisiae* assays for recombination, positive and negative results have been found (Fahrig 1974; Fahrig et al. 1978; Waters et al. 1982), and positive results were found for induction of gene mutations (Fahrig et al. 1978). In *in vivo* studies, negative results have been found for gene mutations in a mouse spot test assay (Fahrig and Steinkamp-Zucht 1996), sex-linked recessive lethal mutations in *Drosophila melanogaster* (Sai-Kato et al. 1995; Umemura et al. 1996), and micronuclei occurrence in mouse and rat bone marrow (NTP 1999). Given the availability of a number of genetic toxicology studies, there is no apparent need for additional genotoxicity testing at this time.

**Reproductive Toxicity.** The possible association between pentachlorophenol exposure and reproductive effects in women has been investigated by Gerhard et al. (1991). Elevated blood levels of pentachlorophenol were found in women with histories of reproductive effects (e.g., habitual abortions, unexplained infertility, menstrual disorders). However, a causal relationship cannot be established due to limitations such as the lack of information on the exposure route and exposure to other chemicals (e.g., increased levels of PCBs were detected in the blood). In addition, matched controls were not used and

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other confounding factors were not controlled. No other human studies examined reproductive end points.

Adverse reproductive effects were observed in animals following oral exposure to technical-grade and pure pentachlorophenol. In a two-generation reproductive toxicity study in rats, decreased fertility was observed the first generation exposed to 60 mg/kg/day pentachlorophenol (purity not reported) (Argus 1997/Bernard et al. 2001c). Decreased frequency of second mating, decreased birth rate for the second mating, and increased severity of cystic uterine gland were observed in mink exposed to 1 mg/kg/day (Beard et al. 1997). In contrast, no reproductive effects were observed in a multigeneration study in mink using the same dietary concentration (Beard and Rawlings 1998). No effect on fertility was observed in sheep exposed to 1 mg/kg/day prior to mating and throughout gestation and lactation (Beard et al. 1999b). No animal studies examined the reproductive toxicity of pentachlorophenol following inhalation or dermal exposure; studies by the inhalation and dermal routes would be valuable in establishing an exposure-response relationship for these exposure routes. The intermediate-duration oral MRL is based on a LOAEL for reproductive effects observed in the single-generation mink study (Beard et al. 1997).

**Developmental Toxicity.** An increased risk of congenital eye cataracts was observed in the children of male sawmill workers presumably exposed to CDD-contaminated mixtures of the sodium salts of pentachlorophenol and tetrachlorophenol (chlorophenate) (Dimich-Ward et al. 1996). Interpretation of the study results is limited because exposure levels were not measured and a surrogate for chlorophenate exposure was used. No other human developmental toxicity studies were located.

A number of animal studies reported developmental effects following oral exposure to pure or technical-grade pentachlorophenol. The observed effects included fetal/neonatal mortality (Argus 1993b/Bernard et al. 2001b, Argus 1997/Bernard et al. 2001c; Schwetz et al. 1974; Welsh et al. 1987), malformations/anomalies (Argus 1993b/Bernard et al. 2001b; Schwetz et al. 1974), and decreased growth (Argus 1993b/Bernard et al. 2001b; Beard et al. 1993b; Courtney et al. 1976; Larsen et al. 1975; Schwetz et al. 1974; Welsh et al. 1987). A threshold for developmental toxicity has not been identified. A comparison between the adverse effects levels for developmental effects with those for systemic, immune, and reproductive effects, suggests that the fetus/neonate is a sensitive target for pentachlorophenol. Note that the acute duration oral MRL is based on a LOAEL for developmental effects (Schwetz et al. 1974). A common limitation of these developmental toxicity studies is that only one dose level was tested in most of these studies. Additional studies using a range of doses would be useful for establishing the threshold for developmental toxicity. Additionally, several oral studies provide evidence that the thyroid

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gland is sensitive to the toxicity of pentachlorophenol (Beard and Rawlings 1998; Beard et al. 1999; Jekat et al. 1994; Rawlings et al. 1998). It is not known whether this would also be a sensitive target in the developing organism. Developmental studies that assessed thyroid function and tested for potential neurobehavioral and neuropathological effects would be useful since deficiencies in thyroxine during prenatal and postnatal periods can cause decrements in intellectual function in children (Bargagna et al. 1997; Birrell et al. 1983; Kooistra et al. 1994). The available developmental toxicity studies involve maternal exposure; no studies have examined the potential developmental effect of paternal exposure. No animal inhalation or dermal developmental toxicity studies are available for pentachlorophenol. Studies by these exposure routes would be useful for establishing dose-response relationships.

**Immunotoxicity.** Several human studies provide suggestive evidence that pentachlorophenol is an immunotoxicant. Impaired mitogen-induced lymphocyte stimulation was observed in individuals exposed to pentachlorophenol-containing pesticides (Daniel et al. 1995); T-cell activation, autoimmunity, immunosuppression, and B-cell dysregulation were observed in family members living in pentachlorophenol-treated log homes (McConnachie and Zahalsky 1991); and decreased proliferative response to a mitogen was observed in factory workers exposed to high levels of pentachlorophenol (Colosio et al. 1993b). Oral studies in animals provide strong evidence that technical-grade pentachlorophenol is an immunotoxicant, although none of the identified studies performed a complete immunotoxicity battery. Humoral and cellular immunity (Holsapple et al. 1987; Kerkvliet et al. 1985a; NTP 1989), susceptibility to tumor induction (Kerkvliet et al. 1982), and complement activity (White and Anderson 1985) have been adversely affected following oral exposure. Studies that tested both technical-grade and pure pentachlorophenol provide strong evidence that the immune effects are related to the level of impurities in the technical-grade product (e.g., CDDs, CDFs). Support for the immunotoxicity of pure pentachlorophenol is less conclusive, with some rat and mouse studies reporting altered immune function (Blakley et al. 1998; Kerkvliet et al. 1982) and other studies reporting no effects (Kerkvliet et al. 1985a; NTP 1989). No studies that tested the immunotoxicity of pentachlorophenol following inhalation or dermal exposure were located. The available data suggest that the immune system may be a sensitive target of toxicity following oral exposure to technical-grade pentachlorophenol and possibly pure pentachlorophenol.

**Neurotoxicity.** In a number of case reports, neurological effects have been described in individuals likely exposed via inhalation and dermal contact. The symptoms of central nervous system neurotoxicity include intermittent delirium, fever, convulsions, profuse sweating, and increased respiratory rate and labored breathing (Chapman and Robson 1965; Robson et al. 1969; Smith et al. 1996). Similar neurological symptoms were reported in an individual intentionally ingesting a weed killer containing

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12% pentachlorophenol (Haley 1977). These effects are probably due to hyperthermia resulting from uncoupling of oxidative phosphorylation, rather than to a direct effect on the central nervous system. Neurological effects have also been observed in animals ingesting pentachlorophenol. Although a study examining a complete neurotoxicology battery of tests has not been identified, the available oral exposure data provide evidence that pentachlorophenol is a neurotoxicant at high doses. Oral exposure to relatively high doses of technical-grade or pure pentachlorophenol resulted in impaired motor activity and startle response in mice exposed to pentachlorophenol for 26 weeks, but not after 5 weeks (NTP 1989). Degenerative changes in the sciatic nerve myelin sheath were observed in rats administered pentachlorophenol of unspecified purity (Villena et al. 1992). No neurological studies involving inhalation or dermal exposure to pentachlorophenol were identified.

**Epidemiological and Human Dosimetry Studies.** A number of studies have reported adverse health effects in humans following short- or long-term exposure to pentachlorophenol. The short-term data comes from case reports involving home use of pentachlorophenol-containing products such as wood preservative or herbicides in the garden (Gordon 1956; Hassan et al. 1985) or a series of reports of newborn infants exposed to pentachlorophenol from diapers and linens treated with an antimildew agent (Robson et al. 1969; Smith et al. 1996). Long-term toxicity information comes from families living in log homes that were treated with pentachlorophenol (McConnachi and Zahalsky 1991) and occupational exposure in agricultural and wood-treatment industries (Baader and Bauer 1951; Cheng et al. 1993; Colosio et al. 1993b; Hryhorczuk et al. 1998; Klemmer et al. 1980). As discussed previously, these studies are limited by incomplete exposure characterization. In general, information on exposure concentrations, exposure route, duration of exposure, possible concomitant exposure to other chemicals, and impurities present in technical-grade pentachlorophenol are not available. In most cases, exposure was by the inhalation and dermal routes. The consistently observed effects include death (Cretny 1976; Dreisbach 1980; Gordon 1956; Roberts 1981, 1990; Rugman and Cosstick 1990), inflammation of the upper respiratory tract and bronchitis (following inhalation exposure) (ACGIH 1991; Baader and Bauer 1951; Klemmer et al. 1980), symptoms of hyperthermia generated by uncoupling of oxidative phosphorylation (e.g., tachycardia, increased respiratory rate, labored breathing, profuse sweating, fever, metabolic acidosis) (Bergner et al. 1965; Gordon 1956; Gray et al. 1985; Haley 1977; Hassan et al. 1985; Menon 1958; Robson et al. 1969; Smith et al. 1996), hemolytic anemia (Hassan et al. 1985; Roberts 1981, 1990; Rugman and Cosstick 1990), hepatic enlargement (Bergner et al. 1965; Cheng et al. 1993; Colosio et al. 1993b; Gordon 1956; Hassan et al. 1985; Hryhorczuk et al. 1998; Smith et al. 1996), impaired immune function (Colosio et al. 1993b; Daniel et al. 1995; McConnachi and Zahalsky 1991), and dermal

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toxicity (irritation and chloracne) (Baader and Bauer 1951; Hosenfeld et al. 1986; Klemmer et al. 1980; Lambert et al. 1986; O'Malley et al. 1990).

Additionally, several epidemiology studies have examined the carcinogenic potential of pentachlorophenol. These data are inconclusive with some studies reporting no association between cancer risk and exposure to pentachlorophenol (Gilbert et al. 1990; Jappinen et al. 1989; Johnson et al. 1990; Robinson et al. 1985) and other studies indicating a significant risk of soft tissue sarcoma (Eriksson et al. 1990; Hardell et al. 1995; Hoppin et al. 1998; Lampi et al. 1992) or non-Hodgkin's lymphoma (Hardell et al. 1994; Hertzman et al. 1997; Lampi et al. 1992). Hepatotoxicity (Blakley et al. 1998; Chhabra et al. 1999; Greichus et al. 1979; Johnson et al. 1973; Kerkvliet et al. 1982; Kimbrough and Linder 1978; Knudsen et al. 1974; Nishimura et al. 1982; NTP 1999; Schwetz et al. 1978; Umemura et al. 1996), impaired immune function (Blakley et al. 1998; Holsapple et al. 1987; Kerkvliet et al. 1982, 1985a, 1985b; NTP 1989; White and Anderson 1985), and increased incidence of malignant tumors (Chhabra et al. 1999; NTP 1989, 1999) have also been reported in animal studies involving oral exposure. A number of other sensitive end points for animals, including thyroid toxicity, reproductive toxicity, and developmental toxicity, have not been fully investigated in humans. Additional epidemiological studies that provide sufficient information for exposure characterization and examine a number of systemic end points would be useful for establishing sensitive targets of toxicity in humans and dose-response relationship data.

**Biomarkers of Exposure and Effect.**

**Exposure.** Pentachlorophenol is excreted in the urine largely unchanged (Ahlborg et al. 1974; Braun et al. 1979; Larsen et al. 1972) and can easily be detected and quantified in the urine at concentrations as low as <1 ppb (Chou and Bailey 1986; Drummond et al. 1982; Edgerton et al. 1979; EPA 1980a; Holler et al. 1989; NIOSH 1984b; Pekari and Aitio 1982; Rick et al. 1982; Siqueina and Fernicola 1981). Thus, measurement of pentachlorophenol in the urine is a useful biomarker of exposure. In addition, pentachlorophenol can be easily detected and quantified in blood serum at concentrations as low as <1 ppb (Bevenue et al. 1968; EPA 1980a; Needham et al. 1981; NIOSH 1984b) and adipose tissue (Kuehl and Dougherty 1980; Needham et al. 1981; Ohe 1979; Shafik 1973). However, measuring pentachlorophenol in body fluids and tissues is not a specific biomarker for pentachlorophenol exposure because other compounds to which exposure may occur (e.g., hexachlorobenzene and lindane) may be metabolized to pentachlorophenol in the body. In addition, the available data do not permit the establishment of a quantitative relationship between levels of pentachlorophenol in the environment and levels in human fluids or tissues. Additionally, a major pentachlorophenol urinary metabolite, TCHQ,

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has potential use as an indicator of exposure to pentachlorophenol (Ahlborg et al. 1974; Braun et al. 1977; Juhl et al. 1985; Reigner et al. 1991; Renner 1989), although this biomarker is not specific for pentachlorophenol. Additional studies are needed to establish a relationship between exposure level and urinary concentration of TCHQ.

**Effect.** The liver is a target organ for both humans and animals exposed to pentachlorophenol. Clinical manifestations of hepatic and renal toxicity include elevated serum ALT and AST levels for toxicity to the liver (Armstrong et al. 1969; Bergner et al. 1965; Gordon 1956; Gray et al. 1985; Klemmer 1972; Robson et al. 1969). Indices of changes in hepatic oxidative phosphorylation may also be useful as biomarkers for pentachlorophenol-induced liver changes (Ellinger et al. 1991). These effects are not specific for exposure to pentachlorophenol and have been associated with exposure to other compounds, such as some chlorinated hydrocarbons. Therefore, the major use of these biomarkers is restricted to comparisons in which pentachlorophenol-exposed and control groups can be identified (e.g., between workers exposed to chemical in the workplace and control subjects). Oral exposure of animals to pentachlorophenol induces a decrease of thyroxine levels in serum (Beard et al. 1999b; Jekat et al. 1994; Rawlings 1998). Comparison of the levels of thyroxine in control and pentachlorophenol-exposed populations could also serve as a nonspecific biomarker of pentachlorophenol effect. In general, there is no simple relationship between nonfatal health effects and levels of pentachlorophenol detected in serum and urine. Development of additional, more sensitive biomarkers that are specific for pentachlorophenol effects would be useful in monitoring populations at high risk.

**Absorption, Distribution, Metabolism, and Excretion.** The absorption, distribution, metabolism, and excretion of pentachlorophenol have been investigated in humans and animals. Evidence for absorption of pentachlorophenol by humans after exposure by the inhalation and dermal routes is provided by the observation of elevated urine and plasma levels in workers (Casarett et al. 1969; Jones et al. 1986; Pekari et al. 1991) and residents of log homes treated with pentachlorophenol (Cline et al. 1989; Hosenfeld et al. 1986). A study of two humans exposed to pentachlorophenol vapors for 45 minutes provides evidence that it is well absorbed (Casarett et al. 1969). Similarly, human studies also indicate that pentachlorophenol is readily absorbed following oral exposure (Braun et al. 1979; Uhl et al. 1986). The results of inhalation (Hoben et al. 1976c) and oral (Ahlborg et al. 1974; Braun and Sauehoff 1976; Braun et al. 1977; Meerman et al. 1983; Reigner et al. 1991) exposure studies in animals confirm the results of the human studies that pentachlorophenol is well absorbed following inhalation or oral exposure. *In vivo* animal studies (Qiao et al. 1997; Wester et al. 1993) are sufficient to characterize the extent of absorption of pentachlorophenol in soil. However, additional animal studies would be useful for

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determining the absorption efficiency of an aqueous solution of pentachlorophenol and neat pentachlorophenol.

No human studies examined the distribution of pentachlorophenol following inhalation, oral, or dermal exposure. The distribution of pentachlorophenol following inhalation (Hoben et al. 1976c), oral (Braun et al. 1977; Gómez-Catalán et al. 1991; Larsen et al. 1975), or dermal (Qiao et al. 1997) exposure has been characterized in acute-duration studies in animals. Long-term studies examining distribution would be useful to determine if there are any duration-related differences in distribution. Pentachlorophenol has been found in human breast milk from German and Slovakian women (Gebefugi and Korte 1983; Veningerova et al. 1996).

Results from human and animal studies indicate that pentachlorophenol is not extensively metabolized, as evidenced by a large portion of the administered dose being excreted in urine unchanged in humans exposed by the inhalation (Ahlborg et al. 1974) and oral (Braun et al. 1979; Uhl et al. 1986) routes and in animals exposed to pentachlorophenol by the inhalation (Hoben et al. 1976a) and oral (Ahlborg et al. 1974; Braun et al. 1977; Renner 1989; Renner and Hopfer 1990) routes. The major metabolite is tetrachloro-*p*-hydroquinone (TCHQ) in humans exposed to pentachlorophenol by the inhalation route (Ahlborg et al. 1974) and in animals exposed to pentachlorophenol by the oral route (Ahlborg et al. 1974; Braun et al. 1977; Reigner et al. 1991; Renner and Hopfer 1990). Additional studies of metabolites formed in humans after exposure to pentachlorophenol by the dermal and oral routes and in animals after exposure to pentachlorophenol by the inhalation and dermal routes would be useful. The available human and animal data indicate that metabolism of pentachlorophenol occurs in the liver, and the major pathways are glucuronide conjugation and oxidative dechlorination to form TCHQ. However, recent studies in rats and mice following oral administration of pentachlorophenol (Lin et al. 1997; Waidyanatha et al. 1994, 1996) suggest that the metabolism of pentachlorophenol can also proceed through the quinols, TCHQ, and tetrachlorocatechol, via microsomal cytochrome P 450 enzymes, and that these quinols can be oxidized via semiquinone intermediates. Both the quinones and semiquinones are electrophilic and can bind to cellular macromolecules (Lin et al. 1997). Additional studies in animals to determine if chlorinated quinones and semiquinones are produced following inhalation and dermal exposures to pentachlorophenol would be useful. Studies in animals by the inhalation, oral, or dermal routes to examine the potential role of peroxidases in pentachlorophenol metabolism would also be useful. Additional studies examining the metabolism of pentachlorophenol following inhalation and dermal exposure would be useful for determining if there are route-specific differences in metabolism.



## 3. HEALTH EFFECTS

No information was found on the relative amounts of excreted pentachlorophenol and its metabolites in urine and feces after humans or animals were exposed to pentachlorophenol by inhalation.

Approximately 74 and 12% (total of 86%) of pentachlorophenol ingested by humans was eliminated in the urine as pentachlorophenol and its glucuronide conjugate, respectively (Braun et al. 1979). In rodents, from 60–83% of the administered oral dose is eliminated in the urine (Ahlborg et al. 1974; Braun et al. 1977; Larsen et al. 1972; Reigner et al. 1991); in monkeys, 45–75% of the administered oral dose is eliminated in the urine (Braun and Sauerhoff 1976). Fecal elimination of pentachlorophenol and its metabolites accounted for 4% of the administered oral dose in humans (Braun et al. 1979), 8–34% of the administered oral dose in rodents (Braun et al. 1977; Larsen et al. 1972; Reigner et al. 1991, 1992), and 3–20% in monkeys (Ballhorn et al. 1981; Braun and Sauerhoff 1976; Rozman et al. 1982). Only trace amounts were eliminated in expired air. Excretion data in animals indicate that the kinetics of pentachlorophenol elimination in humans following oral exposure is similar to that seen in monkeys in that they are first order (Braun and Sauerhoff 1976; Braun et al. 1979); additional studies examining potential species differences would be useful. No studies were located regarding excretion in humans after dermal exposure to pentachlorophenol. After application of radioactively-labeled pentachlorophenol in a soil-based mixture to the skin of swine, one-third to one-half of the absorbed dose was almost equally excreted through urinary and fecal routes (Qiao et al. 1997). Additional studies on routes of elimination of pentachlorophenol following exposures of animals by the dermal and inhalation routes would be useful. Two animal studies (Braun and Sauerhoff 1978; Braun et al. 1974) found an apparent difference in elimination kinetics between males and females. Additional studies examining potential sex-related differences would be useful.

**Comparative Toxicokinetics.** A series of studies conducted by Braun and associates (Braun and Sauerhoff 1976; Braun et al. 1977, 1979) suggest that there are toxicokinetic differences between humans, monkeys, and rats. The results of these studies suggest that the excretion of pentachlorophenol follows a linear, one-compartment model in humans and monkeys. In contrast, excretion in the rats was biphasic (two-compartment model). However, other pharmacological properties, such as maximum plasma concentration, absorption rate constant, volume of distribution, steady-state concentration, and the excretion of glucuronide conjugates were similar for humans and rats, but not for humans and monkeys. These data suggest that the rat may be a better model for humans than the monkey. Additional studies are needed to further evaluate species differences in the toxicokinetics of pentachlorophenol and to identify the most appropriate model for humans.

### 3. HEALTH EFFECTS

**Methods for Reducing Toxic Effects.** Pentachlorophenol can be absorbed through inhalation, oral, or dermal routes. Methods are available for reducing absorption following oral and dermal exposure to pentachlorophenol; however, since gastrointestinal absorption of pentachlorophenol in humans is rapid (Braun et al. 1979), these methods (washing skin and eyes, emesis, lavage, activated charcoal, and catharsis) (EPA 1989, 1989b) are useful only immediately following exposure to the chemical. Based on animal studies, cholestyramine administration is recommended in cases of human pentachlorophenol overexposure to enhance elimination of pentachlorophenol (Goodman et al. 1990); however, its use in humans has not been sufficiently tested. Data on cholestyramine administration, hemoperfusion, and administration of sedatives and antipyretics as treatment methods would be useful.

The mechanism of toxicity of pentachlorophenol is not clear. Although pentachlorophenol has been shown to uncouple oxidative phosphorylation, affect thyroid homeostasis, and produce oxidative damage to DNA, the extent to which these effects contribute to toxicity in the various organs and systems affected by pentachlorophenol is not clear. It is possible that these effects contribute to the toxicity spectrum seen in some organs, but are secondary unrelated to toxic effects seen in other organs. Therefore, additional studies on the relative contributions of these effects (uncoupling of oxidative phosphorylation, disturbances in thyroid homeostasis, and oxidative damage to DNA) to pentachlorophenol toxicity and examination of other potential mechanisms of toxicity (e.g., interactions with specific cell or tissue receptors) would be useful steps toward identifying methods that may reduce the toxic effects of pentachlorophenol.

**Children's Susceptibility.** Adverse effects on the nervous system, liver, kidneys, and respiratory system, and some deaths were associated with exposure of newborn children to pentachlorophenol in diapers and bedding (Smith et al. 1996), and suppression of the immune system was seen in older children exposed to pentachlorophenol (McConnachie and Zahalsky 1991). Additional studies to confirm and expand these findings would be useful. In animals, pentachlorophenol also causes a decrease in serum thyroxine levels, adverse effects on thyroid homeostasis, and inhibition of the uptake of thyroid hormone into the central nervous system. Long-term epidemiological studies of possible health effects in large cohorts of individuals who were exposed to pentachlorophenol as children would be useful, particularly with regard to reproductive function, the immune system, neurobehavioral testing, and cancer.

Oral exposure studies in animals provide evidence that pentachlorophenol is a developmental toxicant. Gestational exposure to pentachlorophenol has resulted in decreased fetal and neonatal survival (Schwetz et al. 1978), decreased fetal and neonatal body weight (Argus 1993b/Bernard et al. 2001b, Argus 1997/

## 3. HEALTH EFFECTS

Bernard et al. 2001c; Beard et al. 1999b; Courtney et al. 1976; Larsen et al. 1975; Schwetz et al. 1978; Welsh et al. 1987), increased male:female sex ratio (Schwetz et al. 1974), delayed ossification (Schwetz et al. 1974), and skeletal anomalies (Schwetz et al. 1974, 1978). There is some suggestive evidence that effects on the thyroid can lead to neurological deficiencies in the offspring; a neurodevelopmental toxicity study is needed to assess this potentially sensitive end point.

There are no studies to indicate whether the pharmacokinetics and metabolism of pentachlorophenol in children are different from those in adults, and there are no PBPK models for pentachlorophenol. However, given the large number of potential reactive metabolites that can be formed from pentachlorophenol and the different levels of active metabolites among rodent species (Lin et al. 1997), well-conducted studies on potential pharmacokinetic and metabolic differences between children and adults would be useful. A rationale for such studies is that UDP-glucuronosyl transferase and sulfotransferases, which are involved in phase II metabolism of pentachlorophenol, and two of the cytochrome P-450s, which are involved in the phase I metabolism of pentachlorophenol, are all thought to be developmentally regulated (Leeder and Kearns 1997). The need for a PBPK model for pentachlorophenol is not apparent at this time. There are some data to show that radiolabeled pentachlorophenol may cross the placenta of animals and enter the developing fetus (Larsen et al. 1975), and can be present in human breast milk (Gebefugi and Korte 1983; Veningerova et al. 1996). However, studies to confirm that pentachlorophenol crosses the placenta into developing fetuses and to characterize levels of pentachlorophenol in human breast milk in the United States would be useful. There are no studies to evaluate whether the mechanism of action of pentachlorophenol is different in children, but there is no apparent reason to suspect that it would be different. However, studies to determine whether children have a different susceptibility to health effects from pentachlorophenol than adults would be useful, starting with studies that compare immature animals to adult animals.

Child health data needs relating to exposure are discussed in 6.8.1 Identification of Data Needs: Exposures of Children.

### 3.12.3 Ongoing Studies

Information on the ongoing studies cited in this section was obtained from FEDRIP (2001).

Dr. I. Hertz-Picciotto at the University of North Carolina is assessing the feasibility of self-administered devices for collection of breath, urine, tap water, and indoor air monitoring samples in studies of penta-

### 3. HEALTH EFFECTS

chlorophenol; generating data on background variability of body burdens and protein adducts from exposures to pentachlorophenol; and determining factors that influence such variability, including point sources of contamination and workplace, in addition to background factors such as sociodemographic, geographic, lifestyle, and home characteristics.

Dr. S. M. Rappaport of the University of North Carolina at Chapel Hill is investigating the development and application of biomarkers of exposure to pentachlorophenol, including the levels of the parent compound in blood, exhaled air, and urine, and the levels of adducts with hemoglobin and serum albumin.

## **4. CHEMICAL AND PHYSICAL INFORMATION**

### **4.1 CHEMICAL IDENTITY**

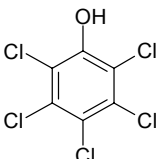
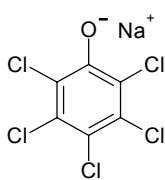
Information regarding the chemical identity of pentachlorophenol is located in Table 4-1.

### **4.2 PHYSICAL AND CHEMICAL PROPERTIES**

Information regarding the physical and chemical properties of pentachlorophenol is located in Table 4-2.

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-1. Chemical Identity of Pentachlorophenol and Pentachlorophenate<sup>a</sup>**

Characteristic	Pentachlorophenol	Sodium pentachlorophenate
Synonym(s)	PCP; penchlorol; penta; pentachlorophenate; 2,3,4,5,6- pentachlorophenol <sup>b</sup>	Pentachlorophenol sodium; pentachlorophenol sodium salt; pentachlorophenoxy sodium; pentaphenate
Registered trade name(s) For 37% aqueous solution <sup>a</sup>  For polymeric form <sup>b</sup>	Chlon; Dowicide 7; Dowicide EC-7; Dura Treet II; EP 30; Fungifen; Grundier Arbezol; Lauxtol; Liroprem; Penta Concentrate; Penta Ready; Penta WR; Permasan; Santophen 20; Woodtreat <sup>b</sup>	Dow Dormant Fungicide; Dowicide G; Dowicide G-St; Mystox D; Napclor-G; Santobrite; Sapco25 Weedbeads
Chemical formula	C <sub>6</sub> HCl <sub>5</sub> O	C <sub>6</sub> Cl <sub>5</sub> ONa
Chemical structure		
Identification numbers:		
CAS Registry	87-86-5	131-52-2
NIOSH RTECS	SM6300000	SM6490000
EPA Hazardous Waste	U242; FO27	No data
OHM/TADS	7216842	No data
DOT/UN/NA/IMCO	NA 2020	UN 2567; IMO6.1
HSDB	894	761
NCI	C54933; C55378; C56655	No data

<sup>a</sup>All information obtained from HSDB 2001 except where noted.<sup>b</sup>RTECS 1991

CAS = Chemical Abstracts Services; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency;  
 HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; OHM/TADS = Oil and Hazardous Materials/Technical Assistance Data System;  
 RTECS = Registry of Toxic Effects of Chemical Substances

## 4. CHEMICAL AND PHYSICAL INFORMATION

**Table 4-2. Physical and Chemical Properties of Pentachlorophenol and Sodium Pentachlorophenate<sup>a</sup>**

Property	Pentachlorophenol	Sodium pentachlorophenate
Molecular weight	266.35	288.34
Color	Colorless or white (pure); dark gray to brown (crude product)	White or tan
Physical state	Crystalline solid (pure); pellets or powder (crude product) <sup>b</sup>	Flakes or powder
Melting point	190 EC	No data
Boiling point	309–310 EC (decomposes)	No data
Density	1.978 g/mL at 22 EC/4 EC	No data
Odor	Phenolic; very pungent (only when hot)	No data
Odor threshold: Water	0.857 mg/L at 30 EC; 12.0 mg/L at 60 EC <sup>b,c</sup>	No data
Solubility: Water	14 mg/L at 20 EC	330,000 mg/L at 25 EC
Organic solvent(s)	Very soluble in alcohol and ether; soluble in benzene; slightly soluble in cold petroleum ether <sup>d</sup>	Soluble in acetone and ethanol
Partition coefficients: Log K <sub>ow</sub>	5.01 <sup>b</sup>	No data
Log K <sub>oc</sub>	4.5 <sup>e</sup>	No data
Vapor pressure at 25 EC	0.00011 mmHg <sup>f</sup>	No data
Photolysis	t <sub>1/2</sub> = 48 h <sup>g</sup>	t <sub>1/2</sub> = 0.70 h <sup>h</sup>
Henry's law constant at 25 EC	3.4x10 <sup>-6</sup> atm-m <sup>3</sup> /mol <sup>i</sup>	No data
Autoignition temperature	No data	No data
Flashpoint	No data	No data
Flammability limits at 25 EC	No data	No data
Incompatibilities	No data	No data
Conversion factors (25 EC)	No data	No data
Explosive limits	No data	No data

<sup>a</sup>All information obtained from HSDB 2001 unless otherwise noted.<sup>b</sup>Verschueren 1983<sup>c</sup>Hoak 1957<sup>d</sup>Budavari et al. 1989<sup>e</sup>Schellenberg et al. 1984<sup>f</sup>EPA 1979e<sup>g</sup>Wong and Crosby 1981<sup>h</sup>Pignatello et al. 1983<sup>i</sup>Lyman et al. 1982





## 5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

### 5.1 PRODUCTION

Vulcan Chemicals, a division of Vulcan Materials Company (Wichita, Kansas), is the only current domestic manufacturer of pentachlorophenol (SRI 1998). Pentachlorophenol is produced by the stepwise chlorination of phenols in the presence of catalysts (anhydrous aluminum chloride or ferric chloride). Outside of the United States, it is also produced by the alkaline hydrolysis of hexachlorobenzene. Typically, commercial grade pentachlorophenol is 86% pure. Contaminants generally consist of other polychlorinated phenols, polychlorinated dibenzo-*p*-dioxins, and polychlorinated dibenzofurans, which are formed during the manufacturing process (see Table 3-2). Pentachlorophenol has also been marketed in the past as a water-soluble sodium salt, a 5% emulsifiable concentrate, or a 3–40% solution in formulation with other chlorophenols, methylene bithiocyanate, or copper naphthenate (IARC 1979). Production volumes for 1983–1986 were as follows: 45 million pounds in 1983; 42 million pounds in 1984; 38 million pounds in 1985; and 32 million pounds in 1986 (Mannsville 1987). About 24 million pounds were manufactured in 1987 by Vulcan Materials (HSDB 2001). More recent production data are not available. For further information on facilities in the United States that manufacture or process pentachlorophenol, refer to Table 5-1. Table 5-1 is derived from Toxics Release Inventory (TRI) data and reports only those facilities that release pentachlorophenol.

### 5.2 IMPORT/EXPORT

The U.S. consumption of pentachlorophenol for 1986 was reported to be 28 million pounds (CMR 1987). In 1982, 121,000 pounds of pentachlorophenol were imported to the United States (328,000 pounds were imported in 1980). In 1985, 3 million pounds of pentachlorophenol were exported, and in 1986, 2 million pounds were exported (Mannsville 1987). More recent data on the import/export volumes of pentachlorophenol are not available.

### 5.3 USE

Pentachlorophenol was one of the most widely used biocides in the United States. It was registered for use by EPA as an insecticide (termiticide), fungicide, herbicide, molluscicide, algicide, disinfectant, and as an ingredient in antifouling paint (Cirelli 1978a), but it has been a restricted-use pesticide since July 1984 (CELDS 1992; EPA 1984a). The principal use of pentachlorophenol is as a wood preservative

## 5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

**Table 5-1. Facilities that Produce, Process, or Use Pentachlorophenol**

State <sup>a</sup>	Number of facilities	Minimum amount on site in pounds <sup>b</sup>	Maximum amount on site in pounds <sup>b</sup>	Activities and uses <sup>c</sup>
AL	2	10,000	999,999	9
AR	2	1,000	999,999	9, 13
CA	1	100	999	13
GA	1	10,000	99,999	9
ID	1	10,000	99,999	13
IL	1	1,000	9,999	13
KY	1	10,000	99,999	13
LA	2	10,000	999,999	9
MD	1	10,000	99,999	1, 5
MN	1	10,000	99,999	8
MO	1	100,000	999,999	9
MS	4	10,000	9,999,999	9, 12
NC	2	10,000	999,999	8, 9
NE	1	10,000	99,999	9
NJ	1	1,000	9,999	13
NV	1	10,000	99,999	9
OH	1	1,000	9,999	13
OR	3	10,000	99,999	9, 12, 13
SC	2	10,000	999,999	9, 13
SD	1	100,000	999,999	9
TX	2	1,000	99,999	13
UT	2	1,000	99,999	13

Source: TRI99 2001

<sup>a</sup>Post office state abbreviations used<sup>b</sup>Amounts on site reported by facilities in each state<sup>c</sup>Activities/Uses:

- |                          |                          |                             |
|--------------------------|--------------------------|-----------------------------|
| 1. Produce               | 6. Impurity              | 10. Repackaging             |
| 2. Import                | 7. Reactant              | 11. Chemical Processing Aid |
| 3. Onsite use/processing | 8. Formulation Component | 12. Manufacturing Aid       |
| 4. Sale/Distribution     | 9. Article Component     | 13. Ancillary/Other Uses    |
| 5. Byproduct             |                          |                             |

## 5. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

(registered by EPA for power-line poles, cross arms, fence posts, and the like). The treatment of wood for utility poles represents 80% of the U.S. consumption of pentachlorophenol (CMR 1987). However, pentachlorophenol is no longer contained in wood preserving solutions or insecticides and herbicides available for home and garden use since it is a restricted-use pesticide. Pentachlorophenol is used for the formulation of fungicidal and insecticidal solutions and for incorporation into other manufactured pesticide products. These nonwood uses account for no more than 2% of U.S. pentachlorophenol consumption (Mannsville 1987). This wide spectrum of uses was partially attributed to the solubilities of the nonpolar pentachlorophenol in organic solvents, and the sodium salt in water.

**5.4 DISPOSAL**

After treatment with sodium bicarbonate or a sand-soda ash mixture, pentachlorophenol can be incinerated. Incineration of pentachlorophenol is one of the most important sources of polychlorinated dibenzo-*p*-dioxins and dibenzofurans, so care must be taken during this process (Karasek and Dickson 1987). Pentachlorophenol has been designated as a hazardous substance, a hazardous pollutant, a toxic pollutant, and a hazardous waste by EPA. Disposal of pentachlorophenol is subject to EPA restrictions (EPA 1991, 1992).



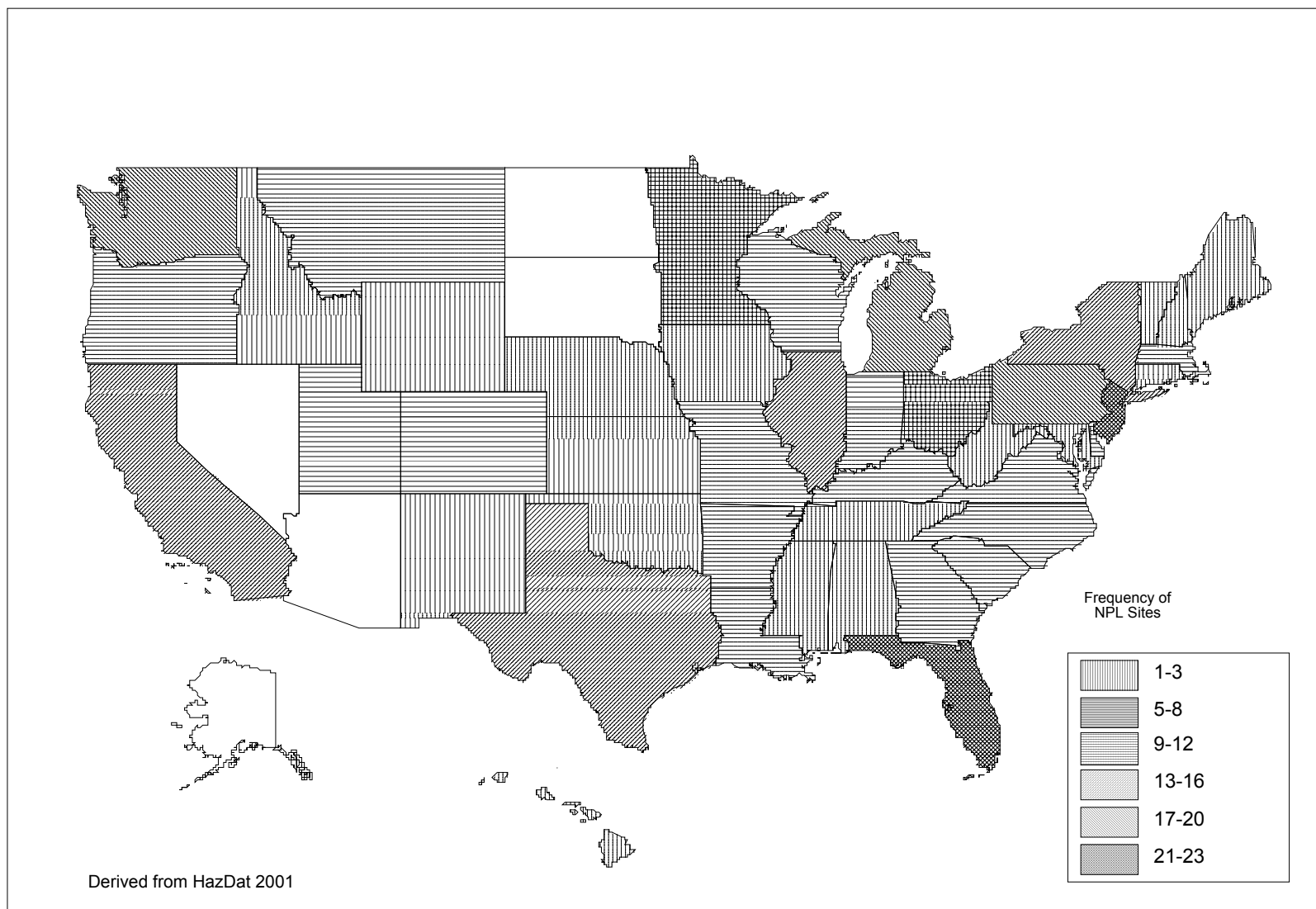
## 6. POTENTIAL FOR HUMAN EXPOSURE

### 6.1 OVERVIEW

Pentachlorophenol has been one of the most heavily used pesticides in the United States. The compound is found in all environmental media (air, soil, and water) as a result of its past widespread use. In addition, a number of other chemicals, including hexachlorobenzene, pentachlorobenzene, and benzene hexachloride isomers, are known to be metabolized to pentachlorophenol. Current releases of pentachlorophenol to the environment are more limited as a result of decreasing volumes used, changing use patterns (e.g., phase-out of slimicide use in water cooling towers), and waste treatment practices (e.g., closing of on-site evaporation ponds at wood-treatment facilities). Pentachlorophenol is currently regulated as a restricted-use pesticide.

Pentachlorophenol is stable to hydrolysis and oxidation, but the compound is rapidly photolyzed by sunlight and can be metabolized by microorganisms, animals, and plants. Adsorption to soils and sediments is more likely to occur under acidic conditions than under neutral or basic conditions. The compound has been found to bioaccumulate to modest levels (e.g., bioconcentration factors of <1,000), but food chain biomagnification has not been observed. In recent decades, pentachlorophenol has been widely detected in human urine, blood, and adipose tissue among members of the general population. Human exposure to pentachlorophenol is believed to occur via inhalation of indoor and workplace air, ingestion of contaminated water and food, and direct dermal contact with pentachlorophenol-treated wood products. Since pentachlorophenol is no longer used in the treatment of wood products used in new residences and agricultural buildings, future indoor air exposure to this compound from these sources is likely to be minimal.

Pentachlorophenol has been identified in at least 313 of the 1,585 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 2001). However, the number of sites evaluated for pentachlorophenol is not known. The frequency of these sites can be seen in Figure 6-1. Of these sites, 312 are located within the United States and 1 is located in the Commonwealth of Puerto Rico (not shown).

**Figure 6-1. Frequency of NPL Sites with Pentachlorophenol Contamination**

## 6. POTENTIAL FOR HUMAN EXPOSURE

**6.2 RELEASES TO THE ENVIRONMENT**

Pentachlorophenol is ubiquitously distributed in the environment. It has been detected in surface waters and sediments, rainwater, drinking water, aquatic organisms, soils, and food, as well as in human milk, adipose tissue, and urine. The compound has been identified in at least 313 of the 1,585 hazardous waste sites on the NPL (HazDat 2001).

The majority of pentachlorophenol annual releases during production and use are to the atmosphere (about 1.4 million pounds [620 metric tons]) from wood preservation plants and cooling towers, and to land (about 1.9 million pounds [890 metric tons]) from wood preservation and domestic use as a preservative. Pentachlorophenol is also released into the aquatic environment, especially in runoff waters and wood-treatment plant effluents. Based on the available information, discharges to water, both direct and through municipal waste water treatment facilities, were estimated to be about 26,000 pounds (12 metric tons) and 11,000 pounds (5 metric tons), respectively (EPA 1980f). It should be noted, however, that much of these data, and data discussed in the following sections, were collected before pentachlorophenol became a restricted-use pesticide. Current releases are more limited, as indicated by the releases reported to the Toxics Release Inventory (TRI). However, total current environmental releases may be higher than the TRI estimates because only certain types of facilities are required to report; the list of facilities is not exhaustive.

The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

**6.2.1 Air**

Pentachlorophenol is released directly into the atmosphere via volatilization from treated wood products. Evaporation of pentachlorophenol-treated industrial process waters from cooling towers was an additional source of historical atmospheric releases of the compound. Historical atmospheric releases included those from cooling towers, where pentachlorophenol and its sodium salt were used as slimicides in cooling tower waters. However, pentachlorophenol and its salt are no longer commonly used for this purpose (Vulcan Chemicals 1989) since the early 1980s, when its use was restricted (EPA 1984b).

Emissions during production are considered to be relatively insignificant in volume, and are geographically restricted to the Vulcan Materials facility in Wichita, Kansas (SRI 1998). Physical

## 6. POTENTIAL FOR HUMAN EXPOSURE

removal mechanisms, such as wet deposition, are important processes that decrease pentachlorophenol concentrations in the atmosphere.

Pentachlorophenol has historically been estimated to volatilize from the surface of pentachlorophenol-treated wood products at an estimated rate of 760,000 pounds (344 metric tons) annually, or roughly 2% of the total amount of preservative applied. These estimates are representative of usage of the compound in those applications in the 1970s (EPA 1980f).

As much as 500,000 pounds annually (228 metric tons) of pentachlorophenol, used in cooling tower waters as an anti-fouling agent, have been released to the atmosphere through volatilization with heated water and steam in the past (EPA 1980f). However, pentachlorophenol is no longer commonly used for this purpose (Vulcan Chemicals 1989).

According to the TRI, an estimated total of 1,306 pounds of pentachlorophenol, amounting to 1.3% of the total environmental release, was discharged to the atmosphere from manufacturing and processing facilities in the United States in 1999 (TRI99 2001) (Table 6-1). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Volatilization from treated wood poles and other outdoor-use wood also occurs; 30–80% of the pentachlorophenol applied to coniferous wood by dip or brush treatments may be lost by volatilization within 12 months (Bunce and Nakai 1989). Ingram et al. (1986) reported increased volatilization of pentachlorophenol from treated wood with increased temperature; similar results with temperature change were seen with each of numerous solvent systems utilized for application of the compound. Volatilization of pentachlorophenol was dependent on the carrier solvents and the wood coatings utilized; maximum volatilization occurred when methylene chloride or 100% mineral spirits were used as carrier solvents, while the minimum volatilization occurred with the use of the cosolvent WC-144.

Pentachlorophenol may be formed during the incineration of chlorine-containing waste material. Heeb et al. (1995) found that pentachlorophenol constituted 8% of polychlorinated phenols formed in the flue gas and 10% of the stack gas during the incineration of chlorine-containing waste material. It may also be released in stack emissions as a result of pyrolysis of polyvinyl chlorides (Blankenship et al. 1994).



**Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Pentachlorophenol**

State <sup>b</sup>	Number of facilities	Reported amounts released in pounds per year <sup>a</sup>						Total on and off-site release
		Air <sup>c</sup>	Water	Underground injection	Land	Total on-site release <sup>d</sup>	Total off-site release <sup>e</sup>	
AL	7	459	813	No data	0	1,272	331	1,603
AR	2	250	5	No data	No data	255	115	370
CA	2	5	No data	No data	No data	5	No data	5
FL	1	No data	No data	No data	2,000	2,000	No data	2,000
GA	2	13	5	No data	No data	18	122	140
ID	1	5	No data	No data	43,000	43,005	No data	43,005
IL	1	2	No data	No data	0	2	74	76
KY	1	10	No data	No data	0	10	250	260
LA	2	8	34	No data	No data	42	23	65
MD	1	No data	No data	No data	No data	No data	No data	No data
MN	1	1	No data	No data	No data	1	No data	1
MO	1	255	0	No data	No data	255	1	256
MS	4	10	112	No data	0	122	15	137
NC	2	3	3	No data	No data	6	1,480	1,486
NE	1	255	No data	No data	No data	255	No data	255
NJ	1	2	0	No data	0	2	15	17
NV	1	2	No data	No data	No data	2	No data	2
OH	1	2	1	No data	No data	3	5	8
OR	4	16	251	No data	26,793	27,060	14,654	41,714
SC	2	6	0	No data	11,911	11,917	8	11,925

**Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use Pentachlorophenol  
(continued)**

State <sup>b</sup>	Number of facilities	Reported amounts released in pounds per year <sup>a</sup>						Total on and off-site release
		Air <sup>c</sup>	Water	Underground injection	Land	Total on-site release <sup>d</sup>	Total off-site release <sup>e</sup>	
SD	1	1	53	No data	No data	54	160	214
TX	2	0	0	5	No data	5	No data	5
UT	2	1	No data	No data	15,133	15,134	255	15,389
WA	4	No data	No data	No data	No data	No data	No data	No data
Total	47	1,306	1,277	5	98,837	101,425	17,508	118,933

Source: TRI99 2001

<sup>a</sup>Data in TRI are maximum amounts released by each facility.

<sup>b</sup>Post office state abbreviations are used.

<sup>c</sup>The sum of fugitive and stack releases are included in releases to air by a given facility.

<sup>d</sup>The sum of all releases of the chemical to air, land, water, and underground injection wells.

<sup>e</sup>Total amount of chemical transferred off-site, including to publicly owned treatment works (POTW).

## 6. POTENTIAL FOR HUMAN EXPOSURE

**6.2.2 Water**

Pentachlorophenol releases to surface water occur through direct discharge and direct entry from numerous nonpoint sources, including treated wood. In addition, pentachlorophenol is transported to surface waters from the atmosphere by wet deposition, and from soil by runoff and leaching.

Approximately 90% of wood-treatment plants evaporate their waste water and, consequently, have no direct discharge to surface waters. The remainder of the plants discharge to municipal waste water treatment facilities. Total annual pentachlorophenol releases to municipal waste water treatment facilities were estimated to be 12,000 pounds (5.3 metric tons) (EPA 1980g).

About 2 metric tons of pentachlorophenol used as a biocide in cooling tower waters were estimated to have been discharged to surface waters in 1978 (EPA 1979a). In addition, industries such as leather tanning and textile factories may have released up to 4,400 pounds (2 metric tons) and 12,000 pounds (5.5 metric tons) of pentachlorophenol, respectively, in their waste water discharges to surface waters on an annual basis in the 1970s (EPA 1980f). Pentachlorophenol is no longer used in these applications (Weinberg 1997).

Chlorination of phenolic compounds during water treatment has been reported to produce detectable levels of pentachlorophenol (Detrick 1977; Smith et al. 1976). In addition, common pesticides such as lindane, hexachlorobenzene, pentachlorobenzene, and pentachloronitrobenzene are known to be metabolized to pentachlorophenol by plants, animals, and/or microorganisms, but the contribution of the metabolism of these pesticides to environmental levels of pentachlorophenol is unknown (Dougherty 1978).

According to the TRI, an estimated total of 1,277 pounds of pentachlorophenol, amounting to 1.25% of the total environmental release, was discharged to water from manufacturing and processing facilities in the United States in 1999 (TRI99 2001) (Table 6-1). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

**6.2.3 Soil**

Pentachlorophenol is released to soils as a result of its past use as a herbicide, leaching from treated wood products, atmospheric deposition in precipitation (such as rain and snow), spills at industrial facilities using pentachlorophenol, and at hazardous waste sites.

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Most of the pentachlorophenol removed from effluent streams by waste water treatment processes is adsorbed to sludge solids. Sludges from wood preservation industries historically have been estimated to contain up to 31,500 pounds (14.3 metric tons) of pentachlorophenol annually. Pentachlorophenol in solid wastes from wood-treatment facility evaporation ponds was estimated to total an additional 133,000 pounds (60.2 metric tons) annually in the 1970s (EPA 1980f). However, most wood-treatment facilities have closed, or are in the process of closing, on-site evaporation ponds (Vulcan Chemicals 1989).

According to the TRI, an estimated total of 98,837 pounds of pentachlorophenol, amounting to 97.5% of the total environmental release, was discharged to soil from manufacturing and processing facilities in the United States in 1999 (TRI99 2001) (Table 6-1). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

### 6.3 ENVIRONMENTAL FATE

Pentachlorophenol released into the atmosphere from treated wood can be transported back to surface waters and soils via wet and dry deposition. Atmospheric pentachlorophenol is transformed via photolysis; the compound may slowly undergo free radical oxidation with an estimated half-life of approximately 2 months.

In surface waters, pentachlorophenol undergoes biotransformation and photolysis, and is adsorbed to sediments. Hydrolysis, oxidation, and volatilization do not significantly affect surface water concentrations.

In soils and sediments, pentachlorophenol is metabolized by acclimated microbes, under both aerobic and anaerobic conditions, or is adsorbed. Pentachlorophenol may also be methylated to form pentachloroanisole, a more lipid soluble compound. Adsorption of pentachlorophenol in soils is pH dependent. The compound has a  $pK_a$  value of 4.7 and consequently exists in the ionic forms at environmentally relevant pH values. For example, at pH 4.7, pentachlorophenol is 50% ionized, whereas at pH 6.7, the compound is about 99% ionized (Crosby 1981). Adsorption decreases in neutral and basic soils and is strongest in acidic soils. Therefore, the compound is most mobile in neutral-to-basic mineral soils and least mobile in acidic organic soils. Volatilization and photolysis do not appear to be important transport and transformation processes for pentachlorophenol in soils.

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**6.3.1 Transport and Partitioning**

A Henry's law constant of  $2.75 \times 10^{-6}$  atm m<sup>3</sup>/mol has been reported for pentachlorophenol; the value for the salt or ionic form of this compound is expected to be much less. Therefore, volatilization of the solvated anionic form from an aqueous system is not considered to be a significant transport mechanism under ambient conditions. Pignatello et al. (1983) reported that volatilization loss of pentachlorophenol as vapor and aerosol from treated river water in outdoor manufactured channels was #0.006% of the initial test concentration. Volatilization of pentachlorophenol from soil is also not expected to be a major transport pathway. Kilzer et al. (1979) determined the volatilization rates of pentachlorophenol from water and three soil types under laboratory conditions. The volatilization rates (expressed as percentage of applied pentachlorophenol per mL evaporated water) from water, sand, loam, and humus were 2.57, 0.13, 0.31, and 0.10%, respectively, in the first hour after application of 50 µg/L pentachlorophenol. During the second hour, the volatilization rates were 2.11, 0.12, 0.15, and 0.12%, respectively.

Pentachlorophenol is volatilized from treated wood surfaces. Walls in a closed room treated with pentachlorophenol released the chemical into the air, with concentrations reaching 1 ng/m<sup>3</sup> on the first day after treatment and 160 ng/m<sup>3</sup> on the fourth day (Gebefugi et al. 1976).

The adsorption or mobility of pentachlorophenol in soils is controlled primarily by soil pH. The amount of pentachlorophenol adsorbed at a given pH increases with increasing organic content of the soil (Chang and Choi 1974). Pentachlorophenol is adsorbed to soil or sediment under acidic conditions, but the compound is mobile under neutral or alkaline conditions (Kuwatsuka and Igarashi 1975). Maximum adsorption has been reported at soil pH values of 4.6–5.1, with no adsorption above pH 6.8 (Choi and Aomine 1974).

Schellenberg et al. (1984) investigated the adsorption of chlorinated phenols to natural sediments and aquifer materials. These authors demonstrated that adsorption of pentachlorophenol was highly dependent on the organic content of the adsorbent. An average  $K_{oc}$  of 32,900 was measured for pentachlorophenol in lake sediment, river sediment, and aquifer materials.

However, normalized partition coefficients (i.e.,  $K_{oc}$ ) do not accurately predict adsorption for ionizable compounds such as pentachlorophenol since its adsorption does not increase linearly with increasing concentration (Christodoulatos et al. 1994). The use of the equation to normalize partition coefficients is not valid in such cases. Davis et al. (1994) investigated the retardation of pentachlorophenol in

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groundwater at a former wood treating facility. Data were not well represented by the Freundlich or Langmuir isotherms. The authors observed that retardation of the compound in the aquifer was greater at lower concentrations ( $<40 \mu\text{g/L}$ ) than at higher ones ( $>1000$  or  $10,000 \mu\text{g/L}$ ), indicating that pentachlorophenol will move at rates closer to that of the groundwater when present at higher concentrations ( $>10,000 \mu\text{g/L}$ ). The authors stated that the results indicated that at the lower concentrations found at plume peripheries, pentachlorophenol would be attenuated and then biodegraded, while at higher concentrations such as at the source, the compound would be mobile.

Pentachlorophenol is applied to wood as a liquid formulation composed of pentachlorophenol dissolved in hydrocarbon diluents such as oils, kerosene, or mineral spirits. The presence of cosolvents such as alcohols or petroleum hydrocarbons decreases the adsorption of pentachlorophenol in soils by increasing its solubility in the soil solution (Christodoulatos et al. 1994). This may also be important at spill, storage, and hazardous waste sites where a large amount of cosolvent would be expected. Based on the results of a study of the mobility of pentachlorophenol, pentachlorodibenzodioxins, and pentachlorodibenzofurans in soils contaminated with wood-preserving oil, Jackson and Bisson (1990) indicated that decreased adsorption of the compounds in soil would result from the presence of a subsurface, contaminated oil phase. They predicted that upon contact with groundwater, the compounds would be partitioned into the aqueous phase. In a study of desorption of chlorophenols in contaminated soils, pentachlorophenol was desorbed more readily in the presence of methanol and exhibited a positive correlation with increasing methanol concentration (You and Liu 1996).

Decreased adsorption may also occur without the presence of a cosolvent/contaminant such as methanol or a petroleum hydrocarbon. The release of soil organics and colloids in the presence of dissolved pentachlorophenol was investigated. When pentachlorophenol was added to soil at aqueous concentrations of  $1,000\text{--}10,000 \mu\text{g/L}$ , surface organics (tentatively identified as fulvic acids) were solubilized and acted as a cosolvent, decreasing the adsorption of pentachlorophenol (Galil and Novak 1995). Enhanced mobility of pentachlorophenol was also predicted from the observed increased stability of soil colloids that adsorbed 3–13% of the compound, but were released from soil particle surfaces into the soil solution.

Pentachlorophenol can be leached from treated wood into surrounding soil. For example, Arsenault (1976) reported that pentachlorophenol migrated from the surface of utility poles to the adjacent soil, which had an average pentachlorophenol concentration of  $654 \text{ mg/L}$ . However, mobility in soil was

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limited, as indicated by the average soil concentration of 3.4 mg/L pentachlorophenol at a distance of 12 inches from the poles.

In a review paper, McAllister et al. (1996) reported that available data on the plant uptake and transformation of pentachlorophenol are inconsistent among studies and are inconclusive with regard to the abilities of specific plants to take up the compound. It was observed that the biodegradation of pentachlorophenol by microorganisms and its adsorption to soil limit the availability of the compound for plant uptake. Among the pentachlorophenol metabolites found in plants are tetrachlorophenols and anisoles (McAllister et al. 1996); additionally, oxidation products (tetrachlorobenzenes), conjugated forms of chlorinated phenols, and insoluble metabolites (lignin-incorporated residues) have been observed (Engelhardt et al. 1986).

Veith et al. (1985) demonstrated that chemicals with a log  $K_{ow}$  value greater than 4.0 are likely to bioaccumulate in organisms and food chains. The log  $K_{ow}$  presented in Chapter 4 is 5.01 for the un-ionized form, which suggests that pentachlorophenol will bioaccumulate. However, the extent of bioaccumulation will depend on the pH of the medium and physiological pH, since at higher pH levels, pentachlorophenol converts to the more water-soluble pentachlorophenate anion. Bluegill sunfish exposed to 100  $\mu\text{g/L}$  pentachlorophenol accumulated the compound in various tissues (edible, nonedible, or whole fish) to levels of 10–350 times the ambient water concentration in a 16-day static/renewal bioassay. Pentachlorophenol was rapidly eliminated upon transfer of the test organisms to clean water (Pruitt et al. 1977). Pentachlorophenol was reported to have a bioconcentration factor (BCF) of 81–461 in the soft tissue of a freshwater mussel; however, the compound was rapidly cleared by the test organisms (52% loss within 12 hours) (Makela et al. 1991). Other bioaccumulation tests with aquatic organisms include BCF values of 30–40 in carp muscle tissue and 300–400 in all other tissues (Gluth et al. 1985) and BCF values of 218 (whole fish) to 1,633 (fish lipid basis) for juvenile American flagfish (Smith et al. 1990). In the latter test, which was a flow-through bioassay, the half-life of pentachlorophenol in the tissues was reported to be about 16 hours. Bioaccumulation of pentachlorophenol in algae, aquatic invertebrates, and fish (with BCFs of up to 10,000) has been demonstrated. Representative BCFs are as follows: goldfish, 1,000; polychaete, 3,830; bluegill sunfish, 13; blue mussel, 324; and eastern oyster, 78 (EPA 1986c).

Biomagnification of pentachlorophenol in terrestrial or aquatic food chains has not been observed. In a 110-day study with rainbow trout, where pentachlorophenol was administered in the diet at a maximum concentration of 3,000  $\mu\text{g/kg}$ , maximum concentrations of the compound in fish tissues were 40  $\mu\text{g/kg}$

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after 50 days and 20 µg/kg at the end of the test period. In a 28-day depuration test, tissue half-life of the compound was about 7 days. According to the investigators, these results suggest that pentachlorophenol bioconcentration in fish occurs primarily through direct uptake from water rather than through ingestion of food. The similar pentachlorophenol tissue concentration levels of prey and predator salmonid fish from Lake Ontario were cited as additional evidence of the limited food chain bioaccumulation of the compound (Niimi and Cho 1983).

Pentachlorophenol bioconcentration by earthworms has also been studied by several investigators. In 14-day exposure tests, BCFs of 3.4–13 were reported for uptake of pentachlorophenol adsorbed to soil particulates (Haque and Ebing 1988; van Gestel and Ma 1988). However, when bioconcentration was calculated on the basis of concentration of test compound in soil solution, BCF values of 426–996 were obtained (van Gestel and Ma 1988).

### 6.3.2 Transformation and Degradation

#### 6.3.2.1 Air

Atmospheric pentachlorophenol is probably photolyzed in the absence of water, although mechanisms for this reaction are not well known (Crosby and Hamadad 1971; Gab et al. 1975). Photolysis of sorbed or film-state pentachlorophenol in the presence of oxygen has also been observed (Gab et al. 1975). The reaction products were similar to those found in aqueous photolysis. Bunce and Nakai (1989) estimated the rate of photolysis in the atmosphere based on measured quantum yields (254 nm) in the laboratory, molar absorptivity values, and solar intensity values for midday in summer at 40 EN; the estimated loss of pentachlorophenol to vapor-phase photolysis was 6.2% per hour. This rate represents the maximum rate at 40 EN; the average rate of photolysis for pentachlorophenol will be lower.

No empirical data were found describing the reactivity of pentachlorophenol to free radical oxidation in the atmosphere. Bunce and Nakai (1989) calculated the potential atmospheric degradation of pentachlorophenol due to hydroxyl radical attack. The estimated loss rate was 1.5% per hour (half-life of 66 hours) as calculated from an estimated rate constant of  $4.7 \times 10^{-13} \text{ cm}^3/\text{molecule-sec}$ , assuming a peak noon summer hydroxyl radical concentration of  $6.2 \times 10^6 \text{ radicals/cm}^3$ . Based on the estimated relative rates of photolysis and degradation by hydroxyl radicals, it was concluded that the former process would likely be the dominant of the two. It is noted that the estimate by Bunce and Nakai did not take into account the adsorption of the compound to particulates in the atmosphere. Using the method of Meylan



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and Howard (1993), a half-life of 58 days for the vapor-phase reaction of pentachlorophenol with hydroxyl radicals can be obtained from an estimated rate constant of  $5.5 \times 10^{-12}$  cm<sup>3</sup>/molecule-sec and an average hydroxyl radical concentration of  $5.5 \times 10^5$  molecule/cm<sup>3</sup>. Adsorption of pentachlorophenol to particulate matter, however, will attenuate the rate of this process in the atmosphere.

**6.3.2.2 Water**

Photolysis and biodegradation are believed to be the dominant transformation processes for pentachlorophenol in aquatic systems. Hydrolysis and oxidation are not important mechanisms for removal of the compound from surface waters.

The molecular structure of pentachlorophenol is indicative of its stability to hydrolysis or oxidation (EPA 1979e). Wong and Crosby (1981) reported that pentachlorophenol did not hydrolyze in aqueous solutions (serving as dark controls in an aqueous photolysis study) at pH 3.3 or 7.3 when held at 26 EC for up to 100 hours.

Wong and Crosby (1981) reported that pentachlorophenol in aqueous solutions at 100 mg/L was photolyzed under laboratory ultraviolet (UV)-light irradiation with estimated half-lives of about 100 hours at pH 3.3 and 3.5 hours at pH 7.3. Photolysis of pentachlorophenol in aqueous solution following exposure to sunlight was also rapid; in laboratory experiments, concentrations of pentachlorophenol in water were reduced from 9.3 to 0.4 mg/L in 24 hours, and approached zero at the end of 48 hours (Arsenault 1976). Wong and Crosby (1981) also reported rapid photolysis in sunlight (July); pentachlorophenol in pH 7.3 aqueous solution at 100 mg/L photolyzed with a half-life of 48 hours (total elapsed time) and a total disappearance time of 10 days. Degradates formed during photolysis included tetrachlorophenols, three tetrachlorodiolis and their respective quinones, chloranilic acid, and eventually 2,3-dichloromaleic acid, which also undergoes photolysis, but at a slightly slower rate than pentachlorophenol. The final products from the complete photolytic degradation of pentachlorophenol were carbon dioxide and chloride ions. In outdoor tests conducted with river water in manufactured channels, Pignatello et al. (1983) demonstrated that photolysis of pentachlorophenol (applied as the sodium salt) was rapid at the water surface (half-life of 0.70 hour at a depth of 0.5 cm). However, photolysis was greatly attenuated with increasing depth of the water column (half-life of 9.63 hours at a depth of 13.8 cm). Photolytic degradation accounted for a 5–28% decrease in the initial test concentration of the compound after 3 weeks.

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Pentachlorophenol is biotransformed in aqueous systems by acclimated microorganisms. In a 40-day study of sterile and nonsterile stream water samples that were not amended with acclimated microbial cultures, Baker et al. (1980) reported negligible biodegradation of pentachlorophenol at 0 and 20 EC. Pignatello et al. (1983) reported that microbial transformation became the primary removal mechanism of pentachlorophenol (applied as the sodium salt) added to river water in tests conducted in outdoor manufactured channels. After about a 3-week acclimation period, microbial transformation accounted for a 26–46% decline in the initial test concentration of pentachlorophenol. The majority of the microbes responsible for the mineralization of pentachlorophenol were associated with rock and macrophyte surfaces or surface sediments rather than existing in the water phase. In a follow-up study utilizing the same type of outdoor tests, Pignatello et al. (1985) found that biotransformation accounted for a 55–74% decrease in concentration of applied pentachlorophenol after a 3–5-week adaptation period. Biotransformation in the water column above sediments occurred at a greater rate under aerobic than under anaerobic conditions. Ingerslev et al. (1998) reported that in a study utilizing a battery of shake flasks tests, pentachlorophenol at 1 and 100 mg/L biodegraded in 10–30 days under aerobic conditions in surface water from an unpolluted stream after an acclimation period of approximately 55 days. The addition of either sterilized or unsterilized sediment to the samples resulted in reduced acclimation periods, but did not affect the postacclimation degradation rates in water.

In a study using radiolabeled pentachlorophenol, Arsenault (1976) demonstrated that the compound was transformed to carbon dioxide, water, and hydrochloric acid in an activated sludge treatment plant. On a pilot-plant scale, the same investigator also showed that a waste stream from a wood-preserving facility containing 23 mg/L of pentachlorophenol could be treated successfully to produce a final effluent concentration of 0.4 mg/L of pentachlorophenol.

In a microcosm study of unfiltered aquifer samples (geologic material and groundwater) contaminated with polycyclic aromatic hydrocarbons and pentachlorophenol, a loss was observed. Although reductions in the parent compound concentration occurred, only 1% of the applied radiolabeled pentachlorophenol had mineralized by 56 days (Mohammed et al. 1998). Neither nutrient addition nor sample sterilization had a significant effect on mineralization. The observed decreases in the pentachlorophenol concentrations were attributed to adsorption to particulate material and not to biodegradation.

In four simulated lentic environments, Boyle et al. (1980) tested the effects of dissolved oxygen, light, pH, and the presence of a hydrosol (i.e., pond soil/sediment) on the transformation of pentachlorophenol (applied as the sodium salt). The persistence of pentachlorophenol was associated with three

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environmental variables: absence of light and hydrosol; pH near or below pKa; and low oxygen concentration. Major reaction products were pentachloroanisole, 2,3,4,5-tetrachlorophenol, 2,3,4,6-tetrachlorophenol, and 2,3,5,6-tetrachlorophenol; only pentachloroanisole was found in the water phase, and then only in the aerobic systems maintained in light.

**6.3.2.3 Sediment and Soil**

Photolysis of pentachlorophenol on soil surfaces is not a major transformation process. Hebert and Miller (1990) reported that UV light was >90% attenuated in the surface 0.2 mm of soil. However, while they will not approach rates of photolysis observed in aqueous solution, photolytic losses on the soil surface may be increased under certain conditions. The effect of upward evaporative flux on the rates of photolytic loss of pentachlorophenol, applied at 1,500 µg/L, was examined in soils maintained at various moisture levels. It was observed that the rates of photolysis on soil increased when near-saturated conditions were utilized, which increased the evaporative flux and translocated the compound to the surface 0.5 mm of the soil where photochemical degradation occurs (Donaldson and Miller 1997). Under near-saturated flow conditions in loamy sand soil, up to 55% more degradation was observed in the irradiated samples than in the dark controls in 14 days.

The rate of pentachlorophenol degradation from adsorption and metabolism in soil is not dependent on soil texture, clay content, free iron oxides, or the degree of base saturation; however, it is partially dependent on the ion exchange capacity of the soil (Engelhardt et al. 1986). The rate of pentachlorophenol transformation in laboratory tests is more rapid in soils with high organic content than in those with low organic content, and greater when moisture content is high and soil temperature approaches the optimum for microbial activity (Young and Carroll 1951).

Biodegradation is considered the major transformation mechanism for pentachlorophenol in soil. Half-lives are usually on the order of 2–4 weeks. Pentachlorophenol is metabolized rapidly by most acclimated microorganisms (Kaufman 1978). In a study by Edgehill and Finn (1983) inocula of a strain of pentachlorophenol-acclimated *Arthrobacter* bacteria was added to soils in laboratory and enclosed outdoor tests. The soils were amended with 120–150 mg pentachlorophenol/L and 34 kg pentachlorophenol/hectare, respectively. In the laboratory test conducted in the dark at 30 EC, the half-life of pentachlorophenol in inoculated samples was about 1 day, whereas the half-life in uninoculated samples was 12–14 days. Pentachlorophenol loss from uninoculated control plots in outdoor tests was 25% after 12 days at ambient temperatures (8–16 EC), while losses from inoculated plots were 50–85%.

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*Pseudomonas* biotransformed [ $^{14}\text{C}$ ]-pentachlorophenol rapidly and released radiolabeled carbon dioxide as well as the intermediate metabolites tetrachlorophenol and tetrachlorohydroquinone. In another study, strains of *Pseudomonas putida* and *Acinetobacter calcoaceticus* sp. were found to be able to use pentachlorophenol as a sole carbon and energy source (Martins et al. 1997)

An investigation was conducted by Frisbie and Nies (1997) to determine whether aged pentachlorophenol residues from contaminated soil at a former wood-treatment site would be biodegraded in the laboratory under aerobic and anaerobic conditions by indigenous microbes from that site. Under aerobic conditions, both existing and newly added pentachlorophenol was biodegraded following a short acclimation period. The degradates 2-monochlorophenol and 4-monochlorophenol were rapidly degraded, but 3-monochlorophenol did not undergo significant degradation. Under anaerobic conditions, pentachlorophenol was degraded to 3-monochlorophenol, which accumulated and was then further degraded; however, approximately 30% of the initial pentachlorophenol was not degraded.

Pentachlorophenol has been observed to degrade more rapidly in anaerobic environments than in aerobic ones. Pentachlorophenol degraded in a paddy soil at 28 EC with a half-life of about 3 weeks; reducing conditions increased the rate of reaction slightly (Ide et al. 1972). These observations were confirmed by Kuwatsuka and Igarashi (1975) in 10 different soil types. Pentachlorophenol biotransformation rates were higher under anaerobic (flooded) conditions than under aerobic (upland) conditions. The half-life for pentachlorophenol under flooded conditions ranged from 10 to 70 days, while under upland conditions, the range was 20–120 days, and the rate of reaction increased with the organic matter content. Pentachlorophenol transformation was assumed to proceed by both chemical and microbial means, based on the effects of sterilization, soil temperature, and nature of the reaction products, which included pentachloroanisole; 2,3,4,5-, 2,3,4,6-, and 2,3,5,6-tetrachlorophenol; and 2,3,4-, 2,3,5-, 2,3,6-, 2,4,5-, 2,4,6-, and 3,4,5-trichlorophenol. The major products were 2,3,4,5-tetrachlorophenol, and 2,3,6- and 2,4,6-trichlorophenol. Tetrachloro-*p*-benzoquinone and 2,6-dichlorohydroquinone have also been implicated as metabolic intermediates for pentachlorophenol (Reiner et al. 1978).

The degradates 3,4- and 3,5-dichlorophenol were also observed in biodegradation studies of pentachlorophenol (Engelhardt et al. 1986). These authors noted that pentachloroanisole was a major degradate in aerobic soils, but was present in minor amounts in anaerobic soils. In anaerobic systems, pentachlorophenol is biodegraded only through reductive dechlorination, and the degradates 3,5-dichlorophenol and 3-monochlorophenol may accumulate; complete dechlorination to phenol and its subsequent mineralization to methane and carbon dioxide have been observed (Frisbie and Nies 1997). In

## 6. POTENTIAL FOR HUMAN EXPOSURE

a review paper on microbial degradation of pentachlorophenol, McAllister et al. (1996) reported that the various intermediates found in numerous studies indicated that microbial degradation of the compound occurs by different mechanisms which are associated with specific microbial consortia.

Pentachlorophenol is degraded under anaerobic conditions in sewage sludge and sediments. After 6 months of operation, about 60% of the initial concentration of pentachlorophenol added to laboratory-scale, fixed-film reactors containing a digested municipal sewage sludge microbial inoculum was removed. Removal from reactors supplemented with glucose attained 98% of the initial charge over the same time frame. Trichlorophenol and tetrachlorophenol were observed as degradation products (Hendriksen et al. 1991). In other laboratory tests, reductive dechlorination of pentachlorophenol was found to be more rapid in freshwater sediments containing microbial communities adapted to dechlorinate 2,4-dichlorophenol and 3,4-dichlorophenol than in nonadapted sediment microbial communities. Degradation products identified included 2,3,5,6-tetrachlorophenol, 2,3,5-trichlorophenol, 3,5-dichlorophenol, 3-chlorophenol, and phenol (Bryant et al. 1991). Ingerslev et al. (1998) also reported more rapid degradation and shorter or no acclimation periods in freshwater sediments amended with activated sludge which was preexposed to pentachlorophenol at various levels. At concentrations ranging from 10 to 20,000 µg/L, the acclimation periods were reduced from 8.6–21.1 days to 0.1–3.2 days when sediments were amended with preexposed activated sludge compared with activated sludge which was not preexposed to pentachlorophenol; only at a toxic concentration of 74,000 µg/L was the acclimation period increased (15.5–59.4 days). At concentrations of 10, 100–2,500, and 20,000 µg/L, preexposure reduced the respective postacclimation half-lives from 32, 3.7–5.6, and 108 days to #2.2 days; at 74,000 µg/L, the postacclimation half-life decreased from 80 days to >51.6 days.

#### 6.3.2.4 Other Media

Laboratory studies were conducted to determine the effect of artificial light and sunlight on concentrations of pentachlorophenol and chlorinated dibenzo-*p*-dioxins in wood treated with pentachlorophenol (Lamparski et al. 1980). Although chlorinated dibenzo-*p*-dioxins are known to be present in pentachlorophenol products as impurities, formation of octachlorodibenzo-*p*-dioxin (OCDD) as well as heptachlorodibenzo-*p*-dioxin (HpCDD) and hexachlorodibenzo-*p*-dioxin (HxCDD) was observed even when purified pentachlorophenol was irradiated. Based on the relative levels of the isomers observed, HxCDD and HpCDD were presumed to be degradation products of OCDD, not condensation products of tetrachlorophenol and pentachlorophenol. The formation of OCDD was greatly reduced when hydrocarbon oil was utilized as the carrier solvent in place of methylene chloride.

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**6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT**

Pentachlorophenol historically has been widely detected in environmental media as a result of its widespread past use by industry, the agricultural sector, and the general public, as a cooling-tower algicide and fungicide, herbicide, molluscicide, paint preservative, plywood and fiberboard waterproofing agent, and drilling mud and photographic solution biocide. Pentachlorophenol is now regulated as a restricted-use pesticide. Therefore, it can only be purchased and used by certified applicators, and only for the applications covered by the applicator's certification. Pentachlorophenol is no longer available to the general public. Although the compound has been detected in indoor air, surface waters, groundwater, drinking water, soils, rainwater, and a variety of foods in older monitoring studies, current contamination of these media by the compound is probably more limited given the restricted current usage of pentachlorophenol and its limited environmental persistence.

**6.4.1 Air**

Limited information is available on the levels of pentachlorophenol in ambient air. EPA (1980f) estimated atmospheric concentrations of pentachlorophenol using air models. A cumulative concentration estimate based on all emission sources was 0.15–136 ng/m<sup>3</sup>. The lower end of this range coincides with the upper end of the range of computed air concentration estimates based on pentachlorophenol concentrations in rainwater in Hawaii (0.002–0.063 ng/m<sup>3</sup>) where pentachlorophenol has been used extensively as an herbicide and wood preservative. A Canadian study (Cessna et al. 1997) reported the amount of pentachlorophenol in air in Saskatchewan (Regina and Waskesiu) and Northwest Territories (Yellowknife). The concentrations of pentachlorophenol in the vicinity of Yellowknife ranged from 0.43 to 3.68 ng/m<sup>3</sup>, with a mean concentration of 1.53 ng/m<sup>3</sup>. At both the Regina and Waskesiu sites, the concentrations ranged from 0.06 to 0.58 ng/m<sup>3</sup> with a mean value of 0.30 ng/m<sup>3</sup>.

**6.4.2 Water**

Of 497 surface water observations in EPA's STORET database as of March 1979, 82% were at the detection limit; 84% of the remaining observations fell between 0.1 and 10 µg/L, with a total range of 0.01–100 µg/L (EPA 1979b). These data imply that ambient levels of pentachlorophenol in surface water are usually below 1 µg/L, with much higher levels in more industrialized areas.

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Pentachlorophenol levels monitored in surface water include the following: 0.1–0.7 µg/L in the Willamette River (Buhler et al. 1973); 9 µg/L in a river below a paper mill (Rudling 1970); 0.1–1 µg/L in the Great Lakes (EPA 1980f); <1 µg/L in a river at a sewage discharge site in Sacramento, California (Wong and Crosby 1978); 38–10,500 µg/L in a stream running through an industrial district in Pennsylvania (Fountaine et al. 1975); and 0.01–0.48 µg/L in streams in Hawaii (Young et al. 1976).

Pentachlorophenol has also been detected in drinking waters at the following levels: 0.04–0.28 µg/L in Corvallis, Oregon (Buhler et al. 1973); a mean concentration of 0.07 µg/L in 108 samples surveyed by the National Organics Monitoring Survey (NOMS); and <1–800 µg/L (an average of 227 µg/L) in seven drinking water wells in Oroville, California (Wong and Crosby 1978).

Pentachlorophenol was detected in raw effluent from a series of wood-treatment plants at levels ranging from 25,000 to 150,000 µg/L (Dust and Thompson 1972) and in influent (1–5 µg/L) and effluent (1–4 µg/L) at streams at a sewage plant in Corvallis, Oregon (Buhler et al. 1973). The compound has also been detected (concentrations unspecified) in surface water and groundwater samples taken at a wood-treatment facility in Arkansas (McChesney 1988), in the surface water (68 µg/L) at a wood-treatment facility in Louisiana (ATSDR 1995), in groundwater (up to 19,000 µg/L) at a wood-preserving site in South Carolina (ATSDR 1993a), in groundwater (0.6 µg/L) at an inactive landfill in Florida (ATSDR 1993b), and in groundwater (up to 4,300 µg/L) at Camilla Wood Preserving Company, Camilla, Georgia (Anonymous 1999).

#### 6.4.3 Sediment and Soil

Although several investigators (Fountaine et al. 1975; Pierce and Victor 1978) refer to possible soil contamination as a source of pentachlorophenol levels in water samples, very little data are available on actual measurements of pentachlorophenol in soil. Arsenault (1976) reported pentachlorophenol concentrations of 3.4–654 ppm in soil within 12 inches of treated utility poles. Pentachlorophenol was detected in the soil samples taken from a depth of 0–3 inches at (320–2,300 µg/kg) and in subsurface soil (820–200,000 µg/kg) at a wood-treatment facility, a NPL site, in Louisiana (ATSDR 1995). It was also found in soil at an inactive landfill in Florida, also a NPL site, at a maximum concentration of 21,000 µg/kg (ATSDR 1993b). Pentachlorophenol was found in on-site (up to 13,000 µg/kg) and off-site (up to 1,300 µg/kg) soil samples from the Camilla Wood Preserving Company in Camilla, Georgia (Anonymous 1999).

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**6.4.4 Other Environmental Media**

Levels of pentachlorophenol in food are examined as a part of FDA's ongoing food monitoring studies. In 1973–1974, 10 out of 360 composite food samples contained pentachlorophenol at 10–30 ppb: 1 in dairy products, 1 in cereals, 1 in vegetables, and 7 in sugar (Manske and Corneliussen 1976). In the next year, 13 out of 240 composites contained pentachlorophenol (10–40 ppb), again mostly in sugars (Johnson and Manske 1977). Pentachlorophenol was detected in all of a series of random samples of Florida food at levels of 1–1,000 ppb, principally in grain products (Dougherty and Piotrowska 1976). Pentachlorophenol was also detected at low levels in peanut butter (1.8–62 µg/kg) and chicken (6–12 µg/kg) (Farrington and Munday 1976).

Pentachlorophenol concentrations in fish tissue for the years 1976–1979, reported in EPA's STORET database, ranged from below the limit of detection to 50 mg/kg. Mean concentrations by region were as follows: Lake Michigan, 0.002 mg/kg; lower Mississippi, 0.478 mg/kg; Pacific Northwest, 16.38 mg/kg; Alaska, 5.0 mg/kg; Western Gulf, not detected; and south central lower Mississippi, not detected (EPA 1979b).

Levels of pentachlorophenol ranging from 10 to 270 µg/L were reported in 9 out of 65 samples of children's paints in the Netherlands (Van Langeveld 1975).

Another study (Thompson et al. 1997) estimated the amount of pentachlorophenol in the atmosphere by measuring the amount of pentachlorophenol in pine needles. The lipid coating of pine needles has been shown to absorb contaminants from the atmosphere and, therefore, measurement of pollutants in pine needles provides an indirect way of estimating the atmospheric pollutants. The pentachlorophenol concentrations in the vicinity of a utility pole storage site were found to range from 29 to 570 ng/g of the needles. In comparison, pentachlorophenol concentration in the pine needles from sites further away from the pole storage locations was found to be <0.5 ng/g.

It should be noted that most of the data discussed above are 13–17 years old (more recent data are not available). Use of pentachlorophenol has decreased in the intervening years because of restrictions placed on its use. Therefore, levels of pentachlorophenol found in other environmental media have presumably decreased since the time these data were published.



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**6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE**

Humans may be exposed to pentachlorophenol in occupational settings through inhalation of contaminated workplace air and dermal contact with the compound or with wood products treated with the compound. General population exposure may occur through contact with contaminated environmental media, particularly in the vicinity of hazardous waste sites. Important routes of exposure appear to be inhalation of contaminated air, ingestion of contaminated groundwater used as a source of drinking water, ingestion of contaminated food and soils, and dermal contact with contaminated soils or products treated with the compound.

Before being regulated as a restricted-use pesticide, pentachlorophenol was used extensively in treating wood. Today, this use is restricted to the treatment of utility poles, railroad ties, and wharf pilings where it is widely used. Dermal exposure to pentachlorophenol by members of the general population may occur upon contact with these wood products. Since pentachlorophenol is readily absorbed through skin (Qiao et al. 1997; Wester et al. 1993), this represents a relevant route of low level exposure. Pentachlorophenol is known to volatilize from treated wood products (Bunce and Naki 1989) at a rate that is temperature-dependent (Ingram et al. 1986), and low level inhalation exposure may also occur with increased levels expected during the summer months. In older residences constructed with treated wood products, inhalation of contaminated indoor air may also be an important source of exposure. A reduction in volatilization of pentachlorophenol by coating the treated wood surfaces with varnishes and epoxy coatings was demonstrated by Ingram et al. (1986). In past years, pentachlorophenol has been detected in human adipose tissue, blood, and urine.

Data have been collected on pentachlorophenol levels in human urine, blood, adipose tissue, and cerebrospinal fluid for both occupational and nonoccupational groups. While levels are much higher in occupationally exposed groups, tests on the general population consistently show evidence of low-level exposure. In an FDA study in Florida, Cranmer and Freal (1970) found an average pentachlorophenol urine level of 4.9 µg/L in the general population, compared with 119.9 µg/L in carpenters, boat builders, and spraymen. A range of 1,100–5,910 µg/L in the urine of Japanese pest control operators exposed to pentachlorophenol, compared with 10–50 µg/L in nonexposed workers was cited by Bevenue and Beckman (1967). A comparison of results from a study in Hawaii on pentachlorophenol in urine of three groups (occupational, nonoccupational, and a mixed population) was done by Bevenue et al. (1967). The pentachlorophenol level of 1,802 µg/L in the occupationally exposed population was almost 50 times higher than the nonoccupational group level of 40 µg/L. Hill et al. (1989) detected pentachlorophenol in

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100% of urine samples taken from 197 children in Arkansas at a median concentration of 14 µg/L. Ninety-seven of these children lived in the vicinity of a herbicide plant while the remaining one hundred were part of a control group of children who lived elsewhere. No difference was observed in the amount of pentachlorophenol detected in the urine samples of these two groups. Pentachlorophenol was also found in 100% of urine samples taken from 50 members of the general population of Barcelona, Spain, at a mean concentration of 25 µg/L (Gómez-Catalán et al. 1987).

An analysis of the urine samples of 1,000 adults residing in the United States detected pentachlorophenol in 64% of the samples (Hill et al. 1995). The adults tested were a subset of those participating in the National Health and Nutrition Examination Survey (NHANES III). The median pentachlorophenol concentration in urine was found to be 1.5 ng/mL. A Canadian study compared results from urine analysis studies of nonoccupationally exposed individuals residing in Saskatchewan, Canada, a region with little lumber industry. In the first study with normal healthy individuals, performed in September 1992, 100% of the samples analyzed were found to contain detectable amounts of pentachlorophenol with a median concentration of 1.3 ng/mL (Thompson and Treble 1994). A subsequent study, performed in January 1995, also detected pentachlorophenol in 100% of the urine samples (Thompson and Treble 1996). The median concentration in this latter study was 0.5 ng/mL. A third urinary analysis study of nonoccupationally exposed individuals residing in Saskatchewan also detected pentachlorophenol in 94% of the urine samples at a median concentration of 0.5 ng/mL (Treble and Thompson 1996).

Among a group of 16 patients with neurological symptoms, pentachlorophenol was detected in blood serum and cerebrospinal fluid using a gas chromatograph with electron capture detection technique. Mean concentrations in these media were 22 µg/L (range, 4–60 µg/L) and 0.75 µg/L (range, 0.24–2.03 µg/L), respectively. Three people in the study group who reported contact with wood preservative products had the highest serum levels of pentachlorophenol. Cerebrospinal fluid levels were not correlated with serum levels or cerebrospinal protein levels (Jorens et al. 1991).

The National Health and Nutrition Examination Survey II (NHANES II) and the National Human Adipose Tissue Monitoring Survey (NHATS) analyzed blood and urine specimens from approximately 6,000 persons between the ages of 12–74 years in 64 communities throughout the United States for the presence of a number of compounds, including pentachlorophenol, during the period of 1976–1980. The initial results of the survey indicated that pentachlorophenol was detected in about 79% of urine samples tested (Murphy et al. 1983), and that pentachlorophenol-related phenols were also detected at lower frequencies. The mean pentachlorophenol value in urine samples tested during 1976–1979 was 6.3 µg/L

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with the maximum level of 193  $\mu\text{g/L}$  (Kutz et al. 1978). Pentachlorophenol measured in urine was considered to be the result of exposure to pentachlorophenol, lindane, and hexachlorobenzene. More recent results of NHANES II indicate that pentachlorophenol was found in 71.6% of the urine samples collected from the general population at an estimated geometric mean concentration of 6.3  $\text{ng/mL}$ . These results suggest that, during 1976–1980, almost 119 million individuals from the general population were exposed to pentachlorophenol. Males were found to have higher percentage quantifiable levels of pentachlorophenol and higher geometric mean concentrations in urine than females (Kutz et al. 1992). In a study of workers exposed to pentachlorophenol in the wood-preserving industry, Arsenault (1976) reported pentachlorophenol levels of 120–9,680  $\mu\text{g/L}$  in urine, with a mean concentration of 1,683  $\mu\text{g/L}$ . In another study, Ferreira et al. (1997) compared the concentration of pentachlorophenol in the urine and blood of a group of workers occupationally exposed to pentachlorophenol at a wood-transformation unit to those of a control group with no known exposure to pentachlorophenol. The mean level of pentachlorophenol in the occupationally exposed group was found to be 1,197 and 1,273  $\mu\text{g/L}$  in urine and blood, respectively. The mean concentration of pentachlorophenol in the control group was considerably lower at 6.4 and 15.3  $\mu\text{g/L}$  in urine and blood, respectively. The urine samples of wood workers from a wood factory in northern Italy were monitored before work at 8 a.m. and after the work shift at 5 p.m (Colosio et al. 1993a). The results indicated that a greater amount of pentachlorophenol was excreted in the morning (175  $\mu\text{g/L}$ ) than in the evening (106  $\mu\text{g/L}$ ). A subsequent study by Barbieri et al. (1995) obtained similar results from which a half-life of about 10 days was estimated for pentachlorophenol excretion in urine.

A mean pentachlorophenol blood serum level of 420  $\mu\text{g/L}$  was reported for residents of log homes, whereas a mean level of 40  $\mu\text{g/L}$  was reported for members of the general public with no known exposure to the compound. For residents of the log homes, pentachlorophenol serum levels of children were found to average 1.8 times those of their parents. Pentachlorophenol urine concentrations for residents of log homes averaged 69  $\mu\text{g/L}$ , whereas urine levels for the general population were found to be 3.4  $\mu\text{g/L}$ . Inhalation was believed to be the most likely route of exposure to pentachlorophenol in log homes (Cline et al. 1989). Pentachlorophenol was also found in serum samples taken from members of the general population of Barcelona, Spain, at a mean concentration of 21.9  $\mu\text{g/L}$  (Gómez-Catalán et al. 1987). In a separate study of 66 residents of log homes treated with pentachlorophenol in Kentucky, Hosenfeld et al. (1986) reported a geometric mean pentachlorophenol blood serum level of 47.6  $\mu\text{g/L}$  and a geometric mean urine concentration of 21  $\mu\text{g}$  per gram urinary creatinine. Pentachlorophenol was detected in blood and urine of all 66 residents.

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Mean pentachlorophenol blood serum levels in workers using pentachlorophenol or pentachlorophenol-treated materials were found to range from 83 to 57,600 µg/L by Cline et al. (1989). This upper limit is approximately 100 times the value expected from exposure to the threshold limit value (TLV) (Braun et al. 1979). Workers were involved in the construction of log homes, repair of telephone lines, custodial care of log cabin museums, and in various operations in wood-preservative and chemical-packaging facilities. One worker from a chemical-packaging facility, with a whole blood pentachlorophenol level of 23,000 µg/L, died of pentachlorophenol poisoning (Cline et al. 1989).

A mean level of 26.3 µg/kg was found in adipose tissue from the general U.S. population and it was concluded that humans are continuously exposed to low levels of pentachlorophenol from the environment, food supplies, and disinfectants (Shafik 1973). The distribution and bioconcentration of pentachlorophenol in different tissues of humans was investigated by Geyer et al. (1987). By comparing daily intake of pentachlorophenol with tissue concentrations, bioconcentration ratios of 5.7, 3.3, 1.4, 1.4, and 1.0 were obtained in liver, brain, blood, spleen, and adipose tissue, respectively. Pentachlorophenol has also been found in human milk samples from West Germany at 0.03–2.8 µg/kg (Gebefugi and Korte 1983). In a study of human tissues removed at autopsy, including testes, kidney, prostate glands, livers, and adipose tissue, pentachlorophenol was found in all tissues examined at a range of 7 ppb in subcutaneous fat to 4,140 ppb in testes (Wagner et al. 1991).

Based on the pentachlorophenol levels in their 1977 food survey, FDA estimated an average dietary intake of 0.76 mg/day for a typical 15–20-year-old male, and EPA (1978a) calculated an average dietary intake of 1.5 mg/day and a maximum dietary intake of 18 mg/day. However, the actual intake will be lower than estimates because average dietary intakes were based on mean concentration of positive samples. Considering pentachlorophenol levels in fish, peanut butter, food packaging materials, jar lids, etc., the average intake of pentachlorophenol in food has been estimated to be 1.5 mg/day (EPA 1980f). Daily dietary intake of pentachlorophenol from contaminated food has been estimated by another source to be 0.1–6 µg/day (WHO 1987). Using a six-compartment environmental partitioning model, Hattemen-Frey and Travis (1989) reported that the food chain is the most important source of exposure to pentachlorophenol for the general population. They estimated average daily dietary intake of the compound to be 16 µg/day from ingestion of contaminated food, primarily root vegetables. Pentachlorophenol was detected in 15% of the foods collected in eight market basket surveys from different regions of the United States during the period of April 1982 to April 1984 (Gunderson 1988). Foods representative of the diets of eight different age/gender population groups were prepared for consumption prior to analysis in a revision to FDA's Total Diet Study methodology. Estimated mean

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daily intakes (ng/kg/day) of pentachlorophenol for these groups in 1982–1984 were as follows:

(1) 6–11-month-old infants, 59.0; (2) 2-year-old children, 48.5; (3) 14–16-year-old females, 16.2; (4) 14–16-year-old males, 20.7; (5) 25–30-year-old females, 15.9; (6) 25–30-year-old males, 18.2; (7) 60–65-year-old females, 13.9; and (8) 60–65-year-old males, 15.5. In a later survey of the Total Diet Study, Gunderson (1995a) estimated mean daily intakes (ng/kg/day) of pentachlorophenol for these same eight age/gender population groups during a 1986–1991 study as follows: (1) 6–11-month-old infants, 0.9; (2) 2-year-old children, 1.4; (3) 14–16-year-old females, 0.5; (4) 14–16-year-old males, 0.5; (5) 25–30-year-old females, 0.8; (6) 25–30-year-old males, 0.7; (7) 60–65-year-old females, 0.8; and (8) 60–65-year-old males, 0.8. A substantial reduction in the amount of pentachlorophenol in the estimated mean daily intake has been observed since the 1982–1984 study. In a monitoring program conducted by the Danish National Pesticide Monitoring Program from 1995 to 1996, no pentachlorophenol was detected in the samples of fruits, vegetables, cereals, bran, fish, or animal products such as meats, butter, cheese, fat, and eggs.

In earlier surveys of pentachlorophenol exposure, food was found to be the most important source of intake for members of the general population (Coad and Newhook 1992; Wild and Jones 1992). In a multimedia analysis of pentachlorophenol exposure for the general population of Canada, food sources (mostly dairy products, grains, and cereals) accounted for an estimated 74–89% of the total daily intake of pentachlorophenol. Inhalation exposure, especially of indoor air, accounted for an estimated 10–25% of total daily intake, whereas water and soil/household dust were found to be negligible sources. Daily exposure of recreational fishermen consuming about twice as much fish as members of the general population was estimated to be only about 2% higher than that of the general population. However, lifetime dietary intakes of pentachlorophenol for aboriginal subsistence fishermen, relying on traditional diets of fish and fish products were estimated to be about twice those of members of the general Canadian population (Coad and Newhook 1992). In the United Kingdom, dietary sources are believed to account for greater than 90% of the estimated total daily intake of 5.7 µg pentachlorophenol/day by members of the general population. This value is considerably smaller than the 39 µg/day estimate for occupationally-exposed individuals. Inhalation is believed to be the most important route of exposure in workplace settings (Wild and Jones 1992). In a study that used the clearance concept to estimate net daily intake (i.e., net daily intake=clearance times average steady state concentration in plasma), the net daily intake of pentachlorophenol for members of the general U.S. population not specifically exposed to the compound was estimated to be 12.3–135.9 µg/day. For members of the general U.S. population residing in log homes, net intake was estimated to be 140–157 µg/day. Daily intake estimates for occupationally-

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exposed individuals varied widely depending on the type of work involved; estimates ranged from 35 to 24,000  $\mu\text{g}/\text{day}$  (Reigner et al. 1992a).

The National Organic Monitoring Survey conducted in 1976 found pentachlorophenol residues in 86 of 108 drinking water samples, with a mean of 0.07  $\mu\text{g}/\text{L}$  and a maximum of 0.7  $\mu\text{g}/\text{L}$  (EPA 1978a); however, the median concentration was less than 0.01  $\mu\text{g}/\text{L}$ , the minimum detectable limit. In another survey, pentachlorophenol was detected at 1.3–12.0  $\mu\text{g}/\text{L}$  in 8 out of 135 systems surveyed (EPA 1980a, 1980c). Assuming an intake of 2 L of drinking water/day, exposure for most people would be less than 0.02  $\mu\text{g}/\text{day}$ , while the maximum exposure would be 24  $\mu\text{g}/\text{day}$ .

Inhalation of estimated ambient levels of pentachlorophenol in the atmosphere has an associated exposure level of 6  $\mu\text{g}/\text{day}$  for the general population (EPA 1980f). Subpopulations in the vicinity of pentachlorophenol sources and workers may be exposed to significantly higher levels. For example, workers in the vicinity of a cooling tower may have been exposed to 14.4 mg pentachlorophenol/day, and those in wood-treatment plants may have been exposed to 0.9–14 mg pentachlorophenol/day (EPA 1980f). Pentachlorophenol levels in the air of an experimentally treated room varied greatly (1–160  $\mu\text{g}/\text{m}^3$ ) with temperature and ventilation (Gebefugi et al. 1976).

Pentachlorophenol was detected at a geometric mean concentration of 0.080 ng/L in 62 of 63 air samples taken in 21 log homes treated with the compound. The homes, all located in Kentucky, were categorized into six treatment types: (1) "never treated"; (2) external treatment; (3) manufacturer treated; (4) treated and sealed; (5) treated, sealed, and neutralized; and (6) treated and neutralized. Concentrations in "never treated" homes, which were lower than those in treated homes, were believed to be the result of the application of pentachlorophenol to logs during storage to prevent fungal growth. Treated logs were found to be the source of pentachlorophenol in indoor air; air concentrations were highly correlated with pentachlorophenol concentrations in wood cores (geometric mean, 15,900 ng/g wood) and log surface wipes (geometric means, 89.6 and 187 ng/100  $\text{cm}^2$ ) (Hosenfeld et al. 1986). Concentrations of pentachlorophenol in older structures built with pressure-treated wood brushed with pentachlorophenol were reported to range from 0.5 to 10  $\mu\text{g}/\text{m}^3$  (EPA 1984b). Use of sealers decreased this concentration by 85%. Indoor air interiors of structures built with industrially dipped nonpressure-treated wood were reported to contain levels of pentachlorophenol that ranged from 34 to 104  $\mu\text{g}/\text{m}^3$  (EPA 1984b). Logs used for home construction are no longer treated with pentachlorophenol. Pentachlorophenol in air samples taken from 75 rooms in 30 buildings with suspected use of pentachlorophenol-containing wood

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preservatives in Germany ranged from  $<0.03$  to  $576 \text{ ng/m}^3$ . Pentachlorophenol in the dust samples taken from the same sites ranged from  $0.083$  to  $79 \text{ ng/kg}$  (Schnelle-Kreis et al. 2000).

Dermal absorption is another potential exposure pathway. Pentachlorophenol is readily absorbed through skin (Qiao et al. 1997; Wester et al. 1993). EPA (1984) has assumed a dermal absorption efficiency in humans of 50% for pentachlorophenol in organic solvents and 10% for an aqueous solution of sodium pentachlorophenate. Dermal exposure is potentially an occupational problem; the general public is not expected to be exposed to pentachlorophenol via dermal contact. Santodonato (1986) suggested that dermal contact is the most important route of occupational exposure to pentachlorophenol because of the manner in which the compound is used (i.e., manual handling of solutions and treated materials) and its low vapor pressure. Workers such as carpenters, lumberyard workers, and loading-dock laborers who handle treated materials could be exposed continually via this route as well as by inhalation. The potential for dermal exposure to pentachlorophenol at hazardous waste sites is unknown.

The National Occupational Hazard Survey (NOHS), conducted by the National Institute for Occupational Safety and Health (NIOSH), estimated that 179,243 workers in 22,347 plants were potentially exposed to pentachlorophenol in the workplace in 1970 (NIOSH 1976). The largest numbers of exposed workers were employed in the following fields: general building contractors; special trade contractors; chemicals and allied products industries; electric, gas, and sanitary services; and medical and other health services industries.

Preliminary data from a second workplace survey, the National Occupational Exposure Survey (NOES) conducted by NIOSH from 1980 to 1983 indicated that 26,463 workers (including 3,916 women) in 1,490 plants employed in lumber and wood products, business services, wholesale trade, general building contractors, and chemicals and allied products industries were potentially exposed to pentachlorophenol in the workplace in 1980 (NIOSH 1984a). Most of these workers were pest controllers, electrical power installers and repairers, laborers, assemblers, carpenters, miscellaneous precision workers, janitors, engineers, and engineering technicians.

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**6.6 EXPOSURES OF CHILDREN**

This section focuses on exposures from conception to maturity at 18 years in humans. Differences from adults in susceptibility to hazardous substances are discussed in 3.7 Children's Susceptibility.

Children are not small adults. A child's exposure may differ from an adult's exposure in many ways. Children drink more fluids, eat more food, breathe more air per kilogram of body weight, and have a larger skin surface in proportion to their body volume. A child's diet often differs from that of adults. The developing human's source of nutrition changes with age: from placental nourishment to breast milk or formula to the diet of older children who eat more of certain types of foods than adults. A child's behavior and lifestyle also influence exposure. Children crawl on the floor, put things in their mouths, sometimes eat inappropriate things (such as dirt or paint chips), and spend more time outdoors. Children also are closer to the ground, and they do not use the judgment of adults to avoid hazards (NRC 1993).

Children are likely to be exposed to pentachlorophenol via the same routes that affect adults, such as inhalation of contaminated air, ingestion of contaminated groundwater used as a source of drinking water, ingestion of contaminated food, and dermal contact with contaminated soils or products treated with the compound. In addition, small children are more likely than adults to come into intimate contact with yard dirt, lawns, and house (carpet) dust. Dislodgeable pesticide residues in carpets or on uncovered floors may present a relatively important exposure route for infants and toddlers through dermal contact and oral ingestion. The tendency of young children to ingest soil, either intentionally through pica or unintentionally through hand-to-mouth activity, is well documented. These behavioral traits can result in ingestion of pentachlorophenol present in soil and dust. Though pentachlorophenol is known to:

- (1) adsorb to soil, especially at lower pH (Chang and Choi 1974; Choi and Aomine 1974; Kuwatsuka and Igarashi 1975);
- (2) have an insignificant rate of volatilization from soil (Kilzer et al. 1979); and
- (3) biodegrade at a moderately rapid rate, very little data are available on the actual measurements of pentachlorophenol in soil.

No studies are available that describe the dermal absorption of pentachlorophenol in children. Two studies are available, however, that show that absorption of pentachlorophenol occurs in both Rhesus monkeys and swine when dermally exposed to soil amended with pentachlorophenol (see Section 3.4.1.3). Therefore, it is possible that children may absorb pentachlorophenol dermally when exposed to soil contaminated with pentachlorophenol.

Hill et al. (1989) compared the amounts of chlorinated phenols and phenoxy acids found in the urine of 97 children living in the vicinity of a herbicide manufacturing plant to those found in the urine of a



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control group of 100 children living away from the herbicide plant. There was no significant difference in the amounts of pentachlorophenol or other herbicide residues detected in the two groups with the median pentachlorophenol concentration of 14 µg/L. This insignificant difference in the amounts of pentachlorophenol between the two groups indicated that the children living in the vicinity of the herbicide plant were not at a greater risk of exposure. Cline et al. (1989) measured the pentachlorophenol in the serum and urine of adults and children living in pentachlorophenol-treated log houses. The pentachlorophenol serum levels of children were found to average 1.8 times those of their parents. The mean concentrations were: (1) 2–5-year-old children, 600 µg/L; (2) 6–10-year-olds, 490 µg/L; (3) 11–15-year-olds, 370 µg/L; and (4) adults, 310 µg/L. The higher concentration of pentachlorophenol detected in children was attributed to their greater body surface-to-weight ratio and a higher respiratory rate as compared to adults. An East German study (Rehwagen et al. 1999), comparing urban versus rural exposure, detected a lower concentration of pentachlorophenol in the urine of children from the city of Leipzig than in the urine of children from the towns of Hettstedt, Wippa, Roitzsch, and Greppin. Although the inhalation of house dust was a possible source of exposure to pentachlorophenol, no correlation could be established between the amount of pentachlorophenol detected in the urine and the amount of pentachlorophenol in the house dust.

Pentachlorophenol was used extensively in treating wood. Today, though no longer used in treatment of wood products in residences and agricultural buildings, pentachlorophenol is still widely used in the treatment of utility poles and railroad ties. Playing near a utility pole such as a telephone or an electrical pole may pose a risk of dermal exposure. Pentachlorophenol is also known to volatilize from treated wood (Bunce and Nakai 1989) with emissions expected to be highest in the hottest months of the summer (Ingram et al. 1986). Therefore, low-level inhalation exposure may occur for children playing nearby. The soil samples, within a distance of 8 inches from the utility poles, were found to have a higher concentration of pentachlorophenol relative to those further away, indicating that leaching is occurring from their bases (Weinberg 1997). This indicated a downward migration of pentachlorophenol down the poles, which would result in a higher concentration in the lower sections. Higher than expected dermal exposure of children may, therefore, also occur since children may touch the lowest sections of utility poles while playing. Old and unpainted playground equipment constructed with pentachlorophenol-treated wood may be another mode of dermal exposure for children.

Lewis et al. (1994) conducted a nine-home pilot study to monitor the potential exposure of small children to pesticides in the residential environment. Pentachlorophenol was found to be one of the most frequently occurring pesticides and was detected in all of the samples in all nine houses irrespective of the

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age of the house (year of construction ranged from 1930 to 1989). The mean concentration of pentachlorophenol reported by the authors at various sites around a house is as follows: entryway soil, 0.03 µg/g; walkway soil, 0.02 µg/g; and play area soil, 0.02 µg/g. It was also detected in house dust, 0.83 µg/g; child hand rinse, 0.02 µg; and air, 0.05 µg/m<sup>3</sup>. No attempts were made by the authors to estimate the amounts of carpet dust or soil that the children who participated in the study may have ingested. The authors concluded that dust ingestion could constitute a substantial portion of a child's exposure to pesticides along with dermal absorption from house dust or yard soil.

A potential source of exposure in infants is the presence of pentachlorophenol in breast milk or formula. No data were located on the presence of pentachlorophenol in breast milk in the United States. However, in a study from Upper Bavaria, Gebefugi and Korte (1983) detected pentachlorophenol in 100% of the samples of breast milk, with a median concentration of 1.43 µg/kg. No significant sources of pentachlorophenol exposure were identified. In a more recent study from Bratislava, Slovakia (a city with a highly concentrated chemical industry and intensive agriculture), human milk obtained from 50 mothers was analyzed for the presence of chlorophenols (Veningerova et al. 1996). The median concentration of pentachlorophenol was found to be 2.21 µg/kg. The main source of pentachlorophenol exposure was through the ingestion of contaminated foods. No pesticide residues (including pentachlorophenol) were detected in ready to serve milk-based infant formula, with and without iron (Gunderson 1995b; Yess et al. 1993).

Van Langeveld (1975) reported levels of pentachlorophenol ranging from 10 to 270 µg/L in 9 out of 65 samples of children's paints in the Netherlands. It is not known whether these paints are imported into the United States. No data were available about the presence of pentachlorophenol in children's paints made in the United States.

Percutaneous pentachlorophenol absorption from the pentachlorophenol used in the laundry can be a significant source of pentachlorophenol exposure in infants. Smith et al. (1996) reported an occurrence of pentachlorophenol poisoning in newborn infants in St. Louis, Missouri during April–August 1967. The infants were exposed to pentachlorophenol through the diapers, which were rinsed in the hospital laundry room with an anti-mildew agent containing 22.9% sodium pentachlorophenate. Pentachlorophenol has, since then, been regulated as a restricted-use pesticide. It is not likely to be used in the laundry today.

Foods representative of the diets of eight different age/gender population groups, including children (6–11-month-old infants, 2-year-old children, and 14–16-year-old males and females), were prepared for

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consumption prior to analysis in a revision to the FDA's Total Diet Study methodology (Gunderson 1988). Estimated mean daily intakes (ng/kg/day) of pentachlorophenol for children in 1982–1984 were as follows: (1) 6–11-month-old infants, 59.0; (2) 2-year-old children, 48.5; (3) 14–16-year-old females, 16.2; and (4) 14–16-year-old males, 20.7. In comparison, the intake for adults ranged from 15.5 to 18.2 ng/kg/day. In a later survey of the Total Diet Study during 1986–1991, Gunderson (1995a) estimated mean daily intakes (ng/kg/day) of pentachlorophenol for these population groups as follows: (1) 6–11-month-old infants, 0.9; (2) 2-year-old children, 1.4; (3) 14–16-year-old females, 0.5; (4) 14–16-year-old males, 0.5; and (5) 25–30-year-old females, 0.8. In comparison, the intake for adults ranged from 0.7 to 0.8 ng/kg/day. A substantial reduction in the amount of pentachlorophenol in the estimated mean daily intake has been observed since the 1982–1984 study. No data are available for the exposure to and the effect of pentachlorophenol through specific food sources such as fish, animal products, cereals, etc. FDA also tested the presence of pesticide residues in a variety of infant and adult foods eaten by infants and children (Yess et al. 1993). Since whole and unpeeled fruits and vegetables were tested, the results were not indicative of pesticide residues in foods as consumed. Pentachlorophenol was found in plain milk (6.5% of the samples, maximum residue of 100 ppb), vitamin D milk (3% of the samples, maximum residue of 20 ppb), pork (7% of the samples, maximum residue of 6 ppb), grape jelly (4% of the samples, maximum residue of 4 ppb), raw pears (4% of the samples, maximum residue of 7 ppb), and in canned, evaporated milk (7% of the samples, maximum residue of 7 ppb). No data are available on children and their weight-adjusted intake of pentachlorophenol.

The children of pesticide applicators who use pentachlorophenol may potentially be exposed to elevated levels from contact with their parents' skin, hair, work clothes, and/or other workplace objects. In addition, pentachlorophenol adsorbed onto the parent or the parent's clothing may contaminate household objects when they come in contact with them, potentially exposing children to pentachlorophenol. Although pentachlorophenol is a restricted-use pesticide and is only supposed to be used by an EPA-certified applicator for specified uses, there have been instances in which children were exposed to pesticides (methyl parathion) from the illegal application of pesticides. No monitoring data are available on this route of exposure to pentachlorophenol.

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**6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES**

Pentachlorophenol levels in human tissues are much higher in occupationally exposed groups than in the general public. Populations with potentially high exposure include individuals involved in the manufacture and use of the compound. Residents near pentachlorophenol manufacturing plants and waste water treatment sludge disposal sites may also be exposed to the chemical at higher concentrations than the general public. Residents around the 313 NPL sites known to have pentachlorophenol contamination may also be exposed to the chemical at higher levels ( $>1,000 \mu\text{g/kg}$ ) in contaminated environmental media.

Pentachlorophenol is found as a residue in treated wood that has been preserved with this chemical. Examples of consumer items containing pentachlorophenol-treated wood have included boats, furniture, and log homes. In fact, some families living in homes historically treated with pentachlorophenol have been reported to have symptoms of chronic exposure (Jagels 1985). Since the compound is no longer used in the treatment of wood products for log homes, outdoor furniture, or playground equipment, human exposure from these sources is probably limited to contact with materials treated in the past.

**6.8 ADEQUACY OF THE DATABASE**

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of pentachlorophenol is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of pentachlorophenol.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

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**6.8.1 Identification of Data Needs**

**Physical and Chemical Properties.** The physical/chemical properties of pentachlorophenol are well characterized and allow the prediction of the environmental fate of the compound (see Chapter 4). Estimates of the distribution of pentachlorophenol in the environment based on available constants (e.g., water solubility, Log  $K_{ow}$ , Log  $K_{oc}$ , vapor pressure) are generally in good agreement with experimentally determined values. No additional studies are required at this time.

**Production, Import/Export, Use, Release, and Disposal.** Pentachlorophenol is currently being produced by only one manufacturer (SRI 1998). Current production volume data are not available; however, it is known that production volumes steadily decreased from 45 million pounds in 1983 (Mannsville 1987) to 9.1 million pounds in 1996 (IARC 1999). No recent data are available on the production, export, and use volumes of pentachlorophenol. In the past, pentachlorophenol was one of the most heavily used pesticides in the United States but is now regulated as a restricted use pesticide (CELDS 1992; EPA 1984b). The compound is found in all environmental media (air, soil, and water) as a result of its past widespread use. The only disposal method located in the literature is incineration, which releases polychlorinated dibenzo-*p*-dioxins and dibenzofurans at unspecified levels (Karasek and Dickson 1987). Disposal of pentachlorophenol is subject to EPA restrictions (EPA 1991, 1992).

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The TRI, which contains this information for 1999, became available in 2001. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

**Environmental Fate.** Information on environmental fate of pentachlorophenol is sufficient to permit a general idea of transport and transformation of the chemical in the environment. Atmospheric or vapor-phase pentachlorophenol is expected to photolyze at an estimated (midday in summer at 40 EN) maximum rate of 6.2% per hour, and to degrade through reactions with hydroxyl radicals at an estimated (midday in summer) loss rate of 1.5% per hour (Bunce and Nakai 1989). Meylan and Howard (1993) estimated a half-life of 58 days for the vapor-phase reaction of pentachlorophenol with hydroxyl radicals. However, the data need still exists for actual rates of vapor-phase photolysis and atmospheric degradation due to hydroxyl radical attack. Volatilized pentachlorophenol may also be lost from the atmosphere through deposition. The compound is expected to partition to soils and sediment (Kuwatsuka and Igarashi 1975), and to be transported in surface water and groundwater (Davis et al. 1994; Mohammed et al. 1998).

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Pentachlorophenol is transformed by photolysis in water, with half-lives of 3.5 hours (pH 7.3) to 100 hours (pH 3.3) under UV light and a half-life of 48 hours (pH 7.3) in sunlight (Wong and Crosby 1981). Aqueous photolysis of the compound occurs more rapidly at the water surface (half-life of 0.7 hours at 0.5-cm depth), with attenuated rates occurring at greater depths in the water column (half-life of 9.6 hours at 13.8-cm depth; Pignatello et al. 1983). Pentachlorophenol does not photolyze to a significant extent in soils, but may be photolyzed at the soil surface (top 0.5 mm) when near-saturated conditions exist; total degradation in near-saturated irradiated soils was 55% greater than in the dark controls (Donaldson and Miller 1997). Additional information on soil photolysis rates at various soil moisture contents may be helpful in determining the potential for degradation of the compound at sites with pentachlorophenol-contaminated areas which are flooded intermittently. A more important mechanism for the transformation of pentachlorophenol in soils is the adsorption of the compound to soil mineral particles and soil organic matter. Pentachlorophenol is a weakly acidic compound (pKa of 4.74) that is adsorbed to the largest extent under acidic soil conditions (where it is present in the unionized form which it is less soluble in water), and has greater mobility in neutral or alkaline soils where it is present as the phenolate anion (Kuwatsuka and Igarashi 1975). Maximum adsorption has been reported at soil pH values of 4.6–5.1, with no adsorption above pH 6.8; at a given pH, adsorption increases with increasing organic matter content (Choi and Aomine 1974). In aquifers, the retardation or decreased mobility of the compound has been observed to be greater in areas of lower pentachlorophenol concentrations (<0.04 mg/L) than in areas of high concentrations (>1 or 10 mg/L; Davis et al. 1994). Although it was determined in previously conducted studies of natural sediments and aquifer materials that the adsorption of pentachlorophenol was highly dependent on the organic matter content of the adsorbent, with an average  $K_{oc}$  of 32,900 measured (Schellenberg et al. 1984), the use of normalized partition coefficients ( $K_{oc}$ ) do not accurately predict the adsorption of ionizable compounds such as pentachlorophenol since the adsorption of such does not increase linearly with the increasing concentration of the compound (Christodoulatos et al. 1994). For this reason, the need exists for a more accurate means of measuring and/or interpreting the potential mobility of pentachlorophenol in aquifers and in surface soils which are either intermittently subjected to flooding or are in contact with overland runoff. Because the presence of alcohols and petroleum compounds such as oils and kerosene (all of which are utilized as cosolvents in the application of pentachlorophenol) may decrease the adsorption of pentachlorophenol in soils (Christodoulatos et al. 1994; Jackson and Bisson 1990), and because pentachlorophenol has also been observed to desorb more readily from contaminated soils in the presence of compounds such as methanol (You and Liu 1996), there is a need for data that indicate the potential mobility of pentachlorophenol when it is present in the soil or water in combination with such cosolvents. Additionally, data are necessary on the adsorption of pentachlorophenol when it is present in combination with other

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contaminants expected to occur in the same environment. Biodegradation is another major mechanism for the transformation of pentachlorophenol in the environment (Englehardt et al. 1986; McAllister et al. 1996; Pignatello et al. 1983). In water, pentachlorophenol may be biodegraded with observed first half-lives of less than 1 month following acclimation periods of 5–7 weeks; the presence of sediment generally decreases the acclimation period (Ingerslev et al. 1998; Pignatello et al. 1985). The biotransformation of pentachlorophenol in groundwater, and possibly in surface water may not be significant in the absence of nonacclimated microbial populations. Decreases in the observed aqueous concentration of the compound may be attributed to adsorption to sediment or particulate material rather than to degradation of the compound (Mohammed et al. 1998). Additional information, such as biodegradation half-lives in both surface water and groundwater, is necessary to evaluate the potential for the degradation of the compound in water that is not in contact with sediment, rock, or macrophyte surfaces and where acclimated microbial populations do not exist. In soils, biodegradation of pentachlorophenol is generally rapid, with half-lives of 2–4 weeks. The metabolism of the compound is more rapid in soils with acclimated microbial populations (Kaufman 1978). Biodegradation of pentachlorophenol and aged residues of the compound occurs in both aerobic and anaerobic soils, usually following an acclimation period, but may occur more completely and rapidly in aerobic soils (Frisbie and Nies 1997). In other studies, biodegradation of the compound was observed to be more rapid in anaerobic environments (Ide et al. 1972; Kuwatsuka and Igarashi 1975). McAllister et al. (1996) reported that there are multiple pathways for the biodegradation of pentachlorophenol, which differ according to the microbial populations present in the soil. While the biodegradation of pentachlorophenol has been studied extensively, there may still be a need for data that elucidate the effect of anaerobic environments (and alternating aerobic/anaerobic environments) on the rate and extent of the degradation of the compound and its metabolites. Additionally, information on the uptake and transformation of the compound in plants is necessary to improve the current understanding of pentachlorophenol's environmental fate; currently existing data on plant uptake and transformation are inconsistent between studies and are inconclusive with regard to the ability of specific plants to remove the compound from the soil (McAllister et al. 1996).

**Bioavailability from Environmental Media.** Pentachlorophenol is readily and completely absorbed following inhalation (Casarett et al. 1969; Cline et al. 1989; Hosenfeld et al. 1986; Jones et al. 1986), oral (Braun et al. 1979; Uhl et al. 1986), and dermal exposure (Hosenfeld et al. 1986; Qiao et al. 1997; Wester et al. 1993). Using Rhesus monkeys, Wester et al. (1993) demonstrated the dermal absorption from pentachlorophenol-treated soil. It was also shown that when [ $^{14}\text{C}$ -UL]-pentachlorophenol in a soil-based mixture was applied occlusively or nonocclusively to a clipped 7.5-cm<sup>2</sup> abdominal site of 8 to 10-week-old female pigs, total radiolabel absorption was 29.08% under nonocclusive conditions and

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100.72% under occlusive conditions 408 hours after dosing (Qiao et al. 1997). Additional information on the bioavailability of pentachlorophenol adsorbed to soils would be helpful in assessing the relative importance of ingestion of contaminated soils as a potential route of human exposure. Additional information is also necessary on the desorption of the compound from soils when the soil pH is altered or when pentachlorophenol-contaminated soil comes into contact with cosolvents (such as alcohols or petroleum compounds), which may enhance desorption and/or increase the solubility of pentachlorophenol. Cline et al. (1989) detected elevated levels of pentachlorophenol in the urine of log-home residents. They believed inhalation to be the most likely route of exposure. Additional information is required to correlate the presence of pentachlorophenol in contaminated air and the exposure via inhalation.

**Food Chain Bioaccumulation.** The log  $K_{ow}$  of pentachlorophenol presented in Chapter 4 is 5.01, suggesting that pentachlorophenol is likely to bioaccumulate. However, the extent of bioaccumulation will depend on the pH of the medium since pentachlorophenol converts at higher pH levels to the more water-soluble pentachlorophenate anion. Pentachlorophenol is bioconcentrated by terrestrial and aquatic organisms (EPA 1986c; Makela et al. 1991; Smith et al. 1990). However, biomagnification of the compound in terrestrial and aquatic food chains has not been demonstrated as a result of the fairly rapid metabolism of the compound by exposed organisms (Niimi and Cho 1983). BCF values of 218 (whole fish) to 1,633 (fish lipid basis) for juvenile American flagfish were demonstrated by Smith et al. (1990). The half-life of pentachlorophenol in the tissues was reported to be about 16 hours. The food chain bioaccumulation potential of pentachlorophenol can currently be characterized without generating additional data.

**Exposure Levels in Environmental Media.** Pentachlorophenol has been detected in ambient air, surface water, drinking water, soils, and foods. Estimates of dietary intake of the compound have been made by the World Health Organization (WHO 1987), EPA (EPA 1978a), and FDA (FDA 1989; Gunderson 1988). In a comparison of the 1986–1991 study to the 1982–1984 study, Gunderson (1995a) observed a substantial reduction in the amount of pentachlorophenol in the estimated mean daily intake. Lewis et al. (1994) detected low levels of pentachlorophenol in air, dust and soil in a nine-home (year of construction ranged from 1930 to 1989) pilot study to monitor the potential exposure of small children to pesticides in the residential environment. Further monitoring is required to be able to evaluate the risk of exposure from pentachlorophenol-treated wood in homes. Limited information is available regarding the levels of pentachlorophenol in air in the United States. More ambient monitoring data of air is required to estimate the exposure of the general population via inhalation of pentachlorophenol in the 1990s.



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Contemporary monitoring studies demonstrating the presence or absence of pentachlorophenol in various sources of surface and drinking water are also needed.

Reliable monitoring data for the levels of pentachlorophenol in contaminated media at hazardous waste sites are needed so that the information obtained on levels of pentachlorophenol in the environment can be used in combination with the known body burden of pentachlorophenol to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites.

**Exposure Levels in Humans.** Pentachlorophenol has been measured in blood (NHANES III) (Ferreira et al. 1997; NHANES II), urine (Barbieri et al. 1995; Bevenue et al. 1967; Colosio et al. 1993a; Ferreira et al. 1997; Hill et al. 1989, 1995; Thompson et al. 1994, 1996; Treble and Thompson 1996), cerebrospinal fluid (Jorens et al. 1991), and tissues of humans (Bevenue et al. 1967). Quantitative data that correlate varying levels in the environment with levels in body fluids and health effects are not available. One study exists for residents of log homes treated with pentachlorophenol; levels in blood and urine were highly correlated with levels in indoor air (Lewis et al. 1994). Additional information on exposure levels for populations living near hazardous waste sites would be helpful. Information regarding the exposure levels for populations near pentachlorophenol-treated utility poles would be useful. This information is necessary for assessing the need to conduct health studies on these populations.

**Exposures of Children.** No monitoring studies have been performed to investigate the exposure to and the body burden of pentachlorophenol in children. No studies are available on the dermal absorption of pentachlorophenol in infants and toddlers due to activities such as crawling, which will result in contact with the floor (carpet) and soil. Since pentachlorophenol is likely to be adsorbed to these materials, more information would allow the estimation of a child's exposure to pentachlorophenol to be more rigorously determined. A pilot study measured the amounts of pentachlorophenol in dust and soils that are found in areas where children may play, such as carpets and playgrounds (Lewis et al. 1994). As part of the FDA total diet study, mean daily intake of pentachlorophenol by 6–11-month-old infants, 2-year-old children, and 14–16-year-old males and females were determined (Gunderson 1995a). Studies dealing with the weight-adjusted intake of pentachlorophenol by children would help in assessing the effects of pentachlorophenol in children. No studies are available on the amounts of pentachlorophenol present in the breast milk of women in the United States. The estimation of the amounts of soil and house dust that are ingested by children needs to be determined. No information is available on the exposure of

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children to pentachlorophenol from the parent's body, work clothes, and other objects from work. Studies are required to identify childhood-specific means of decreasing exposure to pentachlorophenol.

Child health data needs relating to susceptibility are discussed in 3.12.2 Identification of Data Needs: Children's Susceptibility.

**Exposure Registries.** No exposure registries for pentachlorophenol were located. This substance is not currently one of the compounds for which a subregistry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for subregistries to be established. The information that is amassed in the National Exposure Registry facilitates the epidemiological research needed to assess adverse health outcomes that may be related to exposure to this substance.

### 6.8.2 Ongoing Studies

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environment Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control and Prevention, will be analyzing human urine samples for pentachlorophenol and other phenolic compounds. These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.

The U.S. Department of Agriculture is sponsoring several studies on the degradation, adsorption, and uptake of pentachlorophenol. At the Agricultural Research Service, Fargo, North Dakota, research is being conducted to identify and quantitate residues of chlorinated organics (congeners of dioxins, furans, and polychlorinated biphenyls) in beef, milk, and animal feeds, particularly forages. In another study at Ohio Agricultural Research and Development Center, Wooster, Ohio, models for the transport of dioxins that are contained in feed and in other environmental matrices to beef that is intended for human consumption are being developed. At Xenometrix, Inc., research is being focused on the microbial dehalogenation of pentachlorophenol by *Flavobacterium*. Researchers at University of Florida, Gainesville, Florida, are studying the soil processes that regulate the fate of chlorophenols in wetlands. Research is underway at Forest and Wildlife Research Center, Mississippi, to develop a rapid biological technique for cleanup of organic wood preservatives in groundwater using oxygen, surfactants, cofactors, and micronutrients; and to evaluate different commercial surfactants for enhancing the biodegradation of wood-preserving process water containing high concentrations of pentachlorophenol, polyaromatic

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hydrocarbons, oil, and grease. At Texas A&M University, College Station, Texas, research is being conducted to develop a method for dechlorinating pentachlorophenol from contaminated water and soil, and to refine the use of bioassays as monitoring tools to assess the changes in toxicity occurring as a result of remedial activities at Superfund waste sites. At Oregon State University, Corvallis, Oregon, researchers are working on determining the effects of estrogenic environmental pollutants on chemical carcinogenesis using rainbow trout as a model system.

In a study sponsored by the National Institute of General Medical Sciences, at University of Colorado, Boulder, Colorado, research is being performed to determine the mechanism of the enzyme, tetrachloro-hydroquinone dehalogenase, that plays a critical role in biodegradation of pentachlorophenol. A similar study, sponsored by National Science Foundation, investigating the role of tetrachloro-1,4-hydroquinone dehalogenase in the degradation of pentachlorophenol is underway at University of Colorado, Boulder, Colorado. The biochemistry of 2,4,5-trichlorophenoxyacetate and pentachlorophenol is being investigated in a National Science Foundation sponsored study at Washington State University, Richland, Washington.

In addition, ongoing remedial investigations and feasibility studies at NPL sites known to be contaminated with pentachlorophenol should add to the available database for environmental levels, environmental fate, and human exposure.



## 7. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring pentachlorophenol, its metabolites, and other biomarkers of exposure and effect to pentachlorophenol. The intent is not to provide an exhaustive list of analytical methods. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used for environmental samples are the methods approved by federal agencies and organizations such as EPA and the National Institute for Occupational Safety and Health (NIOSH). Other methods presented in this chapter are those that are approved by groups such as the Association of Official Analytical Chemists (AOAC) and the American Public Health Association (APHA). Additionally, analytical methods are included that modify previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

### 7.1 BIOLOGICAL MATERIALS

Exposure to pentachlorophenol is most commonly evaluated by analysis of urine, blood, feces, or adipose or other tissues, using gas chromatography (GC) combined with electron capture detection (ECD) or high-performance liquid chromatography (HPLC) combined with ultraviolet (UV) detection. Recovery is generally high and sensitivity using GC/ECD and HPLC/UV is in the parts per billion (ppb) range. Some efforts are currently in development to detect pentachlorophenol metabolites in urine as a biological marker.

Many purification schemes take advantage of the fact that pentachlorophenol is a weak organic acid. These methods involve extracting the compound into the organic phase under acidic conditions, and/or extracting into alkaline solution as phenolate salts (Chou and Bailey 1986; EPA 1986b). Thus, the standard methods involve multiple extractions, with potential for sample loss; some of these methods derivatize pentachlorophenol prior to analysis (EPA 1980b; NIOSH 1984b). Derivatization often involves diazomethane or diazoethane, which are toxic substances (Bevenue et al. 1968; Holler et al. 1989; Morgade et al. 1980; Shafik 1973; Wagner et al. 1991). Recent methods have tried to simplify the purification scheme and avoid using toxic chemicals for derivatization (Maris et al. 1988).

In an effort to use less toxic materials, blood and urine samples were derivatized with acetic anhydride (Needham et al. 1981). The detection limit was 1–2 ppb using GC/ECD. Penta- and tetrachlorophenols were analyzed simultaneously in urine using HPLC (Pekari and Aito 1982). This method was used for

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3 years in Finland in the biological monitoring of workers exposed to chlorophenols. It is more rapid than GC and does not involve the use of chemicals such as benzene, diazomethane, or pyridine, which pose health risks to the analyst. A rapid extraction method followed by GC/ECD had a detection limit of 0.5 ppb (Kalman 1984).

Because pentachlorophenol exists in urine as both free pentachlorophenol and conjugated pentachlorophenol (glucuronide and sulfate), hydrolysis of urine is necessary to determine total pentachlorophenol (Edgerton and Moseman 1979; Pekari et al. 1991). Acid hydrolysis is preferable to enzymatic hydrolysis because the pentachlorophenol metabolite TCHQ is an inhibitor of  $\beta$ -glucuronidase (Drummond et al. 1982). Although pentachlorophenol and other chlorinated phenols are stable in frozen urine samples, they are degraded by repeated thawing and refreezing (Edgerton 1981). Acid hydrolysis followed by reverse phase HPLC/UV and GC/ECD have been used to measure total pentachlorophenol in urine of people occupationally exposed to pentachlorophenol (Drummond et al. 1982; Pekari et al. 1991). The detection limits for HPLC/UV and GC/ECD were 0.20 and 0.01 ppm, respectively, which are sufficiently sensitive to detect occupational exposure. Using a simplified method without derivatization, total pentachlorophenol and free pentachlorophenol were measured in plasma and urine, with a detection limit of 1.5 pg (Rick et al. 1982). This modification shortens analysis time and allows the use of GC/ECD, which increases sensitivity.

The pentachlorophenol metabolites, TCHQ and tetrachloropyrocatechol, were identified in human urine samples using GC/MS (Edgerton et al. 1979). The detection limit was 1 ppb and recovery was about 95%. Pentachlorophenol and TCHQ were also detected using a cheaper GC/ECD method following a simple extraction (Reigner et al. 1990), but the detection limit was at least 50 ppb.

Negative chemical ionization (NCI) mass spectrometry (MS) was used to detect pentachlorophenol in human serum (Kuehl and Dougherty 1980). The NCI mass spectrometer was reported to be uniquely suited for screening partially purified samples. High sensitivity was obtained by dansylating purified compound and using HPLC/UV detection (de Ruiter et al. 1990).

Hexane extraction, cleanup on thin layer chromatography (TLC) plates, and HPLC/UV detection were used to isolate and characterize pentachlorophenol in human fat, demonstrating that pentachlorophenol is present in human adipose tissue as an ester of palmitic acid (Ansari et al. 1985). Fatty acid conjugates of pentachlorophenol and other chlorinated phenols could be separated by reverse-phase HPLC (Kaphalia 1991). TLC followed by GC/ECD was used to analyze pentachlorophenol in adipose tissue (Ohe 1979).

## 7. ANALYTICAL METHODS

GC/ECD has been used to quantify pentachlorophenol residues in tissues (Wagner et al. 1991). The sensitivity of this method is in the sub-ppm range; >100% recoveries were obtained. GC/MS (NCI) was then used to confirm the identity of the pentachlorophenol residues in the samples. Precision data were not reported.

Analytical methods for determining pentachlorophenol in biological fluids and tissues are shown in Table 7-1.

## 7.2 ENVIRONMENTAL SAMPLES

Concerns about contamination of environmental media, plants, and animals with pentachlorophenol have led to the need for more rapid, sensitive, and selective methods of analysis. As with biological samples, the most common methods of analysis are GC/ECD, high resolution gas chromatography (HRGC)/ECD, and HPLC/UV detection. Under EPA's Contract Laboratory Program for semivolatiles such as pentachlorophenol, the Contract Required Quantitation Levels (CRQL) for water and low soil sediments are 50 mg/L (50 ppm) and 160 mg/kg (160 ppm), respectively (EPA 1986a). Methods are available that detect pentachlorophenol in water or sediment at the 1–10-ppb range.

Pentachlorophenol could be detected in marine water at concentrations ranging from 0.2 to 200 ppb in volumes as small as 5 mL using a simplified monitoring procedure with HPLC/UV detection (Giam et al. 1980). This method reduces costs and analysis time, and can also be used in other aquatic toxicity studies. Differential pulse polarography was used for direct determination of trace amounts of pentachlorophenol (Wade et al. 1979). It was demonstrated that pentachlorophenol is electrochemically reduced and direct determinations are possible at levels as low as 0.27 ppm. HPLC/UV was used to distinguish among 10 different phenolic compounds at mg/L levels in water (Realini 1981). HPLC/UV was also used to measure chlorinated phenols in surface-treated lumber and to distinguish between tetra- and pentachlorophenol (Daniels and Swan 1979). Automated HPLC is 10 times faster than wet chemical techniques. Once the method for analysis has been established and tested thoroughly, the HPLC method requires neither extensive pretreatment nor highly trained laboratory personnel (Ervin and McGinnis 1980).

For relatively clean water samples, HPLC offers a rapid and sensitive method, but its advantages are lost when a complex matrix such as municipal waste water has to be analyzed (Buisson et al. 1984). The resolution possible with capillary gas chromatography and the selectivity of the ECD towards halogenated

**Table 7-1. Analytical Methods for Determining Pentachlorophenol and Metabolites in Biological Samples**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood	Add sulfuric acid. Extract with hexane, derivatize with diazomethane, elute pentachloroanisole from alumina with benzene/hexane	GC/ECD	1 µg/L	90%	NIOSH 1984b (Method 8001)
Blood	Extract with benzene and convert PCP to its methyl ether derivative	GC/ECD	10 µg/L	92%	EPA 1980b
Blood	Add H <sub>2</sub> SO <sub>4</sub> and benzene to the sample and stir while heating; centrifuge; collect benzene layer, evaporate and add diazomethane to make methyl ether derivative	GC/ECD	20 µg/L	87–100%	Bevenue et al. 1968
Blood	Add benzene and conc H <sub>2</sub> SO <sub>4</sub> to the sample and rotate. Transfer benzene layer and add methylating agent and vortex. Dilute with isooctane or hexane.	GC/ECD	No data	No data	EMMI 1997
Serum	Acidify with phosphoric acid; elute from reverse phase column with dichloromethane; dansylate; concentrate	LC/UV	0.4 ppb	85%	de Ruiter et al. 1990
Serum	Acidify sample to pH 1 with hydrochloric acid; extract with dichloromethane; concentrate; derivatize with diazoethane; cleanup using silica gel	GC/ECD	30.0 µg/L	99%	Morgade et al. 1980



**Table 7-1. Analytical Methods for Determining Pentachlorophenol and Metabolites in Biological Samples (*continued*)**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Serum, urine	Acidify to pH 2 with HCl, digest at 100EC, extract with toluene	GC/ECD	0.5 µg/L	105% (urine); 80% (serum)	Kalman 1984
Plasma, urine	Sample collected into tubes containing EDTA and ascorbic acid; plasma mixed with citrate buffer, pH 3, extracted with diethyl ether, and concentrated. Urine was buffered with phosphate buffer pH 7.4 and processed as above	GC/ECD	100 µg/L (urine); 50 µg/L (plasma)	89-93%	Reigner et al. 1990
Urine	ADD HCl and NaHSO <sub>4</sub> , extract with benzene, derivatize with diazomethane, add hexane; elute pentachloroanisole from alumina with benzene/hexane	GC/ECD	1 µg/L	94.7%	NIOSH 1984b (method 8303)
Urine	Acidify urine; hydrolyze; extract with benzene; methylate phenolic group	GC/ECD	5 µg/L	90%	EPA 1980b
Urine	Add HCl to sample; boil; extract with hexane/isopropanol; centrifuge; dry; collect residue in methanol/water	HPLC/UV	26 ppb	84%	Pekari and Aitio 1982
Urine	Add HCl to sample; boil; extract with hexane/isopropanol; centrifuge; back extract to basic borate buffer; derivatize with acetic acid anhydride and pyridine	GC/ECD	10 µg/L	No data	Pekari et al. 1991
Urine	Acidify with HCl; boil; add Na bisulfite; centrifuge; extract with benzene	GC/ECD	<1 µg/L	91–97%	Edgerton et al. 1979

**Table 7-1. Analytical Methods for Determining Pentachlorophenol and Metabolites in Biological Samples (*continued*)**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine	Add H <sub>2</sub> SO <sub>4</sub> ; collect distillate and add NaCl and NaOH; acidify aqueous layer; extract with methylene chloride	RPHPLC/UV	200 ppb	>85%	Drummond et al. 1982
Urine	Add HCl to sample; extract twice with benzene; add hexane	GC/ECD	<10 pg	88%	Siqueina and Fernicola 1981
Urine	Add internal standard to sample; mix	HPLC/UV	250 µg/L	89–96%	Chou and Bailey 1986
Urine	Acidify with H <sub>2</sub> SO <sub>4</sub> ; extract with hexane	GC/ECD	1.5 pg	102%	Rick et al. 1982
Urine	Acid hydrolysis; extract with benzene; derivatize with diazoethane; column cleanup	MS (NCI)	1 µg/L	- 100%	Holler et al. 1989
Urine	Add NaHSO <sub>4</sub> , acidify with HCl, boil, add more NaHSO <sub>4</sub> , extract with benzene, concentrate, column clean-up	GC/ECD	No data	No data	EMMI 1997
Body fluids	Acidify sample and extract with hexane; add acetic anhydride; wash with boric acid / NaOH	GC/ECD	1–2 µg/L	No data	Needham et al. 1981
Human semen and adipose tissue	Macerate sample/tissue with sulfuric acid, complete steam distillation into 2,2,4-trimethylpentane; concentrate organic layer	MS (NCI)	low ng	>90%	Kuehl and Dougherty 1980

**Table 7-1. Analytical Methods for Determining Pentachlorophenol and Metabolites in Biological Samples (*continued*)**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Adipose tissue	Grind tissue; add hexane; add NaOH; extract with hexane; add concentrated HCl; extract with diethyl ether; mix; add diazoethane; concentrate; add hexane and anhydrous sodium sulfate; analyze hexane layer	GC/ECD	5 ppb	75%	Shafik 1973
Adipose tissue	Homogenize sample; rehomogenize in hexane; combine supernatants; separate extracted fat on TLC; scrape appropriate area and suspend in hexane; evaporate	GC/ECD	5 ppb	85–98%	Ohe 1979
Adipose tissue	Add hexane; homogenize; add aqueous sodium hydroxide; extract with hexane; add diethyl ether; extract; derivatize with diazoethane	GC/ECD	140 ppb	91%	Morgade et al. 1980
Feces	Collect sample into tubes containing EDTA and ascorbic acid; acidify in warm sulfuric acid, extract with diethyl ether; concentrate	GC/ECD	100 ppb	No data	Reigner et al. 1990
Liver	Homogenize, incubate with sulfuric acid at 100°C; extract with hexane/toluene	LC/ECD	1.5 ppb	60–70%	Maris et al. 1988

**Table 7-1. Analytical Methods for Determining Pentachlorophenol and Metabolites in Biological Samples (*continued*)**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Fat, liver muscle, serum	Fat: homogenize with HCl; extract with ethyl acetate-hexane; elute from florisil chlorophenol with methanol-chloroform	RPHPLC/UV	<100 ppb	73–108% maximum	Mundy and Machin 1981
	Other tissues: homogenize; reflux with Na <sub>2</sub> SO <sub>4</sub> and NaOH; add TBAH and ether extract; concentrate extract; elute from silica column with methanol chloroform				
Tissues (testes, kidney, prostate, liver and omentum fat)	Homogenize tissue sample, extract with hexane/propanol and centrifuge; remove hexane layer; repeat extraction twice; partition into potassium hydroxide; acidify aqueous layer; extract with hexane; derivatize with diazomethane; cleanup on Florisil column; elute with hexane; additional clean up on activated silica gel column; elute with benzene in hexane	GC/ECD; GCMS (NCI)	4 ppb	115%	Wagner et al. 1991

ECD = electron capture detection; EDTA = ethylenediaminetetraacetic acid; GC = gas chromatography; HCl = hydrochloric acid; HPLC = high-performance liquid chromatography; H<sub>2</sub>SO<sub>4</sub> = sulfuric acid; LC = liquid Chromatography; MS = mass spectrometry; Na = sodium; NaCl = sodium chloride; NaHSO<sub>4</sub> = sodium bisulfite; NaOH = sodium hydroxide; Na<sub>2</sub>SO<sub>4</sub> = sodium sulphate; NCI = negative chemical ionization; PCP = pentachlorophenol; RPHPLC = reverse phase high performance liquid chromatography; TBAH = tetrabutylammonium hydroxide; TLC = thin layer chromatography

## 7. ANALYTICAL METHODS

compounds make HRGC/ECD the method of choice for the detection and quantification of chlorinated phenols at trace levels in complex matrices. Derivatization with a halogen-containing reagent enhances the ECD response. For measuring pentachlorophenol in waste water using HRGC/ECD, sensitivity is in the ppt range. Recoveries are adequate and precision is good.

Similar results were obtained in a comparison of HPLC and GC techniques for determination of pentachlorophenol in animal materials (Mundy and Machin 1981). Pentachlorophenol could be separated from acidic pesticides and other organic acids possibly present in a mill effluent by extraction with an acetylating agent (Rudling 1970). A similar single step extraction and acetylation procedure was used to determine several chlorinated phenolic compounds in paper mill effluent without interference (Lee et al. 1989). GC/MS has been used to measure pentachlorophenol in honey (Muiño and Lozano 1991). This method is simple, accurate, and rapid. Sensitivity is in the low-ppb range. Good recoveries (84–102%) and precision (2.8–6.3% relative standard deviation ([RSD])) were obtained.

A study comparing several methods for rapidly extracting pentachlorophenol from water or soil reported high recovery from all methods using HPLC/UV (Wall and Stratton 1991). A method combining extraction with derivatization by acetic anhydride had a detection limit of about 0.1 ppb for GC/ECD (Xie 1983).

Immunochemical personal exposure monitors (PEMs) are currently being developed for assaying pentachlorophenol sampled from ambient air (Hall et al. 1992). This method is highly selective and involves direct, antibody-based sampling of analytes from air with subsequent quantitation of the analyte by enzyme immunoassay. The lower limit of detection for measuring pentachlorophenol in the assay is approximately 0.5 ng/mL. Recovery and precision data were not reported.

Methods for analyzing pentachlorophenol in environmental samples are shown in Table 7-2.

### 7.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of pentachlorophenol is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a

**Table 7-2. Analytical Methods for Determining Pentachlorophenol and Metabolites in Environmental Samples**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Stack samples	Extract sample with hexane; derivatize with acetic anhydride, collect organic layer; concentrate	GC/MS	No data	80–104%	Cuiu et al. 1986
Air	Air samples collected in PEMs; analyte diffuses across semipermeable membrane into antibody reservoir; analyte is bound by antibody in PEM; antibody is removed from PEM device and quantified by enzyme immunoassay	ELISA	0.5 ng/mL	No data	Hall et al. 1992
Air	Air samples collected in ethylene glycol contained in bubbler using sampler pump, add methanol	GC/UV	8 µg/sample	No data	NIOSH 1994
Waste water	Acidify waste water sample with H <sub>2</sub> SO <sub>4</sub> ; extract with chloroform	HPLC/UV	11 µg/L	No data	Ervin and McGinnis 1980
Water	Acidify sample with HCl extract with methylene chloride	HPLC/UV	1 µg/L	90%	Realini 1981
Water, mill effluent	Acidify sample with H <sub>2</sub> SO <sub>4</sub> ; extract with hexane; extract organic phase with borax; add hexane, acetylate, and analyze the organic phase	GC/ECD	0.1 µg/L	84–93%	Rudling 1970
Pulp mill effluent	Extract onto solid phase sorbents; elute with acetonitrile	LC-ED	No data	>100%	Butler and Dal Pont 1992

**Table 7-2. Analytical Methods for Determining Pentachlorophenol and Metabolites in Environmental Samples (*continued*)**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Marine water	Take 5 mL water and acidify with H <sub>2</sub> SO <sub>4</sub> ; extract with petroleum ether/diethyl ether; evaporate solvent; dissolve residue in CH <sub>3</sub> CN; measure at 254 nm	HPLC/UV	0.2 µg/L	84%	Giam et al. 1980
Drinking water	Acidify water sample; extract with dichloromethane and hexane; derivatize with diazoethane; cleanup on silica gel	GC/ECD	300 ng/L	64%	Morgade et al. 1980
Waste water	Acidify to pH <2; extract with methylene chloride; exchange into 2-propanol. For ECD, derivatize with pentafluorobenzyl bromide	GC/FID GC/ECD	7.4 µg/L 0.59 µg/L	36–134% 36–134%	EPA 1986b (Method 8040)
Water and waste water	Homogenize with dichloromethane; cleanup by sample concentration; back extract with alkali; derivatize by extractive alkylation with pentafluorobenzoyl chloride	HRGC/ECD	5 ng/L	64–80%	Buisson et al. 1984
Effluent	Mix sample with potassium carbonate, acetic anhydride, and petroleum ether; dry organic layer and concentrate	GC/ECD	#0.6 µg/L	92–104%	Lee et al. 1989
Sludge/soil	Add Na <sub>2</sub> SO <sub>4</sub> ; soxhlet extract using toluene/methanol or acetone/hexane; acid-base partition cleanup. For ECD derivatize with pentafluorobenzylbromide	GC/FID GC/ECD	7.4 µg/L 0.59 µg/L	36–134% 36–134%	EPA 1986b (Method 8040)

**Table 7-2. Analytical Methods for Determining Pentachlorophenol and Metabolites in Environmental Samples (*continued*)**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Sediment	Mix with sodium carbonate with or without hexane ("pretreatment"); discard organic phase if present; derivatize by adding acetic anhydride in hexane; centrifuge	GC/ECD	- 0.1 ng/g	96–99% (without pretreatment); 89% (with pretreatment)	Xie 1983
Soil	(1) Soxhlet extract in ethanol/toluene; (2) extract with hexane/acetone acidified to pH 2 with HCl centrifuge; (3) add water to sample and acidify with HCl ultrasonically extract with hexane/acetone; centrifuge; (4) vortex extract with acetonitrile; centrifuge; dry extracts and dissolve in acetonitrile	HPLC/UV	No data	(1) 94.3–98% (2) 94.8–97.8% (3) 94.4–98.5% (4) 96.1–100%	Wall and Stratton 1991
Soil/sediment	Add Na <sub>2</sub> SO <sub>4</sub> and methanol, centrifuge. To 2 mL of extract, add pentafluorobenzyl bromide, hexacyclooctadecane, Na <sub>2</sub> SO <sub>4</sub>	GC/ECD	No data	No data	EMMI 1997 (AOB Method 0-001-1)
Soil	Add acidified water, MTBE, and centrifuge. Derivatize with N-nitrosomethyl urea, concentrate	GC/ECD	No data	No data	EMMI 1997 (AOB (0-008-1))
Surface-treated lumber	Grind dried lumber sample; extract with acetonitrile containing <i>p</i> -bromophenacyl derivative of ββ-dimethylahyic acid	HPLC/UV	0.1 mg/cm <sup>3</sup>	No data	Daniels and Swan 1979



**Table 7-2. Analytical Methods for Determining Pentachlorophenol and Metabolites in Environmental Samples (*continued*)**

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Egg	Homogenize sample; extract with ethyl acetate-hexane; elute chlorophenol with methanol chloroform	RPHPLC/ UV	<100 µg/kg	73–108% maximum	Mundy and Machin 1981
Fish tissue	Homogenize in water; acidify to pH 2 with HCl extract with methylene chloride; extract with 0.1 N NaOH; acidify; extract with toluene, dry	GC/ECD	0.5 ppb	86%	Kalman 1984
Honey	Dissolve sample in acidified water; extract onto Sep-Pak C <sub>18</sub> cartridge; elute with hexane/diethyl ether	GC/MS	7.6 µg/kg	84–102%	Muiño and Lozano 1991
Gelatin	Add 12 N H <sub>2</sub> SO <sub>4</sub> , extract with hexane-isopropanol, partition into 1 N KOH, acidify with 12 NH <sub>2</sub> SO <sub>4</sub> , extract with hexane	GC/ECD	10 ppb	No data	Helrich 1990 (AOAC Method 985.24)
General	Add internal standard, sonicate and separate	HPLC/UV	No data	No data	EMMI 1997 (EPA Method B)
General	Add internal standard and acetone	GC/FID-IS	No data	No data	EMMI 1997 (EPA Method B)

CH<sub>3</sub>CN = acetonitrile; ECD = electron capture detection; FID = flame ionization; GC = gas chromatography; HCl = hydrochloric acid; HPLC = high-performance liquid chromatography; H<sub>2</sub>SO<sub>4</sub> = sulfuric acid; MS = mass spectrometry; MTBE = methyl-tertiary-butyl ether; NaOH = sodium hydroxide; Na<sub>2</sub>SO<sub>4</sub> = sodium sulphate; RPHPLC = reverse phase high performance liquid chromatography; UV = ultra-violet detection

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program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of pentachlorophenol.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

### 7.3.1 Identification of Data Needs

**Methods for Determining Biomarkers of Exposure and Effect.** Methods are available to detect and quantify pentachlorophenol in blood (Bevenue et al. 1968; EMMI 1997; EPA 1980b; NIOSH 1984b), serum (Kalman 1984; Morgade et al. 1980), urine (Chou and Bailey 1986; Edgerton et al. 1979; EMMI 1997; EPA 1980b; Holler et al. 1989; Kalman 1984; NIOSH 1984b; Rick et al. 1982; Siqueina and Fernicola 1981), adipose tissue (Kuehl and Dougherty 1980; Morgade et al. 1980; Ohe 1979; Shafik 1973), feces (Reigner et al. 1990), liver (Maris et al. 1988) and tissue including the liver, muscle, testes, prostate, and omentum fat (Wagner et al. 1991). Chromatographic techniques, such as GC and HPLC were used to isolate the pentachlorophenol, its derivatives, and its degradation products. ECD and MS were coupled with the separation techniques to detect these compounds. Sensitivity was high (blood: 1–20 ppb; serum: 0.4–30 ppb; urine: 0.5–250 ppb; adipose tissue: low ng–140 ppb; feces: 100 ppb; and other tissues: 1.5–<100 ppb) and recovery was good (blood: 87–100%; serum: 80–99%; urine: 84–105%; adipose tissue: 75–98%; and other tissues: 60–115%). These methods can accurately detect pentachlorophenol at background concentrations in blood, urine, and adipose tissue. Only limited data exist on methods for metabolite characterization. TCHQ, tetrachloropyrocatechol, and palmitoyl-pentachlorophenol are the known metabolites of pentachlorophenol. These compounds can be monitored using GC/ECD (Reigner et al. 1990) or MS (Edgerton et al. 1979). GC/ECD is more economical than MS, but using GC/ECD for metabolite detection has been reported in only one study (Reigner et al. 1990). However, since the majority of pentachlorophenol is excreted unchanged, monitoring of metabolites might not provide useful additional information on exposure concentrations. In general, no attempts have been made to correlate levels of pentachlorophenol in the body with levels absorbed through skin or via inhalation. However, data from a study in log homes demonstrate a positive correlation between serum and urine concentrations of pentachlorophenol and indoor air concentrations of this compound (Hosenfeld et al. 1986; Hill et al. 1989).

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No identified biomarkers of effect (e.g., increased SGOT or SGPT enzyme levels in serum, increased blood urea nitrogen, or neurological symptoms) are specific for pentachlorophenol. The identification of specific biomarkers of effect may be useful.

**Methods for Determining Parent Compounds and Degradation Products in Environmental**

**Media.** Methods are available to measure pentachlorophenol in stack samples (Cuiu et al. 1986), air (Cuiu et al. 1986; Hall et al. 1992; NIOSH 1994), water (Giam et al. 1980; Morgade et al. 1980; Realini 1981), waste water and effluent (Buisson et al. 1984; Butler and Dal Pont 1992; EPA 1986b; Ervin and McGinnis 1980; Lee et al. 1989; Rudling 1970), soil, sludge and sediment (EMMI 1997; EPA 1986b; Wall and Stratton 1991; Xie 1983), surface-treated lumber (Daniels and Swan 1979), fish tissue (Kalman 1984), honey (Muiño and Lozano 1991), and gelatin (Helrich 1990). Sensitivity of detection is as follows: air: 5 ppb; water: 0.1–30 ppb; waste water: 0.1 ppb–7.4 ppm; soil/sludge: 0.1 ppb–7.4 ppm; and foods: 0.5–100 ppb. The recovery of pentachlorophenol varies depending on the method of isolation and detection, and the source of the sample (water: 64–102%; waste water: 36–134%; and soil/sludge: 36–134%). The available methods are, in general, sensitive enough to measure both the background levels and the higher levels of acute exposure. However, even though inhalation is considered to be a major route of human exposure, only limited data concerning methods for determining pentachlorophenol in air were located (Cuiu et al. 1986; Hall et al. 1992), and recovery data were not reported for these methods. Although both occupational exposure and exposure from sources such as log cabins are known to occur, methods for measuring ambient concentrations of pentachlorophenol in air are lacking. An additional source of pentachlorophenol exposure is food; methods are available for analyzing pentachlorophenol in animal tissue and honey (Kalman 1984; Muiño and Lozano 1991), though the recovery is not very good. More methods are required to accurately measure the levels of pentachlorophenol (low ppb levels or lower) in foods.

**7.3.2 Ongoing Studies**

L.L. Ingram, Jr., of the Forest Products Utilization Laboratory at Mississippi State University, is conducting research on the development of mass spectrometric methods for analysis of creosote and pentachlorophenol (CRISP 1992).

The Environmental Health Laboratory Sciences Division of the National Center for Environmental Health and Injury Control, Centers for Disease Control, is developing methods for the analysis of pentachlorophenol and other phenolic compounds in urine. These methods use high resolution gas chromatography

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and magnetic sector mass spectrometry, which gives detection limits in the low parts per trillion (ppt) range.

## 8. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding pentachlorophenol in air, water, and other media are summarized in Table 8-1.

An acute-duration oral MRL of 0.005 mg/kg/day has been derived for pentachlorophenol. This MRL is based on a LOAEL of 5 mg/kg/day for developmental effects (increased occurrence of delayed ossification of the skull) in the offspring of rats (Schwetz et al. 1974). The MRL was derived by dividing the LOAEL by an uncertainty factor of 1,000 (10 to account for the use of a LOAEL, 10 for interspecies extrapolation, and 10 for human variability).

An intermediate-duration oral MRL of 0.001 mg/kg/day has been derived for pentachlorophenol. This MRL is based on a LOAEL of 1 mg/kg/day for reproductive effects (increased severity of cystic uterine glands and decreased proportions of mink accepting a second mating and number of mink whelping) in mink (Beard et al. 1997). The MRL was derived by dividing the LOAEL by an uncertainty factor of 1,000 (10 to account for the use of a LOAEL, 10 for interspecies extrapolation, and 10 for human variability).

An MRL of 0.001 mg/kg/day has been derived for chronic-duration oral exposure to pentachlorophenol. The MRL is based on a LOAEL of 1 mg/kg/day for decreased serum thyroxine concentrations and decreased relative thyroid weight in mink (Beard and Rawlings 1998). The LOAEL was divided by an uncertainty factor of 1,000 (10 to account for the use of a LOAEL, 10 for interspecies extrapolation, and 10 for human variability) to derive the MRL.

EPA (IRIS 2001) derived an oral reference dose (RfD) of 0.03 mg/kg/day for pentachlorophenol. The RfD was based on a NOAEL of 3 mg/kg/day for liver and kidney pathology in rats (Schwetz et al. 1978). The MRL was derived by dividing the NOAEL by an uncertainty factor of 100 (10 for interspecies extrapolation and 10 for human variability).

EPA (IRIS 2001) has assigned pentachlorophenol a weight-of-evidence classification of B2, probable human carcinogen.

The International Agency for Research on Cancer (IARC 2001) assigned pentachlorophenol a group 2B cancer classification, possibly carcinogenic to humans.

## 8. REGULATIONS AND ADVISORIES

EPA has restricted the sale and use of pesticide products containing pentachlorophenol (EPA 1987d).

This was effective July 13, 1984 (EPA 1984a).

## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to Pentachlorophenol**

Agency	Description	Information	References
<u>INTERNATIONAL</u>			
Guidelines:			
IARC	Carcinogenicity classification	Group 2B <sup>a</sup>	IARC 2001
WHO	Drinking water quality	9 µg/L	WHO 2001
<u>NATIONAL</u>			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV–TWA <sup>b</sup>	0.5 mg/m <sup>3</sup>	ACGIH 2000
EPA	RAC	30 µg/m <sup>3</sup>	EPA 2001k 40CFR266 Appendix IV
NIOSH	REL (TWA) <sup>b</sup>	0.5 mg/m <sup>3</sup>	NIOSH 2001a
	IDLH	2.5 mg/m <sup>3</sup>	NIOSH 2001b
OSHA	PEL (8-hour TWA) <sup>b</sup> General industry	0.5 mg/m <sup>3</sup>	OSHA 2001b 29CFR1910.1000 Table Z-1
	PEL (8-hour TWA) <sup>b</sup> Construction industry	0.5 mg/m <sup>3</sup>	OSHA 2001c 29CFR1926.55 Appendix A
	PEL (8-hour TWA) <sup>b</sup> Shipyard construction	0.5 mg/m <sup>3</sup>	OSHA 2001a 29CFR1915.100 Table Z
USC	HAP		USC 2001 42USC7412
b. Water			
DOT	Marine pollutant— pentachlorophenol and sodium pentachlorophenate		DOT 2001b 49CFR172.101 Appendix B
EPA	Drinking water standard	1x10 <sup>-3</sup> ppm	EPA 2001j 40CFR141.32
	Groundwater monitoring list—standards for TSD Suggested method PQL	8040 8270 5 µg/L 50 µg/L	EPA 2001i 40CFR264 Appendix IX

## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to Pentachlorophenol  
(continued)**

Agency	Description	Information	References
<u>NATIONAL</u> (cont.)			
EPA	MCL—applies to community and non-transient, non-community water systems	$1 \times 10^{-3}$ mg/L	EPA 2001h 40CFR141.61
	MCLG	0 mg/L	EPA 2001i 40CFR141.50
	Effluent guidelines—toxic pollutant		EPA 2001a 40CFR401.15
	1-Day health advisory (10-kg child)	1.0 mg/L	EPA 2000d
	10-Day health advisory (10-kg child)	0.3 mg/L	
	DWEL	1.0 mg/L	
	Concentration at cancer risk of $10^{-4}$	0.03 mg/L	EPA 1999b  EPA 2001o 40CFR131.36
	Organoleptic effect criteria	30 µg/L	
	Toxic criteria for those states not complying with Clean Water Act section 303(c)(2)(B)		
	Freshwater		
	Maximum concentration	20 µg/L	
	Continuous concentration	13 µg/L	
	Saltwater		
	Maximum concentration	13 µg/L	
	Continuous concentration	7 µg/L	
	Water pollution—designation of hazardous substance		
	Water programs—determination of reportable quantities of hazardous substances	10 pounds	EPA 2001q 40CFR177.3
c. Food			
FDA	Bottled water—allowable level	$1 \times 10^{-3}$ mg/L	FDA 2000a 21CFR165.110
	Indirect food additives— adhesives and components of coatings		FDA 2000b 21CFR175.105
	Indirect food additives—animal glue Sodium pentachlorophenate		FDA 2000c 21CFR178.3120 (d)(3)



## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to Pentachlorophenol  
(continued)**

Agency	Description	Information	References
<u>NATIONAL</u> (cont.)			
FDA	Indirect food additives—rubber articles intended for repeated use Sodium pentachlorophenate		FDA 2000e 21CFR177.2600 (c)(4)
	Indirect food additives—textiles and textile fibers Sodium pentachlorophenate		FDA 2000f 21CFR177.2800 (d)(5)
	Indirect food additives—preservatives for wood Pentachlorophenol and sodium pentachlorophenate	Not to exceed 50 ppm in the treated wood	FDA 2000d 21CFR177.3800 (b)
d. Other			
ACGIH	BEI Total pentachlorophenol in urine Free pentachlorophenol in plasma	2 mg/g creatinine 5 mg/L	ACGIH 2000
	Carcinogenicity classification	A3 <sup>c</sup>	
DOT	Hazardous material—pentachlorophenol and sodium pentachlorophenate		DOT 2001a 49CFR172.101
	Use of tank cars—hazardous substance		DOT 2001c 49CFR173.31 (f)(2)
EPA	Carcinogenicity classification	B2 <sup>d</sup>	IRIS 2001
	Oral slope factor	12 (mg/kg/day) <sup>-1</sup>	
	RfD	3x10 <sup>-2</sup> mg/kg/day	EPA 2001b 40CFR403 Appendix G
	General pretreatment regulations for existing and new sources of pollution—pollutants eligible for a removal credit (land application)	30 mg/kg	
	Identification and listing of hazardous waste—comparable/ Syngas fuel exclusion Minimum required detection limit for comparable fuel specification	2,400 mg/kg	

## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to Pentachlorophenol  
(continued)**

Agency	Description	Information	References
<u>NATIONAL</u> (cont.)			
EPA	Identification and listing of hazardous waste—hazardous constituent		EPA 2001e 40CFR261 Appendix VIII
	Identification and listing of hazardous waste—maximum concentration of contaminant for the toxicity characteristic	100 mg/L	EPA 2001g 40CFR261.24
	Hazardous waste—concentration limits for health based limits for exclusion of waste-derived residues	1 mg/kg	EPA 2001c 40CFR266 Appendix VII
	Health and environmental protection standards for uranium and thorium mill tailings	Listed constituent	EPA 2001d 40CFR192 Appendix I
	Superfund—reportable quantity	10 pounds	EPA 2001m 40CFR302.4
	Toxic chemical release reporting; Community Right-to-Know—effective date	01/01/87	EPA 2001n 40CRF372.65
<u>STATE</u>			
Regulations and Guidelines:			
a. Air:			
Arkansas	RAC	30 µg/m <sup>3</sup>	BNA 2001
California	RAC	30 µg/m <sup>3</sup>	BNA 2001
	Toxic air contaminant		
Colorado	Hazardous air pollutant		BNA 2001
	8 hour	10 µg/m <sup>3</sup>	
	30 minute	50 µg/m <sup>3</sup>	
Delaware	RAC	30 µg/m <sup>3</sup>	BNA 2001
Idaho	Toxic air pollutant		BNA 2001
	OEL	0.5 mg/m <sup>3</sup>	
	EL	0.033 pounds/hour	
	AAC	0.025 mg/m <sup>3</sup>	
Illinois	RAC	30 µg/m <sup>3</sup>	BNA 2001
	Toxic air contaminant		

## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to Pentachlorophenol  
(continued)**

Agency	Description	Information	References
<u>STATE (cont.)</u>			
Kansas	HAP		BNA 2001
	Maximum air emissions allowed	0.7 tons/year	CDC 1999a
Kentucky	RAC	30 µg/m <sup>3</sup>	BNA 2001
Minnesota	HAP threshold	0.7 tons/year	BNA 2001
New Hampshire	Regulated toxic air pollutant OEL	0.5 mg/m <sup>3</sup>	BNA 2001
North Carolina	Emission rates requiring a permit Chronic toxicants Acute systemic toxicants	0.063 pounds/day 0.0064 pounds/day	BNA 2001
	Toxic air pollutants Chronic toxicants (24 hour) Acute systemic toxicants (1 hour)	0.003 mg/m <sup>3</sup> 0.025 mg/m <sup>3</sup>	BNA 2001
Rhode Island	HAP		BNA 2001
South Carolina	RAC	30 µg/m <sup>3</sup>	BNA 2001
	Toxic air emissions—maximum allowable concentration	5 µg/m <sup>3</sup>	BNA 2001
Tennessee	RAC	30 µg/m <sup>3</sup>	BNA 2001
Vermont	Hazardous ambient air standard Annual average Action level	1.19 µg/m <sup>3</sup> 0.10 µg/m <sup>3</sup>	BNA 2001
Washington	Threshold for HAPs	0.35 tons/year	BNA 2001
Wisconsin	Proposed thresholds 24 hour <25 ft 24 hour \$25 ft <75 ft 24 hour \$75 ft	0.0269 pounds/hour 0.104 pounds/hour 0.811 pounds/hour	Wisconsin DNR 2001
	Proposed standard—AAC	12 µg/m <sup>3</sup>	
Wyoming	RAC	30 µg/m <sup>3</sup>	BNA 2001
b. Water:			
Alabama	MCL	1 ppb	BNA 2001
	Toxic pollutant criteria Marine acute Marine chronic	13 µg/L 7.9 µg/L	BNA 2001

## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to Pentachlorophenol  
(continued)**

Agency	Description	Information	References
<u>STATE (cont.)</u>			
Alaska	MCL	0.001 mg/L	BNB 2001
	Groundwater clean-up level	0.001 mg/L	BNB 2001
Arizona	MCL	0.001 mg/L	BNB 2001
	Aquifer water quality standard	0.001 mg/L	BNB 2001
	Drinking water guideline	220 µg/L	HSDB 2001
Arkansas	Groundwater monitoring (PQL)	5 mg/L	BNB 2001
Colorado	MCL	0.001 mg/L	BNB 2001
Florida	MCL	0.001 mg/L	BNB 2001
Georgia	MCL	0.001 mg/L	BNB 2001
	Instream concentrations		BNB 2001
	Freshwater	2.1 µg/L	
	Costal and marine estuarine waters	7.9 µg/L	
Hawaii	MCL—community, non-transient, and non-community water systems	1x10 <sup>-3</sup> mg/L	CDC 1999b
Idaho	Groundwater quality standard	0.001 mg/L	BNB 2001
Illinois	MCL	0.001 mg/L	BNB 2001
	Groundwater monitoring	5 µg/L	BNB 2001
Indiana	MCL	0.001 mg/L	BNB 2001
Iowa	MCL	0.001 mg/L	BNB 2001
Kansas	MCL	0.001 mg/L	BNB 2001
Kentucky	MCL	0.001 mg/L	BNB 2001
	Hazardous constituent for groundwater monitoring		BNB 2001
	Maximum allowable instream concentrations	0.28 mg/L	BNB 2001
Maine	Drinking water guideline	1 µg/L	HSDB 2001
Maryland	MCL	0.001 mg/L	BNB 2001
Massachusetts	Groundwater monitoring (PQL)	5 µg/L	BNB 2001
Michigan	MCL	0.001 mg/L	BNB 2001
Minnesota	Drinking water guideline	3 µg/L	HSDB 2001

## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to Pentachlorophenol  
(continued)**

Agency	Description	Information	References
<u>STATE (cont.)</u>			
Mississippi	Groundwater standard	1 ppb	BNA 2001
	Freshwater		BNA 2001
	Acute	3.32 µg/L	
	Chronic	2.1 µg/L	
	Salt water		
	Acute	13 µg/L	
	Chronic	7.9 µg/L	
Missouri	MCL	0.001 mg/L	BNA 2001
Montana	MCL	0.001 mg/L	BNA 2001
Nebraska	MCL	0.001 mg/L	BNA 2001
	Drinking water standard	0.001 mg/L	BNA 2001
Nevada	Standards for toxic materials applicable to municipal or domestic supply	1,010 µg/L	BNA 2001
New Hampshire	MCL	0.001 mg/L	BNA 2001
	MCLG	0	
	Ambient groundwater quality standard	1 µg/L	BNA 2001
New Hampshire	Water quality criteria		BNA 2001
	Fresh acute	5.28 µg/L	
	Fresh chronic	4.05 µg/L	
	Marine acute	13.0 µg/L	
	Marine chronic	7.9 µg/L	
	Water and fish ingestion	0.28 µg/L	
	Fish consumption only	8.2 µg/L	
New Jersey	Groundwater quality criteria	0.3 µg/L	BNA 2001
	PQL	1.0 µg/L	
New Mexico	MCL	0.001 mg/L	BNA 2001
	Groundwater parameters (PQL)	0.005 mg/L	BNA 2001
New York	MCL	0.001 mg/L	BNA 2001
	Groundwater monitoring (PQL)	5 µg/L	BNA 2001
North Dakota	MCL	0.001 mg/L	BNA 2001
Ohio	MCL	0.001 mg/L	BNA 2001
Oklahoma	MCL	0.001 mg/L	BNA 2001
	Water column criteria to protect for the consumption of fish flesh	29,370 µg/L	BNA 2001

## 8. REGULATIONS AND ADVISORIES

**Table 8-1. Regulations and Guidelines Applicable to Pentachlorophenol  
(continued)**

Agency	Description	Information	References
<u>STATE (cont.)</u>			
Oklahoma	Hazardous constituent (PQL)	5 µg/L	BNA 2001
Rhode Island	MCLG	0	BNA 2001
	MCL	0.001 mg/L	
	Groundwater quality standard Preventive action limit	0.001 mg/L 0.0005 mg/L	BNA 2001
South Carolina	Groundwater monitoring (PQL)	5 µg/L	BNA 2001
	Water quality criteria		BNA 2001
	MCL Organism consumption	1.0 µg/L 82 µg/L	
South Dakota	MCL	0.001 mg/L	BNA 2001
	Groundwater standard	1x10 <sup>-3</sup> mg/L	FSTRAC 1999b
Tennessee	Toxic substance criteria	1.0 µg/L	BNA 2001
	Maximum concentration	20 µg/L	
	Continuous concentration	13 µg/L	
	Water and organism	2.8 µg/L	
	Organism only	82 µg/L	
Texas	MCL	0.001 mg/L	BNA 2001
Utah	MCL	0.001 mg/L	BNA 2001
	Groundwater quality standard	0.001 mg/L	BNA 2001
Vermont	MCL	0.001 mg/L	BNA 2001
	MCLG	0	BNA 2001
Vermont	Consumption of water and organism	0.28 µg/L	BNA 2001
	Consumption of organism only	8.2 µg/L	
	Enforcement standard	1.0 µg/L	BNA 2001
	Preventive action level	0.3 µg/L	
Virginia	Hazardous constituent (PQL)	5 µg/L	BNA 2001
	Public water supplies	2.8 µg/L	BNA 2001
	All other surface waters	82 µg/L	
Washington	MCL	0.001 mg/L	BNA 2001
West Virginia	Groundwater standard	0.001 mg/L	BNA 2001
Wisconsin	MCLG	0.003 mg/L	BNA 2001
<b>c. Food</b>			
Nebraska	Standards for bottled water	0.001 mg/L	BNA 2001

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**Table 8-1. Regulations and Guidelines Applicable to Pentachlorophenol  
(continued)**

Agency	Description	Information	References
<u>STATE (cont.)</u>			
d. Other			
Arizona	Soil remedial level Residential Non-residential	25.0 mg/kg 79.0 mg/kg	BNA 2001
Connecticut	Direct exposure criteria for soil Residential Industrial/commercial	5.1 ppm 48 ppm	BNA 2001
Hawaii	Restricted use pesticide	Restricted concentration above 5%	BNA 2001
Massachusetts	RfD Oral slope factor  Toxic pollutant	$3 \times 10^{-2}$ mg/kg/day $12 \text{ (mg/kg/day)}^{-1}$	BNA 2001
Minnesota	Slope factor Health risk limit	$0.12 \text{ (mg/kg/day)}^{-1}$ 3 µg/L	BNA 2001
Missouri	Hazardous constituent		BNA 2001
New Hampshire	Restricted use pesticide	All concentrations	BNA 2001
New Jersey	Restricted use pesticide	All concentrations above 5%	BNA 2001
New York	Restricted use pesticide	All concentrations above 5%	BNA 2001

<sup>a</sup>Group2B: possibly carcinogenic to humans<sup>b</sup>Skin notation: danger of cutaneous absorption<sup>c</sup>A3: confirmed animal carcinogen with unknown relevance to humans<sup>d</sup>Group B2: probable human carcinogen

AAC = acceptable ambient concentrations; ACGIH = American Conference of Governmental Industrial Hygienists; BEI = biological exposure index; BNA = Bureau of National Affairs; CDC = Center for Disease Control; CFR = Code of Federal Regulations; DNR = Department of Natural Resources; DOT = Department of Transportation; DWEL = drinking water equivalent level; EL = emissions level; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; FSTRAC = Federal–State Toxicology Risk Analysis Committee; HAP = hazardous air pollutant; HSDB = Hazardous Substances Data Bank; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life and health; IRIS = Integrated Risk Information System; MCL = maximum contaminant level; MCLG = maximum contaminant level goal; NIOSH = National Institute of Occupational Safety and Health; OEL = occupational exposure level; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; PQL = practical quantitation limit; RAC = reference air concentration; REL = recommended exposure release; RfD = reference dose; TLV = threshold limit value; TSD = treatment, storage, and disposal; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization





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## 10. GLOSSARY

**Absorption**—The taking up of liquids by solids, or of gases by solids or liquids.

**Acute Exposure**—Exposure to a chemical for a duration of 14 days or less, as specified in the Toxicological Profiles.

**Adsorption**—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

**Adsorption Coefficient ( $K_{oc}$ )**—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

**Adsorption Ratio ( $K_d$ )**—The amount of a chemical adsorbed by a sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

**Benchmark Dose (BMD)**—Usually defined as the lower confidence limit on the dose that produces a specified magnitude of changes in a specified adverse response. For example, a  $BMD_{10}$  would be the dose at the 95% lower confidence limit on a 10% response, and the benchmark response (BMR) would be 10%. The BMD is determined by modeling the dose response curve in the region of the dose response relationship where biologically observable data are feasible.

**Benchmark Dose Model**—A statistical dose-response model applied to either experimental toxicological or epidemiological data to calculate a BMD.

**Bioconcentration Factor (BCF)**—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

**Biomarkers**—Broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility.

**Cancer Effect Level (CEL)**—The lowest dose of chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

**Carcinogen**—A chemical capable of inducing cancer.

**Case-Control Study**—A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

**Case Report**—Describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

**Case Series**—Describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research but are not actual research studies.

## 10. GLOSSARY

**Ceiling Value**—A concentration of a substance that should not be exceeded, even instantaneously.

**Chronic Exposure**—Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

**Clastogenic**—An agent capable of causing breakage of chromosomes.

**Cohort Study**—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

**Cross-sectional Study**—A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

**Data Needs**—Substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

**Developmental Toxicity**—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

**Dose-Response Relationship**—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

**Embryotoxicity and Fetotoxicity**—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and *in utero* death.

**Endocrine System**—A system of ductless hormone-secreting glands that includes the hypothalamus, pituitary gland, adrenal glands, thyroid glands, parathyroid glands, and pancreatic islets.

**Environmental Protection Agency (EPA) Health Advisory**—An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

**Epidemiology**—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

**FEFR<sub>25-75</sub>**—Forced expiratory flowrate between 25 and 75%.

**FEV<sub>1.0</sub>**—Forced expiratory volume in 1.0 seconds.

**FVC**—Forced vital capacity.

**Genotoxicity**—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

## 10. GLOSSARY

**Half-life**—A measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

**Immediately Dangerous to Life or Health (IDLH)**—The maximum environmental concentration of a contaminant from which one could escape within 30 minutes without any escape-impairing symptoms or irreversible health effects.

**Immune System**—A cellular complex that forms the basis of the body's defenses to both biological and chemical exogenous substances.

**Incidence**—The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

**Intermediate Exposure**—Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

**Immunologic Toxicity**—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

**Immunological Effects**—Functional changes in the immune response.

***In Vitro***—Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo***—Occurring within the living organism.

**Lethal Concentration<sub>(LO)</sub> (LC<sub>LO</sub>)**—The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

**Lethal Concentration<sub>(50)</sub> (LC<sub>50</sub>)**—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

**Lethal Dose<sub>(LO)</sub> (LD<sub>LO</sub>)**—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

**Lethal Dose<sub>(50)</sub> (LD<sub>50</sub>)**—The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

**Lethal Time<sub>(50)</sub> (LT<sub>50</sub>)**—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

**Lowest-Observed-Adverse-Effect Level (LOAEL)**—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

**Lymphoreticular Effects**—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

**Malformations**—Permanent structural changes that may adversely affect survival, development, or function.

## 10. GLOSSARY

**Minimal Risk Level (MRL)**—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

**Modifying Factor (MF)**—A value (greater than zero) that is applied to the derivation of a minimal risk level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

**Morbidity**—State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

**Mortality**—Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

**Mutagen**—A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

**Necropsy**—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

**Neurotoxicity**—The occurrence of adverse effects on the nervous system following exposure to a chemical.

**No-Observed-Adverse-Effect Level (NOAEL)**—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

**Octanol-Water Partition Coefficient ( $K_{ow}$ )**—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

**Odds Ratio (OR)**—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

**Organophosphate or Organophosphorus Compound**—A phosphorus containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

**Permissible Exposure Limit (PEL)**—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40 hour workweek.

**Pesticide**—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

**Pharmacokinetics**—The science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

## 10. GLOSSARY

**Pharmacokinetic Model**—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereby the physiologically-based model compartments represent real anatomic regions of the body.

**Physiologically Based Pharmacodynamic (PBPD) Model**—A type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

**Physiologically Based Pharmacokinetic (PBPK) Model**—Comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

**ppbv**—Parts per billion by volume.

**ppmv**—Parts per million by volume.

**Prevalence**—The number of cases of a disease or condition in a population at one point in time.

**Proportionate Mortality Ratio (PMR)**—The ratio of a cause-specific mortality proportion in an exposed group to the mortality proportion in an unexposed group; mortality proportions may be adjusted for confounding variables such as age. Cause-specific mortality proportions can be calculated when the cohort (the population at risk) cannot be defined due to inadequate records, but the number of deaths and the causes of deaths are known.

**Prospective Study**—A type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

**$q_1^*$** —The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The  $q_1^*$  can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually  $\mu\text{g/L}$  for water,  $\text{mg/kg/day}$  for food, and  $\mu\text{g/m}^3$  for air).

**Recommended Exposure Limit (REL)**—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a 10-hour workday during a 40-hour workweek.

**Reference Concentration (RfC)**—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of  $\text{mg/m}^3$  or ppm.

**Reference Dose (RfD)**—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious

## 10. GLOSSARY

effects during a lifetime. The RfD is operationally derived from the No-Observed-Adverse-Effect Level (NOAEL- from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

**Relative Risk (RR)**—The risk expressed as a ratio of the incidence of diseased subjects exposed to a particular risk factor to the incidence of diseased subjects in a non-exposed referent group.

**Reportable Quantity (RQ)**—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

**Reproductive Toxicity**—The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

**Retrospective Study**—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

**Risk**—The possibility or chance that some adverse effect will result from a given exposure to a chemical.

**Risk Factor**—An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that is associated with an increased occurrence of disease or other health-related event or condition.

**Risk Ratio**—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

**Short-Term Exposure Limit (STEL)**—The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

**Standardized Mortality Ratio (SMR)**—The ratio of a cause-specific mortality rate in an exposed cohort during a given period to the mortality rate of an unexposed cohort; mortality rates are often adjusted for age or other confounding variables.

**Standardized Proportionate Incidence Ratio (SPIR)**—Similar to a Proportionate Mortality Ratio (PMR) in that it is a ratio of a proportion of a specific disease in an exposed group compared with the proportion in an unexposed group.



## 10. GLOSSARY

**Target Organ Toxicity**—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

**Teratogen**—A chemical that causes structural defects that affect the development of an organism.

**Threshold Limit Value (TLV)**—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

**Time-Weighted Average (TWA)**—An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

**Toxic Dose<sub>(50)</sub> (TD<sub>50</sub>)**—A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

**Toxicokinetic**—The study of the absorption, distribution and elimination of toxic compounds in the living organism.

**Uncertainty Factor (UF)**—A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using Lowest-Observed-Adverse-Effect Level (LOAEL) data rather than No-Observed-Adverse-Effect Level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UF of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10 and 1.

**Xenobiotic**—Any chemical that is foreign to the biological system.



## **APPENDIX A**

### **ATSDR MINIMAL RISK LEVELS AND WORKSHEETS**

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99–499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

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MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agency wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical Name: Pentachlorophenol  
CAS Number: 87-86-5  
Date: June 22, 2001  
Profile Status: Final  
Route: ☐ Inhalation ☒ Oral  
Duration: ☒ Acute ☐ Intermediate ☐ Chronic  
Key to Figure: 14  
Species: Rats

Minimal Risk Level: 0.005 ☒ mg/kg/day ☐ mg/m<sup>3</sup>

Reference: Schwetz BA, Keeler PA, Gehring PJ. 1974. The effect of purified and commercial grade pentachlorophenol on rat embryonal and fetal development. Toxicol Appl Pharmacol 28:151-161.

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Purified (98%+) and commercial-grade (88.4%) pentachlorophenol were administered by gavage in corn oil to groups of 20–40 pregnant Sprague-Dawley rats on days 6–15 of gestation at doses of 0 (corn oil control), 5, 15, 30, and 50 mg/kg/day. At the 5 and 30 mg/kg/day dose levels, the actual amount of pentachlorophenol administered was 5.8 and 34.7 mg/kg/day, which was equivalent to 5 and 30 mg/kg/day pure pentachlorophenol.

Effects noted in study and corresponding concentrations: Maternal body weight gain was significantly decreased at 30 and 50 mg/kg/day with both pure and commercial-grade pentachlorophenol. Otherwise, no signs of maternal toxicity were noted. Significant increases in incidences of resorptions were seen at 15, 30, and 50 mg/kg/day commercial-grade pentachlorophenol and at 30 and 50 mg/kg/day with the pure pentachlorophenol. There was 100% resorption of implantations at the 50 mg/kg/day pure pentachlorophenol dose level. The sex ratio was significantly altered at 30 mg/kg/day pure pentachlorophenol and 50 mg/kg/day of the commercial-grade pentachlorophenol, with the majority of the survivors being male offspring.

Significant decreases in fetal body weight were observed at 30 and 50 mg/kg/day of commercial-grade pentachlorophenol and significant decreases in fetal body weight and crown-rump length were seen with 30 mg/kg/day of pure pentachlorophenol. Fetal malformations and/or variations were observed at 15 mg/kg/day and higher for the commercial-grade pentachlorophenol and 5 mg/kg/day and higher for the pure pentachlorophenol. The observed effects for the commercial-grade groups included subcutaneous edema and lumbar spurs at \$15 mg/kg/day, rib, sternebrae, and vertebrae anomalies at \$30 mg/kg/day. In the pure pentachlorophenol offspring, the incidence of delayed ossification of the skull was significantly increased at \$5 mg/kg/day, and significant increases in the occurrence of subcutaneous edema, lumbar spurs, and skeletal anomalies in the ribs, sternebrae, and vertebrae were observed at \$15 mg/kg/day.

Concentration and end point used for MRL derivation: This MRL is based on a LOAEL of 5 mg/kg/day for delayed ossification of the skull in rat pups when the dams were given pure pentachlorophenol by corn oil gavage on gestation days 6 through 15.

☐ NOAEL ☒ LOAEL

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Uncertainty Factors used in MRL derivation:

- [X] 10 for use of a LOAEL
- [X] 10 for extrapolation from animals to humans
- [X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: NA

Was a conversion used from intermittent to continuous exposure? NA

Other additional studies or pertinent information that lend support to this MRL: Similar developmental effects have been observed in another developmental toxicity study (Argus 1993b/Bernard et al. 2001b). In this study, significant increases in the occurrence of resorptions, soft tissue and skeletal malformations and variations and decreases in fetal body weight were observed in the offspring of rats were administered by gavage 80 mg/kg/day technical grade (89% pure) pentachlorophenol on gestational days 6–15. This study identified a NOAEL of 30 mg/kg/day. Intermediate-duration oral developmental toxicity studies in rats have also reported increased fetal/neonatal mortality, malformations, and/or variations, and decreased growth (Argus 1997/Bernard et al. 2001c; Courtney et al. 1976; Exon and Koller 1982; Schwetz et al. 1978; Welsh et al. 1987).

Agency Contact (Chemical Manager): Lori L. Miller, M.P.H.

## APPENDIX A

**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical Name: Pentachlorophenol  
CAS Number: 87-86-5  
Date: June 22, 2001  
Profile Status: Final  
Route: ☐ Inhalation ☒ Oral  
Duration: ☐ Acute ☒ Intermediate ☐ Chronic  
Key to Figure: 47  
Species: Mink

Minimal Risk Level: 0.001 ☒ mg/kg/day ☐ mg/m<sup>3</sup>

Reference: Beard AP, McRae AC, Rawlings NC. 1997. Reproductive efficiency in mink (*Mustela vison*) treated with the pesticides lindane, carbofuran, and pentachlorophenol. J Reprod Fertil 111:21-28.

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Groups of 10 female mink were exposed to 1 mg/kg/day pentachlorophenol in the diet for 3 weeks prior to mating with unexposed males and throughout pregnancy and lactation. The females were mated twice at 7–8 day intervals. The purity of the pentachlorophenol was not reported.

Effects noted in study and corresponding concentrations: A decrease in the proportion of mated females accepting a second mating and the proportion of mink that whelped were observed. No effect on the proportion of mink accepting the first mating or the proportion of mink with visible implantation sites were found. An increase in the severity cystic uterine glands was also observed in the pentachlorophenol-exposed mink.

Concentration and end point used for MRL derivation: This MRL is based on a LOAEL of 1 mg/kg/day for reproductive effects in mink exposed to pentachlorophenol (purity not reported) in the diet.

☐ NOAEL ☒ LOAEL

Uncertainty Factors used in MRL derivation:

- ☒ 10 for use of a LOAEL
- ☒ 10 for extrapolation from animals to humans
- ☒ 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Dose was calculated by the study authors.

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: NA

Was a conversion used from intermittent to continuous exposure? NA

Other additional studies or pertinent information that lend support to this MRL: Several other studies have examined the reproductive toxicity of pentachlorophenol. Decreased fertility has been observed in

## APPENDIX A

the first generation of rats exposed to 60 mg/kg/day, but not in the parental or second generations; the NOAEL for this effect is 30 mg/kg/day (Argus 1997/Bernard et al. 2001c). A significant decrease in testicular spermatid count, decreases in absolute testes weight and the ratio of testes weight to brain weight, and focal/multifocal mononuclear cell infiltrate in the epididymis were observed in the F1 rats administered 30 or 60 mg/kg/day. However, no alterations in the average number of motile or nonmotile sperm, epididymal or testicular sperm counts, or sperm morphology were observed in either generation (Argus 1997/Bernard et al. 2001c). No alterations in reproductive tissues were observed in the female rats. Significant increases in the average day of preputial separation and vaginal patency were observed in the F1 generation, suggesting that *in utero* exposure to pentachlorophenol disrupted the normal development of the reproductive system. No adverse reproductive effects were observed in another mink study in which the animals were also fed a diet containing 1 mg/kg/day pentachlorophenol (purity not reported) (Beard and Rawlings 1998). Additionally, no significant alterations in mating response, ovulation rate, follicle and corpus luteum size, gestation length, pregnancy rate, lambing rate, and lamb birth rate were observed in sheep exposed to 1 mg/kg/day pentachlorophenol in the diet for 5 weeks pre mating and throughout the gestation and lactation periods (Beard et al. 1999b). No effect on fertility was observed in the offspring of these sheep, later mated to unexposed males (Beard and Rawlings 1999).

Several reproductive toxicity and nonreproductive toxicity studies have reported histological alterations in reproductive tissues. The observed effects include focal degeneration of the seminiferous tubules and decreased sperm density in the epididymis body (but not in caput or cauda epididymis) in sheep exposed to 1 mg/kg/day pentachlorophenol (purity not reported) in the diet during gestation, lactation, and for 20 weeks postnatally (Beard et al. 1999a), minimal to marked germinal epithelial degeneration and lack of spermatozoa in the seminiferous tubules of rats exposed to 270 mg/kg/day pure pentachlorophenol in the diet for 28 days (effects may have been secondary to poor condition of animals) (Chhabra et al. 1999; NTP 1999), increased severity of oviductal intraepithelial cysts in sheep administered 2 mg/kg/day pure pentachlorophenol by gavage twice weekly for 43 days (Rawlings et al. 1998), and lymphocyte infiltration into the endometrium in sheep exposed to 1 mg/kg/day pentachlorophenol (purity not reported) in the diet for 5 weeks pre mating and during the gestation and lactation periods (Beard et al. 1999b). No histological alterations in reproductive tissues were observed in male or female rats chronically exposed to 30 mg/kg/day pure pentachlorophenol in the diet for 2 years (Chhabra et al. 1999; NTP 1999). Additionally, no alterations in reproductive hormones (estradiol, testosterone, progesterone, follicle stimulating hormone, and/or luteinizing hormone levels) have been observed in mink (Beard et al. 1997) or sheep (Beard et al. 1999a).

Liver and developmental effects also appear to be sensitive end points of pentachlorophenol following intermediate-duration oral exposure; the lowest adverse effect levels for these effects are 10-fold higher than the reproductive effects reported in mink. Significant increases in relative liver weight and the occurrence of centrilobular hepatocellular hypertrophy have been reported in rats and mice exposed to <10 mg/kg/day pure or technical-grade pentachlorophenol (Blakley et al. 1998; Kerkvliet et al. 1982; Kimbrough and Linder 1978; Knudsen et al. 1974). At higher doses, hepatocyte degeneration and necrosis have been observed (Kerkvliet et al. 1982; NTP 1989, 1999). Developmental effects (decreased pup body weight) have also been observed in rat offspring at 10–15 mg/kg/day (Argus 1997/Bernard et al. 2001c; Welsh et al. 1987).

Agency Contact (Chemical Manager): Lori L. Miller, M.P.H.



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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical Name: Pentachlorophenol  
CAS Number: 87-86-5  
Date: June 22, 2001  
Profile Status: Final  
Route: ☐ Inhalation ☒ Oral  
Duration: ☐ Acute ☐ Intermediate ☒ Chronic  
Key to Figure: 54  
Species: Mink

Minimal Risk Level: 0.001 ☒ mg/kg/day ☐ mg/m<sup>3</sup>

Reference: Beard AP, Rawlings NC. 1998. Reproductive effects in mink (*Mustela vison*) exposed to the pesticides lindane, carbofuran and pentachlorophenol in a multigeneration study. J Reprod Fertil 113:95-104.

Experimental design (human study details or strain, number of animals per exposure/control groups, sex, dose administration details): Pentachlorophenol (Sigma, St. Louis, Missouri; purity not indicated) was administered at a dose of 1 mg/kg/day in the diet to parental-generation female mink from 3 weeks prior to mating (with untreated males) until weaning of first-generation offspring. Male and female offspring in the first and second generations were continued on the pentachlorophenol diet effectively from conception until sexual maturity. As with the parental generation, females of the first generation were mated with untreated males. The number of control and treated females in the parental generation was not indicated. Ten control and 8 pentachlorophenol-treated females of the first generation, continued on the pentachlorophenol diet throughout growth, mating, pregnancy, lactation, and for 3 months after the end of lactation, were mated to produce the second generation. Ten control and 6 pentachlorophenol males of the first generation were killed when their testis development was maximal at about 42 weeks of age. The study group in the second generation consisted of 8 males and 10 females given control diet and 8 males and 10 females continued on the pentachlorophenol diet. At necropsy of the first-generation males, weights of the testes, epididymides, and penis were recorded, and these organs and samples of the pancreas, liver, and pituitary gland were fixed for microscopic examination; dimensions of the testes and penis were also recorded. At necropsy of the first-generation females, weights of the ovaries, oviduct, uterus, pituitary, thyroid, parathyroid, and adrenals were recorded, and samples of these and the pancreas were fixed for microscopic examination. Weights of the heart, brain, liver, and kidney were also recorded. In the second-generation animals, the same tissues were weighed and measured, but no tissues were examined histologically in the females and only endocrine and reproductive tissues were examined histologically in the males. Serum from blood samples collected at necropsy of first and second generation males and females was analyzed for estradiol and thyroxine. Serum cortisol was also measured in first-generation females and serum testosterone was measured in first- and second-generation males.

Effects noted in study and corresponding concentrations: No overt signs of toxicity were seen and no reproductive effect end points were altered in the pentachlorophenol-treated groups compared with controls. The only effects noted in the pentachlorophenol-treated groups were significantly-decreased serum thyroxine concentrations in males of the first generation and in males and females of the second generation, and significantly-decreased relative thyroid weight in females of the second generation.

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Concentration and end point used for MRL derivation: This MRL is based on a LOAEL of 1 mg/kg/day (only dose tested) for significantly-decreased serum thyroxine concentrations in males of the first generation and males and females of the second generation and decreased relative thyroid weight in females of the second generation when mink were administered pentachlorophenol of unspecified purity continuously in the diet in a multigeneration reproduction study.

[ ] NOAEL [X] LOAEL

Uncertainty Factors used in MRL derivation:

- [X] 10 for use of a LOAEL
- [X] 10 for extrapolation from animals to humans
- [X] 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? No. The dose of 1 mg/kg/day was estimated by the study authors. Details of the method of dose estimation were not provided.

If an inhalation study in animals, list conversion factors used in determining human equivalent concentration: NA

Was a conversion used from intermittent to continuous exposure? NA

Other additional studies or pertinent information that lend support to this MRL: Single intraperitoneal injections of pentachlorophenol of unspecified purity at doses up to 28 mg/kg caused marked, statistically significant, dose-related decreases in the serum total thyroxine level in male rats (van Raaij et al. 1991a). The decreases were maximal at 6–24 hours after administration, and thyroxine levels slowly returned to control values within 96 hours after administration. Further in vitro studies by these investigators revealed that the likely mechanism of action for this anti-thyroid effect was competition for serum protein thyroxine binding sites (van Raaij et al. 1991b). A decrease in maternal serum thyroxine (T4) concentration throughout pregnancy and lactation and a significant increase in maternal thyroid gland follicle size were found in female sheep administered 1 mg/kg/day pentachlorophenol (purity not indicated) in the diet 5 weeks prior to mating and throughout pregnancy and lactation until 2 weeks after weaning of the lambs (Beard et al. 1999b). Additionally, increased thyroxine levels were observed in their ewe and ram lambs that also received postnatal exposure to pentachlorophenol (Beard and Rawling 1999; Beard et al. 1999a). Oral gavage administration of pure pentachlorophenol to young adult female rats over a 28-day period at doses of 3 or 30 mg/kg produced decreases in circulating and free concentrations of the thyroid hormones triiodothyronine (T3) and T4 in serum, a decrease in serum thyroid stimulating hormone, decreases in intrathyroidal levels of T3 and T4, a decrease in the T4:T3 ratio in serum, and a reduction in thyroidal hormone stores. Technical-grade pentachlorophenol, tested only at a dose of 3 mg/kg, produced the same effects except the reduction in free T3 in serum (data for free serum T4 were not reported) (Jekat et al. 1994). Single intraperitoneal injections of pentachlorophenol of unspecified purity into adult male rats at doses of 7, 14, or 28 mg/kg also caused marked, statistically significant, dose-related decreases in the uptake of radiolabeled T4 into cerebrospinal fluid compared with control (van Raaij et al. 1994).

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## APPENDIX B

### USER'S GUIDE

#### Chapter 1

##### Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

#### Chapter 2

##### Relevance to Public Health

This chapter provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The chapter covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this chapter. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

## APPENDIX B

**Interpretation of Minimal Risk Levels**

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

**Chapter 3****Health Effects****Tables and Figures for Levels of Significant Exposure (LSE)**

Tables (3-1, 3-2, and 3-3) and figures (3-1 and 3-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

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The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

**LEGEND****See LSE Table 3-1**

- (1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.
- (2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.
- (3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).
- (4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 3-1).
- (5) Species The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.
- (6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.
- (7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.

## APPENDIX B

- (8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").
- (9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.
- (10) Reference The complete reference citation is given in Chapter 9 of the profile.
- (11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.
- (12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

**LEGEND****See Figure 3-1**

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

- (13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.
- (14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.
- (15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m<sup>3</sup> or ppm and oral exposure is reported in mg/kg/day.
- (16) NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).
- (17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

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- (18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels ( $q_1^*$ ).
- (19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

# SAMPLE

1 6

**Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

	Key to figure <sup>a</sup>	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference	
						Less serious (ppm)	Serious (ppm)		
2	6	INTERMEDIATE EXPOSURE							
		5	6	7	8	9		10	
3	6	Systemic	9	9	9	9		9	
4	6	18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3 <sup>b</sup>	10 (hyperplasia)	Nitschke et al. 1981	
CHRONIC EXPOSURE									
							11		
		Cancer					9		
	38	Rat	18 mo 5 d/wk 7 hr/d				20 (CEL, multiple organs)	Wong et al. 1982	
	39	Rat	89–104 wk 5 d/wk 6 hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982	
	40	Mouse	79–103 wk 5 d/wk 6 hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982	

<sup>a</sup> The number corresponds to entries in Figure 3-1.

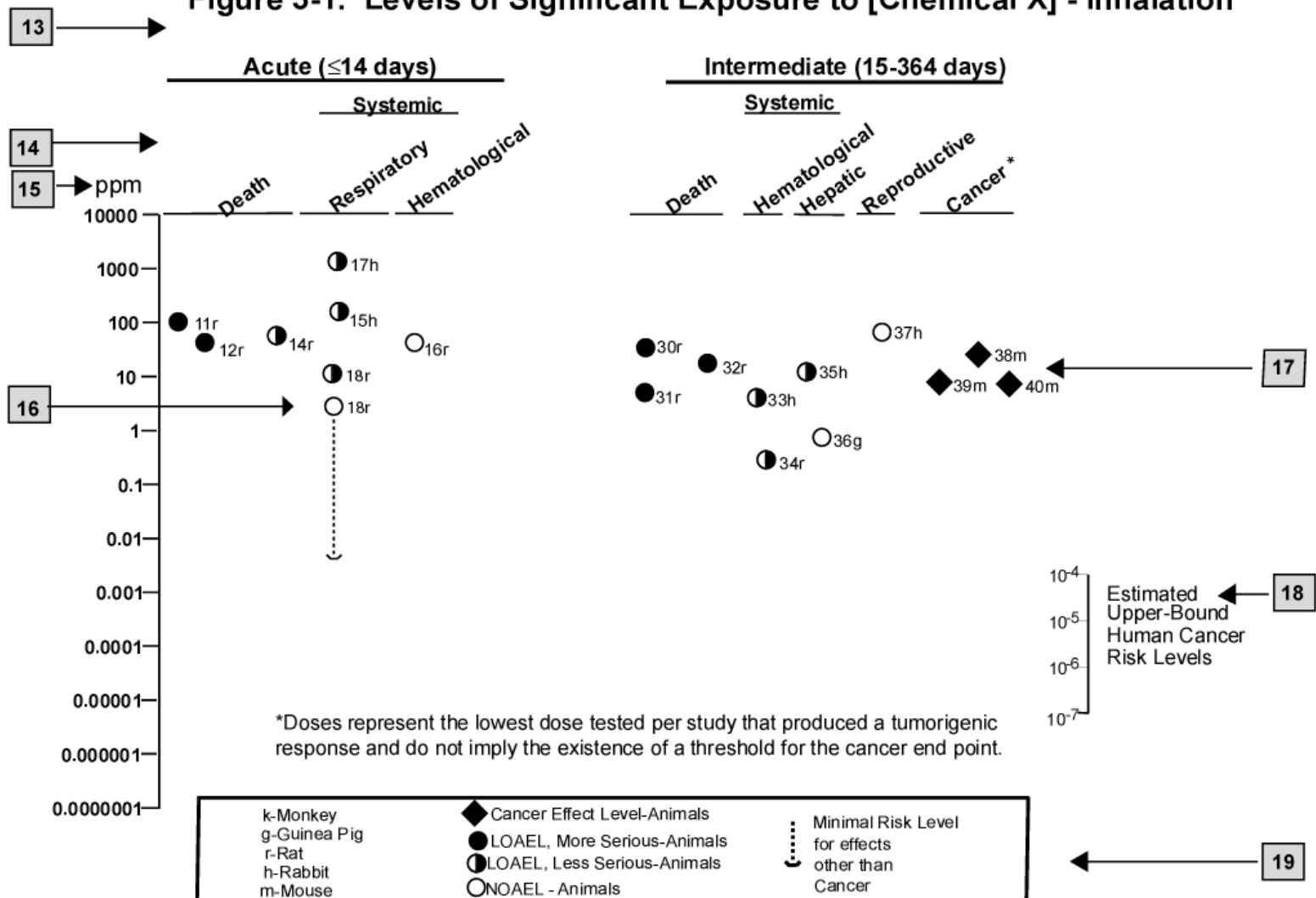
12 6

<sup>b</sup> Used to derive an intermediate inhalation Minimal Risk Level (MRL) of  $5 \times 10^{-3}$  ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).



# SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation





## APPENDIX C

### ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	Best Available Technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	Cancer Effect Level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/	Department of Transportation/United Nations/
NA/IMCO	North America/International Maritime Dangerous Goods Code
DWEL	Drinking Water Exposure Level
ECD	electron capture detection
ECG/EKG	electrocardiogram

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EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F <sub>1</sub>	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
ft	foot
FR	<i>Federal Register</i>
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
K <sub>d</sub>	adsorption ratio
kg	kilogram
kkg	metric ton
K <sub>oc</sub>	organic carbon partition coefficient
K <sub>ow</sub>	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC <sub>Lo</sub>	lethal concentration, low
LC <sub>50</sub>	lethal concentration, 50% kill
LD <sub>Lo</sub>	lethal dose, low
LD <sub>50</sub>	lethal dose, 50% kill
LT <sub>50</sub>	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	<i>trans,trans</i> -muconic acid
MAL	Maximum Allowable Level
mCi	millicurie
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	milligram
min	minute
mL	milliliter

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mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	Polycyclic Aromatic Hydrocarbon
PBPD	Physiologically Based Pharmacodynamic
PBPK	Physiologically Based Pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector

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pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard mortality ratio
SNARL	Suggested No Adverse Response Level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD <sub>50</sub>	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer

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$\mu\text{g}$	microgram
$q_1^*$	cancer slope factor
—	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result





## APPENDIX D

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