TOXICOLOGICAL PROFILE FOR CHLOROPHENOLS

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

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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:

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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
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*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 prepare 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.

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: Health Effects: Specific health effects of a given hazardous compound are reported by *route of exposure*, by *type of health effect* (death, systemic, immunologic, reproductive), 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 Chlorophenols Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to Chlorophenols?
Section 2.6 Children's Susceptibility
Section 5.6 Exposures of Children

Other Sections of Interest:

Section 2.7 Biomarkers of Exposure and Effect
Section 2.10 Methods for Reducing Toxic Effects

ATSDR Information Center

Phone: 1-800-447-1544 (to be replaced by 1-888-42-ATSDR in 1999)
or 404-639-6357 ***Fax:*** 404-639-6359
E-mail: ***atsdric@cdc.gov*** ***Internet:*** ***http://atsdr1.atsdr.cdc.gov:8080***

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.

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.

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@dgs.dgsys.com*** • AOEC Clinic Director: http://occ-env-med.mc.duke.edu/oem/aoec.htm.

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: 847-228-6850 • FAX: 847-228-1856.

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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 chlorophenols. The panel consisted of the following members:

1. Dr. Joseph Gould, Research Scientist, Georgia Institute of Technology, Atlanta, GA.

2. Dr. Arthur Gregory, Private Consultant, Sterling, VA.

3. Dr. Norman Trieff, Professor of Environmental Toxicology, University of Texas, Galveston, TX.

These experts collectively have knowledge of chlorophenols' 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 chlorophenols 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. Chlorophenols has been found in at least 116 of the 1,467 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 chlorophenols are 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 chlorophenols, 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 ARE CHLOROPHENOLS?

Chlorophenols are a group of chemicals in which chlorines (between one and five) have been added to phenol. Phenol is an aromatic compound derived from benzene, the simplest aromatic hydrocarbon, by adding a hydroxy group to a carbon to replace a hydrogen. There are five basic types of chlorophenols: mono[one]chlorophenols, di[two]chlorophenols, tri[three]chlorophenols, tetra[four]chlorophenols, and penta[five]chlorophenols. In all, there are 19 different chlorophenols. Eight are discussed in this document: 2-chlorophenol, 4-chlorophenol, 2,4-dichlorophenol, 2,4,5-trichlorophenol, 2,4,6-trichlorophenol, 2,3,4,5-tetrachlorophenol, 2,3,4,6-

tetrachlorophenol, and 2,3,5,6-tetraohlorophenol. Pentachlorophenol is discussed in another document.

Except for 2-chlorophenol, which is a liquid at room temperature, all of the chlorophenols are solids. The chlorophenols have a strong medicinal taste and odor; small amounts (at parts per billion [ppb] to parts per million [ppm] concentrations) can be tasted in water. Very small amounts of chlorophenols can also make fish taste bad. All the compounds discussed are or were produced commercially.

Chlorophenols with at least two chlorines either have been used directly as pesticides or converted into pesticides. Also, chlorophenols, especially 4-chlorophenol, have been used as antiseptics. In addition to being produced commercially, small amounts of some chlorophenols, especially the mono- and dichlorophenols, may be produced when waste water or drinking water is disinfected with chlorine, if certain contaminants are present in the raw water. They are also produced during the bleaching of wood pulp with chlorine when paper is being produced. More information on the physical and chemical properties and on the production and use of chlorophenols is found in Chapters 3 and 4.

1.2 WHAT HAPPENS TO CHLOROPHENOLS WHEN THEY ENTER THE ENVIRONMENT?

Chlorophenols can enter the environment while they are being made or used as pesticides. Most of the chlorophenols released into the environment go into water, with very little entering the air. The compounds that are most likely to go into the air are the mono- and dichlorophenols because they are the most volatile (that is, have the greatest tendency to form vapors or gases). Once in the air, sunlight helps destroy these compounds and rain washes them out of the air. Chlorophenols stick to soil and to sediments at the bottom of lakes, rivers, or streams. However, low levels of chlorophenols in water, soil, or sediment are broken down by microorganisms and are removed from the environment within a few days or weeks. Further information regarding the release and environmental fate of chlorophenols can be found in Chapters 4 and 5.

1.3 HOW MIGHT I BE EXPOSED TO CHLOROPHENOLS?

Most people are exposed to very low levels of chlorophenols in drinking water that has been ' disinfected with chlorine (chlorinated drinking water). Chlorophenols have been measured in chlorinated drinking water at parts per trillion (ppt) concentrations (that is, the amount [weight] of chlorophenols per trillion parts [volume] of water). In lakes, rivers, and streams, chlorophenols were found in less than 1 percent of the water that was tested. Chlorophenols have been measured in city air at concentrations of less than a part per trillion (the amount of chlorophenols [volume] per trillion parts [volume] of air).

It has been estimated during the National Occupational Exposure Survey (NOES) from 1981-1983 that about 5,000 people in the United States are exposed to 4-chlorophenol, 2,4,5-trichlorophenol, or 2,4,6-trichlorophenol at work (NOES 1990). It has not been estimated how many people are exposed at work to the other chlorophenols. People who make chlorophenols or use them as pesticides are most likely to have high exposure to these chemicals. For example, mixtures of tetrachlorophenols are used at sawmills as wood preservatives. Skim contact while treating wood with the tetrachlorophenols is the most likely route of exposure. Another likely route of exposure is breathing air contaminated by mono- and dichlorophenols. Further information regarding exposure to chlorophenols can be found in Chapter 5.

1.4 HOW CAN CHLOROPHENOLS ENTER AND LEAVE MY BODY?

When chlorophenols are eaten, almost all of the compounds quickly enter the body. Chlorophenols also rapidly enter the body through the skin. Little is known about how much of the chlorophenols enter the body if one breathes air containing them. The monochlorophenols do not stay inside the body very long. They are changed to less harmful products, and most leave through the urine within 24 hours. The other chlorophenols (dichlorophenol, trichlorophenols, tetrachlorophenols), which also leave through the urine as less harmful chemicals, can stay in the body for several days. For further discussion about how the chlorophenols enter and leave the body, see Chapter 2.

1, PUBLIC HEALTH STATEMENT

1.5 HOW CAN CHLOROPHENOLS 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.

One man who splashed pure 2,4-dichlorophenol on his arm and leg died shortly after the accident. Workers who made pesticides from chlorophenols and were exposed to chlorophenols as well as other chemicals through breathing and through the skin developed acne and mild injury to their livers. According to some studies, the risk of cancer was also slightly higher among workers who had made pesticides for a long time. These workers were exposed to very high levels of other chemicals as well as chlorophenols, so it is not certain whether the effects were caused by the chlorophenols or the other chemicals.

Animals that were given food or drinking water containing chlorophenols at high levels developed adverse or negative health effects. The major effects with exposure to high levels of chlorophenols were on the liver and the immune system. Also, the animals that ate or drank chlorophenols did not gain as much weight as the animals that ate food and drank water not containing chlorophenols.

Feeding rats and mice high doses of 2,4-dichlorophenol for a long time did not cause cancer. However, long-term treatment of rats and mice with high doses of 2,4,6-trichlorophenol in food caused leukemia in rats and liver cancer in mice, suggesting that 2,4,6-trichlorophenol may be a

carcinogen. The Department of Health and Human Services has determined that 2,4,6-trichlorophenol may reasonably be anticipated to be a carcinogen. The International Agency for Research on Cancer (IARC) has determined that the chlorophenols as a group, are possibly carcinogenic to man. The Environmental Protection Agency (EPA) has determined that 2,4,6-trichlorophenol is a probable carcinogen.

Putting chlorophenols on the skin or eyes of animals causes severe injuries. Injury is greatest with exposure to the mono- and dichlorophenols. The signs of severe skin injury include redness, swelling, scabbing, and scar formation. The cornea was damaged when monochlorophenols were placed directly onto the eyes of rabbits. Further information about the health effects following exposure to chlorophenols can be found in Chapter 2.

1.6 HOW CAN CHLOROPHENOLS AFFECT CHILDREN?

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans. Potential effects on children resulting from exposures of the parents are also considered.

The most likely source from which children could be exposed to chlorophenols is water that has been disinfected with chlorine. Children could receive larger doses because they consume more fluids per bodyweight than adults. Children may also be exposed in areas where chlorophenols have been sprayed as pesticides or herbicides. Children playing outdoors in areas with contaminated soil could be at risk for exposure because they often put objects or hands in their mouths. Monochlorophenols are used as household antiseptics, and 2,4-DCP is used for mothproofing. More complex chlorophenols are used as biocides. Biocides are substances used to kill organisms.

We do not know whether chlorophenols cause birth defects in humans; chlorophenols have not been shown to cause birth defects in animals, even at high doses. High levels of chlorophenols given to pregnant female rats in the drinking water have tended to reduce the number of their

newborn animals and to decrease the weights of the newborn. In one study animals exposed to chlorophenols showed delayed hardening of some bones. Section 2.6 of this profile contains further details on animal-based developmental effects studies. We do not know whether chlorophenols can cross the placenta or get into breast milk.

1.7 HOW CAN FAMILIES REDUCE THE RISK OF EXPOSURE TO CHLOROPHENOLS?

If your doctor finds that you have been exposed to significant amounts of chlorophenols, ask if children may also be exposed. When necessary your doctor may need to ask your state department of public health to investigate.

The chlorophenols presented in this profile exist in eight different forms, each one having different properties and uses. Therefore, different routes exist in which a family may be exposed to chlorophenols. Chlorophenols are primarily used as antiseptics, disinfectants, herbicides, pesticides, and wood preservatives. People are at greater risk of exposure if they live near industrial facilities that use or manufacture chlorophenols or waste sites that could be releasing it into the environment. Most released chlorophenols are found in surface water or in soil near the release point. Children should be kept from coming in contact with water or dirt in an area that could be contaminated. You should prevent your children from eating dirt. Make sure they wash their hands frequently and before eating. Discourage your children from putting their hands in their mouths or other hand-to-mouth activity.

People who do not live near production or waste sites can still be exposed to chlorophenols through other routes. Chlorophenols can be present in drinking water when chlorine is used to disinfect it. The safe drinking water standard for 2-chlorophenol is included in Table 7-l. At low concentrations, chlorophenols give water an unpleasant, medicinal taste.

Chlorophenols and other related chemicals are often used as herbicides and pesticides. 2,4-D and 2,4,5-T, the latter of which has been banned, are herbicides often used on food crops that can break down to form 2,4-DCP. Children should be deterred from playing in areas where 2,4-D or

other chlorophenol based herbicides or pesticides have been sprayed. Children are lower to the ground than adults and may be exposed because they often get dirt, grass, and other outdoor material on their skin and in their mouths. Also, your children may be exposed to chlorophenols if an unqualified person applies pesticides containing them 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 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.

If you buy over-the-counter pesticide products to apply yourself, be sure the products are in unopened pesticide containers that are labeled and contain an EPA registration number. Carefully follow the instructions on the label. If you plan to spray inside, make sure the pesticide is intended for indoor use.

If you feel sick after a pesticide has been used in your home, consult your doctor or local poison control center.

Chlorophenols may also be present in many household products. 2,4-DCP is commonly used for mothproofing. 4-CP is used as a disinfectant in homes, farms, hospitals, and as an antiseptic for root canal treatment. Monochlorophenols have been used as antiseptics, although they have largely been replaced by other chemicals. Pesticides and household chemicals should be stored out of reach of young children to prevent unintentional poisonings. Always store pesticides and household chemicals in their original labeled containers. Never store pesticides or household chemicals in containers children would find attractive to eat or drink from, such as old soda bottles.

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

There is no medical test that is specific for chlorophenols to determine whether you have been exposed to these chemicals. Compounds that have been made by your body from chlorophenols can be measured in the urine. However, these compounds can also be found in the urine when you are exposed to other chemicals such as lindane (an insecticide) or to 2,4-dichlorophenoxyacetic acid (a chemical that kills weeds). More information about measuring exposure to chlorophenols can be found in Chapter 2.

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).

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 chlorophenols include the following:

The EPA recommends that drinking water concentrations of 2-chlorophenol should not be more than 0.04 part per million (ppm), and concentrations of 2,4-dichlorophenol should not be more than 0.02 ppm; these are levels that can be tasted. In order for chlorophenols to be lower than levels that can be tasted, the EPA recommends levels of 0.1 part per billion (ppb; the amount of chlorophenols per billion parts of water) for monochlorophenols, 0.3 ppb for 2,4-dichlorophenols, and 1 ppb for 2,4,5-trichlorophenol and 2,3,4,6-tetrachlorophenol. More information about regulations and guidelines for chlorophenols can be found in Chapter 7.

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: l-800-447-1544
Fax: (404) 639-6359

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.

1. PUBLIC HEALTH STATEMENT

* To order toxicological profiles, contact

National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161
Phone: (800) 553-6847 or (703) 487-4650

2. HEALTH EFFECTS

2.1 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 chlorophenols. 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.

2.2 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 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 (LOAEL) 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 chlorophenols are indicated in Table 2-1 and Figure 2-1. Because cancer effects could occur at lower exposure levels, the figure 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}-10^{-7}), as developed by EPA.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for chlorophenols. 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.

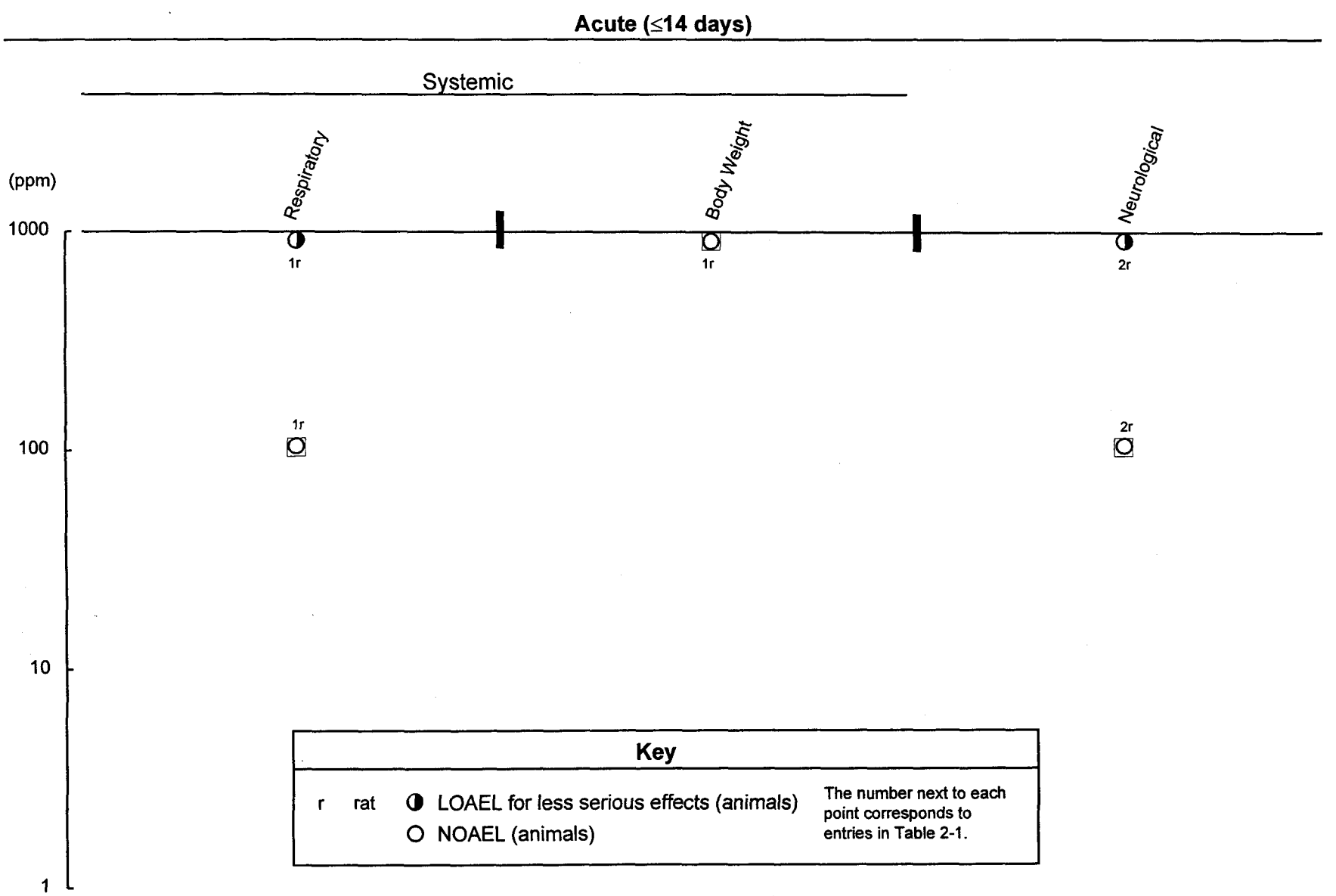
TABLE 2-1. Levels of Significant Exposure to Chlorophenols - Inhalation

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)	LOAEL (effect) Serious (ppm)	Reference/ Compound
ACUTE EXPOSURE							
Systemic							
1	Rat (Wistar)	4 hr	Resp	104	908 M (tachypnea 1/5 rats)		Duchosal and Biedermann 1991
							2-chlorophenol
			Bd Wt	908			
Neurological							
2	Rat (Wistar)	4 hr		104	908 (restlessness, hunched posture)		Duchosal and Biedermann 1991
							2-chlorophenol

[a] The number corresponds to entries in Figure 2-1.

Bd Wt = body weight; hr = hour(s); LOAEL= lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; Resp = respiratory

Figure 2-1. Levels of Significant Exposure to Chlorophenols - Inhalation



2. HEALTH EFFECTS

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.

There are 19 isomers of the chlorophenols, each containing between 1 and 5 chlorines. All members of the series are chlorine derivatives of phenol, the simplest aromatic alcohol, i.e., hydroxybenzene. They possess both acute and chronic toxicity which varies with the number of chlorines present. However, this profile is concerned with only eight of these isomers, chosen on the basis of the following three criteria: (1) toxicity, (2) potential for human exposure, and (3) frequency of occurrence at NPL hazardous waste sites.

Because many of the isomers typically co-occur in the environment and have qualitatively (but not quantitatively) similar toxicological effects, they are combined into one profile to avoid repetition across multiple profiles. The isomers discussed include two monochlorinated compounds (2- and 4-chlorophenol, or 2-CP and 4-CP), one dichlorinated compound (2,4-dichlorophenol, or 2,4-DCP), two trichlorinated compounds (2,4,5- and 2,4,6-trichlorophenol, or 2,4,5-TCP and 2,4,6-TCP), and three tetrachlorinated compounds (2,3,4,5-, 2,3,4,6-, and 2,3,5,6-tetrachlorophenol, or 2,3,4,5-TeCP, 2,3,4,6-TeCP, and 2,3,5,6-TeCP). The information in the profile is organized by isomer (mono-, di-, tri-, tetrachlorophenols), and for each isomer the available data are then presented by duration (acute [14 days or less], intermediate [15 to 364 days], chronic [365 days or more]). In this text, the term "chlorophenols" will refer to any two or more of these eight isomers. The most commercially and toxicologically significant isomer, pentachlorophenol, is not included in this document because it is the subject of a separate profile.

2.2.1 Inhalation Exposure

2.2.1.l Death

Mortality studies of workers at phenoxy herbicide factories where exposure to chlorinated phenols (2,4,5-TCP, 2,4,6-TCP, and 2,4-DCP) occurred, have not shown increased mortality from any cause (Coggen et al. 1991; Ott et al. 1987). Additional occupational studies that focus on cancer-related deaths are discussed in Section 2.2.1.8. No studies were located regarding death in humans following inhalation exposure to any of the chlorophenols discussed in this profile.

Nose-only exposure of male and female Wistar rats to 2-CP for 4 hours to a concentration of 908 ppm (Duchosal and Biederman 1991) and whole-body exposure of Sprague-Dawley rats to 2-CP for 6 hours

at 620 ppm (Younger Labs 1975) did not result in any deaths. These studies are limited by a lack of experimental detail. Additional studies regarding lethality in animals following inhalation exposure to chlorophenols were not located.

2.2.1.2 Systemic Effects

No studies were located regarding musculoskeletal or renal effects in humans or animals after inhalation exposure to any of the eight chlorophenols discussed in this profile.

The limited studies examining systemic effects following inhalation exposure to chlorophenols are described below. The NOAEL and LOAEL values from the single reliable study are recorded in Table 2-1 and plotted in Figure 2-1.

Respiratory Effects. No studies were located regarding respiratory effects in humans after inhalation exposure to any of the eight chlorophenols discussed in this profile. Very limited studies of respiratory effects in workers exposed by inhalation to one or more of the chlorophenols in conjunction with other substances have been completed.

When compared to 260 unexposed referents, 281 workers involved in the production of sodium trichlorophenol and its derivatives for 18 years had no increased incidence of chronic bronchitis, chronic obstructive pulmonary disease, or altered measures of pulmonary function (Calvert et al. 1991). Exposure occurred 15 years before pulmonary function was examined. Because trichloro-phenols are rapidly cleared, serum 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), which was produced as a contaminant in the manufacture of 2,4,5-TCP and its derivatives, was used to indicate that the workers had actually been exposed. The mean lipid adjusted TCDD serum concentration in exposed workers was 200 ppt relative to 7 ppt in the controls.

Occupational exposure of seven workers to an unspecified trichlorophenol isomer, in addition to other chemicals, by chronic inhalation was associated with adverse upper airway and chest symptoms (cough, chronic bronchitis, chest wheezing), altered pulmonary function (reduced expiratory flow rate of the lung, increased closing volume of the lung, increased elastic recoil pressure of the lung), and pulmonary lesions (interstitial densities) (Alexandersson and Hedenstierna 1982). The workers were exposed for 2-10 years and exposure concentrations were not well characterized. The study indicates that exposure concentrations were 0.003 mg/L (0.02 ppm) or less, and they may have varied considerably. The study was also limited

because of the small number of subjects (seven), which included three smokers. Therefore, it is not possible to determine whether the exposure to TCP alone induced the reported respiratory effects or whether smoking contributed to the effects. The authors (Alexandersson and Hedenstierna 1982) concluded that inhalation exposure to trichlorophenol may cause pulmonary dysfunction and possibly fibrosis following chronicduration exposure.

Lumber mill workers exposed to a mixture of tetrachlorophenols (specific isomers not stated) and pentachlorophenol reported upper respiratory tract irritation more frequently than unexposed workers (Kleinman et al. 1986). Tetrachlorophenol air concentrations ranged from 0.8 to 12.2 μg/m^3, and pentachlorophenol concentrations were below the limit of detection (0.5 μg/m^3).

Tachypnea was observed in one of five male rats exposed (nose-only) to 2-CP at 908 ppm for 4 hours (Duchosal and Biederman 1991). Tachypnea was not observed in any female rats exposed in the same manner. Dark red foci observed in the lungs (right caudal, median, or left lobe) of male and female rats exposed to 17 (2/5 males, 2/5 females) or 104 ppm (4/5 males, 2/5 females) were not found at 908 ppm (Duchosal and Biederman 1991). No controls were used in this study. The LOAEL for tachypnea and a NOAEL for respiratory effects identified in this limited study are presented in Table 2-l and Figure 2-l.

Cardiovascular Effects. Electrocardiograms were normal in three individuals who developed chloracne following occupational exposure (inhalation and dermal) to chlorophenols and other compounds during the manufacture of 2,4-DCP and 2,4,5-TCP (Bleiberg et al. 1964). No additional studies were located regarding cardiovascular effects in humans following inhalation exposure to any of the eight chlorophenols discussed in this profile.

No studies were located regarding cardiovascular effects in animals following inhalation exposure to any of the eight chlorophenols discussed in this profile.

Gastrointestinal Effects. The self-reported prevalence of gastrointestinal disease was not increased among 281 TCP production workers with elevated serum TCDD levels (Calvert et al. 1992). The workers had been exposed to a mixture of TCPs at least 15 years prior to the survey. However, the long time lag between exposure and examination of gastrointestinal symptoms may invalidate the study.

2. HEALTH EFFECTS

No studies were located regarding gastrointestinal effects in animals after inhalation exposure to any of the eight chlorophenols discussed in this profile.

Hematological Effects. Clinical assessment of two patients occupationally exposed during the manufacture of 2,4-DCP- and 2,4,5-TCP-based herbicides revealed hematology and blood chemistry parameters (blood counts, bleeding and clotting time, serum bilirubin, blood urea nitrogen, and others) to be within normal ranges (Bleiberg et al. 1964).

No studies were located regarding hematological effects in animals after inhalation exposure to any of the eight chlorophenols discussed in this profile.

Hepatic Effects. Porphyria cutanea tarda has been reported in workers employed in the manufacture of 2,4-DCP and 2,4,5-TCP (Bleiberg et al. 1964). Exposure to chlorophenols and intermediates was probably through inhalation and dermal contact. Eleven cases of porphyria were identified, based on urinary porphyrin excretion, in a survey of 29 workers. Elevated serum transaminase levels and evidence of liver damage, e.g., regeneration of liver cells and hemofuscin (a brownish-yellow pigment that results from the decomposition of hemoglobin) deposition, were detected from liver biopsies in two cases that were studied in detail. Thus, the exposure was probably related to liver injury. Definitive conclusions regarding the connection between the porphyria or liver injury and exposure to chlorophenols in this group of workers cannot be made since the workers were exposed to a variety of chlorinated compounds, including a highly volatile chlorinated phenolic ether with six chlorines formed during the manufacturing process. The data provide an alert for potential human risk, however. Information on exposure to other liver toxicants, including the chronic ingestion of alcohol, was not obtained.

The results of a cross-sectional study of trichlorophenol production workers indicated an increased risk of elevated gamma-glutamyltransferase (GGT) activity in these workers (Calvert et al. 1992). GGT is a liver enzyme that is a potential marker of hepatobiliary disease. An interaction between alcohol consumption and exposure was related to increased GGT activity in these production workers (Calvert et al. 1992). However, the absence of increases in other hepatic enzymes may limit the diagnostic potential of the GGT findings in this study.

No studies were located regarding hepatic effects in animals following inhalation exposure to any of the eight chlorophenols discussed in this profile.

Dermal Effects. Chloracne, evidence of acquired porphyria cutanea tardia, hyperpigmentation, folliculitis, keratosis, and hirsutism have been observed in workers employed in the manufacture of 2,4-DCP- and 2,4,5-TCP-based herbicides (Bleiberg et al. 1964; Bond et al. 1989). As noted above in the discussion of hepatic effects, exposure to chlorophenols may have been through either inhalation or dermal contact or both. Furthermore, the subjects were exposed to several chlorinated compounds (e.g., dioxin) in addition to chlorophenols; therefore, the chloracne and other dermal effects cannot be ascribed specifically to chlorophenol exposure since chloracne is known to occur following exposure to TCDD.

No studies were located regarding dermal effects in animals following inhalation exposure to any of the eight chlorophenols discussed in this profile.

Ocular Effects. Lumber mill workers exposed to a mixture of tetrachlorophenols (specific isomers not stated) and pentachlorophenol reported eye irritation more frequently than unexposed workers (Kleinman et al. 1986). Tetrachlorophenol air concentrations ranged from 0.8 to 12.2 $\mu g/m^3$, and pentachlorophenol concentrations were below the limit of detection (0.5 $\mu g/m^3$). Industrial hygienists indicated that improvements in protective equipment were necessary at this mill, which suggests that ocular irritation could have resulted in part from contact with contaminated surfaces (e.g., hands, clothing).

No studies were located regarding ocular effects in animals following inhalation exposure to any of the eight chlorophenols discussed in this profile.

Body Weight Effects. No studies were located regarding body weight effects in humans following inhalation exposure to any of the eight chlorophenols discussed in this profile.

No changes in body weight were observed during the 15-day observation period after rats were exposed (nose-only) to 2-CP at 908 ppm for 4 hours (Duchosal and Biedermann 1991). No controls were included in this study. This NOAEL for body weight effects is recorded in Table 2-l and plotted in Figure 2-1.

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans or animals after inhalation exposure to any of the eight chlorophenols discussed in this profile.

Dermal Effects. Chloracne, evidence of acquired porphyria cutanea tardia, hyperpigmentation, folliculitis, keratosis, and hirsutism have been observed in workers employed in the manufacture of 2,4-DCP- and 2,4,5-TCP-based herbicides (Bleiberg et al. 1964; Bond et al. 1989). As noted above in the discussion of hepatic effects, exposure to chlorophenols may have been through either inhalation or dermal contact or both. Furthermore, the subjects were exposed to several chlorinated compounds (e.g., dioxin) in addition to chlorophenols; therefore, the chloracne and other dermal effects cannot be ascribed specifically to chlorophenol exposure since chloracne is known to occur following exposure to TCDD.

No studies were located regarding dermal effects in animals following inhalation exposure to any of the eight chlorophenols discussed in this profile.

Ocular Effects. Lumber mill workers exposed to a mixture of tetrachlorophenols (specific isomers not stated) and pentachlorophenol reported eye irritation more frequently than unexposed workers (Kleinman et al. 1986). Tetrachlorophenol air concentrations ranged from 0.8 to 12.2 $\mu g/m^3$, and pentachlorophenol concentrations were below the limit of detection (0.5 $\mu g/m^3$). Industrial hygienists indicated that improvements in protective equipment were necessary at this mill, which suggests that ocular irritation could have resulted in part from contact with contaminated surfaces (e.g., hands, clothing).

No studies were located regarding ocular effects in animals following inhalation exposure to any of the eight chlorophenols discussed in this profile.

Body Weight Effects. No studies were located regarding body weight effects in humans following inhalation exposure to any of the eight chlorophenols discussed in this profile.

No changes in body weight were observed during the 15-day observation period after rats were exposed (nose-only) to 2-CP at 908 ppm for 4 hours (Duchosal and Biedermann 1991). No controls were included in this study. This NOAEL for body weight effects is recorded in Table 2-l and plotted in Figure 2-1.

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans or animals after inhalation exposure to any of the eight chlorophenols discussed in this profile.

2.2.1.4 Neurological Effects

Lumber mill workers exposed to a mixture of tetrachlorophenols (specific isomers not stated) and pentachlorophenol reported headaches more frequently than unexposed workers (Kleinman et al. 1986). Monitoring of air and urinary concentrations of tetrachlorophenols suggested that exposure was principally through the skin.

Rats exposed for 4 hours to 908 ppm 2-CP using nose-only exposure showed restlessness, a hunched posture, and ruffled fur (Duchosal and Biedermann 1991). These effects were not observed at 104 ppm. The LOAEL and NOAEL for neurological effects is recorded in Table 2-l and plotted in Figure 2-l.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after inhalation exposure to any of the eight chlorophenols discussed in this profile.

2.2.1.6 Developmental Effects

No studies were located regarding developmental health effects in humans or animals after inhalation exposure to any of the eight chlorophenols discussed in this profile.

2.2.1.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

A number of investigators have studied the potential association between chlorophenol-based pesticide production and carcinogenicity (Eriksson et al. 1981, 1990; Hardell et al. 1981; Hoar et al. 1986; Honchar and Halperin 1981; Kogevinas et al. 1992; Lynge 1985; Smith et al. 1984; Woods et al. 1987). Reports from Sweden indicate significantly increased relative risk ratios for soft tissue sarcomas (STS) and/or non-Hodgkin's lymphomas (NHLs) in exposed workers (Eriksson et al. 1981, 1990; Hardell et al. 1981). In a retrospective cohort study on Danish workers exposed to 2,4-DCP and 4- chloro-*o*-tolyloxy-acetic

The composite human results represent studies from a variety of occupational settings, with various degrees of exposure to chlorophenols, dioxins, intermediates, and final products, such as chlorophenoxy pesticides. The data are not sufficiently sensitive to support a relationship, per se, between any of the chlorophenol exposures and tumor incidence. However, taken in composite, the human study results do suggest a possible concern for increased tumorigenic risk in farm workers and production workers exposed to chlorophenols or their end-use products (Woods et al. 1987).

No studies were located regarding cancer in animals after inhalation exposure to any of the eight chlorophenols discussed in this profile.

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding death in humans after oral exposure to any of the eight chlorophenols discussed in this profile.

The lowest reported LD_{50} for a chlorophenol isomer was 89 mg/kg for male mice treated with 2,3,5,6 TeCP in ethanol (Ahlborg and Larsson 1978). The highest reported LD_{50} was 2,960 mg/kg for male rats treated with 2,4,5-TCP in corn oil (McCollister et al. 1961). The range of LD_{50} values indicates that the chlorophenols are slightly or moderately toxic according to the classification scheme of Hodge and Sterner (1949). Ahlborg and Larssen (1978) examined the acute oral toxicity of the TeCPs in both ethanol and propylene glycol. The LD_{50}s were higher when propylene glycol was used as the vehicle rather than ethanol (e.g., the LD_{50} for 2,3,4,6-TeCP in female mice was 131 when administered in ethanol and 735 mg/kg when administered in propylene glycol). The Ahlborg and Larssen (1978) study highlights the importance of vehicle effects in acute gavage studies, and because vehicles were different across studies and chlorophenol isomers, it is not possible to make definitive conclusions about which isomer is more toxic following a single oral dose.

In the only known toxicity study involving repeated dosing of monochlorophenols, groups of male and female ICR mice received daily gavage doses of 35, 69, or 175 mg/kg/day 2-CP in corn oil for 14 days. No exposure-related deaths occurred at the two lower treatment levels. All mice exposed at 175 mg/kg/day died,

suggesting a steep dose-response relationship between the mid- and high-treatment doses (Borzelleca et al.1985a).

In repeated-dose studies of 2,4-DCP in corn oil, 4 out of 34 pregnant Fischer-344 rats treated by gavage at 750 mg/kg/day on gestation days 6-15 died (Rodwell et al. 1989), while all non-pregnant rats treated with 2,000 mg/kg/day in the diet for 14 days survived (NTP 1989). Although pregnant rats may be more susceptible, the difference in effect may also be a result of differences in the rate of exposure between gavage and dietary dosing.

All rats and mice exposed to 2,4-DCP in the diet for 13 weeks at doses of 2,000 or 2,600 mg/kg/day survived (NTP 1989). However, all mice died when exposed to 5,200 mg/kg/day for 3 weeks (NTP 1989). In a 2-year study, decreased survival was not observed in rats fed 2,4-DCP in the diet at doses up to 440 mg/kg/day or in mice fed 2,4-DCP in the diet at doses up to 1,300 mg/kg/day for 103 weeks (NTP 1989).

No deaths were observed among rats treated by gavage (18 doses in olive oil) or in the diet with 2,4,5-TCP at doses up to 1,000 mg/kg/day for 90 days (McCollister et al. 1961). In addition, no deaths were observed in rabbits treated with 20 gavage doses of 500 mg/kg/day 2,4,5-TCP over 28 days (McCollister et al. 1961).

Deaths were observed during the first 4 weeks of treatment among female rats (3/40) and male rats (8/25) exposed to 2,4,6-TCP in corn oil by gavage for 11 weeks at 1,000 but not at 500 mg/kg/day (Blackbum et al.1986). The females were treated 2 weeks prior to pregnancy and then throughout gestation. No deaths were observed in rats treated by gavage with 2,4,6-TCP in corn oil at 720 mg/kg/day for 90 days (Bercz et al. 1990). In a 7-week dietary study, 1 of 5 rats died at 1,075 mg/kg/day and 4 of 10 mice died at 4,095 mg/kg/day, with no deaths observed at 735 mg/kg/day among rats or at 2,795 mg/kg/day among mice (NCI 1979). In a chronic study, no increased mortality trend was observed in rats or mice treated with 2,4,6-TCP in the diet at concentrations up to 500 mg/kg/day for 106-107 weeks for rats and 1,356 mg/kg/day for 105 weeks for mice (NCI 1979).

No deaths were observed in rats treated by gavage with 200 mg 2,3,4,6-TeCP/kg/day during gestation (RTI 1987) or among male and female rats treated at 200 mg/kg/day for 90 days (American Biogenics 1988). In both studies the 2,3,4,6-TeCP was given in olive oil.

The LD_{50} values and all reliable LOAEL values for death in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category for oral exposures to chlorophenols are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. No studies were located regarding respiratory effects in humans after oral exposure to any of the eight chlorophenols discussed in this profile.

Lung hemorrhaging occurred in rats treated with a single lethal gavage dose of 2,4-DCP (Wil Research Laboratories 1982). Nasal lesions were noted in male but not female rats exposed to 210 mg/kg/day for 103 weeks. Nasal lesions were not observed in mice fed as much as 1,300 mg/kg/day for the same exposure period (NTP 1989). This effect may, therefore, be specific to the male rat or may have been a result of aspiration while eating. Histopathological changes have not been observed in the lungs of rats or mice orally exposed to 2,4-DCP (Borzelleca et al. 1985a; NTP 1989), 2,4,5-TCP (McCollister et al. 1961), 2,4,6-TCP (Bercz et al. 1990; Blackburn et al. 1986; NCI 1979), or 2,3,4,6-TeCP (American Biogenics 1988).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after oral exposure to any of the eight chlorophenols discussed in this profile.

No change in heart weight was noted in mice fed 2,4-DCP at doses up to 230 mg/kg/day for 6 months (Kobayashi et al. 1972). Histopathological examinations of the heart have not revealed any effects in rats fed 2,4-DCP at 2,000 mg/kg/day or in mice fed 2,4-DCP at 2,600 mg/kg/day for 13 weeks (NTP 1989). Studies on rats exposed to 2,4-DCP at doses as high as 440 mg/kg/day and mice exposed to as much as 1,300 mg/kg/day for 103 weeks also showed no histological changes in the heart (NTP 1989).

Heart weight changes were not observed in rats treated with 18 gavage doses of 1,000 mg 2,4,5-TCP/kg, nor were.histological changes observed in the hearts of rats treated with 2,4,5-TCP in the diet at doses up to1,000 mg/kg/day for 98 days (McCollister et al. 1961).

TABLE 2-2. Levels of Significant Exposure to Chlorophenols - Oral

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference/ Compound
	ACUTE EXPOSURE						
	Death						
1	Rat (Fischer-344)	10 d 1x/d Gd 6-15 (GO)				750 F (4/34 maternal deaths)	Rodwell et al. 1989 2,4-dichlorophenol
2	Rat (NS)	once (GO)				2960 M (LD50)	McCollister et al. 1961 2,4,5-trichloropheno
3	Mouse (CD-1 ICR)	14 d (GO)				175 (24/24 died)	Borzelleca et al. 1985a 2-chlorophenol
4	Mouse (CD-1 ICR)	once (GW)				345 F (LD50)	Borzelleca et al. 1985a, 1985b 2-chlorophenol
5	Mouse (CD-1 ICR)	once (GO)				1373 M (LD50)	Borzelleca et al. 1985a, 1985b 4-chlorophenol
6	Mouse (CD-1)	once (GO)				1276 M (LD50)	Borzelleca et al. 1985b, 1985c 2,4-dichlorophenol

TABLE 2-2. Levels of Significant Exposure to Chlorophenols - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference/ Compound
7	Mouse (B6C3F1)	14 d (F)				5200 M (1/5 deaths)	NTP 1989
							2,4-dichlorophenol
8	Mouse (C57 black)	once (G)				400 F (LD50)	Ahlborg and Larsson 1978
							2,3,4,5-tetraCP
9	Mouse (C57 black)	once (G)				131 F (LD50)	Ahlborg and Larsson 1978
							2,3,4,6-tetraCP
10	Mouse (C57 black)	once (G)				89 M (LD50)	Ahlborg and Larsson 1978
							2,3,5,6-tetraCP
11	Gerbil (NS)	once (G)				533 F (LD50)	Ahlborg and Larsson 1978
							2,3,4,5-tetraCP
12	Gerbil (NS)	once (G)				698 F (LD50)	Ahlborg and Larsson 1978
							2,3,4,6-tetraCP
13	Gerbil (NS)	once (G)				979 F (LD50)	Ahlborg and Larsson 1978
							2,3,5,6-tetraCP

TABLE 2-2. Levels of Significant Exposure to Chlorophenols - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference/ Compound
	Systemic						
14	Rat (Sprague-Dawley)	2 wk 2x/d (GO)	Hepatic	1.28 [b] M	2.58 M (hepatocytes: foamy cytoplasm, clustering of mitochondria and endoplasmic reticulum)		Phornchirasilp et al. 1989b 4-chlorophenol
15	Rat (Fischer-344/N)	14 d (F)	Bd Wt	500 M	1000 M (19% decrease in body weight)	2000 M (52% decrease in body weight)	NTP 1989 2,4-dichlorophenol
16	Rat (Sprague-Dawley)	14 d 1x/d (GO)	Hepatic	400			Carlson 1978 2,4,5-trichlorophenol
17	Rat (Sprague-Dawley)	14 d 1x/d (GO)	Hepatic	400			Carlson 1978 2,4,6-trichlorophenol
18	Rat (Wistar)	once (GO)	Gastro	410	432 (mild necrosis)	632 (mucosal hyperemia of stomach, severe necrosis of intestine)	Hattula et al. 1981 2,3,4,6-tetraCP
			Musc/skel	632			
			Renal	632			

TABLE 2-2. Levels of Significant Exposure to Chlorophenols - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference/ Compound
19	Mouse (CD-1 ICR)	14 d (GO)	Hemato	69			Borzelleca et al. 1985a 2-chlorophenol
			Hepatic	69			
			Renal	69			
			Bd Wt	35	69 (unspecified decreased body weight)		
20	Mouse (B6C3F1)	14 d (F)	Bd Wt	2600		5200 M (25% decrease body weight, reduced food intake)	NTP 1989 2,4-dichlorophenol
	Immuno/Lymphor						
21	Mouse (CD-1 ICR)	14 d (GO)		69			Borzelleca et al. 1985a 2-chlorophenol
	Neurological						
22	Rat (Fischer 344)	once (GO)		1000	2000 F (lethargy, ataxia, sensitivity to touch and sound, twitches)		Wil Research Laboratories, Inc. 1982 2,4-dichlorophenol
23	Mouse (CD-1 ICR)	14 d (GO)			35 (hyperactivity)		Borzelleca et al. 1985a 2-chlorophenol

TABLE 2-2. Levels of Significant Exposure to Chlorophenols - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)		LOAEL (effect) Serious (mg/kg/day)		Reference/ Compound
24	Mouse (ICR)	2 doses 18 hr apart (GO)					1500	(central nervous system depression)	Kobayashi et al. 1972 2,4-dichlorophenol
25	Mouse (B6C3F1)	14 d (F)		2600			5200	(lethargy)	NTP 1989 2,4-dichlorophenol
	Developmental								
26	Rat (Sprague-Dawley)	once Gd 11 (G)		667 F	1000 F	(maternal toxicity: 10 g loss at 24 hrs compared to 0 in controls recovered by 72 hrs, no fetal toxicity noted)			Kavlock 1990 4-chlorophenol
27	Rat (Fischer-344)	Gd 6-15 1x/d (GO)		200	750	(fetal toxicity: delayed ossification, 3% reduced fetal body weights)			Rodwell et al. 1989 2,4-dichlorophenol
28	Rat (CD)	Gd 6-15 1x/d (GO)		25 F	100 F	(13% decrease in corrected maternal body weight gain; no fetal effects)	200 F	(26% decrease in corrected maternal body weight gain; no fetal effects)	RTI 1987 2,3,4,6-tetraCP

TABLE 2-2. Levels of Significant Exposure to Chlorophenols - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference/ Compound
	INTERMEDIATE EXPOSURE						
	Death						
29	Rat (Long-Evans, hooded)	11 wk 5d/wk 1x/d (GO)				1000 M (8/25 died)	Blackburn et al. 1986 2,4,6-trichlorophenol
30	Mouse (B6C3F1)	3 wk (F)				5200 (20/20 died)	NTP 1989 2,4-dichlorophenol
31	Mouse (B6C3F1)	7 wk 7d/wk (F)				4095 (4/10 died)	NCI 1979 2,4,6-trichlorophenol
	Systemic						
32	Rat (Sprague-Dawley)	10 wk premating Gd 1-21 13 wk post-weaning (W)	Hepatic	3	30 (increased liver weight)		Exon and Koller 1985; Exon et al. 1984 2,4-dichlorophenol

TABLE 2-2. Levels of Significant Exposure to Chlorophenols - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference/ Compound
33	Rat (Fischer-344/N)	13 wk (F)	Resp	2000			NTP 1989
							2,4-dichlorophenol
			Cardio	2000			
			Gastro	2000			
			Hemato	250 F		500 F (bone marrow atrophy: both erythroid and myeloid elements)	
			Musc/skel	2000			
			Hepatic	2000			
			Renal	2000			
			Endocr	2000			
			Derm	2000			
			Ocular	2000			
			Bd Wt	500	1000 M (20% reduction in body weight)		
34	Rat (Wistar)	98 d (F)	Resp	1000			McCollister et al. 1961
							2,4,5-trichlorophenol
			Cardio	1000			
			Hemato	1000			
			Hepatic	100	300 (mild centrilobular degeneration, focal necrosis)		
			Renal	100	300 (mild degenerative change in epithelium)		
			Endocr	1000			
			Bd Wt	300 F		1000 F (24% decrease in body weight gain)	

TABLE 2-2. Levels of Significant Exposure to Chlorophenols - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference/ Compound
35	Rat Sprague-Dawley	90 d (GO)	Resp	720			Bercz et al. 1990
							2,4,6-trichlorophenol
			Cardio	720			
			Gastro	720			
			Hemato	720			
			Hepatic	80	240M (14 % increased relative liver weight)		
			Renal	240	720M (increased kidney weight, decreased urinary pH)		
			Endocr	720			
			Ocular	720			
			Bd Wt	720			
36	Rat (Long-Evans hooded)	11 wk 5d/wk 1x/d (GO)	Resp	1000 M			Blackburn et al. 1986
							2,4,6-trichlorophenol
			Cardio	1000 M			
			Hepatic	1000 M			
			Renal	1000 M			
			Endocr	1000 M			
			Bd Wt	1000 M			
37	Rat (Sprague-Dawley)	24-25 wk 7d/wk (W)	Hepatic	0.3	3 (15% increase in liver weight)		Exon and Koller 1985
							2,4,6-trichlorophenol
			Bd Wt	30			

TABLE 2-2. Levels of Significant Exposure to Chlorophenols - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)		Serious (mg/kg/day)		Reference/ Compound
38	Rat (Fischer-344)	7 wk 7d/wk (F)	Hemato	1575	2300	(increase splenic hematopoiesis)			NCI 1979 2,4,6-trichlorophenol
			Hepatic	1575	2300M	(midzonal vacuolation of hepatocytes; 2/5)			
			Bd Wt	500	735	(11-16% decrease in body weight)	1075	(27% decrease in body weight)	
39	Rat (Sprague-Dawley)	90 d (GO)	Resp	200					American Biogenics Corp 1988 2,3,4,6-tetraCP
			Cardio	200					
			Gastro	200					
			Hemato	200					
			Musc/skel	200					
			Hepatic	25	100	(increased liver weights and centrilobular hypertrophy)			
			Renal	25	100	(increased kidney weights)			
			Endocr	200					
			Ocular	200					
			Bd Wt	100	200M	(body weight gain decreased by 11%)			
40	Rat (Wistar)	55 d, 7d/wk (GO)	Gastro	50	100	(focal necrosis of small intestine)			Hattula et al. 1981 2,3,4,6-tetraCP
			Musc/skel	100					
			Hepatic	10			50	(necrosis, thrombosed veins)	
			Bd Wt	100					

TABLE 2-2. Levels of Significant Exposure to Chlorophenols - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference/ Compound
41	Mouse (ICR, ddN)	6 mo (F)	Cardio	230 M			Kobayashi et al. 1972
							2,4-dichlorophenol
			Hemato	230 M			
			Hepatic	100 M	230M (swelling of hepatic cells)		
			Renal	230 M			
			Bd Wt	230 M			
42	Mouse (B6C3F1)	13 wk (F)	Resp	2600			NTP 1989
							2,4-dichlorophenol
			Cardio	2600			
			Gastro	2600			
			Hemato	2600			
			Musc/skel	2600			
			Hepatic		325M (minimal hepatocellular necrosis 4/10)	2600 M (hepatocellular necrosis 10/10)	
			Renal	2600			
			Endocr	2600			
			Derm	2600			
			Ocular	2600			
			Bd Wt	1300	2600 (10-15% reduction in body weight)		
	Immuno/Lymphor						
43	Rat (Sprague-Dawley)	16 wk: Gd 1-21 ppd 1-91 (W)		50			Exon and Koller 1983, 1985
							2-chlorophenol

TABLE 2-2. Levels of Significant Exposure to Chlorophenols - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference/ Compound
44	Rat (Sprague-Dawley)	15 wk premating Gd 1-21, 15 wk post-weaning (W)		0.3 c	3 (decreased delayed-type hypersensitivity)		Exon and Koller 1985; Exon et al. 1984 2,4-dichlorophenol
45	Rat (Sprague-Dawley)	24-25 wk 7d/wk 24hr/d (W)		3	30 (increased spleen weight)		Exon and Koller 1985 2,4,6-trichlorophenol
46	Rat (Sprague-Dawley)	90 d (GO)		200			American Biogenics Corp 1988 2,3,4,6-tetraCP
47	Mouse (CD-1)	90 d (W)		491 F			Borzelleca et al. 1985a 2,4-dichlorophenol
	Neurological						
48	Rat (Fischer-344/N)	13 wk (F)		1000	2000 (hunched posture)		NTP 1989 2,4-dichlorophenol
49	Rat (Sprague-Dawley)	90 d (GO)		200			American Biogenics Corp 1988 2,3,4,6-tetraCP

TABLE 2-2. Levels of Significant Exposure to Chlorophenols - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)		LOAEL (effect) Serious (mg/kg/day)		Reference/ Compound
50	Mouse (B6C3F1)	13 wk (F)		2600					NTP 1989 2,4-dichlorophenol
	Reproductive								
51	Rat (Sprague-Dawley)	13 wk: 10 wk premating Gd 1-21 (W)		5			50	(increase in the percentage of stillborn pups; decrease in live litter size)	Exon and Koller 1982, 1985 2-chlorophenol
52	Rat (Sprague-Dawley)	13 wk: 10 wk premating Gd 1-21 (W)		3	30	(decreased mean litter size)			Exon and Koller 1985; Exon et al. 1984 2,4-dichlorophenol
53	Rat (Long-Evans hooded)	11 wk 5d/wk 1x/d (GO)		1000 M					Blackburn et al. 1986 2,4,6-trichlorophenol
54	Rat (Sprague-Dawley)	13 wk: 10 wk premating Gd 1-21 (W)		3			30	(decreased mean litter size)	Exon and Koller 1985 2,4,6-trichlorophenol
55	Rat (Sprague-Dawley)	90 d (GO)		200					American Biogenics Corp 1988 2,3,4,6-tetraCP

TABLE 2-2. Levels of Significant Exposure to Chlorophenols - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference/ Compound
56	Mouse (CD-1)	90 d (W)		500 M			Seyler et al. 1984 2,4-dichlorophenol
	Developmental						
57	Rat (Sprague-Dawley)	31 wk: 10 wk, Gd 1-21 ppd 1-21 ad lib (W)		50			Exon and Koller 1981 2-chlorophenol
58	Rat (Sprague-Dawley)	16 wk: 3 wk (Gd 1-21) ppd 1-91 (W)		50			Exon and Koller 1983, 1985 2-chlorophenol
59	Rat (Sprague-Dawley)	13 wk: 10 wk premating Gd 1-21 (W)		30			Exon and Koller 1985; Exon et al. 1984 2,4-dichlorophenol
60	Rat (Long-Evans hooded)	2 wk 5d/wk 1x/d then Gd1-21 7d/wk 1x/d (GO)		100	500 (10-11% reduction in litter weight)		Blackburn et al. 1986 2,4,6-trichlorophenol

TABLE 2-2. Levels of Significant Exposure to Chlorophenols - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference/ Compound
	CHRONIC EXPOSURE						
	Systemic						
61	Rat (Sprague-Dawley)	27 mo, 10 wk premating Gd 1-21 Ld 1-21 (W)	Hemato	50			Exon and Koller 1985 *2-chlorophenol*
62	Rat (Fischer-344)	103 wk (F)	Resp			210 M (nasal lesions; multifocal degeneration of respiratory epithelium)	NTP 1989 2,4-dichlorophenol
			Cardio	440 M			
			Gastro	440 M			
			Hemato	440 M			
			Musc/skel	440 M			
			Hepatic	440 M			
			Renal	440 M			
			Endocr	440 M			
			Derm	440 M			
			Ocular	440 M			
			Bd Wt	120 F	250 F (6-12% reduced body weight)		

TABLE 2-2. Levels of Significant Exposure to Chlorophenols - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference/ Compound
63	Rat (Fischer-344)	107 wk 7d/wk (F)	Resp	500			NCI 1979
							2,4,6-trichlorophenol
			Cardio	500			
			Gastro	500			
			Hemato			250 M (bone marrow hyperplasia)	
			Hepatic	500			
			Renal	500			
			Endocr	500			
			Derm	500			
			Bd Wt		250 F (approximate 10% decrease in body weight)	500 F (approximate 29% decrease in body weight)	
64	Mouse (B6C3F1)	103 wk (F)	Resp	1300 M			NTP 1989
							2,4-dichlorophenol
			Cardio	1300 M			
			Gastro	1300 M			
			Hemato	1300 M			
			Musc/skel	1300 M			
			Hepatic	1300 M			
			Renal	1300 M			
			Endocr	1300 M			
			Ocular	1300 M			
			Derm	1300 M			
			Bd Wt	430 F	820 F (maximum 19% decrease in body weight relative to controls)		

TABLE 2-2. Levels of Significant Exposure to Chlorophenols - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference/ Compound
65	Mouse (B6C3F1)	105 wk 7d/wk (F)	Resp	1300 M			NCI 1979
							2,4,6-trichlorophenol
			Cardio	1300 M			
			Gastro	1300 M			
			Hemato	1300 M			
			Hepatic			650 M (hepatic hyperplasia)	
			Renal	1356			
			Endocr	1356			
			Derm	1356			
			Bd Wt			658 F (approximately 24% decrease in body weight)	
	Immuno/Lymphor						
66	Rat (Fischer-334)	103 wk (F)		440 M			NTP 1989
							2,4-dichlorophenol
67	Rat (Fischer-344)	107 wk 7d/wk (F)		500			NCI 1979
							2,4,6-trichlorophenol
68	Mouse (B6C3F1)	103 wk (F)		1300 M			NTP 1989
							2,4-dichlorophenol

TABLE 2-2. Levels of Significant Exposure to Chlorophenols - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference/ Compound
	Neurological						
69	Rat (Fischer-334)	103 wk (F)		440 M			NTP 1989 2,4-dichlorophenol
70	Rat (Fischer-344)	107 wk 7d/wk (F)		500			NCI 1979 2,4,6-trichlorophenol
71	Mouse (B6C3F1)	103 wk (F)		1300 M			NTP 1989 2,4-dichlorophenol
72	Mouse (B6C3F1)	105 wk 7d/wk (F)		1356 F			NCI 1979 2,4,6-trichlorophenol
	Reproductive						
73	Rat (Fischer-344)	103 wk (F)		440 M 250 F			NTP 1989 2,4-dichlorophenol
74	Rat (Sprague-Dawley)	107 wk 7d/wk (F)		500			NCI 1979 2,4,6-trichlorophenol

TABLE 2-2. Levels of Significant Exposure to Chlorophenols - Oral (continued)

Key to[a] figure	Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference/ Compound
75	Mouse (B6C3F1)	103 wk (F)		1300 M 820 F			NTP 1989 2,4-dichlorophenol
76	Mouse (B6C3F)	105 wk 7d/wk (F)		1300 M 1356 F			NCI 1979 2,4,6-trichlorophenol
	Cancer						
77	Rat (Fischer-344)	107 wk 7d/wk (F)				250 M (CEL: monocytic leukemia 23/50)	NCI 1979 2,4,6-trichlorophenol
78	Mouse (B6C3F1)	105 wk 7d/wk (F)				650 M (CEL: 7/47 hepatocellular carcinomas or adenomas)	NCI 1979 2,4,6-trichlorophenol

[a]The number corresponds to entries in Figure 2-2.
[b]Used to derive an acute oral Minimal Risk Level (MRL) of 0.01 mg/kg/day for chlorophenols; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). This MRL, based on 4-CP, should be protective for all chlorophenols discussed in the profile, but could be overprotective.
[c]Used to derive an intermediate oral Minimal Risk Level (MRL) of 0.003 mg/kg/day for chlorophenols; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability). This MRL, based on 2,4-DCP, should be protective for all chlorophenols discussed in the profile, but could be overprotective.

Bd Wt = body weight; Cardio = cardiovascular; CEL = cancer effect level; d = day(s;) Derm = dermal; Endocr = endocrine; F= female; (F) = feed; (G) = gavage; Gastro = gastrointestinal; (GO) = gavage-oil; (GW) = gavage-water; Gd = gestation day; Hemato = hematological; hr = hour(s); Immuno/Lymphor =immunological/ lymphoreticular; Ld = lactation day; LD50 = 50% lethal concentration dose; LOAEL = lowest-observed-adverse-effect level; M= male; mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not stated; ppd = post parturition day; Resp = respiratory; tetraCP = tetrachlorophenol; (W) = water; wk = week(s); x = time(s)

Figure 2-2. Levels of Significant Exposure to Chlorophenols - Oral

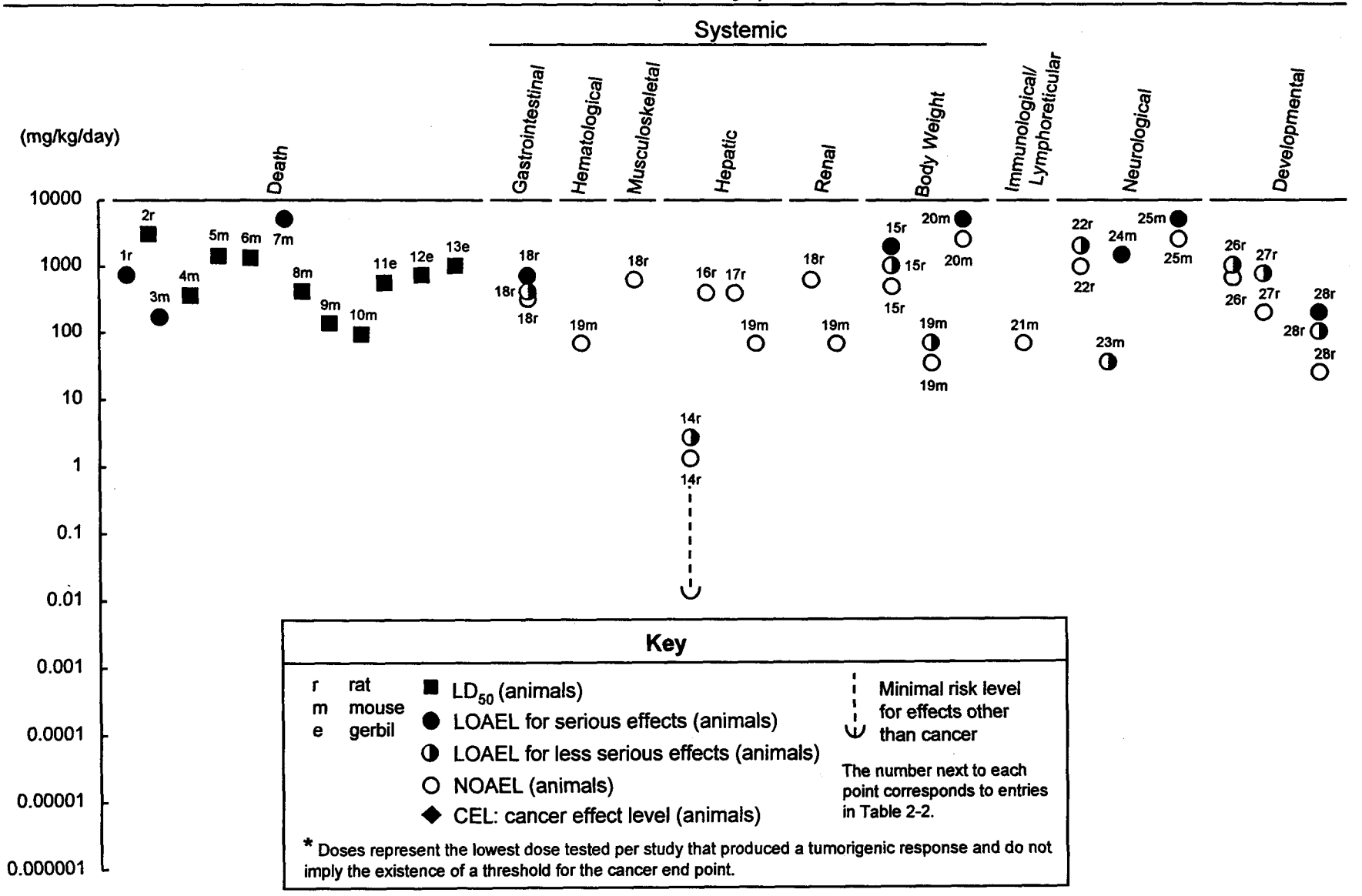


Figure 2-2. Levels of Significant Exposure to Chlorophenols - Oral (cont.)

Intermediate (15-364 days)

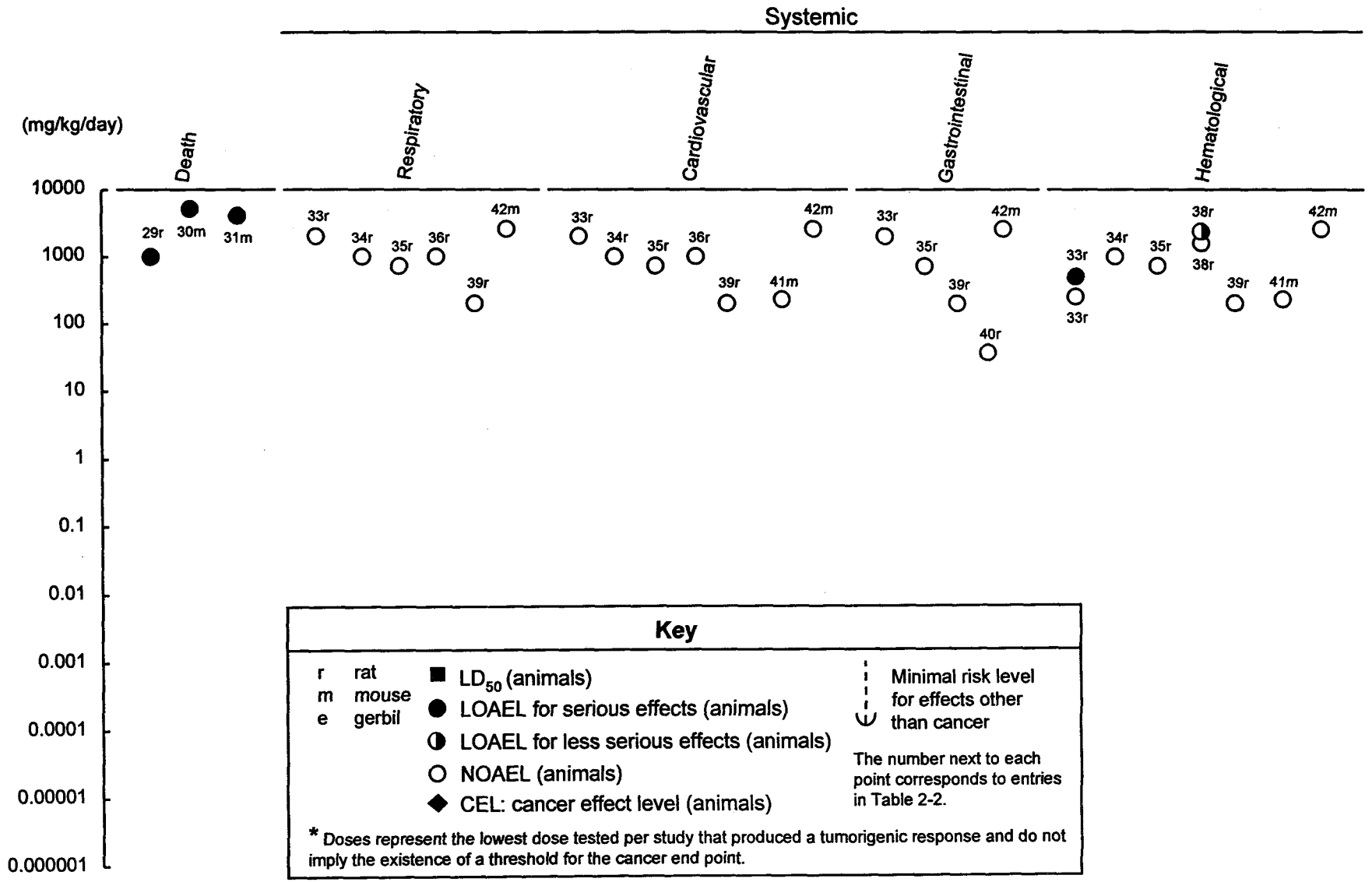


Figure 2-2. Levels of Significant Exposure to Chlorophenols - Oral (cont.)

Intermediate (15-364 days)

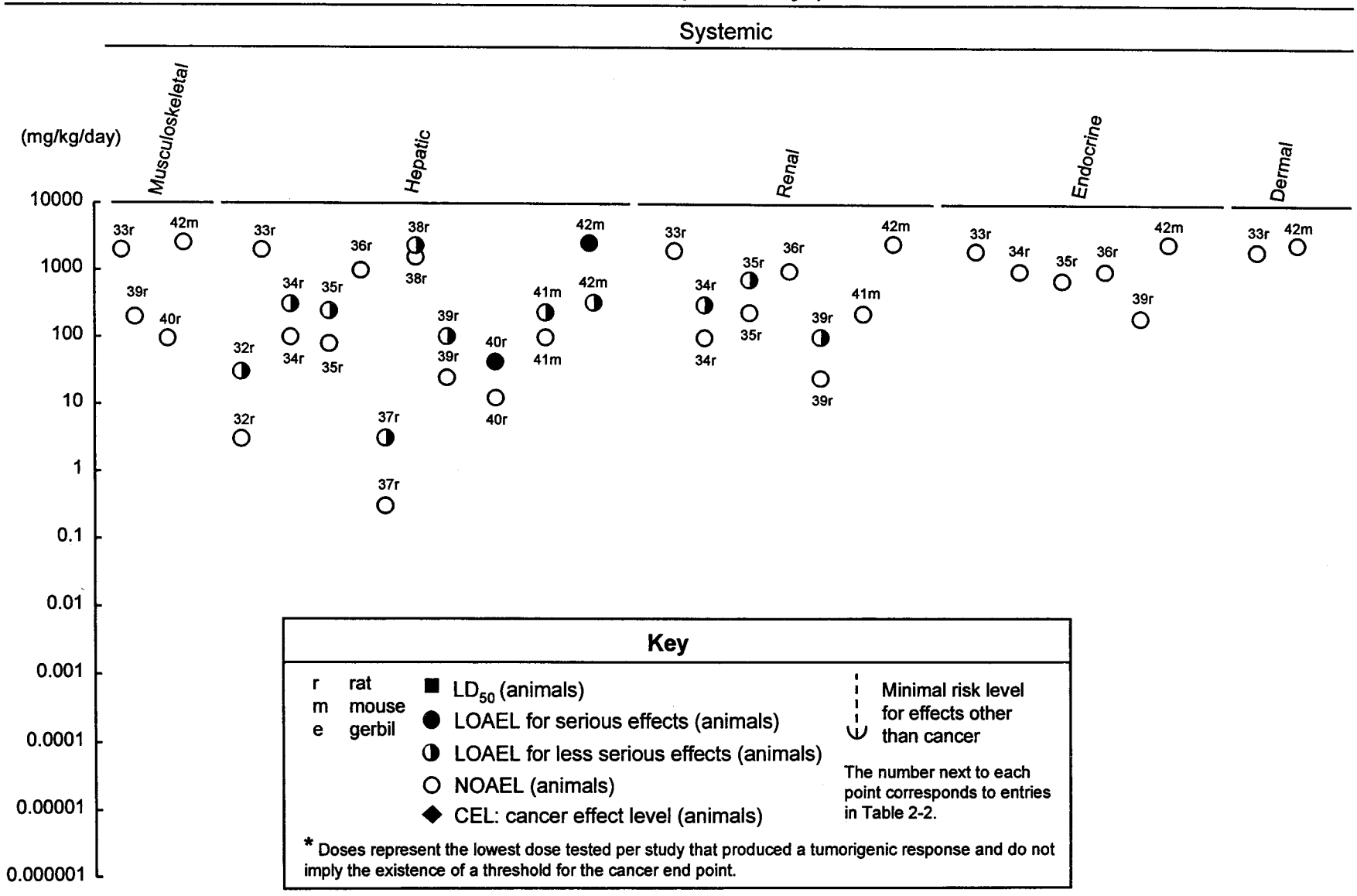


Figure 2-2. Levels of Significant Exposure to Chlorophenols - Oral (cont.)

Intermediate (15-364 days)

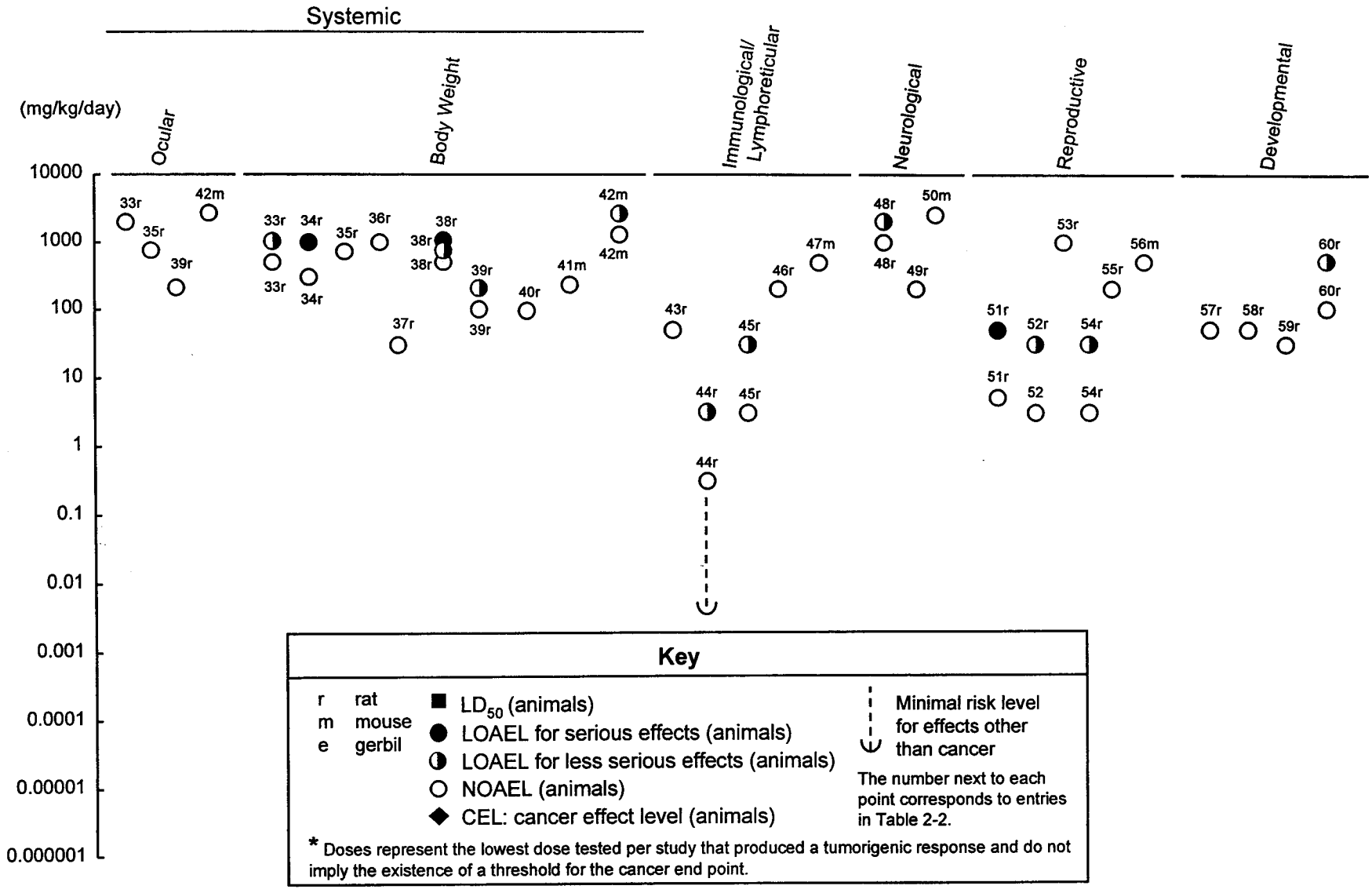


Figure 2-2. Levels of Significant Exposure to Chlorophenols - Oral (cont.)

Chronic (≥365 days)

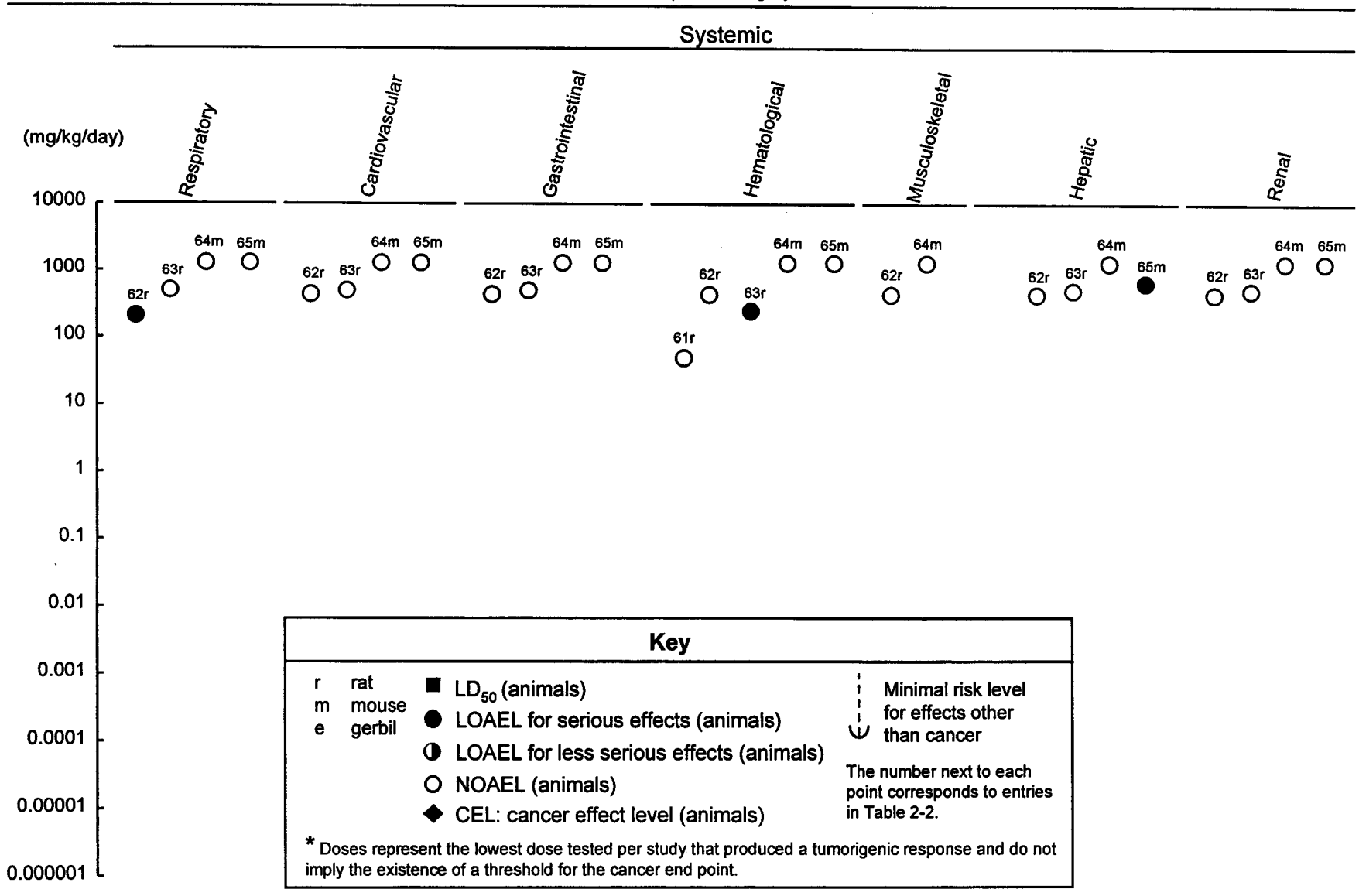
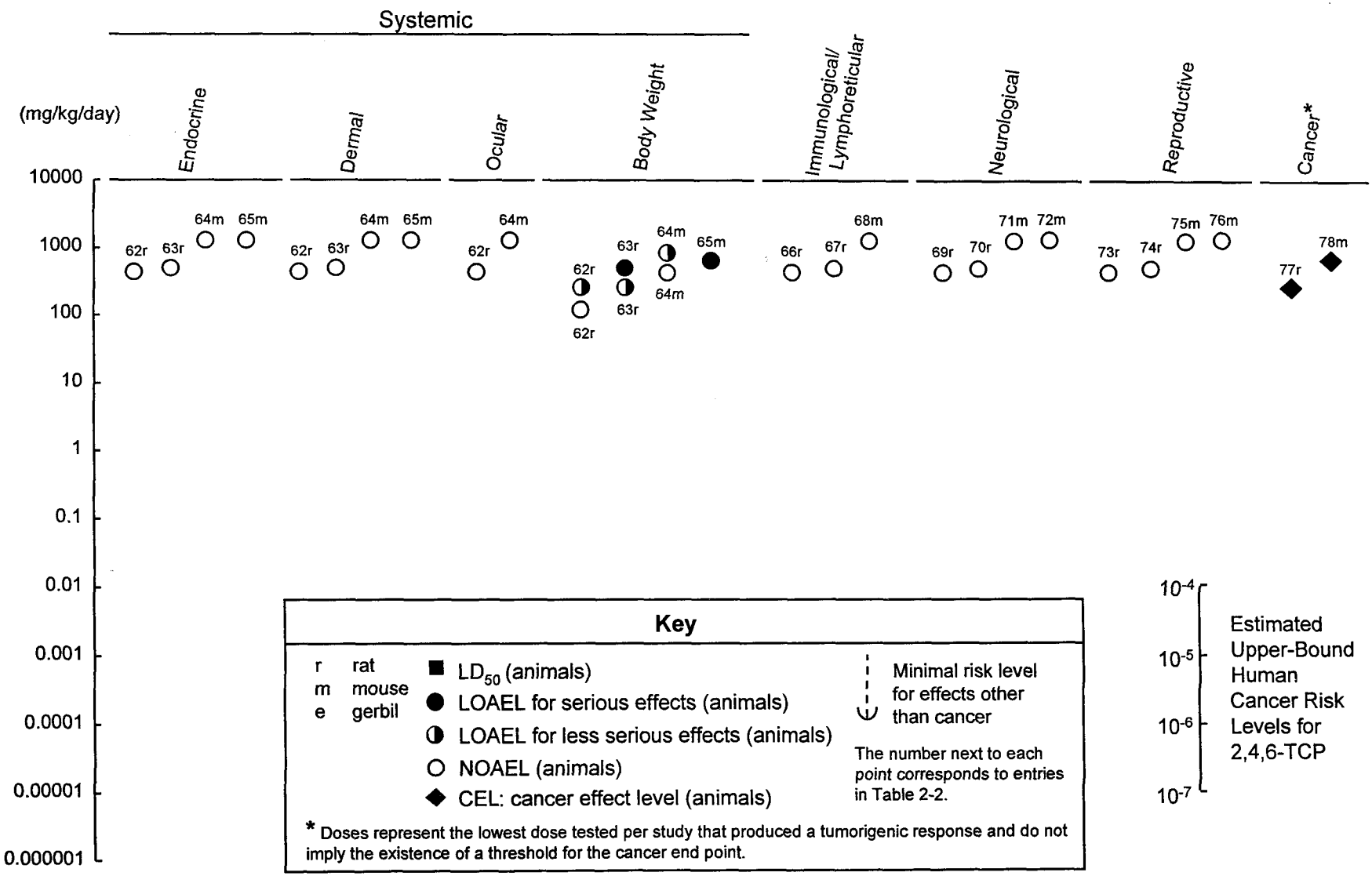


Figure 2-2. Levels of Significant Exposure to Chlorophenols - Oral (cont.)

Chronic (≥365 days)



Heart weight did not increase in rats exposed orally to 2,4,6-TCP over an intermediate (10 or 13 weeks) exposure period to doses as high as 1,000 mg/kg/day (Bercz et al. 1990; Blackburn et al. 1986). No treatment-related lesions were evident upon histopathologic examination of the hearts of rats and mice exposed to doses as high as 720 and 1,356 mg/kg/day of 2,4,6-TCP, respectively for 90 days (Bercz et al.1990) or 105 weeks (NCI 1979).

No changes in heart weight or histology were observed in rats treated with 2,3,4,6-TeCP for 90 days (American Biogenics 1988).

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after oral exposure to any of the eight chlorophenols discussed in this profile.

Mild catarrhal enteritis was observed in female Sprague-Dawley albino rats given a single gavage dose of 316-5,000 mg/kg/day 2,4-DCP in corn oil and sacrificed 24 hours later (Henke and Lockwood 1978). No pathology reports were provided for rats that were sacrificed on day 7 or day 14. In another study, gross necropsy revealed reddened hind, stomach and intestines in Fischer-344 rats given a single gavage dose of 2,400 mg/kg/day 2,4-DCP in corn oil. Both studies demonstrated that this compound can be irritating to the gastrointestinal tract (Wil Research Laboratories 1982). The observation of gastrointestinal effects at lower doses in Sprague-Dawley compared to Fischer-344 rats suggests that Sprague-Dawley rats may be more sensitive to the acute gastrointestinal effects of 2,4-DCP. No significant histopathological changes were observed in the gastrointestinal tracts of Fischer-344 rats fed 2,000 mg/kg/day 2,4-DCP or mice fed 2,600 mg/kg/day 2,4-DCP for 13 weeks, or in rats fed 440 mg/kg/day 2,4-DCP or mice fed 1,300 mg/kg/day 2,4-DCP for 103 weeks (NTP 1989).

In a 90-day study, no significant histopathological changes were observed in the gastrointestinal tracts of rats treated by gavage with 2,4,6-TCP at 720 mg/kg/day (Bercz et al. 1990). Histopathologic examination of the stomach and intestines of rats and mice exposed to 2,4,6-TCP for 2 years at doses as high as 500 and 1,356 mg/kg/day, respectively, revealed no treatment-related lesions (NCI 1979).

Wistar rats administered a single gavage dose of 632 mg/kg 2,3,4,6-TeCP had mucosal hyperemia of the stomach and severe necrosis of the intestine (Hattula et al. 1981). At a dose of 432 mg/kg, mild necrosis was observed in the intestines of 1/10 rats, with no effects observed at 410 mg/kg. Focal necrosis of the small intestines was observed in Wistar rats treated by gavage for 55 days with 100 mg/kg/day 2,3,4,6- TeCP. No

effects were observed at 10 mg/kg/day (Hattula et al. 1981). In contrast, no histopathological changes were observed in the gastrointestinal tracts of Sprague-Dawley rats treated with 2,3,4,6-TeCP at 200 mg/kg/day for 90 days (American Biogenics 1988). 2,3,4,6-TeCP was administered in olive oil in both the Hattula et al. (1981) (concentrations not reported) and American Biogenics (1988) studies (maximum concentration of 20 mg/mL). Because olive oil was used as a vehicle for both studies, the differences in effects to the gastrointestinal tract may likely be due to the dissimilar dosing solution concentrations and rodent strains.

Hematological Effects. No studies were located regarding hematological effects in humans after oral exposure to any of the eight chlorophenols discussed in this profile.

Groups of 12 male and 12 female mice, administered once daily by gavage with up to 69 mg/kg/day 2-CP or up to 638 mg/kg/day 2,4-DCP for 14 days, showed no adverse effects on standard hematological parameters, including total and differential white blood cells, red blood cells, platelets, hematocrit, hemoglobin, and coagulation measures relative to unexposed controls (Borzelleca et al. 1985a). However, when groups of 20 male and 20 female mice were dosed with up to 383 mg/kg/day of 2,4-DCP (male), and 49 mg/kg/day (female) in drinking water for 90 days, the number of white blood cells was increased in the high-dose males (Borzelleca et al. 1985c). No changes in red or white blood cell counts were noted in mice exposed to 2,4-DCP at doses up to 230 mg/kg/day for 6 months (Kobayashi et al. 1972). After 13 weeks of prenatal exposure and up to 15 weeks of postnatal exposure to 2-CP in drinking water, rat weanlings showed no adverse effects on red cell count, hematocrit, mean corpuscular volume, white cell count, or hemoglobin concentration; the highest exposure dose was 50 mg/kg/day (Exon and Koller 1982). Chronic prenatal/postnatal exposure to either 50 mg/kg/day 2-CP or 30 mg/kg/day 2,4-DCP resulted in increased erythrocyte count, packed cell volume, and hemoglobin concentration. The increases for erythrocyte count and hemoglobin (>10%) were statistically significant ($p \leq 0.05$) (Exon and Koller 1985). However, the investigators suggested that the increase may be secondary to effects on liver enzymes or on hematopoietic stem cells and did not consider these effects biologically significant,

In an NTP study (NTP 1989), bone marrow atrophy was observed in male rats treated with 2,4-DCP in the diet at 1,000 mg 2,4-DCP/kg/day for 13 weeks and in female rats at 500 mg/kg/day. The atrophy resulted in depletion of both erythroid and myeloid elements, with no effects observed at 250 mg/kg/day. No hematological effects were noted in mice treated with 2,4-DCP in the diet for 13 weeks at doses up to 2,600 mg/kg/day or in rats or mice treated with 2,4-DCP for 103 weeks (rats, 440 mg/kg/day; mice, 1,300 mg/kg/day) (NTP 1989).

Treatment of rats with 2,4,5-TCP in the diet at doses up to 1,000 mg/kg/day for 98 days resulted in no changes in hematocrit, hemoglobin, or white blood cell counts(McCollister et al. 1961). Administration of up to 720 mg/kg/day 2,4,6-TCP to rats for 90 days resulted in no adverse effects on erythrocyte count, leukocyte count, corrected leukocyte count, hemoglobin, hematocrit, platelet count, or a differential analysis of leukocytes (Bercz et al. 1990). Rats exposed orally for 7 weeks to 2,4,6-TCP exhibited a "moderate to marked increase" in splenic hematopoiesis (NCI 1979). A high incidence of bone marrow hyperplasia and leukocytosis occurred in rats chronically exposed to 2,4,6-TCP in their diet at 250 mg/kg/day (NCI 1979). Further discussion of these hematological effects in rats can be found in Section 2.2.2.8. No hematological effects were evident in mice exposed chronically to 2,4,6-TCP in their diet at doses up to 1,300 mg/kg/day (NCI 1979).

Treatment of rats by gavage with doses of 200 mg/kg/day 2,3,4,6-TeCP for 90 days significantly ($p<0.05$) reduced hemoglobin and hematocrit in both sexes (American Biogenics 1988). Although the effects were statistically significant, the investigators did not consider the effects to be toxicologically significant because the group mean data were within the normal range of reference control data for the laboratory where the study was conducted. In addition, no gross or histopathologic evidence was found to support the decreases in hemoglobin and hematocrit.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after oral exposure to any of the eight chlorophenols discussed in this profile.

Ninety-day (up to 2,600 mg/kg/day) and 2-year (up to 1,300 mg/kg/day) exposure of rats and mice to 2,4-DCP did not result in any histopathological changes in the muscle or ribs (NTP 1989). Single dose and 55-day exposure to 2,3,4,6-TeCP produced no adverse histopathological effects on muscle in Wistar rats (Hattula et al. 1981). The highest single and intermediate-duration exposure levels were 632 mg/kg and 100 mg/kg/day, respectively (Hattula et al. 1981).

Hepatic Effects. No studies were located regarding hepatic effects in humans after oral exposure to any of the eight chlorophenols discussed in this profile.

Treatment of mice by gavage with 2-CP in corn oil at doses up to 69 mg/kg/day for 14 days resulted in a significant decrease in liver weights in females with no effects on serum glutamic-oxaloacetic transaminase (SGOT); serum glutamic-pyruvic transaminase (SGPT); liver microsomal proteins; cytochrome P-450;

cytochrome b5; or activities of liver aminopyrine demethylase, aniline hydroxylase, or arylhydrocarbon hydroxylase (Borzelleca et al. 1985a). The study authors did not consider the change in liver weight to be adverse because biologically or statistically significant compound-related adverse effects were not observed.

In Sprague-Dawley rats, twice daily administration of as little as 0.32 mg/kg 4-CP for 2 weeks (0.64 mg/kg/day) resulted in significant activation of hepatic enzymes including cytochrome P-450 (Phomchirasilp et al. 1989b). Microsomal protein and cytochrome P-450 levels were also elevated in the treated rats. The magnitude of increases over 2 weeks in liver microsomal protein and cytochrome P-450 content declined at doses above 0.64 mg/kg/day. Following additional experiments in which treatment was given two times per day, both a 2-week exposure to 2.58 mg/kg/day and an 8-week exposure to 0.64 mg/kg/day resulted in a foamy cytoplasm and the clustering of mitochondria and endoplasmic reticulum. The electron microscopic changes were not observed in the livers of rats treated at 1.28 mg/kg/day for 2 weeks. In separate studies, similar treatment doses of 4-CP had no effect on relative liver weights, microsomal zoxazolamine 6-hydroxylase activity, or measures of serum lipid and lipidlipoprotein concentrations, but did increase fasting glucose levels (Phomchirasilp et al. 1989a). Light microscopy was not reported in this study. Based on the electron microscopic changes following 2 weeks of exposure, 2.58 mg/kg/day is considered a LOAEL and 1.28 mg/kg/day is considered a NOAEL. As described in footnote "b" of Table 2-2, an acute duration oral MRL of 0.01 mg/kg/day was calculated for the chlorophenols based on 4-CP. The LOAEL for 4-CP was the lowest LOAEL among all the acute-duration LOAELs for all the chlorophenols discussed in this profile.

Sprague-Dawley rats dosed at 20 mg/kg/day of 2,4-DCP in the drinking water had increased liver weights (Exon et al. 1984), an effect that could indicate hyperplasia or enzyme induction. No histopathological changes were observed in the livers of Fischer-344 rats fed 2,4-DCP in the diet at doses up to 2,000 mg/kg/day for 13 weeks or 400 mg/kg/day for 103 weeks (NTP 1989). Liver weights or liver enzymes released to the serum were not measured in the NTP (1989) study. Mice fed 325 mg/kg/day of 2,4-DCP for 13 weeks had dose-related increases in hepatocellular necrosis (not further described) (NTP 1989). When mice were fed 383 or 230 mg/kg/day for 90 days or 6 months, respectively, no effects were noted on SGOT or SGPT activity (these enzymes are released into the bloodstream as a result of liver injury) (Borzelleca et al. 1985a; Kobayashi et al. 1972). One of 10 mice exposed to 230 mg/kg/day 2,4-DCP for 6 months had hepatocellular hyperplasia. No liver effects were observed at 100 mg/kg/day (Kobayashi et al.

1972). Diffuse syncytial alterations occurred in male mice given 800 mg/kg/day 2,4-DCP in the diet for 103 weeks (NTP 1989). The number of cells affected was small, and the affected cells were scattered within the histologic sections.

When guinea pigs were administered 40 mg/kg 2,4-DCP perorally 3 times a week for 2 weeks, lipid peroxidation was increased in the liver (Clerhata et al. 1996). A high intake of ascorbic acid (50 mg/animal/day) significantly decreased lipid peroxidation in the liver in comparison to guinea pigs with low ascorbic acid intake (2 mg/kg/day). 2,4-DCP accumulation was also decreased in the liver of animals with high ascorbic acid intake.

The pretreatment of rats with 2,4,5- or 2,4,6-TCP by gavage at doses up to 400 mg/kg/day for 14 days had no effect on ethylp-nitrophenylphosphonothionate detoxification (Carlson 1978). 2,4,5-TCP but not 2,4,6-TCP at 400 mg/kg/day decreased microsomal NADPH-reductase activity and cytochrome P-450 activity.

Histologic changes in the liver were not observed when rats were treated by gavage with 2,4,5-TCP in corn oil at doses up to 1,000 mg/kg/day for 18 or 24 days (McCollister et al. 1961). Slight pathologic changes, which were not further described, were noted in the livers of rabbits treated by gavage with 2,4,5-TCP in 5% gum acacia solution for 20 or 28 days (McCollister et al. 1961). Over a 98-day period, a dose of 300 mg/kg/day given to rats in the diet resulted in mild centrilobular degeneration and focal necrosis, with no effects observed at 100 mg/kg/day (McCollister et al. 1961).

Increased liver weight and midzonal vacuolation of hepatocytes were evident in rats exposed orally for 7 weeks to 2,300 mg/kg/day 2,4,6-TCP (NCI 1979). Increased relative liver weights were found in groups of male rats exposed to 240 and 720 mg/kg/day of 2,4,6-TCP for 90 days and groups of female rats exposed to 720 mg/kg/day of 2,4,6-TCP for 90 days (Bercz et al. 1990). No treatment-related histopathological evidence of tissue damage was noted. Clinical chemistry results included increased serum albumin and total protein concentrations, which the investigators attributed to either an altered hydration status or dysfunctional hepatic activity (Bercz et al. 1990). The investigators considered 240 mg/kg/day as a LOAEL for hepatic effects and the next lower dose, 80 mg/kg/day, as a NOAEL for acute duration exposure. In contrast, increased liver weight and histopathologic lesions were not evident in rats exposed to 2,4,6-TCP over intermediate or chronic periods at doses up to 1,000 and 500 mg/kg/day, respectively (Blackburn et al. 1986; NCI 1979).

Microscopic examination revealed hepatic hyperplasia and other signs of hepatocellular damage (e.g., liver cell abnormalities, focal areas of cellular alteration) in mice exposed chronically to 2,4,6-TCP in the diet at doses as low as 650 mg/kg/day (NCI 1979). It is possible these lesions were precursors of the hepatocellular adenomas and carcinomas also observed in this study. More information relating to these hepatic neoplasms can be found in Section 2.2.2.8.

Concentration-related increases in absolute liver weight occurred in rats exposed perinatally to 3 or 30 mg/kg/day 2,4,6-TCP for 15 weeks (Exon and Koller 1985). The investigators did not examine functional or anatomical hepatic parameters.

The different effects of 2,4,6-TCP in rats and mice may, in part, be a result of the different methodologies used for exposure, variations in experimental design, and/or possible differences in gastrointestinal absorption because of the nature of the vehicle. In the intermediate oral studies by Bercz et al. (1990) and Blackburn et al. (1986), 2,4,6-TCP was administered in corn oil by gavage. Interpretation of the Blackburn et al. (1986) data is further complicated by the investigators' failure to report sample sizes used in the statistical analysis. The NCI (1979) studies used administration of 2,4,6-TCP in the diet, while 2,4,6-TCP was administered in drinking water in the Exon and Koller (1985) study, therefore, a direct comparison is not very meaningful.

For both acute- (one dose) and intermediate-duration (55 days) administration of 2,3,4,6-TeCP in Wistar rats, the most severe effects occurred in the liver (Hattula et al. 1981). In the single dose study, various adverse histopathological effects occurred at unspecified dose levels up to a maximum dose of 632 mg/kg. Intermediate-duration (55 days) administration of 100 mg/kg/day resulted in both Level III (large confluative necroses with dilated and thrombosed veins) and Level II (bile duct proliferation, focal necrosis, and polymorphonuclear leukocyte infiltration) hepatic damage. At 50 mg/kg/day, 1 out of 10 rats showed Level III damage. The NOAEL for hepatic effects following 55 days of exposure was 10 mg/kg/day (Hattula et al. 1981). The number of animals used in the 55-day study was not stated.

In a study sponsored by the EPA (American Biogenics 1988), increased liver weights and centrilobular hypertrophy were observed in rats treated by gavage with 2,3,4,6-TeCP at 100 or 200 mg/kg/day for 90 days. No effects were observed at 25 mg/kg/day.

2. HEALTH EFFECTS

Renal Effects. No studies were located regarding renal effects in humans after oral exposure to any of the eight chlorophenols discussed in this profile.

In mice, daily administration of 35 or 69 mg/kg/day 2-CP for 14 days had no adverse effects on measures of renal function, including blood urea nitrogen (BUN), total protein, albumin/globulin ratio, or electrolyte balance (Borzelleca et al. 1985a). No significant compound-related adverse effects were noted at necropsy. In the same study, a dose of 175 mg/kg/day was lethal to all exposed mice.

Except for renal tubular necrosis in mice that died following treatment with 2,4-DCP in the diet for 3 weeks at 5,200 mg/kg/day (NTP 1989), kidney effects have not been observed in animals treated with 2,4-DCP. Based on histological examinations, the reported NOAELs for kidney effects are 2,000 and 440 mg/kg/day for rats fed 2,4-DCP in the diet for 13 and 103 weeks, respectively (NTP 1989), and 230,2,600, and 1,300 for mice fed 2,4-DCP in the diet for 90 days, 13 weeks, and 103 weeks, respectively (Kobayashi et al. 1972; NTP 1989). Treatment of mice with 2,4-DCP in drinking water at doses up to 491 mg/kg/day had no effect on kidney weights or clinical chemistry values including urine protein, phosphorus, calcium, sodium, chloride, potassium, or creatinine levels (Borzelleca et al. 1985a). Histopathological examinations were not completed because the clinical chemistry was negative.

Treatment of rats with 2,4,5-TCP at 1,000 mg/kg/day by gavage for 18 days resulted in a significant increase in kidney weight, with no histopathologic changes or changes in BUN (McCollister et al. 1961). Slight pathologic changes (not further described) were observed in rabbits given 20 gavage doses of 100 or 500 mg/kg/day, with no effects noted at 10 mg/kg/day (McCollister et al. 1961). In a go-day study, 2,4,5-TCP administered in the diet at 300 mg/kg/day resulted in mild degenerative changes in the renal epithelium of the convoluted tubules and in proliferation of the interstitial tissue (McCollister et al. 1961). No kidney effects were observed at 100 mg/kg/day.

Administration of 720 mg/kg/day 2,4,6-TCP in corn oil by gavage for 90 days resulted in increased absolute and relative kidney weights in male, but not female, Sprague-Dawley rats and decreased urinary pH in both sexes. No other effects on clinical parameters of renal function were observed (Bercz et al. 1990). Renal weight did not increase in Long-Evans rats administered 2,4,6-TCP in corn oil by gavage at doses as high as 1,000 mg/kg/day for 11 weeks, 5 days per week (Blackburn et al. 1986). Strain differences and daily treatment as opposed to treatment five times per week may account for the differences in renal effects in the Bercz et al. (1990) and Blackburn et al. (1986) studies. No treatment-related lesions were evident upon

histopathologic examination of the kidney in rats and mice exposed to dietary 2,4,6-TCP for 2 years at doses as high as 500 and 1,356 mg/kg/day, respectively (NCI 1979).

A single dose or 55day exposure to 2,3,4,6-TeCP, at doses up to 632 mg/kg or 100 mg/kg/day, respectively, had no adverse effect on the histological appearance of the kidneys of rats (Hattula et al. 1981). Increased kidney weights without any histopathologic changes were observed in rats treated by gavage with 2,3,4,6-TeCP at 100 mg/kg/day for 90 days (American Biogenics 1988). No renal effects were observed at 25 mg/kg/day.

Endocrine Effects. No studies were located regarding endocrine effects in humans after oral exposure to any of the eight chlorophenols discussed in this profile.

Histopathologic examinations did not reveal any changes in the endocrine glands (adrenals, pituitary, thyroid, pancreas) of rats or mice treated with 2,4-DCP in the diets at doses up to 2,000 (rats) or 2,600 (mice) mg/kg/day for 13 weeks, or at doses up to 440 (rats) or 1,300 (mice) mg/kg/day for 103 weeks (NTP 1989). Histopathologic changes of the adrenals were not observed in rats treated with 2,4,5-TCP in the diet at 1,000 mg/kg/day for 98 days (McCollister et al. 1961).

Female rats treated by gavage with 720 mg/kg/day of 2,4,6-TCP for 90 days had slightly, but statistically significant, elevated adrenal weights compared to untreated controls (Bercz et al. 1990). Because no histopathological changes were noted, this dose is considered a NOAEL. Adrenal gland weights were not increased in male rats treated by gavage with 2,4,6-TCP at 1,000 mg/kg/day for 11 weeks (Blackburn et al. 1986), providing further support that the adrenal glands are not a target of 2,4,6-TCP toxicity. However, differences between male and female rats could be due to endocrine differences between males and females. Histopathologic changes were not observed in the adrenal glands, thyroid, pancreas, or parathyroid glands in rats or mice treated with 2,4,6-TCP in the diet at doses of 500 (rats) or 1,356 (mice) mg/kg/day for 105 weeks (NCI 1979). Treatment of rats by gavage with 2,3,4,6-TeCP for 90 days at doses up to 200 mg/kg/day had no effect on the histologic appearance of the adrenal glands, pituitary, pancreas, or thymus (American Biogenics 1988).

Dermal Effects. No studies were located regarding dermal effects in humans after oral exposure to any of the eight chlorophenols discussed in this profile.

Pregnant rats given 750 mg/kg 2,4-DCP by gavage experienced hair loss (Rodwell et al. 1989). No histological changes in the skin were found in rats or mice given as much as 2,000 or 2,600 mg/kg/day, respectively, for up to 13 weeks, nor for these same species fed up to 440 or 1,300 mg/kg/day for up to 103 weeks (NTP 1989). Upon histopathologic examination of the skin, no treatment-related effects were observed in rats or mice exposed chronically to oral doses of 2,4,6-TCP as high as 500 or 1,356 mg/kg/day, respectively (NCI 1979).

Ocular Effects. No studies were located regarding ocular effects in humans after oral exposure to any of the eight chlorophenols discussed in this profile.

Histopathologic examination of the eyes did not reveal any adverse effect in rats or mice either treated with 2,4-DCP (NTP 1989) in the diet or treated by gavage with 2,3,4,6-TeCP (American Biogenics 1988) for intermediate or chronic durations. Ophthalmoscopic examinations did not reveal any treatment-related effects in rats treated by gavage with 2,4,6-TCP at doses up to 720 mg/kg/day for 90 days (Bercz et al. 1990).

Body Weight Effects. No studies were located regarding body weight effects in humans after oral exposure to any of the eight chlorophenols discussed in this profile.

In a 14-day study, both sexes of mice receiving 69 mg/kg/day 2-CP had unspecified body weight decrements (Borzelleca et al. 1985a); the NOAEL was 35 mg/kg/day. No effects on body weight were observed in rats treated with 2-CP in drinking water at doses of 50 mg/kg/day during gestation and lactation as well as 15-weeks postweaning (Exon and Koller 1981,1982). Single-day gestational exposure of gravid Sprague-Dawley rats to 1,000 mg/kg 4-CP resulted in a significant body weight loss (Kavlock 1990). By 72 hours after dosing, the body weight difference was no longer statistically significant, and lower levels did not produce any body weight gain inhibition in gravid Sprague-Dawley rats. The NOAEL for the body weight effect for 4-CP was 667 mg/kg/day. Additional results from this study are discussed in Section 2.2.2.6.

Studies with rats and mice fed 2,4-DCP for acute, intermediate, and chronic durations revealed dose-related decreases in food intake and body weight (NTP 1989). These effects are believed to be due to the bad taste of 2,4-DCP. Body weights were not affected in mice treated with 2,4-DCP in the diet at doses up to 230 mg/kg/day (Kobayshi et al. 1972) or in drinking water at doses up to 491 mg/kg/day (Borzelleca et al.1985a). To improve palatability in drinking water, Borzelleca et al. (1985a) used a 1:9 emulphor:water

solution which is a modified vegetable oil. Body weights of pregnant animals treated on gestation days 6-l5 were reduced at 375 but not 200 mg/kg/day (Rodwell et al. 1989).

Treatment of rats by gavage with 2,4,5-TCP for 18 or 24 days at 1,000 mg/kg/day had no effect on body weight (McCollister et al. 1961). In contrast, treatment with 2,4,5-TCP in the diet at 1,000 mg/kg/day for 90 days resulted in a 24% decrease in body weight gain in female but not in male rats (McCollister et al. 1961). No effects on food intake were measured.

Treatment of rats with 2,4,6-TCP by gavage at 1,000 mg/kg/day for 2 weeks before mating and throughout gestation resulted in reduced body weights through gestation day 14 (Blackburn et al. 1986). Body weights on gestation day 21 were not significantly different from those of the controls. No effect on body weight was observed in rats treated by gavage with 2,4,6-TCP at 1,000 mg/kg/day for 90 days (Bercz et al. 1990) or 11 weeks (Blackburn et al. 1986), suggesting that pregnant animals may be more sensitive to effects on body weight following treatment with 2,4,6-TCP. No effect on body weight was observed in mice treated with 2,4,6-TCP in drinking water at 30 mg/kg/day for 24-25 weeks (Exon and Koller 1985). Body weights were significantly reduced in rats treated with 2,4,6-TCP in the diet for 7 weeks at 735 but not at 500 mg/kg/day and 250 mg/kg/day for 105 weeks (NCI 1979). Body weights were also significantly decreased in mice fed 2,600 mg/kg/day 2,4,6-TCP in the diet for 7 weeks and at 658 mg/kg/day for 105 weeks (NCI 1979). No effects on body weight were observed in mice fed 1,300 mg/kg/day 2,4,6-TCP for 7 weeks (NCI 1979). Food intake data were not provided in the NCI (1979) study. The fact that 2,4,6-TCP affected body weight following dietary intake but had little effect at similar doses following gavage treatment suggests that 2,4,6-TCP may have caused the food to be less palatable and reduced food intake in mice at the concentrations used in the NCI (1979) study. Therefore, decreased body weight may be an effect of decreased food intake rather than an effect of 2,4,6-TCP treatment.

Body weight was significantly decreased in rats treated by gavage with 2,3,4,6-TeCP at 100 mg/kg/day (American Biogenics 1988) for 90 days, but not 100 mg/kg/day for 55 days (Hattula et al. 1981).

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans after oral exposure to any of the eight chlorophenol isomers discussed in this profile.

Rats fed 50 mg/kg/day 2-CP for up to 16 weeks and mice fed 69 mg/kg/day 2-CP for 14 days showed no changes in humoral or cell-mediated immunological assays (Borzelleca et al. 1985a; Exon and Koller 1983,1985). Indices assessed in the Exon and Koller (1983, 1985) studies include antibody production, delayed type hypersensitivity, and phagocytic activity of peritoneal exudate cells. Female mice exposed to 69 mg/kg/day for 14 days had statistically significant decreases in spleen weight but no gross abnormalities in spleen morphology (Borzelleca et al. 1985a). Spleen and thymus weights were not significantly affected in rats that received 50 mg 2,4-DCP kg/day in drinking water for 16 weeks (Exon and Koller 1983, 1985). Perinatal exposure of young rats to 2-CP at doses up to 50 mg/kg/day produced no treatment-related effects on humoral or cell-mediated immunity, thymus weights, or spleen weights (Exon and Koller 1983, 1985).

Histopathological examination of lymph nodes, spleen, and thymus did not reveal any effects in rats or mice treated with 2,4-DCP in the diet at doses up to 2,000 (rats) and 2,600 mg/kg/day (mice) for 13 weeks, or 440 (rats) and 1,300 mg/kg/day (mice) for 103 weeks (NTP 1989). Bone marrow atrophy was observed in rats treated at 500 but not 250 mg/kg/day for 13 weeks (NTP 1989). Because both erythroid and myeloid elements were affected, this study is also discussed in Section 2.2.2.2 under Hematological Effects. No changes in spleen weight were observed in mice treated with 2,4-DCP in the diet at 230 mg/kg/day for 6 months (Kobayashi et al. 1972), and no changes in spleen or thymus weight were noted in mice treated with 2,4-DCP in the drinking water at doses up to 491 mg/kg/day for 90 days.

As shown in Table 2-2 and Figure 2-2, immune system effects have been reported in animals at low doses of 2,4-DCP. Decreased delayed-type hypersensitivity occurred in rats during 15-week-duration exposure to 3 mg/kg/day of 2,4-DCP in drinking water, and increased serum antibodies to key hole limpert nemocyanin were found in the blood of rats during similar exposures to 30 mg/kg/day (Exon and Koller 1985; Exon et al. 1984). Macrophage function, measured by the *in vitro* phagocytosis of sheep red blood cells, showed no effect from 2,4-DCP treatment. These results suggest that the immune system is quite sensitive to 2,4-DCP. No immune system effects occurred with exposure to 0.3 mg/kg/day (Exon et al. 1984). Based on the NOAEL of 0.3 mg/kg/day, an intermediate-duration oral MRL of 0.003 mg/kg/day was calculated for the chlorophenols as described in the footnote in Table 2-2. The LOAEL for 2,4-DCP was the lowest among all the intermediate-duration LOAELs for all the chlorophenols discussed in this profile.

No changes in spleen weight or histological appearance were observed in rats treated with 2,4,5-TCP in the diet at doses of 1,000 mg/kg/day for 98 days (McCollister et al. 1961) or in rats treated by gavage with 720 mg/kg/day 2,4,6-TCP for 90 days (Bercz et al. 1990). Spleen weights were significantly increased in rats exposed to 2,4,6-TCP in the drinking water both pre- and postnatally at doses of 30 mg/kg/day, while no significant effects on immune function (antibody levels, delayed-type hypersensitivity, macrophage numbers) were observed (Exon and Koller 1985). Treatment of rats and mice with 2,4,6-TCP in the diet for 2 years at doses up to 500 mg/kg/day for rats and 1,356 mg/kg/day for mice did not reveal any significant gross or histopathological changes in the spleen, lymph nodes, or thymus (NCI 1979).

Administration of a single gavage dose 632 mg/kg of 2,3,4,6-TeCP in Wistar rats resulted in "slight stasis" in the spleens of rats (Hattula et al. 1981); the toxicological significance of this finding is unknown. No histological changes were observed in the spleen, lymph nodes, or thymus of rats treated with 2,3,4,6-TeCP by gavage at doses up to 200 mg/kg/day for 90 days (American Biogenics 1988).

The highest NOAEL values and all reliable LOAEL values for immunological and lymphoreticular effects in rats and mice for each exposure duration are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to any of the eight chlorophenol isomers discussed in this profile.

In most acute animal studies involving 2-, 4-CP and 2,4-DCP exposure, a common syndrome of effects precedes death (Borzelleca et al. 1985a, 1985b; Kobayashi et al. 1972; Spencer and Williams 1950; Wil Research Laboratories 1982). This syndrome includes restlessness, tremors, convulsions, dyspnea and/or tachypnea, and collapse or coma. In many of these studies, the major effects associated with exposure to high doses of many phenolic compounds are myoclonic convulsions, or spasmodic twitching of a group of muscles. The relationship between chlorophenol exposure and the onset of convulsions is discussed further in Sections 2.4 and 2.5. In general, the sensitivity of these clinical signs (particularly convulsions) decreases with increasing chlorination.

In an LD_{50} study, single oral doses (unspecified) of 2-CP or 4-CP caused restlessness, motor weakness, tremors, convulsion, or central nervous system depression in rats and mice (Borzelleca et al. 1985a, 1985b).

The actual doses used in the study (Borzelleca et al. 1985b) were not stated. A single oral dose of 514 mg/kg 4-CP produced seizures immediately followed by death in male ICR mice (Phornchirasilp et al. 1989b). Single doses of 2-CP >300 mg/kg resulted in distress and twitching in rabbits (Spencer and Williams 1950). Administration of 4-CP produced similar effects at higher, unspecified doses. In male and female ICR mice, repeated administration of 35 and 69 mg/kg/day 2-CP for 44 days resulted in hyperactivity and decreased brain weight, respectively (Borzelleca et al. 1985a); although, the brain tissue appeared grossly normal (Borzelleca et al. 1985a).

Mice treated with 2,4-DCP in the diet at 5,200 mg/kg/day for 14 days were lethargic and 1 out of 5 males died (NTP 1989). Hunched posture was observed in rats treated with 2,4-DCP in the diet at 2,000 mg/kg/day for 13 weeks (NTP 1989) with no histopathological changes in the brain, sciatic nerve, or spinal cord. In mice treated with 2,4-DCP in the diet at doses up to 2,600 mg/kg/day for 13 weeks, no histopathological changes were observed in the brain, sciatic nerve, or spinal cord (NTP 1989). No effect on brain weight was observed in mice treated with 2,4-DCP in the drinking water at doses up to 491 mg/kg/day (Borzelleca et al.1985a). No clinical signs of neurological effects were reported in rats or mice fed doses up to 440 mg/kg/day for rats and 1,300 mg/kg/day for mice, and histopathologic examination of the brains of these animals did not reveal any effects (NTP 1989).

No changes in brain weight or histological appearance of the brain were observed in rats treated with 2,4,5-TCP in the diet at doses up to 1,000 mg/kg/day for 98 days (McCollister et al. 1961).

Histopathologic examination of the brain (cerebrum and cerebellum) of rats and mice exposed repeatedly to oral 2,4,6-TCP at doses as high as 720 and 1,356 mg/kg/day, respectively, revealed no treatment-related effects (Bercz et al. 1990; NCI 1979). Similarly, in Wistar rats exposed acutely to up to 632 mg/kg 2,3,4,6-TeCP, or repeatedly to 200 mg/kg/day 2,3,4,6-TeCP for 90 days, no histopathological effects in the brain were observed (American Biogenics 1988).

The highest NOAEL and all LOAEL values for neurological effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after oral exposure to any of the eight chlorophenol isomers discussed in this profile.

A teratogenicity study in which pregnant rats were treated with 2,4-DCP by gavage on gestation days 6-15 at doses that caused maternal deaths and decreased body weight gain showed neither postimplantation loss nor changes in the numbers of resorptions and viable fetuses (Rodwell et al. 1989). No reproductive organ pathology was observed in rats or mice of either sex fed up to 2,000 or 2,600 mg/kg/day 2,4-DCP, respectively, for 13 weeks (NTP 1989). Reproductive organ pathology was also not observed in male rats fed 440 and female rats fed 250 mg/kg/day 2,4-DCP and male mice fed 1,300 and female mice fed 8,210 mg/kg/day 2,4-DCP for 2 years (NTP 1989). Sperm from male mice fed 500 mg/kg/day 2,4-DCP for 90 days in drinking water were not impaired in their ability to fertilize ova (Seyler et al. 1984).

Using identical experimental protocols, investigators have studied the reproductive effects of 2-CP, 2,4-DCP, and 2,4,6-TCP in Sprague-Dawley female rats (Exon and Koller 1985). Groups of rats received uncontaminated drinking water or one of three concentrations of a chlorophenol in drinking water, beginning at weaning and extending through mating and parturition. The total exposure duration for each group was approximately 13 weeks. The only consistent concentration-related effect observed in all three experiments was a marginal decrease ($p<0.10$) in litter size. In all cases, the individual conceptus, rather than the litter, was the unit of statistical analysis. For 2-CP, 2,4-DCP, and 2,4,6-TCP, the highest concentration in water corresponded to 50,30, and 30 mg/kg/day, respectively; these doses are considered LOAELs for reproductive effects. No significant reproductive effects were observed at 5 mg/kg/day 2-CP and 3 mg/kg/day for 2,5-DCP and 2,4,6-TCP.

In a study designed to look at reproductive function, Blackburn et al. (1986) treated female rats with 2,4,6-TCP by gavage at doses up to 1,000 mg/kg/day for 2 weeks before mating and throughout gestation and treated male rats with 2,4,6-TCP at doses up to 1,000 mg/kg/day for 10 weeks. The treated females were mated with untreated males, and the treated males were mated with untreated females. 2,4,6-TCP had no effects on breeding success, litter size, or litter survival when either sex was treated. Treatment of males had no effect on sperm count, motility, or morphology, nor were there any changes in weights of the testes, prostate, or seminal vesicles. Although treatment-related deaths occurred in both sexes at 1,000 mg/kg/day, this dose can be considered a NOAEL for 2,4,6-TCP reproductive effects in rats.

In 90-day studies, gavage treatment of rats with either 2,4,5-TCP at doses up to 1,000 mg/kg/day (McCollister et al. 1961) or with 2,4,6-TCP up to 720 mg/kg/day (Bercz et al. 1990) had no effect on the weight of the testes or ovaries. Treatment of rats with 2,4,6-TCP in the diet for 2 years had no effects on the histologic appearance of the testis and prostate or of the uterus or ovaries (NCI 1979).

In a study designed to examine developmental effects, pregnant rats were treated by gavage with 2,3,4,6-TeCP at doses up to 200 mg/kg/day on gestation days 6-l 5 (RTI 1987). An increased trend in percent preimplantation loss with dose suggested an effect on the process of implantation or early postimplantation viability. Because this study was not designed to examine the preimplantation/ implantation phase of reproduction, the investigators suggested that the effect requires confirmation. Therefore, a LOAEL or NOAEL for reproductive effects in female rats exposed to 2,3,4,6-TeCP is not clearly defined by this study. No histopathological changes were observed in the testes, ovaries, or uterus and cervix of rats treated by gavage with 2,3,4,6-TeCP at doses up to 200 mg/kg/day for 90 days (American Biogenics 1988).

The highest NOAEL values and all reliable LOAEL values are listed in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans after oral exposure to any of the eight chlorophenol isomers discussed in this profile.

No significant changes in offspring body or liver weights were observed in rats treated with 2-CP in drinking water at doses up to 50 mg/kg/day throughout gestation and up to 91 days post partum (Exon and Keller 1981, 1983, 1985). Groups of 6-13 female Sprague-Dawley rats receiving a single dose of 333,667, or 1,000 mg/kg 4-CP on gestational day 11 showed no adverse changes in litter sizes, perinatal loss, pup weight, or litter biomass (Kavlock 1990). The only treatment-related effect was a transient decrease in maternal body weight at 1,000 mg/kg.

Oral exposure of pregnant rats to 750 mg/kg/day 2,4-DCP for 10 gestational days induced a slight decrease in fetal weight and a statistically significant delayed ossification of sternal and vertebral arches and led to a slight insignificant increase in early embryonic deaths (0.8/average litter controls; 1.2/litter 750 mg/kg/day) (Rodwell et al. 1989). Maternal death occurred at this dose level, indicating that 2,4-DCP was not selectively toxic to embryos or fetuses. The authors indicated that, although the number of deaths and fetal weights

differed from that of the concurrent controls, values were not different from the historical control data from their laboratory. No evidence of malformations in the offspring was found in this study. At 375 mg/kg/day, maternal body weight was reduced, with no effects observed at 200 mg/kg/day.

No effect on immune function parameters (antibody production, delayed type hypersensitivity response, phagocytic activity) was noted in 6-week-old rats treated with 2,4-DCP in the drinking water at doses up to 30 mg/kg/day throughout gestation (Exon and Koller 1985; Exon et al. 1984). Spleen weights were significantly increased at 30 mg/kg/day, although no histological changes in the spleen were observed.

Gavage administration of 650 mg/kg/day 2,4,5-TCP during organogenesis (days 6-15 of gestation) produced no fetotoxicity, malformations, or structural terata in the offspring of Sprague-Dawley rats (Chernoff et al. 1990). Treatment resulted in statistically insignificant increases in maternal lethality and decrements in maternal weight gain (Chernoff et al. 1990). In another developmental study, groups of mice received either a single gavage dose of 800-900 mg/kg 2,4,5-TCP on 1 day of gestation (any of gestation days S-15), or 250-300 mg/kg/day on any 3 days of gestation (gestation days 7-9, 10-12, or 13-15) (Hood et al. 1979). With the exception of a significant increase in the incidence of prenatal mortalities and resorptions in dams dosed on day fourteen, 2,4,5-TCP had no effect on resorption incidence or pup survival. 2,4,5-TCP administration did not affect mean fetal weight or the incidence of gross malformations, skeletal malformations, or cleft palates (Hood et al. 1979).

In a study designed to examine reproductive effects, a 10-11% decrease in litter weights was observed in litters of female rats treated by gavage with 2,4,6-TCP at 500 mg/kg/day for 2 weeks before mating and throughout gestation (Blackburn et al. 1986). No effects on litter weights were observed at 100 mg/kg/day, and no effects on survival to postnatal day 42 were observed. No effects on body weight were observed among offspring of male rats treated by gavage with 2,4,6-TCP at 1,000 mg/kg/day for 10 weeks before mating (Blackburn et al. 1986). Because comprehensive examinations of offspring were not completed, this study is not sufficient to conclude that developmental effects do not occur following exposure to 2,4,6-TCP.

Maternal exposure of rats to 500 mg/kg/day 2,4,6-TCP produced a transient reduction in the body weight of offspring (Blackbum et al. 1986). No developmental effects were noted in the offspring of female rats exposed to 2,4,6-TCP throughout gestation (Blackbum et al. 1986; Exon and Koller 1985). In addition, no developmental effects were noted in the offspring of male rats treated with 2,4,6-TCP and untreated females (Blackbum et al. 1986). These studies were limited by the lack of reporting on the number of animals from

which group means were calculated (Blackburn et al. 1986) and by a lack of reporting on maternal toxicity (Exon and Koller 1985).

In a developmental study in which female Sprague-Dawley rats orally received purified 2,3,4,6-TeCP throughout organogenesis, the only effect on the fetus was delayed ossification of the skull bones (Schwetz et al. 1974). The reported incidences were 14/173 (8%) and 18/104 (17%) at 0 and 30 mg/kg/day, respectively. When analyzed by litter, no statistical difference for delayed ossification was observed. Therefore, 30 mg/kg/day 2,3,4,6-TeCP is considered a NOAEL for developmental effects in rats. In a follow-up study, pregnant CD rats received 0,25, 100, or 200 mg/kg/day, in olive oil, every day during organogenesis (RTI 1987). Administration of the two highest doses resulted in corrected maternal body weight gain (dam body weight-gravid uterus weight) inhibitions of 13% and 26%, respectively, with no effects at 25 mg/kg/day. Measurement of food intake indicated that these effects were not related to decreased food consumption, Minor variations between dose groups in fetal malformation and aberrations were not dose related. The investigators also noted a dose-related trend for 2,3,4,6-TeCP-mediated effects on implantation or postimplantation viability. No further evidence of maternal or fetotoxic effects were observed (RTI 1987). Based on maternal toxicity, this study identifies 100 mg/kg/day as a LOAEL and 25 mg/kg/day as a NOAEL for developmental effects.

The highest NOAEL value and all LOAEL values from each reliable study for developmental effects for each exposure duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after oral exposure to any of the eight chlorophenols discussed in this profile.

In ICR mice, daily gavage administration of 69 mg/kg/day 2-CP or 638 mg/kg/day 2,4-DCP in corn oil for 14 days did not increase sister chromatid exchange (SCE) rates in testicular or bone marrow cells (Borzelleca et al. 1985a). Further details were not provided. Ninety-day exposure,of mice to 2,4DCP in drinking water at doses up to 500 mg/kg/day also had no effect on SCE in bone marrow and testicular cells (Borzelleca et al. 1985a). A single gavage dose of 2,4,5-TCP (164 mg/kg), 2,4,6-TCP (164 mg/kg), or 2,3,4,6-TeCP (28 or 193 mg/kg) given to rats did not damage deoxyribonucleic acid (DNA) as measured by the fraction of DNA eluted from white blood cells or livers (Kitchin and Brown 1988).

Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding cancer in humans after oral exposure to any of the eight chlorophenol isomers discussed in this profile.

In the one oral carcinogenicity study located, groups of Sprague-Dawley rats received prenatal, postnatal, or both pre- and postnatal exposure to 2-CP (Exon and Koller 1985). The exposure concentrations were 0,5, 50, and 500 ppm in drinking water (0, 0.5, 5, 50 mg/kg/day). Under all exposure conditions, 2-CP administration had no effect on the incidence, latency, or types of tumors relative to the untreated controls. Additional groups of gravid dams received ethylurea and nitrite, precursors of the carcinogenic initiator ethylnitrosourea (ENU), on gestation days 14 and 21. No consistent effects on either tumor incidence or latency occurred in rats treated with ENU and then treated either prenatally or postnatally with 2-CP. The groups of males receiving ENU and both prenatal and postnatal 2-CP had increased tumor incidence and decreased tumor latency relative to a control group receiving ENU only. The investigators indicate that the combined changes were marginally statistically significant ($p< 0.10$) in comparison to a group receiving the initiator ENU only. ENU-exposed female rats also exposed pre- and postnatally to 2-CP showed no consistent, concentration-related effects on either tumor incidence or latency (Exon and Koller 1985). Findings in the combined-exposure male treatment groups indicate that 2-CP may be either a cocarcinogen or a tumor promotor. However, an analysis of incidence and latency data suggests that the effects may not be concentration related. No effects on tumorigenicity were found in similar studies with 2,4-DCP given in drinking water at 0.3,3, or 30 mg/kg/day. It is not clear whether a maximum tolerated dose was achieved in these studies (Exon and Koller 1985).

Chronic carcinogenicity bioassays in rats and mice treated with 2,4-DCP in the diet at doses up to 440 mg/kg/day for rats and 1,300 mg/kg/day for mice did not provide any evidence that 2,4-DCP is carcinogenic (NTP 1989). In contrast, carcinogenicity bioassays with rats and mice provide evidence that chronic oral exposure to 2,4,6-TCP is associated with leukemia and liver cancer (NCI 1979). In male rats, chronic oral exposure to 2,4,6-TCP in the diet produced a significant dose-related increase in the incidence of monocytic leukemia (NCI 1979). An increased incidence of leukemia also occurred in female rats; however, the increase was not significant compared to the controls. In addition, leukocytosis and monocytosis as well as hyperplasia of the bone marrow were induced in treated male and female rats that did not develop

leukemia. In rats with leukemia, there were large numbers of circulating monocytes in the blood that ranged from well-differentiated monocytes to immature and blast forms. Monocytes were often observed in the liver, spleen, lymph tissue, and bone marrow and occasionally in the lungs, adrenals, and other organs.

In both male and female $B6C3F_1$ mice treated chronically with 2,4,6-TCP in the diet, a significant doserelated increase in the incidence of hepatocellular adenomas and carcinomas (not further described) was noted (NCI 1979). Liver damage, including individual liver cell abnormalities, focal areas of cellular alteration and focal and nodular areas of hyperplasia were commonly present in the treated mice. Significant limitations of this study included the failure to report the dioxin content of the 2,4,6-TCP formulation, changes in the dosing regimen of mice, and no testing of organ function. Another limitation was the failure to compare the incidence of liver tumors to historical controls as well as concurrent controls. Hepatocellular carcinoma has a high natural incidence in this strain of mouse which tends to vary from one study to the next.

A single oral dose of 2,4,6-TCP (200 mg/kg) did not significantly increase skin tumors in mice treated dermally with a tumor promoter (12-O-tetradecanoylphorbol-13-acetate [TPA]) relative to TPA alone, suggesting that 2,4,6-TCP does not act systemically as an initiator (Bull et al. 1986). Other studies also examined the possible carcinogenic effects of 2,4,6-TCP, but contained limitations that preclude a conclusion (Bionetics Research Labs 1968; Innes et al. 1969; Stoner et al. 1986). The limitations included early termination of the experiment (24 weeks) (Stoner et al. 1986), only one treatment group (Bionetics Research Labs 1968; Innes et al. 1969), a small number of treated animals (Bionetics Research Labs 1968; Innes et al. 1969), and a change in dosing regimen and method of exposure (Bionetics Research Labs 1968; Innes et al. 1969).

The Cancer Effect Levels (CELs) are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.3 Dermal Exposure

2.2.3.1 Death

A worker who splattered pure 2,4-DCP on portions of his right arm and leg while disposing of industrial waste collapsed and experienced a seizure within 20 minutes of the accident and died shortly thereafter. Postmortem examination revealed blood and urine 2,4-DCP concentrations of 24.3 and 5.3 mg/L, respectively. The identity of 2,4-DCP was confirmed by mass spectrometry. The investigators did not

estimate an absorbed dose (Kintz et al. 1992), but assuming a blood volume of 5 liters and a body weight of 70 kg, the dose would be approximately 2 mg/kg as a minimum. A screen for other drugs including ethanol, organic solvents, tranquilizers, and drugs of abuse was negative.

Limited data were located on the lethal effects of dermally applied chlorophenols in experimental animals. Results of a contract laboratory study indicate that the dermal LD_{50} of 2-CP in rabbits is between 1,000 and 1,580 mg/kg (Younger Lab 1975). Antemortem observations included increasing weakness, tremors, collapse, and coma. Gross necropsy in the rabbit studies indicated hemorrhage in the lungs, Liver discoloration, gastrointestinal inflammation, darkened spleens and kidneys, and enlarged gall bladders. The study data do not clearly indicate whether mortality resulted from any of these effects. Conclusions from this study are limited by small test groups and/or the lack of information regarding experimental methodology.

A dermal LD_{50} of 1,415 mg/kg has been reported for male rabbits exposed to 2,4-DCP for 24 hours (Carreon et al. 1980b). Because there were only two rabbits per dose group, the 95% confidence interval on this value is very large (236-8,455 mg/kg). Unoccluded dermal application of 2,000 mg/kg 2,3,4,5-TeCP or 2,3,5,6-TeCP resulted in 1 out of 20 and 2 out of 20 deaths, respectively, in Sprague-Dawley rats (Shen et al. 1983). The purity of each test compound was >99%. Because these preliminary studies indicated that the dermal LD_{50} values for 2,3,4,5-TeCP and 2,3,5,6-TeCP were greater than 2,000 mg/kg, further testing of these compounds was not completed. The LD_{50} for commercial tetrachlorophenol, consisting primarily of the 2,3,4,6-isomer (at least 90%), was 485 mg/kg in males and 565 mg/kg in females. Clinical signs preceding death for all tetrachlorophenol isomers included initial hyperactivity followed by hypoactivity, neuromuscular weakness, and convulsions (Shen et al. 1983).

The LD_{50} values and dermal doses of chlorophenols associated with death are recorded in Table 2-3.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, hematological, musculoskeletal, hepatic, or renal effects in humans or animals after dermal exposure to any of the eight chlorophenols discussed in this profile. The systemic effects that were observed after dermal exposure to chlorophenols are discussed below.

Gastrointestinal Effects. No studies were located regarding gastrointestinal effects in humans after dermal exposure to any of the eight chlorophenols discussed in this profile.

TABLE 2-3. Levels of Significant Exposure to Chlorophenols - Dermal

Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference/ Compound
ACUTE EXPOSURE						
Death						
Rat (Sprague-Dawley)	24 hr				2000 M (1/10 died)	Shen et al. 1983 2,3,4,5-tetraCP
Rat (Sprague-Dawley)	24 hr				485 M (LD50)	Shen et al. 1983 2,3,4,6-tetraCP
Rat (Sprague-Dawley)	24 hr				2000 F (2/10 died)	Shen et al. 1983 2,3,5,6-tetraCP
Rabbit (New Zealand albino)	24 hr				1580 (2/2 rabbits died)	Younger Labs 1975 2-chlorophenol
Rabbit (New Zealand albino)	24 hr				1414 M (LD50)	Carreon et al. 1980b 2,4-dichlorophenol
Systemic						
Mouse (dd)	6 hr	Derm	100 M			Dohi et al. 1989 4-chlorophenol

TABLE 2-3. Levels of Significant Exposure to Chlorophenols - Dermal (continued)

Species/ (strain)	Exposure duration/ frequency (specific route)	System	NOAEL (mg/kg/day)	LOAEL (effect) Less serious (mg/kg/day)	LOAEL (effect) Serious (mg/kg/day)	Reference/ *Compound*
Rabbit (NS)	once	Ocular		0.6 M (slight hyperemia)	1.2 M (severe hyperemia, edema, cloudiness of the cornea)	Harrison and Madonia 1971 4-chlorophenol
Rabbit (New Zealand albino)	24 hr	Derm		250 M (moderate to marked erythema, slight to marked edema and necrosis)		Carreon et al. *1980b* 2,4-dichlorophenol
Rabbit (New Zealand albino)	24 hr	Derm		200 F (moderate to marked erythema, edema, and necrosis)		Hencke and Lockwood 1978 2,4-dichlorophenol
Neurological						
Rabbit (New Zealand albino)	24 hr			250 M (lethargy)		Carreon et al. 1980b *2,4-dichlorophenol*

Derm = Dermal; F = female; hr =hour(s); LD50 = 50% lethal dose; LOAEL = lowest-observable-adverse-effect level; M = male; NOAEL = no-observable-adverse-effect level; NS = not stated

Diarrhea was observed in one of two female rabbits the day after a dermal exposure to a single dose of 398 mg/kg/day 2,4-DCP (Hencke and Lockwood 1978). This limited study suggests that either dermally applied 2,4-DCP, or the stress of being exposed to a skin irritant, can result in gastrointestinal effects in rabbits.

Dermal Effects. Chloracne and evidence of acquired porphyria, hyperpigmentation, and hirsutism have been observed in workers employed in the manufacture of 2,4-DCP- and 2,4,5-TCP-based herbicides (Bleiberg et al. 1964; Bond et al. 1989). The chloracne incidence was greatest in young employees exposed in trichlorophenol production and in chlorophenol production and finishing procedures (Bond et al. 1989). In this study, workers exposed to the highest concentration of the contaminant TCDD were at the greatest risk of developing chloracne.

The results of animal studies indicate that monochlorophenols are corrosive to epithelial tissue (Bioassay Systems 1981; Rhodia 1978). Severe effects have been reported at exposure levels of 242-2,000 mg/kg of 2-CP or 4-CP applied directly to rabbit skin. Corrosion (not further described) is typically accompanied by other signs of severe skin injury, including erythema, edema, and discoloration. A single dermal application of a lower dose (100 mg/kg) of 4-CP to one ear of a mouse did not increase ear weight relative to the untreated ear (Dohi et al. 1989). Because of the inadequacies of the test methodologies used, few conclusions regarding dose-response relationships or comparative isomeric potency can be made.

Dermal lesions were caused by a single direct application of as little as 200 mg/kg 2,4-DCP to bare abdominal skin of New Zealand White rabbits (Carreon et al. 1980a, 1980b; Hencke and Lockwood 1978; Younger Labs 1976). The dose-related dermal damage observed was described as mild-to-moderate erythema and mild-to-marked edema, followed by necrosis and scabbing. No NOAEL values were identified in these studies.

Dermal application of 20 mL/kg (32 g/kg) 2,3,4,5-TeCP on the shaved skin of female rats resulted in dermatosis associated with scar formation. Rats treated with the sodium hydroxide extracted fraction of 2,3,4,5-TeCP had no dermatological lesion, indicating that the adverse effects were attributable to the chlorophenol rather than contaminants, such as dioxins (Shen et al. 1983).

Ocular Effects. Lumber mill workers exposed to a mixture of tetrachlorophenols (specific isomers not stated) and pentachlorophenol reported eye irritation more frequently than unexposed workers (Kleinman et

al. 1986). The eye irritation was likely a direct effect of the tetrachlorophenols, resulting from contact with the airborne chemicals or contact with contaminated surfaces (e.g., hands, clothing).

Monochlorophenols produce effects ranging from slight hyperemia to severe corrosion when applied to the corneas of rabbits. Rabbits administered 0.6 mg/kg 4-CP (a 1% solution) showed slight hyperemia (Harrison and Madonia 1971). At 1.2 mg/kg, rabbits had more severe hyperemia with edematous swelling, corneal cloudiness, and exudation. The maximum response occurred 5 hours after application. Inflammation was no longer apparent at 96 hours. Severe discomfort and corrosion was reported to occur 1 minute after the application of 33 mg/kg undiluted 2-CP to rabbit eyes (Younger Labs 1975). Although the results are inadequate for an assessment of comparative potencies across isomers, the available data indicate that 2-CP and 4-CP produce rapid and severe cornea1 destruction at relatively low concentrations.

Severe cornea1 damage occurred in the eyes of rabbits after a single direct application of 0.1 mL 2,4-DCP (Hencke and Lockwood 1978). Careful washing of the eye 30 seconds after application did not prevent this damage.

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans following dermal exposure to any of the eight chlorophenols discussed in this profile.

The murine local lymph node assay, which is predictive of skin sensitization potential, was completed in mice treated with 2,4,5-TCP (Kimber and Weisberger 1991). A single dermal exposure of 50 mL of 2,4,5-TCP was applied on one shaved flank; 5 days later the mice were given 3 daily doses (140-560 mg/kg/day) applied to the ear. A positive response was observed at all doses, suggesting that 2,4,5-TCP can be a skin sensitizer. This study is limited since only three mice were used in each group and a statistical analysis of the data was not completed.

2.2.3.4 Neurological Effects.

An industrial waste worker who accidentally splashed pure 2,4-DCP on portions of his right arm and leg, experienced a seizure within 20 minutes of the exposure, and died shortly thereafter (Kintz et al. 1992). Lumber mill workers exposed to a mixture of tetrachlorophenols (specific isomers not stated) and

pentachlorophenol reported headaches more frequently than unexposed workers (Kleinman et al. 1986). Industrial hygiene observations of inadequate use of protective equipment to prevent skin exposure led the investigators to suggest that exposure was principally through the skin, with some possibility of oral ingestion.

Rabbits given single applications of 250 mg/kg 2,4-DCP or more became lethargic (Carreon et al. 1980a, 1980b; Younger Labs 1976), and two rabbits in the 2,000-mg/kg group and one in the 4,000-mg/kg group became anorexic (Carreon et al. 1980b). Small sample sizes weaken the validity of these data, but the lethargy observed in this study is in keeping with the signs of central nervous system depression seen in rats and mice orally exposed to 2,4-DCP. In a single-dose dermal study of the tetrachlorophenols in rats, clinical signs observed before death were hyperactivity, neuromuscular weakness, convulsions, and death (Shen et al. 1983). Both 2,3,5,6-TeCP and 2,3,4,5-TeCP that had dermal LD_{50} values >than 2,000 mg/kg were less toxic than 2,3,4,5-TeCP that had a dermal LD_{50} of 468 mg/kg in males and 565 mg/kg in females.

No NOAEL values were identified for neurological effects. The lowest LOAEL values for neurological effects in rabbits are recorded in Table 2-2.

2.2.3.5 Reproductive Effects

No studies were located regarding reproductive effects in humans or animals after dermal exposure to any of the eight chlorophenol isomers discussed in this profile.

2.2.3.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after dermal exposure to any of the eight chlorophenol isomers discussed in this profile.

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

Numerous authors have studied the possible relationship between occupational chlorophenol exposure and the expression of oncogenicity. For all of these studies, the workers were exposed by both the inhalation and dermal routes. The description and results of these studies were provided in Section 2.2.1.8.

Results of case-control studies have suggested increased risks for soft tissue sarcoma, malignant lymphoma, and acute myeloid leukemia in slaughterhouse workers exposed occupationally to a number of chemicals, including 2,4,6-TCP, by dermal exposure during the treatment of animal pelts (Pearce et al. 1988; Smith et al. 1984). Workers in these studies were also exposed to potentially oncogenic viruses (including bovine leukemia virus). Because of the confounding exposures to various agents, no conclusions can be made from these studies as to the causal agent for these cancers.

In 15-week mouse initiation-promotion studies, 2-CP and 2,4-DCP, but not 2,4,6-TCP, showed tumor promoting activity (Boutwell and Bosch 1959). One application of the known tumor initiator 9,10-dimethyl-1,2-benzanthracene (DMBA) to the middorsal region of mice was followed by twice weekly dermal applications of 25 μL of a 20% solution of either 2-CP, 2,4-DCP, or 2,4,6-TCP. Compared to DMBA treatment alone, 2-CP and 2,4-DCP increased the number of skin tumors, with no effect from 2,4,6-TCP exposure (Boutwell and Bosch 1959). In a study in which no initiator was used, 2-CP applied to the backs of mice twice per week for 12 weeks resulted in papillomas in 46% of the mice (Boutwell and Bosch 1959). No carcinomas were observed. The significance of these results is limited by the lack of appropriate vehicle control groups, irritation, and the reporting of only gross pathological effects (EPA 1980a).

2,4,6-TCP did not have initiating activity in an initiation-promotion study in mice (Bull et al. 1986). Mice were treated with a dermal dose of 200 mg/kg/day 2,4,6-TCP followed 2 weeks later by 20 weeks (3 times per week) of dermal 12-0-tetradecanoylphorbol-13-acetate (TPA) treatment.

2.3 TOXICOKINETICS

Tri- and tetrachlorophenol are rapidly absorbed and excreted following occupational exposure, which involves both the inhalation and dermal routes. Studies using human cadaver tissue also suggest rapid absorption after dermal application. Data on the absorption of chlorophenols by the oral route are limited

to animal studies. Based on the results of these studies and the physical properties of chlorophenols, the gastrointestinal absorption of chlorophenols should be rapid and virtually complete. Data are insufficient to quantitatively estimate the absorption rate or to compare absorption following administration in food versus administration in water.

Limited evidence from animal studies suggests rapid clearance of chlorophenols from all body tissues. Intravenous administration of 2,4-DCP to rats resulted in short-lived deposition in the kidney, liver, brain, and fat. The extent of plasma protein binding, which is a major determinant of both the body burden and elimination kinetics, increases with increasing chlorination. Increased plasma protein binding decreases the clearance rate of higher chlorinated phenols (Pekari et al. 1991).

Few systematic metabolic studies were located for chlorophenols. In general, rapid Phase II metabolism to glucuronide and sulfate conjugates seems to be the predominant route of metabolism. The relative proportion of these conjugates may be species-, dose-, and route-related. The most important Phase I metabolites are apparently quinone and semiquinone reactive intermediates. Prominent urinary metabolites after 2,4,6-TCP administration in rats are other trichlorophenols. In at least one *in vitro* study, no evidence of dioxin precursors was found.

After occupational exposure to chlorophenols in a lumber treatment facility, elimination rates were inversely proportional to the degree of chlorination probably because of increased plasma protein binding with increased chlorination. Elimination half-lives of 18 hours and 4.2 days were recorded for 2,4,6-TCP and 2,3,4,6-TeCP, respectively. Elimination occurred according to a two-compartment open model. In rats orally administered radiolabelled 2,4,6-TCP, 92.5% of the administered radioactivity appeared in the urine and 6.4% appeared in the feces within 3 days after exposure cessation.

2.3.1 Absorption

Absorption of chlorophenols has not been studied in children.

2.3.1.l Inhalation Exposure

The identification of 2,4,6-TCP and 2,3,4,6-TeCP in the serum and urine of workers exposed while treating lumber indicates that 2,4,6-TCP and 2,3,4,6-TeCP are absorbed through inhalation (Pekari et al. 1991). No

airborne chlorophenol concentrations were provided. Although inhalation exposure was possible, a study of pullers at a timber mill (Fenske et al. 1987) suggests that 95% of the estimated exposure is by the dermal route.

No studies were located regarding the absorption of chlorophenols in animals after inhalation exposure to any of the eight chlorophenol isomers discussed in this profile.

2.3.1.2 Oral Exposure

No studies were located regarding oral absorption in humans of any of the eight chlorophenol isomers discussed in this profile. These isomers have moderately high lipophilicity and pK_as >5.0; consequently, intestinal ahsorption should be favored (Ambre 1990). Based on chemical properties and on limited animal data, absorption through the gastrointestinal tract after oral intake in humans is expected to be both rapid and virtually complete.

The animal data indicating rapid and complete absorption are based solely on studies reporting recovery of all or most of the orally administered chlorophenols in the urine. Spencer and Williams (1950) recovered ≥100% of a single oral dose of 2- or 4-CP (emulsified in water) given to rabbits. Five days after three daily gavage treatments of rats with radiolabelled 2,4,6-TCP (vehicle not reported), 82.3% of the administered radioactivity was recovered in the urine (Korte et al. 1978). In a 15-day study of 25 μg/day radiolabelled 2,4,6-TCP, 92% of the administered radioactivity was recovered in the urine of the treated rats (Bahig et al. 1981).

2.3.1.3 Dermal Exposure

In vivo and *in vitro* data indicate that the chlorophenols are readily absorbed following dermal exposure. In an industrial accident, 20 minutes after a worker was splashed with a pure solution of 2,4-DCP on less than 10% of his body (arm and leg), he collapsed and shortly thereafter died (Kintz et al. 1992). Postmortem blood and urine concentrations of 2,4-DCP were 24.3 and 5.3 mg/L, respectively. Using a fluorescent tracer, and measures of urinary excretion of TeCP in lumber mill workers exposed to a wood preservative (20% TeCP, 3% pentachlorophenol, <0.4% other CPs), Fenske et al. (1987) estimated that 30-100% of the 2,3,4,6-TeCP deposited on the skin is absorbed. Absorption occurred through the hands and forearms despite the use of chemical-resistant gloves. Fenske et al. (1987) also indicate that the skin regions with

greatest exposure, the hands and forearms, were in frequent contact with wood so that abrasion may have reduced the barrier properties of the stratum corneum.

The results of diffusion experiments using hydrated human cadaver epidermis also indicate that the chlorophenols readily cross the skin at low concentrations. The permeability coefficients determined in excised human abdominal epidermis were 5 .5, 6.1, 10.0, and 9.9 cm mi*N*- $1x10^4$ for 2-CP, 4-CP, 2,4-DCP, and 2,4,6-TCP (Roberts et al. 1977). 2-CP and 4-CP were reported to damage the skin, determined by an increase in the permeability coefficient at aqueous concentrations of 0.8 and 0.75% (w/v), respectively, while no damage was observed with 2,4-DCP and 2,4,6-TCP at concentrations up to saturation. In a study using abdominal skin exposed to air, absorption of 2,3,4,6-TeCP over 24 hours was 33% from an aqueous medium (1.54% 2,3,4,6-TeCP) and 63% from a diesel-oil-based medium (0.96 2,3,4,6-TeCP) (Horstman et al. 1989). These values were determined by assuming that the amount of the applied dose that was not recovered from the skin's surface was the amount absorbed. The actual amounts recovered in the skin and receiving solutions were 9.5 and 3.9% for the aqueous- and oil-based medium, respectively. The authors attribute low recovery to difficulties in extracting 2,3,4,6-TeCP from the skin.

Dermal absorption can be inferred from *in vivo* animal studies resulting in death and/or adverse systemic effects following dermal exposure to 2-CP (Younger Labs 1975) and 2,4-DCP (Carreon et al. 1980a, 1980b; Hencke and Lockwood 1978; Younger Labs 1976).

Chlorophenols are also readily permeable in rodent skin *in vitro* preparations. At solution pHs between 5.0 and 5.74, the apparent 2-CP, 2,4-DCP, and 2,4,6-TCP permeability constants for a hairless mouse skin preparation over a concentration range of 0.05-0.5% varied from 0.14 to 0.36 cm/hour in whole skin and from 0.136 to 0.276 cm/hour in skin stripped of the stratum corneum (Huq et al. 1986). The investigators proposed that permeability is probably greater in the more highly vascularized human tissue because the extensive network of surface capillaries in humans reduces the thickness of the diffusional barrier. They further stated that dermally absorbed phenolic compounds are potentially more toxic than orally absorbed compounds because Phase II detoxification reactions are more rapid after oral exposure. In another *in vitro* diffusion study of 4-CP, 87.4 to 90.5% of the applied dose crossed rat epidermal preparations in 72 hours, indicating extensive absorption (Hughes et al. 1993). Those phenols (both chlorophenols and other substituted phenols) with log K_{ow}, values between 1.4 and 3.5 showed the greatest amount of permeability through the dermal membrane. Although specific data were not identified, dermal absorption of

chlorophenols should also be greater for the neutral acid form than for the phenolate anion as ions do not readily cross cell membranes.

2.3.1.4 Other Routes of Exposure

No studies were located regarding absorption in humans exposed to any of the eight chlorophenol isomers by other routes.

An experiment with rabbits indicated that 2,4,6-TCP is absorbed through the cornea to a minor degree following ocular application (Ismail et al. 1977).

2.3.2 Distribution

Distribution of chlorophenols has not been studied in children.

2.3.2.1 Inhalation Exposure

No studies were located regarding the tissue distribution in humans or animals exposed by inhalation to any of the eight chlorophenol isomers discussed in this profile.

2.3.2.2 Oral Exposure

No studies were located regarding the tissue distribution in humans exposed orally to any of the eight chlorophenol isomers discussed in this profile.

Chlorophenols do not appear to accumulate in animals following oral exposure. For example, liver 2-CP concentrations were 2.2,3.2, and 0.8 ppm, and kidney 2-CP concentrations were 2.6,2.4, and 2.2 ppm in female rats exposed to 2-CP in the drinking water for 16 weeks at 5,50, and 500 ppm, respectively (Exon and Koller 1982). The investigators did not provide an explanation for the low value (0.8 ppm) found in the livers of rats receiving the high dose and did not indicate whether these values were wet or dry weight concentrations. Radioactivity was not recovered in the liver, lung, and subcutaneous fat of rats given three daily gavage doses of radiolabelled 2,4,6-TCP (Korte et al. 1978) or in unspecified tissues of rats given radiolabelled 2,4,6-TCP by gavage for 15 days (Bahig et al. 1981).

The highest concentrations of 2,3,4,6-TeCP were found in the spleen followed by the kidneys and liver 24 hours after a single oral dose was given to rats (Hattula et al. 1981). In a 55day study in which rats were treated by gavage with 2,3,4,6-TeCP at 10,50, or 100 mg/kg/day, tissue levels, measured 24 hours after the last dose, were dose related. For all doses, the concentrations of 2,3,4,6-TeCP in the brain and muscle were lower than those found in the kidney, liver, and spleen. At the 100 mg/kg/day dose, the kidney had the highest 2,3,4,6-TeCP concentrations (5.1 ppm) followed by the spleen (3.2 ppm), liver (2.2 ppm), brain (1.2 ppm), and muscle (0.46 ppm) (Hattula et al. 1981). At the 10 mg/kg/day dose, 2,3,4,6-TeCP was not detected in the brain or muscle (detection limit not stated), while low levels were found in the spleen (0.04 ppm), kidney (0.03 ppm), and liver (0.01 ppm).

2.3.2.3 Dermal Exposure

Concentrations of 2,4-DCP were 24.3, 5.3, 18.7, and 1.2 mg/L in the blood, urine, bile, and stomach contents of a worker who collapsed (within 20 minutes) and died shortly after being splashed with pure 2,4-DCP on his right arm and leg (Kintz et al. 1992).

No studies were located regarding the tissue distribution in animals dermally exposed to any of the eight chlorophenol isomers discussed in this profile.

2.3.2.4 Other Routes of Exposure

A study in which laboratory animals were given intravenous 2,4-DCP provides some insight regarding distribution patterns anticipated in humans (Somani and Khalique 1982). Intravenously administered 2,4-DCP rapidly distributes to the kidney, liver, fat, and brain in rats, with the highest concentrations in the kidney and liver. Elimination from these tissues is also rapid; the elimination half-time for plasma is approximately 10 minutes (Somani and Khalique 1982). The results of *in vitro* binding studies using human serum proteins indicate that both 2,4-DCP and 2,4,6-TCP strongly bind to serum proteins, including albumin and globulin (Judis 1982). The percentage of the compound bound to albumin was slightly greater for 2,4,6-TCP (94.1%) than for 2,6-DCP (87.7%).

In rabbits, following ocular exposure, radiolabelled 2,4,6-TCP was distributed to various compartments of the eye (Ismail et al. 1977). At 30 minutes post exposure, the applied radioactivity was detected in the cornea (4%), aqueous humor (0.37%), lens (0.037%), iris (0.18%), choroid (0.04%), vitreous (0.01%), conjunctiva

(2.14%), limbus (0.96%), and sclera (0.35%). At 60 minutes post exposure the respective percentages were 2.4, 0.17, 0.03, 0.10, 0.13, 0.01, 2.49, 0.88, and 0.53%.

Peak concentrations of 2,4,6-TCP were observed in all tissues assayed (blood, liver, kidney, muscle, fat, and brain) 30 minutes after rats were given a single intraperitoneal injection of 25 mg/kg 2,4,6-TCP (Pekari et al. 1986). The highest concentration observed was in the kidneys, 329 ± 117 nmol/g tissue, a concentration approximately 2, 7, 10, 13, and 26 times the concentrations found in the blood, liver, fat, muscle, and brain, respectively.

2.3.3 Metabolism

Both human and animal studies indicate that sulfation and glucuronidation are the main metabolic pathways of chlorophenols. Among sawmill workers, virtually all the absorbed tri- and tetrachlorophenols were excreted in the urine as conjugated metabolites (Pekari et al. 1991). Sulfate conjugation was predominant.

A number of rabbit studies (Azouz et al. 1953; Bray et al. 1952a, 1952b; Spencer and Williams 1950) have shown that metabolism of the monochlorophenols is principally via conjugation. In the latter study, groups of 6 rabbits were treated by gavage with 171.3 mg/kg of 2-CP or 4-CP emulsified in water as a single dose. For both isomers, the 24-hour urine analysis indicated that between 78.1 and 88.3% of the administered dose was excreted as the glucuronide, and between 12.8 and 20.6% of the administered dose was excreted as the ethereal sulfate. A total of 101.7 and 101.1% of the administered 2-CP or 4-CP doses, respectively, was accounted for as urinary glucuronide and sulfate conjugates. Metabolism was further investigated in 4 rabbits, each treated by gavage with an average dose of 395 mg/kg/day of 4-CP. After 36 hours, 54.1% of the administered dose appeared in the urine as the glucuronide conjugate, and 10.4% of the administered dose appeared in the ethereal sulfate fraction. Only 0.1% of the administered dose was excreted as 4-chlorocatechol. The low total recovery (64.5%) in the latter experiment limits conclusions. Other rabbit studies indicated that chlorocatechols constituted only 1.5-4.5% of the administered doses of 300 mg/kg 2-CP or 500 mg/kg 4-CP (Azouz et al. 1953). In a limited study in dogs (Coombs and Hele 1926) about half of an oral dose of 2- or 4-CP was excreted in the urine as the ethereal sulphate. No evidence for metabolism to mercapturic acid was found.

In contrast to the study in dogs, Phornchirasilp et al. (1989a) has proposed that in mice 4-CP is metabolized by P-450 enzymes to intermediates that react with glutathione to form glutathionyl adducts. This pathway

was proposed based on the observation that 4-CP treatment of mice depleted liver thiol stores. The depletion of liver thiol stores was prevented by a P-450 inhibitor (SKP 525-A) suggesting that P-450 activity is required for this effect.

A study in rats found that glucuronides and other unspecified conjugates were formed following a single intravenous dose of 2,4-DCP (10 mg/kg) (Somani and Khalique 1982). One hour after dosing, only small amounts of 2,4-DCP were found in the tissues studied (plasma, liver, kidneys, fat, brain). Although other unspecified conjugates were found in the fat, glucuronide conjugates were not found in the fat at any time interval. Two minor metabolites of 2,4-DCP, both dichloromethoxy phenols, have been identified in studies using isolated perfused rat livers (Somani et al. 1984). The extent to which the dichloromethoxy phenols are formed *in vivo* has not been determined (Somani et al. 1984).

2,4-DCP has been shown to be metabolized into two major metabolites identified as 2-chloro-1,4-hydroxyquinone and 2-chloro- 1,4-benzoquinone by microsomal fractions and whole cells of yeast *Saccharomyces cerevisiae* expressing human cytochrome P-450 3A4 (Mehmood et al. 1997). Another metabolite, 1,2,4-hydroxybenzene, was also detected during biotransformation by whole cells but was not observed in microsomal fractions. Thus, human CYP3A4 can remove either or both chlorine atoms from the aromatic ring of 2,4-DCP molecule, forming 2-chloro-1,4-hydroxyquinone and 1,2,4-hydroxybenzene, respectively. 2-chloro-1,4-hydroxyquinone was probably acted on by dehydrogenase from yeast microsomes, forming 2-chloro-1,4-benzoquinone (Mehmood et al. 1997).

Little information was located on the metabolism of trichlorophenols. In general, 2,4,6-TCP undergoes biotic isomerization to other trichlorophenol isomers and conjugation with glucuronic acid (Bahig et al. 1981). Male rats eliminated 63% of a gavage dose of 2,4,6-TCP in the urine as 4 trichlorophenol isomers and 28% as conjugates. Three of the trichlorophenol isomers were identified as 2,4,6-TCP (parent compound), 2,3,6-TCP, and 2,4,5-TCP; the fourth isomer was not identified. Glucuronic acid accounts for approximately 80% of the conjugates detected in urine (Bahig et al. 1981).

In vitro studies using rat liver microsomes have shown that 2,4,5-TCP can be metabolized to 3,4,6-trichlorocatechol, 2,5-dichlorohydroquinone, and a dihydroxydichlorobenzene (not further characterized) (Butte et al. 1988; Juhl et al. 1991). Metabolites were also dimerized to a dihydroxyhexachlorobiphenyl, a dihydroxypentachlorodiphenyl ether, two hydroxypentachlorodiphenyl ethers, a hydoxyhexachlorodiphenyl ether, and a Hydroxyhexachlorodioxin or hydroxyhexachlorodiphenoquinone (Butte et al. 1988). Metabolites generated following incubation

of 2,4,6-TCP with rat liver S-9 fraction were 2,6-dichloro-1,4-hydroquinone and two isomers of hydroxypentachlorodiphenyl ether (Juhl et al. 1989). The 2,6-dichloro-1,4-semiquinone free radical was also identified. Although *in vivo* these metabolites may be minor, *in vitro* they were responsible for DNA damage (Juhl et al. 1989, 199l).

Metabolism of 2,4,6-TCP by the skin has not been detected (Huq et al. 1986). Therefore, Huq et al. (1986) have suggested that 2,4,6-TCP absorbed through the skin could be more toxic than a similar ingested dose because the ingested compound is partially converted to glucuronide conjugates.

In a study in rats, a majority (70%) of intraperitoneally administered 2,4,6-TCP detected in the blood was in conjugated form 30 minutes after dosing. The authors speculated that the chemical was conjugated with glucuronic acid (Pekari et al. 1986). The average percentage of the metabolites of 2,4,6-TCP conjugated in the blood over the course of the study was 83±11%.

A study of the metabolism of the TeCP isomers following intraperitoneal injection in rats, indicates that much of the dose is excreted in the urine unchanged (Ahlborg and Larrson 1978). Following treatment with 2,3,4,5- and 2,3,4,6-TeCP, a trichlorohydroquinone was identified in the urine as a minor metabolite. Following treatment with 2,3,5,6-TeCP, about 35% of the recovered dose (total recovery 98.7%) was tetrachloro-*p*-hydroquinone, while the remaining was the unchanged parent compound (Ahlborg and Larrson 1978).

Metabolism of chlorophenols has not been studied in children. In humans, activity of UDP-glucuronosyltransferase (responsible for glucuronide conjugates) does not reach adult levels until about 6-8 months of age, although the development of this activity is isoform specific. Activity of sulfotransferases (responsible for sulfate conjugates) seems to develop earlier, although again, it is isoform specific. The activity of some sulfotransferase isoforms may be greater than that of adults during infancy and early childhood (Leeder and Kearns 1997). Since chlorophenols are detoxified in the liver by conjugation with glucuronic acid and sulfate, the toxicity of chlorophenols may be different in children.

2.3.4 Excretion

Excretion of chlorophenols has not been studied in children.

2.3.4.1 Inhalation Exposure

After occupational exposure by combined dermal and inhalation routes to a chlorophenol dipping solution, maximal urinary concentrations were 1-11.8 μmol/L 3.4-17.3 μmol/L, and 0.2-0.9 μmol/L for tri-, tetra-, and pentachlorophenol, respectively (Pekari et al. 1991). Elimination half-lives were 18 hours, 4.2 days, and 16 days, respectively. The renal clearance rate of 2,3,4,6-TeCP was approximately five times faster than the clearance rate of pentachlorophenol; this finding reflects the increased plasma protein binding of the higher chlorinated compound (Pekari et al. 1991). The clearance rate of 2,4,6-TCP could not be calculated because of highly variable serum concentrations (Pekari et al. 1991).

No animal studies were located regarding the excretion of any of the eight chlorophenol isomers after inhalation exposure.

2.3.4.2 Oral Exposure

The limited available data indicate that orally administered monochlorophenols are rapidly absorbed and excreted in the urine, primarily as glucuronide and sulfate conjugates, in rats, rabbits, and dogs (Bray et al. 1952a, 1952b; Coombs and Hele 1926; Spencer and Williams 1950). Most of the administered dose is excreted in the urine within 24 hours. More comprehensive data, including the kinetics of tissue uptake and distribution, are limited to 4-CP (discussed below). Data are insufficient to identify differences in the excretion of monochlorophenol isomers between animal species.

At oral doses of 150-450 mg/kg, excretion of the glucuronide conjugate of orally administered 4-CP in rabbits followed first-order kinetics (Bray et al. 1952a). The velocity constant k_g, or the rate of glucuronide excretion relative to remaining body burden, was 0.41 $hour^{-1}$. The investigators noted that the value of k_g for 4-CP is apparently not related to the electron withdrawing influence of the substituent group (Bray et al.1952a).

Male rats administered radiolabelled 2,4,6-TCP by gavage for 3 days and observed for 5 days after dosing eliminated a total of 82.3% of the total dose in the urine and 22.2% in the feces (Korte et al. 1978). In a second study using male rats, radiolabelled 2,4,6-TCP was administered by gavage for 15 days, with sacrifice 3 days after administration ended. A total of 92.5% of the administered dose was excreted in the urine, and 6.4% was excreted unchanged in the feces (Bahig et al. 1981). Four trichlorophenol isomers

were detected in the urine and comprised 63% of the total urinary radioactivity. These isomers were the unchanged parent compounds, 2,3,6-TCP, 2,4,5-TCP, and an unidentified compound. The metabolites identified in the polar fraction were trichlorophenol conjugates with glucuronic acid; these products accounted for 28% of the radioactivity eliminated in the urine (Bahig et al. 1981). Free trichlorophenol was identified in the feces. The excretion of radioactivity declined rapidly after dosing ended. By the third day postexposure, only 4.3% of the radioactivity in a daily dose was detected in the urine and 1.9% was detected in the feces (Bahig et al.1981).

2.3.4.3 Dermal Exposure

As discussed in Section 2.3.4.1, combined dermal and inhalation exposure to a chlorophenol-containing wood treatment solution resulted in the urinary excretion of tri-, tetra-, and pentachlorophenol. Rate constants of elimination were inversely proportional to the extent of chlorination (Pekari et al. 1991).

No animal studies were located regarding the excretion of any of the eight chlorophenol isomers after dermal exposure.

2.3.4.4 Other Routes of Exposure

A study in rats showed rapid clearance from the kidney, liver, fat, brain, and plasma of both the parent compound and metabolites after intravenous administration of 10 mg/kg/day 2,4-DCP in an aqueous solution (Somani and Khalique 1982). Half-lives for 2,4-DCP and its conjugates ranged from 4 to 30 minutes in these tissues, with the highest values in kidney, followed by the liver, fat, plasma, and brain (Somani and Khalique 1982). No detectable amounts were found in the brain at 60 minutes. These data suggest that 2,4-DCP does not accumulate in body tissues and is quickly excreted.

In rats administered 2,4,6-TCP by intraperitoneal injection, the majority (70%) of 2,4,6-TCP associated radioactivity detected in the blood 30 minutes after dosing was in a conjugated form (Pekari et al. 1986). The authors speculated that it was conjugated with glucuronic acid. The biological half-life of conjugated 2,4,6-TCP was 1.4 hours in blood and ranged from 1.4 to 1.8 hours in other tissues. Elimination of approximately 90% of the administered dose in the urine occurred within 4-6 hours. Only trace amounts of trichlorophenol were detected in tissues 10 hours after dosing (Pekari et al. 1986).

Ahlborg and Larrson (1978) studied the urinary excretion of TeCPs in rats following intraperitoneal injection of a single dose. The slowest rate of excretion was observed following treatment with 2,3,4,5-TeCP. During the 72 hours after administration, about 60% of the dose was recovered in the urine; the majority of it was excreted unchanged. In contrast, following treatment with 2,3,4,6-TeCP, 95.9% of the dose was excreted in the urine in 72 hours, and 98.7% of the administered 2,3,5,6-TeCP was excreted in the urine within 24 hours after dosing. The investigators (Ahlborg and Larsson 1978) did not provide an explanation regarding the slower excretion of 2,3,4,5-TeCP compared to the excretion of 2,3,4,6-TeCP and 2,3,5,6-TeCP.

2.3.5 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 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 2-3 shows a conceptualized representation of a PBPK model.

If PBPK models for chlorophenols exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

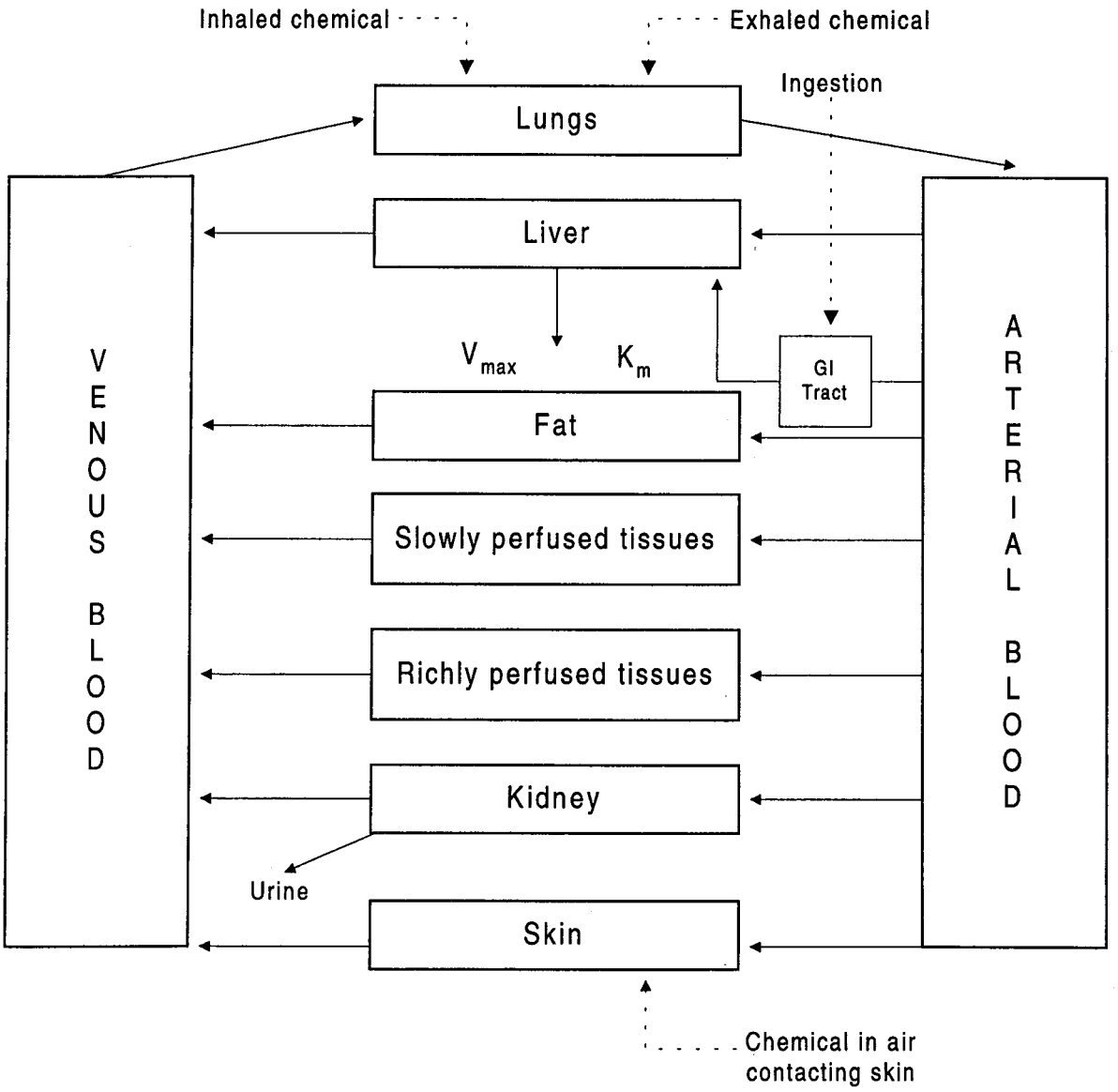
There are no PBPK models for chlorophenols.

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

Chlorophenols have moderately high lipophilicity. They are weak organic acids with pK_a values that range from 5.4 to 8.9 (Shiu et al. 1994); consequently, absorption should be favored in the stomach and the intestine. Absorption through the gastrointestinal tract is by simple diffusion and is expected to be both rapid and virtually complete. The chlorophenols are also readily absorbed after dermal exposure. Dermal absorption should also be greater for the neutral acid form than for the phenolate anion as ions do not readily cross cell membranes. Dermally absorbed doses of chlorophenols are potentially more toxic than orally absorbed doses (Huq et al. 1986). The chlorophenols were not metabolized or conjugated during

Figure 2-3. Conceptual Representation of a Physiologically-Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



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.

their diffusive transport through the skin (Huq et al. 1986); however, they are partially converted to more easily eliminated, less toxic glucuronide conjugates after oral ingestions.

After a single oral dose of 2,3,4,6-TeCP to rats, the kidney had the highest tissue concentration, followed by the spleen, liver, brain, and muscle (Hattula et al. 1981). When administered intravenously to rats, 2,4-DCP rapidly distributes to the kidney, liver, fat, and brain, with the highest concentrations in the kidney and liver (Somani and Khalique 1982). 2,4-DCP and 2,4,6-TCP strongly bind to serum proteins, including albumin and globulin (Judis 1982).

2.4.2 Mechanisms of Toxicity

Chlorophenols uncouple mitochondrial oxidative phosphorylation and produce convulsions. Within 20 minutes of being accidentally splashed with 2,4-DCP on his right arm and leg, a worker experienced seizures, collapsed, and died shortly thereafter (Kintz et al. 1992). Lethargy, tremors, convulsions, and/or central nervous system depression have been reported in chlorophenol-exposed animals (Borzelleca et al. 1985a; Deichmann and Mergard 1948). Within the series including phenols and chlorinated phenols, convulsive effects decreased with increasing chlorination. Limited data were located on the mechanism of phenol- or chlorophenol-induced convulsions. Phenol administration in cats facilitated effects on central synaptic transmission at both excitatory and inhibitory synapses (Banna and Jabbur 1970). The authors proposed that certain phenols increase the amount of neurotransmitter released during synaptic transmission, resulting in convulsions. After intraperitoneal injection of several chlorophenols, convulsions predominated in those mice receiving the 2- and 4-CP compounds (Farquh&son et al. 1958). Because these compounds have pK values of 8.65 or higher and would not be in the ionic form at physiologic pH, the investigators attributed the observed effect to the chlorophenol rather than to the ion.

Particularly for the higher chlorophenols, the primary toxic mechanism associated with exposure is the uncoupling of mitochondrial oxidative phosphorylation (Farquharson et al. 1958; Weinbach and Garbus 1965). Although the kinetics of chlorophenol-induced uncoupling have primarily been studied in *in vitro* mitochondrial preparations, the associated metabolic effects (such as increased body temperature and dyspnea) have been verified *in vivo* (Farquharson et al. 1958). The ability of chlorophenols to uncouple oxidative phosphorylation increases with increasing chlorination. Toxic manifestations include central nervous system depression followed by increased respiration, hyperthermia, a blood pressure rise, progressive euromuscular weakness, and cyanosis. The results of a number of *in vitro* studies (Cascorbi and Ahlers

1989; Izushi et al. 1988; Mitsuda et al. 1963; Narasimhan et al. 1992; Shannon et al. 1991; Stockdale and Selwyn 1971) indicate a concentration-dependent triphasic effect of chlorophenols on phosphorylation and cellular respiration. At low concentrations, uncoupling produces stimulation of state 4 (resting state) respiration as a result of increased adenosine triphosphatase (ATPase) activity in the absence of a phosphate acceptor. Inhibition of state 3 (active) respiration is also observed. At moderate concentrations, resting respiration is neither stimulated nor inhibited. Significant inhibition of respiration, associated with a breakdown of the electron transport process and decreased ATPase activity, occurs at very high concentrations. These concentrations are also associated with mitochondrial swelling and disruption of the mitochondrial matrix structure. Investigators have cited two independent mechanisms to explain these effects on cellular metabolism. Uncoupling activity has been attributed to a protonophoric effect (a disruption of the energy gradient across the mitochondrial membrane resulting from distribution of chlorophenols in the phospholipid bilayer of the membrane), whereas inhibition of cellular respiration has been attributed to a direct action on intracellular proteins.

The results of these and other studies also illustrate that higher order chlorophenols have the greatest effects on cellular metabolism. In general, investigators have found that 2-CP and 4-CP are less than 7% as potent as tetrachlorophenol in uncoupling oxidative phosphorylation and inhibiting cellular respiration (Cascorbi and Ahlers 1989; Janik and Wolf 1992; Narasimhan et al. 1992; Weinbach and Garbus 1965). Within the chlorophenol series, two physicochemical parameters, the a-Hammett constant, a measure of electron withdrawing ability, and the octanol-water partition coefficient (log K_{ow}), accounted for 98% of the variability in the inhibition of ATPase activity (Cascorbi and Ahlers 1989).

Corrosive skin damage resulting from high concentration phenol exposure has been attributed to protein denaturation by protein-solute complexes (Roberts et al. 1977). In this study, various concentrations of 2-CP and 4-CP were applied to samples of human abdominal skin maintained in a diffusion chamber. The estimated threshold concentrations for damage (the aqueous concentration at which the transmembrane permeability coefficient began to increase) were 0.8% and 0.75%, respectively, for these two isomers. The investigators proposed that the extent of damage was related to the concentration of the solute partitioned into the stratum corneum, the diffusivity of the solute, and the pK of the applied phenolic compound.

In a study in rats, Kitchin and Brown (1988) examined the effects of single gavage doses of 2,4,5-TCP, 2,4,6-TCP, and 2,3,4,6-TeCP on markers of carcinogenic initiation (alkaline elution for DNA damage in liver and blood), promotion of carcinogenesis (ornithine decarboxylase activity in the liver), and hepatic cell damage

(serum alanine aminotransferase [SGPT] activity). At a dose one-fifth the LD_{50} (164 mg/kg for 2,4,5 and 2,4,6-TCP; 28 mg/kg for 2,3,4,6-TeCP), no effects were observed. 2,4,6-TCP and 2,3,4,6-TeCP were also tested at higher equimolar concentrations (2,4,6-TCP, 500 mg/kg; 2,3,4,6-TeCP, 193 mg/kg). At the high dose, both compounds resulted in a significant increase in liver ornithine decarboxylase activity. No effects on alkaline elution of DNA or on SGPT activity were observed, suggesting that 2,4,6-TCP and 2,3,4,6-TeCP were weak promoters.

2.4.3 Animal-to-Human Extrapolations

Extrapolating animal toxicity data to predict human risk from chlorophenol exposure appears to be reasonable because of the similarity in metabolic pathways and effects. However, the one case of human death following dermal exposure indicates that animals may be more resistant to the toxic effects of 2,4-dichlorophonol than humans.

2.5 RELEVANCE TO PUBLIC HEALTH

Issues relevant to children are explicitly discussed in 2.6 Children's Susceptibility and 5.6 Exposures of Children.

Overview.

Chlorophenols are used as intermediates in the production of dyes and chlorinated pesticides. Because of its biocidal properties, 4-CP is also used as a dental antiseptic. Runoff from pesticide degradation, contaminated food intake, and the chlorination of both drinking water and waste water are the environmental sources of human exposure to chlorophenols. A chlorophenol-containing waste site may result in groundwater contamination with subsequent introduction into the drinking water supplies. Dermal exposure can occur in occupational settings. Much lower levels of dermal exposure can occur through showering and bathing with water containing chlorophenols. In addition, the environmental dechlorination of the higher chlorophenols can result in exposure to the lower chlorophenols.

Exposed pesticide production workers may be at increased risk for soft tissue sarcoma, Hodgkin's disease, and non-Hodgkin's lymphoma. Although these results have been found in several occupational studies, the majority of studies find no, or only slightly, increased cancer risk associated with exposure. Possible

confounding variables in the positive studies included recall and selection bias. Another major health concern in workers is the development of chloracne, which is probably attributable to the presence of other chlorinated dioxins as contaminants in CP-containing pesticides.

The results of animal studies partially support the human data. 2,4,6-TCP was a carcinogen in 2-year rat and mouse studies. Other studies suggest that chlorophenols, rather than being initiators, may be tumor promoters. This is supported by genotoxicity data that suggest that the chlorophenols are not directly mutagenic. The EPA has classified 2,4,6-TCP as a class B2 carcinogen. Hepatic effects, ranging from enzyme induction to generalized necrosis, are also found in animals. Although 2,4-DCP has been shown to effect cell-mediated immunity in laboratory studies, the toxicological relevance of this finding to individuals exposed near hazardous waste sites is unknown. The higher chlorinated phenols have shown equivocal reproductive and developmental effects only at doses producing maternal toxicity. These findings indicate a possible concern for pregnant women exposed in the workplace or through contaminated environmental media. Observations of corrosion and death after skin application of high doses of chlorophenols reinforces the dermal health hazard concern for workers.

Minimal Risk Levels for Chlorophenols

Exposures to chlorophenols at hazardous waste sites are most likely to be to a mixture of chlorophenols rather than to a single compound. Unfortunately, no information regarding effects following exposure to a mixture of chlorophenols was identified. As a conservative approach, duration-specific MRLs for the chlorophenols as a class were developed based on the single compound with the lowest LOAEL and, therefore, should protect against effects following exposure to all chlorophenols as well as exposure to mixtures of chlorophenols if effects of multiple chlorophenols are additive.

Inhalation

The inhalation data for chlorophenols is limited to a single acute study of 2-CP in which rats were exposed (nose-only) to 17, 104, or 908 ppm for 4 hours (Duchosal and Biederman 1991). Restlessness and hunched posture were observed at the high concentration. Dark red foci were observed at the two lower concentrations.

but not at the high concentration. No controls were used in this study. Because of the lack of a clear doseresponse relationship and the absence of controls, this study was not considered appropriate for the derivation of an inhalation MRL.

Oral

- An MRL of 0.01 mg/kg/day has been derived for acute-duration oral exposure to chlorophenols. This MRL is based on electron microscopic changes (foamy cytoplasm and clustering of rnitochondria and endoplasmic reticulum) observed in the hepatocytes of rats treated with 4-CP at 2.58 mg/kg/day but not at 1.28 mg/kg/day (Phornchirasilp et al. 1989b). The rats were treated by gavage two times per day with the 4-CP in corn oil. There are no additional studies that examine liver effect following oral exposure to 4-CP.

- An MRL of 0.003 mg/kg/day has been derived for intermediate-duration oral exposure to chlorophenols. This MRL is based on a decrease in delayed type hypersensitivity observed in rats treated with 2,4-DCP in the drinking water throughout gestation and 10 weeks after weaning at 3 mg/kg/day but not at 0.3 mg/kg/day (Exon and Keller 1985; Exon et al. 1984).

Chronic

No chronic duration oral MRLs were derived for any of the chlorophenols because the NOAELs identified in the chronic studies were greater than LOAELs identified in the intermediate duration studies.

Death. No data were found on death following inhalation or ingestion of chlorophenols. The only report of death in humans following exposure to chlorophenols is a single case in which a man died shortly after being splashed on less than 10% of his body with 2,4-DCP (Kintz et al. 1992). Postmortem blood and urine concentrations were 24.3 and 5.3 mg/L, respectively. Most data from acute inhalation, oral, and dermal lethality animal studies suggest that chlorophenols are lethal only at high exposure levels. Acute lethality generally occurs at oral doses greater than 100 mg/kg (Ahlborg and Larsson 1978; Bercz et al. 1990; Blackburn et al. 1986; Borzelleca et al. 1985a, 1985b; Carreon et al. 1980a; Kobayashi et al. 1972; NTP 1989; Rodwell et al. 1989). The range of oral LD_{50} values, 89 mg/kg for male mice treated with 2,3,5,6- TeCP in ethanol (Ahlborg and Larsson 1978) to 2,960 mg/kg for male rats treated with 2,4,5-TCP in corn oil (McCollister et al. 1961), indicates that the chlorophenols are slightly or moderately toxic according to the

classification scheme of Hodge and Sterner (1949). The use of different vehicles in oral studies makes it difficult to draw any conclusions about which of the chlorophenols are the most toxic. For example, in studies of the TeCPs, oral LD_{50}s in rats were lower when the compounds were given in 40% ethanol rather than propylene glycol (Ahlborg and Larssen 1978).

More limited dermal LD_{50} data indicate a range of 485 mg/kg for 2,3,4,6-TeCP in rats (Shen et al. 1983) to 1,414 mg/kg/day for 2,4-DCP in rabbits (Carreon et al. 1980b). The range of LD_{50}s following intraperitoneal injection exposure was 48 mg/kg for 2,3,5,6-TeCP given to mice in 40% ethanol (Ahlborg and Larsson 1978) to 430 mg/kg for 2,4-DCP given to rats in olive oil (Farquharson et al. 1958).

Typical signs of severe acute intoxication include ataxia, fatigue, disorientation, tachycardia, and increased respiratory rate followed by dyspnea, myoclonic convulsions, and coma (Borzelleca et al. 1985a, 1985b; Farquharson et al. 1958; Kobayashi et al. 1972). Convulsions are a diagnostic feature of intoxication with certain phenolic compounds, including the lower chlorinated phenols. The mechanism of action of this effect is poorly understood. Furthermore, an adequate dose-response relationship for this end point has not been established. Convulsions have been reported after both oral and dermal administration, indicating that the effect is not route specific.

Given the high doses of chlorophenols required to produce death in laboratory animals, death in humans exposed through contaminated drinking water is unlikely. The taste and odor thresholds of the chlorophenols, which are in the ppb range (Burttschell et al. 1959), would make the likelihood of intoxication via drinking water quite remote because of the unpleasant taste and odor of the contaminated water. In the occupational setting, exposure to more highly concentrated chlorophenols could result in death following inhalation, oral, or dermal exposure as suggested by the case report by Kintz et al. (1992).

Systemic Effects. No data regarding the systemic toxicological effects of exposure to chlorophenols in humans, in isolation from other contaminants, were located in the literature. The discussion provided below will describe systemic effects in humans occupationally exposed to a variety of airborne contaminants (including chlorophenols), laboratory animal studies, and supporting data.

Respiratory Effects. In a small cross-sectional study on workers involved in 2,4,5,-TCP production, no adverse effects on pulmonary function or the incidence of pulmonary lesions were observed (Calvert et al. 1991). Lumber mill workers exposed to a mixture of tetrachlorophenols (specific isomers not stated) and

pentachlorophenol reported upper respiratory tract irritation more frequently than unexposed workers (Kleinman et al. 1986). Acute inhalation exposure of laboratory animals to monochlorophenols has resulted in hemorrhage in the lungs and tachypnea (Duchosal and Biedermann 1991). Rats and mice exposed to high oral doses of 2,4-DCP or 2,4,6-TCP had no adverse effects on lung weight or histopathology (Bercz et al. 1990; Blackburn et al. 1986; NCI 1979; NTP 1989).

The limited data are insufficient to predict the respiratory response of humans exposed either acutely or chronically to chlorophenols.

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans after exposure by any route to any of the eight chlorophenols discussed in this profile. Animal studies have not reported histological changes in the heart following exposure to 2,4-DCP, 2,4,5-TCP, or 2,4,6-TCP (Bercz et al 1990; Blackburn et al. 1986; NCI 1979; NTP 1989), providing limited evidence that these compounds are not cardiovascular toxicants.

Gastrointestinal Effects. Symptomology of gastrointestinal effects has not been reported in production workers exposed to trichlorophenols and other chlorinated organics (Calvert et al. 1992). Single gavage doses of 432 mg/kg or more 2,3,4,6-TeCP has produced intestinal cell necrosis in rats (Hattula et al. 1981). The results of other animal studies, however, did not indicate damage to the intestinal tract after exposure to large oral doses of chlorophenols (NCI 1979; NTP 1989).

Hematological Effects. Adequate data for the assessment of hematological effects in chlorophenol-exposed humans were not located. Results from oral acute- to chronic-duration animal studies indicate that 2-CP has no adverse effects on standard hematological end points at doses up to 50 mg/kg/day (Borzelleca et al. 1985a; Exon and Koller 1985). Consequently, under the conditions of these studies, the hematological system does not appear to be a target organ at moderately high exposure concentrations.

Results of chronic oral studies in rats indicate that various hematopoietic effects, such as bone marrow atrophy, hyperplasia, and leukocytosis, occur in rats exposed chronically to 500 mg/kg/day or more 2,4-DCP or 2,4,6-TCP (NCI 1979; NTP 1989). Furthermore, the results of the NCI (1979) studies indicate that 2,4,6- TCP is associated with an increased incidence of leukemia in rats.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans. Intermediate and chronic oral exposure of animals to 2,4-DCP (NTP 1989) or 2,3,4,6-TeCP (Hattula et al. 1981) did not result in any histopathologic changes in muscle.

Hepatic Effects. Chlorophenol-exposed manufacturing workers have been diagnosed with porphyria, elevated serum transaminase levels, regenerative hepatocellular activity, and hemofuscin deposition (Bleiberg et al. 1964). In another group of production workers, elevated GGT activity has been associated with an interaction between 2,4,5-TCP exposure and alcohol consumption (Calvert et al. 1992). These data indicate a concern for hepatic effects in individuals exposed to chlorophenols.

Acute exposure concentrations of up to 69 mg/kg/day 2-CP for 14 days in mice produced no changes in hepatic microsomal P-450 enzyme levels (Borzelleca et al. 1985a). In contrast, 2-week administration of 0.64 mg/kg/day 4-CP in Sprague-Dawley rats increased microsomal demethylase activities, microsomal protein, and cytochrome P-450 content (Phornchirasilp et al. 1989a). Electron microscopic changes in hepatocytes (foamy cytoplasm, clustering of mitochondria and endoplasmic reticulum) occurred at ≥ 2.58 mg/kg/day, and 1.28 mg/kg/day was considered a NOAEL. The discrepancies in results between these two studies may be related to species differences but is most likely due to a 10-fold difference in test material volume measured on a body weight basis.

Animal data regarding the hepatic effects of the higher chlorinated phenols are conflicting. Mouse studies indicate that chronic exposure to 2,4-DCP is associated with liver necrosis (NTP 1989). There is inconclusive evidence that 2,4-DCP causes hepatocellular hyperplasia in rats and mice and diffuse syncytial alterations in mice exposed for long periods. A possible mechanism for the observed diffuse syncytial alterations was demonstrated in an *in vitro* study (Onfelt 1987) in which 2,4-DCP interfered with normal cell division by disrupting spindle formation. Interference of 2,4-DCP with oxidative phosphorylation, as demonstrated in an *in vitro* study with isolated mitochondria (Stockdale and Selwyn 1971), may be a mechanism for any or all of these liver effects since it can deplete the energy stores available to affected cells.

Hepatic effects observed in rats and mice following intermediate and chronic oral exposure to 2,4,6-TCP include alterations in hepatocytes, increased liver weight, and hepatic hyperplasia (Exon and Koller 1985; NCI 1979). The latter effect may possibly be a precursor to hepatic adenomas and carcinomas also observed in mice chronically exposed to 2,4,6-TCP (NCI 1979). Exposure to mid- to high-oral doses of 2,4,6-TCP has resulted in increased relative liver weights (Bercz et al. 1990; NCI 1979) and midzonal

vacuolation of hepatocytes (NCI 1979). In intermediate-duration oral studies, administration of as low as 50 mg/kg/day was associated with massive hepatocellular necrosis and venous thrombosis in l/10 rats (Hattula et al. 1981).

The mechanism for the observed hepatic alterations is difficult to determine. Various hepatic microsomal drug-metabolizing enzymes were not induced in an acute study in which rats were given several intraperitoneal injections of 2,4,6-TCP (Denomme et al. 1983). Acute oral dosing with as much as 400 mg/kg had no effect on enzyme activities and protein levels that are indicative of either increased metabolic activity or hepatotoxicity (Carlson 1978). Hepatic ornithine decarboxylase activity, a potential marker of tumor promoting capabilities, was elevated over control levels only after administration of lethal doses of 2,4,6-TCP or 2,3,4,6-TeCP (Kitchin and Brown 1988). Despite the inability to specifically ascertain the mechanistic basis of observed hepatotoxic effects, the available *in vivo* data are adequate to indicate that individuals exposed to sufficient levels of chlorophenols near hazardous waste sites are potentially at risk for liver effects ranging from increased enzyme activity to generalized necrosis.

Renal Effects. No data on the renal effects of chlorophenols in humans were located. In animal studies, either no or mild renal effects are evident at oral exposure levels of 720-2,600 mg/kg/day (Bercz et al. 1990; Blackburn et al. 1986; NCI 1979; NTP 1989). Renal tubular necrosis occurred only at lethal exposure concentrations (NTP 1989). The current data suggest that renal toxicity may only occur at doses unlikely in occupational or environmental settings.

Endocrine Effects. There are no reports of endocrine effects in humans occupationally exposed to chlorophenols. Histopathological changes have not been observed in endocrine glands (adrenal gland, pituitary, thyroid, parathyroids, pancreas) in animals exposed to chlorophenols for intermediate and chronic durations, providing limited evidence that endocrine glands are not a target of chlorophenol toxicity (American Biogenics 1988; Bercz et al. 1990; Blackburn et al. 1986; McCollister et al. 1961; NCI 1979; NTP 1989). An *in vitro* study examining the binding of chlorophenols to human transthyretin (a carrier of thyroid hormone) found that increasing chlorination resulted in greater affinity for the thyroxine (T4) binding site of the carrier (van den Berg 1990). The affinities of 2-CP, 2,4,5-TCP, and 2,4,6-TCP compared to T4 were 0.004, 0.15, and 0.33, respectively. Tetrachlorophenols were not tested. Based on the results of this *in vitro* study, van den Berg (1990) suggests that chlorophenols may reduce plasma T4 levels through competition with T4 binding on transthyretin and other T4 carriers (e.g., thyroid binding globulin, albumin).

Dermal Effects. Chloracne and evidence of acquired porphyria cutanea tarda, hyperpigmentation, and hirsutism have been observed in factory workers who were concurrently exposed to chlorophenols in phenoxy-based herbicides and, potentially, to dioxins (TCDD) (Bleiberg et al. 1964; Bond et al. 1989). In at least one study, chloracne incidence was positively correlated with TCDD exposure (Bond et al. 1989). The results of dermal studies with rats and rabbits indicate that chlorophenols can produce various effects, ranging from mild erythema to severe corrosion of the skin (Bioassay Systems 1981; Carreon et al. 1980a, 1980b; Hencke and Lockwood 1978; Rhodia 1978; Shen et al. 1983). The reports describing dermal effects are very limited and do not provide details of the effects observed; additionally, dose-response relationships are not clearly defined. The lowest dose resulting in direct dermal effects was 242 mg/kg/day 2-CP applied to the skin of rabbits (Bioassay Systems 1981).

Dermal exposure may be a special concern because wood treatment workers had measurable tetrachlorophenol levels on the hands and volar surface of the forearm, despite the use of gloves when handling timber (Fenske et al. 1987).

Ocular Effects. Eye irritation was reported among lumber mill workers exposed to a mixture of tetrachlorophenols (specific isomers not stated) and pentachlorophenol (Kleinman et al. 1986). The eye irritation was likely a direct effect of the tetrachlorophenols. The results of ocular toxicity studies in rabbits indicate that 2-CP concentrations as low as 1% can result in mild hyperemia (Rhodia 1978). The extent of tissue damage is concentration-related. Application of a 2% solution resulted in severe hyperemia with edema and cloudy swelling (Rhodia 1978), while administration of undiluted 2-CP produced edema with severe tissue erythema and corrosion (Younger Labs 1975). Severe cornea1 damage in rabbits occurred after the direct application of 0.1 mL 2,4-DCP in the eye (Hencke and Lockwood 1978). Consequently, moderately high vapor concentrations of 2-CP, 2,4-DCP, and possibly other chlorophenols in industry or at hazardous waste sites have the potential to produce ocular irritation and/or damage in unprotected individuals.

Body Weight Effects. Effects on body weight have not been reported in humans occupationally exposed to chlorophenols. Body weight loss has been observed in animals exposed to chlorophenols following acute, intermediate, and chronic duration exposure (American Biogenics 1988; Borzelleca et al. 1985a; Kavlock 1990; McCollister et al. 1961; NCI 1979; NTP 1989; Rodwell et al. 1989). When chlorophenols are administered in the diet, changes in body weight may be in part a result of decreased food intake because of reduced palatability (NTP 1989), although body weight decreases have also been observed following gavage administration (American Biogenics 1988). The lowest dose associated with body weight decrease was

20 mg 2,3,4,6-TeCP given to rats by gavage for 90 days (American Biogenics 1988). The observation that a TeCP has the greatest effect on body weight is consistent with the observation that TeCPs are more potent in uncoupling oxidative phosphorylation than the monochlorophenols (Cascorbi and Ahlers 1989; Narasimhan et al. 1992).

Immunological and Lymphoreticular Effects. No human data were located regarding immunological or lymphoreticular effects of chlorophenols. The results of one animal study indicate that neither humoral nor cell-mediated immunity is affected by oral exposure to 2-CP at doses up to 50 mg/kg/day (Exon and Koller 1985). In contrast, combined pre- and postnatal exposure to 2,4-DCP at 3 mg/kg/day both stimulated antibody production and inhibited a delayed type hypersensitivity response (Exon and Koller 1985). Combined pre- and postnatal exposure to 2,4,6-TCP in drinking water at doses up to 30 mg/kg/day did not significantly affect humoral or cell-mediated immunity in rats (Exon and Koller 1985). As discussed under hematological effects, bone marrow atrophy affecting both erythroid and myeloid elements has been observed in rats treated with 2,4-DCP in the diet at 500 mg/kg/day for 13 weeks (NTP 1989). Histological examination of lymph nodes, spleen, and thymus in chlorophenol-exposed animals has not revealed any effects in intermediate and chronic duration studies (McCollister et al. 1961; NCI 1979; NTP 1989).

Because of limited animal data and knowledge regarding the toxicological significance of many immunological findings, the relevance to public health of immunological effects following exposure to the chlorophenols cannot be determined specifically. However, animal evidence indicates that 2,4-DCP may have an effect on the immune system.

Neurological Effects. Lumber mill workers exposed to a mixture of tetrachlorophenols (specific isomers not stated) and pentachlorophenol reported headaches more frequently than unexposed workers (Kleinman et al. 1986). In animals exposed to chlorophenols by the inhalation, oral, or dermal routes, convulsions (a sign of exposure to high doses of some phenolic compounds) decrease with increasing chlorination. In oral and dermal acute lethality studies, convulsions were noted only as antecedents of death (Borzelleca et al. 1985a, 1985b; Deichmann and Mergard 1948). Consequently, adequate information about dose-response relationships or isomeric potencies were not determined. The mechanisms for these effects are not known, although interference with oxidative energy metabolism in the central nervous system has been suggested, based on *in vitro* studies with rat brain and nerve tissues (Farquharson et al. 1958). After intraperitoneal injection in mice, the median doses producing convulsions were 99 and 116 mg/kg, respectively, for 2-CP and 4-CP (Angel and Rogers 1972). Although this administration route has limited relevance for human exposure, the

data do suggest that humans exposed at hazardous waste sites via drinking water are likely to be at minimal risk of developing convulsions.

Reproductive Effects. No data were located regarding the reproductive effects of chlorophenols in humans. Studies on the reproductive toxicity of chlorophenols in rats suggest that 2-CP, 2,4-DCP, and 2,4,6-TCP, administered on days 6 through 15 of gestation, may reduce liter size (Exon and Koller 1985). However, at the highest dose tested (about 30 mg/kg/day 2,4-DCP and 2,4,6-TCP, and 50 mg/kg/day 2-CP) litter sizes were reduced compared to controls only at the $p \leq 0.1$ level. A study designed to assess the reproductive toxicity of 2,4,6-TCP found no effect on male or female reproductive functions at doses that caused death and reduced body weight (Blackburn et al. 1986). An increasing trend for preimplantation loss was observed in pregnant rats treated with 2,3,4,6-TeCP on gestation days 6-15 (RTI 1987). Because this study was not designed to examine the preimplantation/ implantation phase of reproduction, the issue of whether 2,3,4,6-TeCP affects implantation still needs to be resolved. Histological changes in the testes or ovaries have not been observed in rats or mice exposed to 2,4-DCP, 2,4,5- or 2,4,6-TCP, or 2,3,4,6-TeCP in intermediate- and chronic-duration studies (American Biogenics 1988; Bercz et al. 1990; McCollister et al. 1961; NCI 1979; NTP 1989).

Developmental Effects. No data were located regarding developmental effects in humans following exposure to chlorophenols. The results of developmental studies in animals do not clearly show a selective effect on development at doses lower than those causing maternal toxicity. At maternally toxic doses (750 mg/kg/day) reduced fetal body weight and delayed ossification were observed in the offspring of rats treated with 2,4-DCP on gestation days 6-15 (Rodwell et al. 1989). No developmental effects were noted in rats treated with 2,3,4,6-TeCP even at a dose that caused a 26% reduction in maternal body weight gain. The lack of a specific developmental effect for 2-CP, 2,4,6-TCP (Fu et al. 1990), 4-CP, and 2,3,4,5-TeCP (Mayura et al. 1991) is supported by studies using the *in vitro* hydra assay which showed that the compounds were equally toxic to adult and developing organisms.

In vitro exposure of rat embryos indicates that the chlorophenols can directly affect development. Exposure of rat embryos to 6 mM 4-CP or 2,3,4,5-TeCP resulted in a significant decrease in crown-rump length, somite number, and DNA and protein content (Mayura et al. 1991). The effects of 2,3,4,5-TeCP on development were much greater than 4-CP. 2,3,4,5-TeCP but not 4-CP also resulted in a significant reduction in yolk sac diameter. 4-CP exposure (195-781 nM) of rat embryos reduced measures of growth (somite number, crown rump length, DNA content) and increased structural defects (hind limb bud absence,

hypoplasia of first arch, tail defects) (Oglesby et al. 1992). The effects of 4-CP were ameliorated by coculture with hepatocytes, suggesting that 4CP, rather than a metabolite, was responsible for the effects on development.

In summary, the *in vivo* data suggest marginal effects of chlorophenol exposure on maternal and fetal toxicity and no evidence of teratogenicity. The more highly chlorinated compounds may present the greatest health risk to pregnant women exposed occupationally or through contaminated drinking water.

Genotoxic Effects. Studies regarding genotoxic effects in humans were not available. 2-CP and 4-CP have been tested in one *in vivo* and several *in vitro* genotoxicity assays. Acute administration of up to 69 mg/kg/day 2-CP in mice was not associated with any changes in bone marrow or testicular sister chromatid exchange (SCE) frequency (Table 2-4). Similarly, oral administration of up to 638 mg/kg/day (14 days) or 500 mg/kg/day (90 days) had no effect on SCEs in the testes or bone marrow (Borzelleca et al. 1985a). No further details were provided.

In mammalian *in vitro* systems, 2-CP induced slight-to-moderate increases in c-mitosis (indicating disturbances of the spindle function) and aneuploidy in cultured Chinese hamster lung cells (Onfelt 1987; see Table 2-5). The increase in aneuploidy, compared to controls, was statistically significant ($p<0.025$) by the chisquare test. The results of prokaryotic genotoxicity assays for 2-CP and 4-CP were primarily negative for mutagenicity. In standard *Salmonella typhimurium* reverse mutation assays with strains TA98, TA100, TA1535, TA1537, and TA1538, treatment generally did not produce an increased number of revertants (DeMarini et al. 1990; Haworth et al. 1983; Rapson et al. 1980). Negative findings occurred both in the presence and absence of metabolic activation. In one study, 4-CP had a marginally positive response in strain TA1537 (Seuferer et al. 1979). Neither 2-CP nor 4-CP, either with or without the S9 protein fraction, showed positive gene expression in a *umu* test system (Ono et al. 1992; Sakagami et al. 1988). 2-CP and 4-CP were negative in a prophage induction assay with *Escherichia coli* (DeMarini et al. 1990). 4-CP induced an increased number of revertants in *S. typhimurium* strains TA97 TA98, TAlOO, and TA104 (Strobe1 and Grummt 1987). The effects were most pronounced in strain TA97, in the presence of metabolic activation. Interpretation of these data is confounded by the absence of concentration-effect relationships.

2,4-DCP was negative for SCE induction in the testes and bone marrow after drinking water administration in rats (Borzelleca et al. 1985a; see Table 2-4). As shown in Table 2-5, the compound was mostly negative for mutagenic activity in *S. typhimurium* assays (Haworth et al. 1983; Probst et al. 1981; Rapson et al. 1980;

Table 2-4. Genotoxicity of Chlorophenols *In Vivo*

Species (test system)	End point	Exposure route	Results	Reference	Isomer (purity)
Mammalian systems:					
Mouse (testes and bone marrow)	Sister chromatid exchange	Oral	–	Borzelleca et al. 1985a	2-CP (98+%)
Mouse (testes and bone marrow)	Sister chromatid exchange	Drinking water	–	Borzelleca et al. 1985a	2,4-DCP (98+%)
Mouse (spot test)	Point mutation	Drinking water	–	Borzelleca et al. 1985a	2,4-DCP (98+%)
Rat (alkaline elution WBC and liver DNA)	DNA damage	Oral	–	Kitchin and Brown 1988	2,4,5-TCP (99%)
Rat (alkaline elution WBC and liver DNA)	DNA damage	Oral	–	Kitchin and Brown 1988	2,4,6-TCP (98%)
Rat (alkaline elution WBC and liver DNA)	DNA damage	Oral	–	Kitchin and Brown 1988	2,3,4,6-TeCP (92%)
Insect system:					
Drosophila melanogaster (sex-linked recessive lethal text)	Recessive lethal	Feeding	–	Valencia et al. 1985	2,4,6-TCP (NS)[a]
D. melanogaster (sex-linked recessive lethal text)	Recessive lethal	Injection	–	Valencia et al. 1985	2,4,6-TCP (NS)[a]

[a]The authors reported that "practical grade" 2,4,6-trichlorophenol was tested; however, the purity of this material was not specified (Valencia et al. 1985).

– = negative result; DNA = deoxyribonucleic acid; NS = not specified; WBC = white blood cells

Table 2-5. Genotoxicity of Chlorophenols *In Vitro*

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Isomer (purity)
Prokaryotic organisms:	Mutation	–	–	Haworth et al. 1983	2-CP (NS)
Salmonella typhimurium TA98, TA100, TA1535, TA1537 (preincubation assay)					
S. typhimurium TA100 (plate incorporation)	Mutation	NS	–	Rapson et al. 1980	2-CP ("pure")
S. typhimurium TA1535/pSK1002 (induction of DNA repair genes)	Mutation	–	–	Ono et al. 1992	2-CP (NS)
Escherichia coli WP2s(λ) (microsuspension)	Prophage induction	–	–	DeMarini et al. 1990	2-CP (reagent grade)
S. typhimurium TA97, TA98, TA100, TA104 (plate incorporation)	Mutation	+	+	Strobel and Grummt 1987	4-CP (NS)
S. typhimurium TA98, TA100, TA1535, TA1537 (preincubation assay)	Mutation	–	–	Haworth et al. 1983	4-CP (NS)
S. typhimurium TA98, TA100, TA1535, TA1537, TA1538 (plate incorporation)	Mutation	NS	+/–	Seuferer et al. 1979	4-CP (NS)
S. typhimurium TA1535/pSK1002 (induction of DNA repair genes)	Mutation	NS	–	Rapson et al. 1980	4-CP ("pure")
S. typhimurium TA1535/pSK1002 (induction of DNA repair genes)	Mutation	–	–	Sakagami et al. 1988	4-CP (reagent grade)
E. coli WP2s(λ) (microsuspension)	Prophage induction	–	–	DeMarini et al. 1990	4-CP (NS)

Table 2-5. Genotoxicity of Chlorophenols *In Vitro* (*continued*)

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Isomer (purity)
S. typhimurium TA98, TA100, TA1535, TA1537	Mutation	–	–	DeMarini et al. 1990	4-CP (practical grade)
E. coli WP2s(l) (microsuspension)	Prophage induction	+	–	DeMarini et al. 1990	2,4-DCP (99%)
S. typhimurium TA1535/pSK1002 (induction of DNA repair genes)	Mutation	–	+	Ono et al. 1992	2,4-DCP (NS)
S. typhimurium TA98, TA100, TA1535, TA1537	Mutation	–	–	Rasanen et al. 1977	2,4-DCP (NS)
S. typhimurium TA87, TA100, TA1535, TA1537, TA1538	Mutation	–	–	Simmon et al. 1977	2,4-DCP (NS)
S. typhimurium TA100	Mutation	–	–	Rapson et al. 1980	2,4-DCP ("pure")
S. typhimurium C3076, D3052, G46, TA98, TA1000, TA1535, TA1537, TA1538	Mutation	–	–	Probst et al. 1981	2,4-DCP (NS)
S. typhimurium TA98, TA100, TA1535, TA1537 (preincubation assay)	Mutation	+	–	Haworth et al. 1983; NTP 1989	2,4-DCP (NS)
S. typhimurium TA1535/pSK1002 (induction of DNA repair genes)	Mutation	+	+	Ono et al. 1992	2,4,5-TCP (NS)
E. coli WP2s(l) (microsuspension)	Prophage induction	+	–	DeMarini et al. 1990	2,4,5-TCP (99%)
S. typhimurium TA98, TA100, TA102, TA104	Mutation	–	–	George et al. 1992	2,4,5-TCP ("purified")
λ prophage induction	Mutation	–	+	George et al. 1992	2,4,5-TCP ("purified")

Table 2-5. Genotoxicity of Chlorophenols *In Vitro* (*continued*)

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Isomer (purity)
S. typhimurium TA98, TA100, TA1535, TA1537	Mutation	–	–	Rasanen et al. 1977	2,4,5-TCP (NS)
S. typhimurium TA98, TA100, TA1535, TA1537	Mutation	–	–	Rasanen et al. 1977	2,4,5-TCP (NS)
E. coli WP2s(l) (microsuspension)	Prophage induction	+	+	DeMarini et al. 1990	2,4,6-TCP (practical grade)
S. typhimurium TA1535/pSK1002 (induction of DNA repair genes)	Mutation	–	+	Ono et al. 1992	2,4,6-TCP (NS)
S. typhimurium TA98, TA100, TA1535, TA1537	Mutation	–	–	Rasanen et al. 1977	2,4,6-TCP (NS)
S. typhimurium TA100 (plate incorporation assay)	Mutation	NS	–	Rapson et al. 1980	2,4,6-TCP ("pure")
S. typhimurium TA100, TA1535, TA1537 (preincubation assay)	Mutation	–	–	Haworth et al. 1983	2,4,6-TCP (NS)
S. typhimurium TA98, TA100, TA1537 (plate incorporation assay)	Mutation	–	–	Kinae et al. 1981	2,4,6-TCP (NS)
Bacillus subtilis H-17, M-45 (rec assay)	DNA damage	NS	+	Kinae et al. 1981	2,4,6-TCP (NS)
E. coli WP2s(l) (microsuspension)	Prophage induction	+	–	DeMarini et al. 1990	2,3,4,5-TeCP (98%)
S. typhimurium TA97, TA98, TA100, TA1535 (preincubation assay)	Mutation	–	–	Zeiger et al. 1988	2,3,4,5-TeCP (>99%)
E. coli WP2s(l) (microsuspension)	Prophage induction	+	–	DeMarini et al. 1990	2,3,4,6-TeCP (unknown)

Table 2-5. Genotoxicity of Chlorophenols *In Vitro* (*continued*)

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Isomer (purity)
S. typhimurium TA1535/pSK1002 (induction of DNA repair genes)	Mutation	+	+	Ono et al. 1992	2,3,4,6-TeCP (NS)
S. typhimurium TA98, TA100, TA1535, TA1537	Mutation	–	–	Rasanen et al. 1977	2,3,4,6-TECP (NS)
S. typhimurium TA97, TA98, TA100, TA1535 (preincubation assay)	Mutation	–	–	Zeiger et al. 1988	2,3,4,6-TeCP (>86%)
E. coli WP2s(l) (microsuspension)	Prophage induction	–	–	DeMarini et al. 1990	2,3,5,6-TeCP (99%)
S. typhimurium TA97, TA98, TA100, TA1535 (preincubation assay)	Mutation	–	–	Zeiger et al. 1988	2,3,5,6-TeCP (97%)
Eukaryotic organisms:					
Chinese hamster V79 cells	Chromosomal aberrations	NS	+	Onfelt 1987	2-CP ("purified")
Chinese hamster V79 cells	Mutation	NS	–	Hattula and Knuutinen 1985	2,4-DCP (NS)
Chinese hamster and rat cells (V79 cells cocultured with primary rat hepatocytes; hepatocyte-mediated assay)	Mutation	–	NS	Hattula and Knuutinen 1985	2,4-DCP (NS)
Chinese hamster V79 cells	Chromosomal aberrations	NS	+	Onfelt 1987	2,4-DCP ("purified")

Table 2-5. Genotoxicity of Chlorophenols *In Vitro* (*continued*)

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Isomer (purity)
Adult rat hepatocytes	*Unscheduled DNA* synthesis	*NS*	+	*Probst et al. 1981*	*2,4-DCP* (NS)
Chinese hamster ovary cells	Chromosomal aberrations	+	+	Armstrong et al. 1993	2,4,5-TCP (>99%)
Chinese hamster V79 cells	Mutation	NS	–	Jansson and Jansson 1992	2,4,6-TCP (99.7%)
	Chromosomal aberrations	NS	+		
Saccharomyces cerevisiae MP-1 (plate suspension assay)	Mutation	–	+	Fahrig et al. 1978	2,4,6-TCP (99%)
S. cerevisiae MP-1 (plate suspension assay)	Mitotic crossing over	NS	–	Fahrig et al. 1978	2,4,6-TCP (99%)
S. cerevisiae MP-1 (plate suspension assay)	*Mitotic gene* conversion	*NS*	–	Fahrig et al. 1978	2,4,6-TCP (99%)
Chinese hamster and rat cells (hamster V79 cells cultured with primary rat hepatocytes; hepatocyte-mediated assay)	Mutation	–	NS	Hattula and Knuutinen 1985	2,4,6-TCP (NS)
Chinese hamster V79 cells	Mutation	NS	+	Hattula and Knuutinen 1985	2,4,6-TCP (NS)
Mouse (cultured lymphoma L5178Y tk+/– cells; forward mutation assay)	Mutation	NS	+	McGregor et al. 1988	2,4,6-TCP (NS)
Chinese hamster ovary cells	Sister chromatid exchanges and chromosomal aberrations	NS	–	Galloway et al. 1987	2,4,6-TCP (NS)
Chinese hamster ovary cells	Chromosomal aberrations	+	+	Armstrong et al. 1993	2,4,6-TCP (>99.7%)

Table 2-5. Genotoxicity of Chlorophenols *In Vitro* (*continued*)

Species (test system)	End point	Results: With activation	Results: Without activation	Reference	Isomer (purity)
Chinese hamster V79 cells	Mutation	NS	+	Hattula and Knuutinen 1985	2,3,4,6-TeCP (NS)

– = negative result; + = positive result; +/– = borderline mutagen; DNA = deoxyribonucleic acid; NS = not specified

Rasanen et al. 1977; Simmon et al. 1977) but was positive with activation in a prophage induction assay (DeMarini et al. 1990) and positive without activation in a umu test system (Ono et al. 1992). In mammalian cells (Table 2-5), 2,4-DCP was negative for gene mutation in Chinese hamster V79 cells (Hattula and Knuutinen 1985) but produced chromosomal aberrations in Chinese hamster V79 cells (Onfelt 1987) and induced unscheduled DNA synthesis in rat hepatocytes (Probst et al. 1981).

2,4,5-TCP did not increase DNA damage in mice given a single oral dose (164 mg/kg) as indicated by alkaline elution of DNA from white blood cells and the liver (Kitchin and Brown 1988). 2,4,5-TCP was predominantly negative in standard S. typhimurium reversion bioassays (George et al. 1992; Rasanen et al. 1977) but was positive both with and without activation in a *umu* test system (Ono et al. 1992) and with (DeMarini et al. 1990) and without activation (George et al. 1992) in prophage induction assays (Table 2-5). 2,4,5-TCP did induce chromosome aberrations in Chinese hamster ovary cells both with and without metabolic activation (Armstrong et al. 1993).

2,4,6-TCP has been evaluated for genotoxicity in a variety of *in vitro* and in viva assays. As summarized in Tables 2-4 and 2-5, the results of these various assays have been both positive and negative, with the majority of studies reporting negative results. According to Kitchin and Brown (1988), short-term *in vitro* tests with chlorinated phenols often show weakly positive or no effects. Five different assays have reported positive results. *In vitro,* 2,4,6-TCP has demonstrated genotoxic activity without metabolic activation in bacteria *(Bacillus subtilis),* yeast *(Saccharomyces cervisiae),* and mammalian cells (Chinese hamster V79 cells, mouse lymphoma L5178Y TK +/- cells) (Fahrig et al. 1978; Hattula and Knuutinen 1985; Kinae et al. 1981; McGregor et al. 1988). *In vivo,* 2,4,6-TCP has demonstrated genotoxic activity in somatic cells of mice in the spot test (Fahrig et al. 1978). 2,4,6-TCP has tested positive for chromosomal aberrations in Chinese hamster ovary cells both with and without metabolic activation (Armstrong et al. 1993). Positive results for mutations in Chinese hamster V-79 cells reported by Hattula and Knuutinen (1985) were in contrast to the negative results reported by Jansson and Jansson (1992). Additional negative results occurred in bacteria *(S. typhimurium* without activation), yeast *(S. cervisie),* and mammalian ovary cells (Fahrig et al. 1978; Galloway et al. 1987; Haworth et al. 1983; Kinae et al. 1981; Lawlor et al. 1979; Rasanen et al. 1977). *In vivo* tests using insect systems *(Drosophila melanogaster)* were also negative (Valencia et al. 1985).

An increase in DNA damage was not observed in the white blood cells or livers of mice given a single oral dose of 2,3,4,6-TeCP (193 mg/kg) (Kitchin and Brown 1988). 2,3,4,6-TeCP did test positive for mutation in Chinese hamster V79 cells (Hattula and Knuutinen 1985). All three tetrachlorophenol isomers have

tested negative for mutation in standard *S. typhimurium* strains (Rasanen et al. 1977; Zeiger et al. 1988). 2,3,4,5- and 2,3,4,6-TeCP, but not 2,3,5,6-TeCP, tested positive in a prophage induction assay (DeMarini et al. 1990), and 2,3,4,6-TeCP was positive both with and without activation in *a umu* test system (Ono et al. 1992).

The preponderance of the evidence from *in vivo* (Borzelleca et al. 1985a; Kitchen and Brown 1988; Valencia et al. 1985) and *in vitro* studies with prokaryotes (DeMarini et al. 1990; George et al. 1992; Haworth et al. 1983; Kinae et al. 1979; Ono et al. 1992; Probst et al. 1981; Rapson et al. 1980; Rasanen et al. 1977; Sakagami et al. 1988; Simmon et al. 1977; Zeiger et al. 1988) suggests that as a class the chlorophenols are not directly mutagenic. In contrast, a more limited number of *in vitro* studies with eukaryotic cells have generally been positive for chromosomal aberrations (Armstrong et al. 1993; Jansson and Jansson 1992; Onfelt 1987; Probst et al. 1981) suggesting that chromosome malsegregation may be the mechanism of genotoxicity for the chlorophenols. The lack of effect in the *in vivo* studies may be a result of the rapid urinary excretion of chlorophenols in these single-dose studies (Borzelleca et al. 1985a; Kitchin and Brown 1988).

Cancer. Numerous cohort and case-control studies of wood finishing and chlorophenoxy herbicide workers exposed to higher chlorophenols are available (Coggon et al. 1991; Eriksson et al. 1981, 1990; Hardell et al. 1987; Hoar et al. 1986; Honchar and Halperin 1981; Kogevinas et al. 1992; Lynge 1985; Ott et al. 1980; Pearce et al. 1988; Smith et al. 1984; Woods et al. 1987). The results of these studies vary, but some suggest a relationship between chlorophenol exposure and increased incidence of soft-tissue sarcomas, lung cancers, malignant lymphomas, non-Hodgkin's lymphomas, and nasal/nasopharyngeal cancers. The conclusions from these studies are limited by small cohort sizes, coexposure to other contaminants (including TCDD), and the lack of adequate control groups.

Chronic oral studies of 2,4-DCP in rats and mice (Exon and Koller 1985; NTP 1989) have not resulted in any significant carcinogenic effect, even following both pre- and postnatal exposure (Exon and Koller 1985). A positive result in a dermal initiation promotion study suggests that 2,4-DCP can act as a promoter (Boutwell and Bosch 1959).

The data available are inadequate regarding cancer in humans following exposure to 2,4,6-TCP. Animal data suggest that humans may be at risk of cancer following exposure to 2,4,6-TCP (NCI 1979). A significant dose-related increase in the incidence of leukemia occurred in male rats chronically exposed to

2,4,6-TCP in the diet (NCI 1979). Both female and male mice treated chronically with 2,4,6-TCP in the diet had significantly increased incidences of hepatocellular carcinomas and adenomas when compared to the controls (NCI 1979).

The carcinogenicity of 2,4,6-TCP following both intraperitoneal and subcutaneous exposure has been evaluated in studies with mice. No significant increase in the incidence of pulmonary tumors was noted in mice given repeated intraperitoneal injections of 2,4,6-TCP over an intermediate exposure period and followed over a 24-week observation period (Stoner et al. 1986). No significant increase in the incidence of injection-site tumors or systemic tumors was observed in mice 18 months after a single subcutaneous injection of 2,4,6-TCP (Bionetics Research Labs 1968). These intraperitoneal and subcutaneous studies are limited because the duration of exposures was less than lifetime. In addition, although the intraperitoneal and subcutaneous routes of administration are valuable research methods, their relevance to human exposure pathways is limited.

IARC (1987) considers chlorophenols as a group to have limited evidence for human carcinogenicity (group 2B). The Department of Health and Human Services (NTP 1994) considers that 2,4,6-TCP may reasonably be anticipated to be a carcinogen. Based on the positive NCI (1979) cancer bioassays with rats and mice, EPA (IRIS 1994) has classified 2,4,6-TCP as a B2 agent (probable human carcinogen). This category applies to those chemical agents for which there is sufficient evidence of carcinogenicity in animals and inadequate evidence of carcinogenicity in humans. EPA (IRIS 1994) has calculated a cancer potency factor (q_1* or slope factor) for 2,4,6-TCP of 0.02 (mg/kg/day) for both oral and inhalation exposure. This cancer potency factor is equivalent to a drinking water unit risk value and an inhalation unit risk value of 3.1×10^{-7} $(\mu g/L)^{-1}$ and 3.1×10^{-6} $(\mu g/m^3)^{-1}$, respectively (IRIS 1994). The drinking water concentration of 2,4,6-TCP associated with an excess lifetime cancer risk of 10^{-4}, 10^{-5}, and 10^{-6} is 300 μg/L, 30 μg/L , and 3 μg/L, respectively. The air concentration of 2,4,6-TCP associated with an excess lifetime cancer risk of 10^{-4}, 10^{-5}, and 10^{-6} is 30 $\mu g/m^3$, 3 $\mu g/m^3$, and 0.3 $\mu g/m^3$, respectively (IRIS 1994).

The mechanism(s) by which 2,4,6-TCP induces cancer in animals are not known. However, it has recently been suggested that 2,4,6-TCP causes cancer either by suppressing the immune system, by acting as a weak clastogen, and/or by acting as a weak initiator or promoter of carcinogenesis (Kitchin and Brown 1988). According to Kitchin and Brown (1988), two positive results (direct V-79, *Bacillus subtilus)* support the idea that 2,4,6-TCP may be an initiator. However, three negative results in the Ames test, hepatocyte mediated V-79, and alkaline elution *in vivo* fail to support the idea that 2,4,6-TCP is an initiator. 2,4,6-TCP was also

not an initiator following a single oral, dermal, or subcutaneous dose given to mice followed by 20 weeks of three times per week skin applications of the promotor 12-*O*-tetradecanoylphorbol-13-acetate (Bull et al. 1986). Supporting evidence for 2,4,6-TCP as a promotor includes the observation that ornithine decarboxylase and cytochrome P-450 induction occurs at high doses.

2.6 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 due to 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 5.6 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 pre-natal and post-natal 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 (Widdowson and Dickerson 1964; Foman et al. 1982; Owen and Brozek 1966; Altman and Dittmer 1974; Foman 1966). 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 and 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 (feeder and Kearns 1997; Komori 1990; Vieira et al. 1996; NRC 1993). Whether differences in xenobiotic metabolism make the child more or less susceptible also depend 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 the newborn who has a low glomerular filtration rate and has not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; West et al. 1948; NRC 1993). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer 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, the fact that infants breathe more air per kilogram of body weight than adults may be somewhat counterbalanced by their alveoli being less developed, so there is a disproportionately smaller surface area for absorption (NRC 1993).

No direct information is available regarding the health effects of chlorophenols observed in children. However, health effects observed in adults are also expected to be of potential concern in children. Although no direct information is available on the effects of chlorophenols on the developmental process in humans, studies in animals indicate few developmental effects. No significant changes in offspring body or liver weights were observed in rats treated with 2-CP in drinking water at doses up to 50 mg/kg/day throughout gestation and up to 91 days post par-turn (Exon and Koller 1981, 1985). No adverse changes in litter sizes, perinatal loss, pup weight, or litter biomass were observed when female rats received a single dose of 4-CP as high as 1,000 mg/kg on gestational day 11 (Kavlock 1990). Oral exposure of pregnant rats to a maternal toxic dose of 750 mg/kg/day 2,4-DCP for 10 gestational days induced a slight decrease in fetal weight and a statistically significant delayed ossification of sternal and vertebral arches and led to a slight insignificant increase in early embryonic deaths (Rodwell et al. 1989). No effects on immune function parameters were observed in 6-week old rats treated with 2,4-DCP in the drinking water at doses up to 30 mg/kg/day throughout gestation (Exon and Koller 1985; Exon et al. 1984). Gavage administration of 650 mg/kg/day 2,4,5-TCP during organogenesis (days 6-15 of gestation) produced no fetotoxicity, malformations, or structural terata in the offspring of rats (Chemoff et al. 1990). Administration of 800-900 mg/kg 2,4,5-TCP in mice on 1 day of gestation or 250-300 mg/kg/day on any 3 days of gestation had no effect on resorption incidence, pup survival, mean fetal weight, gross malformations, skeletal malformation, or cleft palates (Hood et al. 1979). Similarly, maternal exposure of rats to 500 mg/kg/day 2,4,6-TCP only produced a

transient reduction in the body weight of offspring (Blackburn et al. 1986). When female Sprague-Dawley rats orally received purified 2,3,4,6-TeCP throughout organogenesis, the only effect on the fetus was delayed ossification of the skull bones (Schwetz et al. 1974). However, this effect was not statistically significant when analyzed by litters. In a follow-up study in pregnant rats receiving 0,25, 100, or 200 mg/kg/day every day during organogenesis, the two highest doses resulted in inhibition of maternal body weight gain. There was also a dose-related trend for 2,3,4,6-TeCP-mediated effects on implantation or postimplantation viability. Chlorophenols do not appear to be teratogenic in animals (Rodwell et al. 1989; Exon and Koller 1981; Schwetz et al. 1974).

Prior maternal exposure to chlorophenols is unlikely to affect the fetus or a nursing neonate. The relative rapid metabolism and excretion of chlorophenols (Keith et al. 1980) should limit their potential to accumulate in maternal tissue; chlorophenols do not appear to accumulate in animals after oral exposure (Korte et al. 1978; Bahig et al. 1981). The accumulation of 2-CP in tissues of dams was found to be minimal (Exon and Koller 1982). However, 2,3,4,6-TeCP was detected in adipose tissues from people not occupationally exposed to chlorophenols (Mussalo-Rauhamaa et al. 1989), probably due to the relatively higher octanolwater partition coefficient of TeCP. Chlorophenols and/or their metabolites might cross the placenta as it has been shown in a reproductive study in rats that transplacental exposure to 2-CP can be feto- or embryotoxic at a high dose, resulting in a significant increase in the number of still births (Exon and Koller 1982), although it is possible that these could be indirect effects of the fetus. In another study, an increase in delayed ossification of the fetal skull bones was observed when pregnant Sprague-Dawley rats were treated with TeCP, supporting that chlorophenols might cross the placenta. No studies are available that measured chlorophenols in breast milk.

As a class, the chlorophenols are not directly genotoxic although a limited number of *in vitro* studies with eukaryotic cells have been positive for chromosomal aberrations. There is no information to indicate that parental exposure may affect children via damage to germ cells.

Metabolism of chlorophenols has not been studied in children. However, sulfation and glucuronidation are the main metabolic pathways for chlorophenols in both human and animal studies. The conjugated metabolites are then eliminated in urine. In humans, activity of UDP-glucuronosyltransferase (responsible for glucuronide conjugates) does not reach adult levels until about 6-8 months of age, although the development of this activity is isoform specific. Activity of sulfotransferases (responsible for sulfate conjugates) seems to develop earlier, although again it is isoform specific. The activity of some sulfotransferase isoforms may be

greater than that of adults during infancy and early childhood (Leeder and Kearns 1997). In rats, while sulfation is almost at adult levels at birth, UDP-glucuronosyltransferase activity towards different xenobiotics varies with maturation (Weiss 1960; Young and Lietman 1978). It is possible that chlorophenols might be eliminated at a slower rate in children, resulting in increased susceptibility of children to their toxicity.

2.7 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 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 chlorophenols are discussed in Section 2.7.1.

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 chlorophenols are discussed in Section 2.7.2.

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 2.9, "Populations That Are Unusually Susceptible."

2.7.1 Biomarkers Used to Identify or Quantify Exposure to Chlorophenols

There are no biomarkers of exposure or effect that have been validated in children or adults exposed as children. The only known biomarkers of chlorophenol exposure are the hydrolyzed urinary extracts of the parent compounds and dechlorinated derivatives. However, these extracts are not unique to chlorophenol exposure. For example, conjugated forms of higher chlorophenols have been observed after laboratory administration of hexachlorocyclohexanes (Engst et al. 1976; Koransky et al. 1975), indicating that urinary chlorophenol levels are not specific to chlorophenol exposure. Similarly, the presence of chlorophenols or their metabolites in urine is not necessarily diagnostic for chlorophenol exposure because these compounds are also detectable in urine after exposure to certain other pesticides, such as lindane (Karapally et al. 1973), VC-13 (Shafik et al. 1973), 2,4-dichloro-phenoxyacetic acid, and 2,4,5-trichlorophenoxyacetic acid (Hill et al. 1989). Finally, metabolic dechlorination of higher chlorophenols to lower chlorophenols occurs under some conditions (Renner and Mucke 1986). Studies to determine the importance of these processes on urinary chlorophenol formation, as either conjugated or unconjugated metabolites, have not been conducted. Consequently, the value of assessing urinary chlorophenol concentrations as measures of potential exposure in workers or residents near hazardous waste sites cannot currently be determined.

2.7.2 Biomarkers Used to Characterize Effects Caused by Chlorophenols

No unique biomarkers of effects are available for chlorophenols. As discussed in Section 2.2, the clinical signs associated with high acute levels of monochlorophenol administration include myoclonic convulsions (Angel and Rogers 1972; Borzelleca et al. 1985a, 1985b; Farquharson et al. 1958) and dermal and ocular lesions (Bioassay Systems 1981; Rhodia 1978; Younger Labs 1975). Both myoclonic convulsions and epithelial tissue corrosion are commonly observed after exposure to numerous phenolic compounds and are therefore not necessarily diagnostic of monochlorophenol exposure. Increasing chlorination results in clinical signs of metabolic derangement, such as hyperthermia and blood pressure decrements (Angel and Rogers 1972; Farquharson et al. 1958). These clinical signs are not specific to chlorophenols; they occur

following exposure to any agent that uncouples mitochondrial oxidative phosphorylation such as nitrophenol (Ahlborg and Thunburg 1980). Other effects of chlorophenols, including effects on the immune system (Exon et al. 1984) and on reproduction (Exon and Koller 1985), are also not specific to chlorophenols.

For more information on biomarkers for renal and hepatic effects of chemicals see ATSDR/CDC Subcommittee Report on Biological Indicators of Organ Damage (1990) and for information on biomarkers for neurological effects see OTA (1990).

2.8 INTERACTIONS WITH OTHER SUBSTANCES

Data regarding the interaction of chlorophenols with other chemical substances in humans or animals were not located. Substances that result in effects similar to those for the chlorophenols have the potential to interact with these compounds. For example, chlorophenols may interact with other carcinogens, promoters, neurotoxic agents, and liver, renal, dermatologic, and ocular toxins.

Factors interfering with Phase II conjugation reactions would inhibit the detoxification of chlorophenols. The results of recent experimentation indicate that the polycyclic aromatic hydrocarbon (PAH), 3-methylcholanthrene (3-MC), stimulates the glucuronidation of phenolic substrates through the induction of glucuronylsyltransferase (Jansen et al. 1992; Wishart 1978a, 1978b). The enzymes induced have a spectrophotometric peak of 448 nanometers (cytochrome P-448) and are characteristically distinct from the phenobarbital-type induced enzymes that have an absorbance maximum at 450 nanometers. These findings suggest that other toxic and/or carcinogenic PAHs, such as benzo(a)pyrene, can significantly enhance the metabolism of phenols. The relationship between PAH particulate and solid material, commonly associated with incinerators and hazardous waste sites, and chlorophenol metabolism has not been studied. In general, the ability of another chemical to affect the toxicity of chlorophenols may depend on its affinity for the cytochrome P-448 substrate binding site.

Chlorophenols are toxic to the liver. Exposure to hepatotoxic drugs such as acetaminaphen (Tylenol®) and chlorophenols may result in additive effect. However, there are no studies that indicate such interaction.

Using an *in vitro* rat liver microsomal preparation, Arrhenius et al. (1977) noted that 2,4-DCP, 2,4,6-TCP, and 2,3,4,6-TeCP in the concentration range of 0.03-3 mM shifted the metabolism of aromatic amines from C-oxygenation to n-oxygenation. The carcinogenic metabolites of aromatic amines can be formed by M-

oxygenation. Therefore, Arrhenius et al. (1977) suggested that the chlorophenols should be considered as possible synergists for the carcinogenicity of aromatic amines.

2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to chlorophenols than will most persons exposed to the same level of chlorophenols in the environment. Reasons include genetic make-up, developmental stage, age, health and nutritional status (including dietary habits that may increase susceptibility, such as inconsistent diets or nutritional deficiencies), and substance exposure history (including smoking). These parameters may result in decreased function of the detoxification and excretory processes (mainly hepatic, renal, and respiratory) or the preexisting compromised function of target organs (including effects or clearance rates and any resulting end-product metabolites). For these reasons we expect the elderly, with declining organ function, and the youngest of the population, with immature and developing organs, will generally be more vulnerable to toxic substances than healthy adults. Populations who are at greater risk due to their unusually high exposure are discussed in Section 5.7, Populations With Potentially High Exposure.

No specific population that would be particularly susceptible to chlorophenol intoxication has been identified. Because of the extensive hepatic conjugation and renal clearance of these compounds, individuals with liver or kidney dysfunction may be the most sensitive population. The results of recent studies indicate that individuals with cirrhosis of the liver (Macdonald et al. 1992; Ohta 1991) or hepatitis (Ohta 1991) show impaired Phase II conjugation. Chronic renal failure is associated with the inability to clear conjugated metabolites, resulting in elevated, steady-state whole body concentrations of glucuronide and sulfate metabolites (Martin et al. 1991). Patients with acute tubular necrosis, with or without cirrhosis, show markedly elevated urinary β-glucuronidase concentrations (Solis-Herruzo et al. 1986) and, theoretically, a high body burden of unconjugated metabolites. These data suggest that chlorophenol-exposed individuals with preexisting liver or kidney disease may be at increased risk from exposure.

Individuals with Gilbert's disease or Crigler-Najjar syndrome, inherited deficiencies of bilirubin UDPglucuronyl transferase (UGT), may have increased sensitivity to the effects of chlorophenol exposure (de Morais and Wells 1988; de Morais et al. 1992). Considerable progress in understanding the genetic control of these abnormalities has recently been made (Jansen et al. 1992). Patients with Type I Crigler-Najjar syndrome may be at the greatest risk following exposure to phenolic compounds. This form of the syndrome

is characterized by unconjugated hyperbilirubinemia and apparently results from a deficiency in the 3-Mcinducible form of the phenolic UGT. Defects in cytochrome P-450 induction occur in Type II (partial hyperbilirubinemia) Crigler-Najjar syndrome and Gilbert disease; consequently, these patients may not be as sensitive to increased plasma concentrations of chlorophenol.

Cigarette smokers are at potentially increased risk from chlorophenol exposure (Alvares 1978; Bock et al. 1987). The incomplete combustion products of smoking, such as PAHs, induce P-448 metabolism, resulting in the potential formation of reactive metabolites and an increased conjugation rate (see Sections 2.3.3 and 2.7). Alternatively, PAHs may accelerate the detoxification of chlorophenol. Consequently, definitive statements about the relationship between cigarette smoking and chlorophenol metabolism cannot be made at the present time.

Evidence from rat studies (Exon et al. 1985) suggests that at least one part of the immune system (delayed hypersensitivity) is sensitive to 2,4-DCP. Persons with immune system deficiencies, therefore, may be more susceptible to the adverse effects of 2,4-DCP exposure.

Fetuses or neonates may also be at increased risk. In humans, activity of UDP-glucuronosyltransferase (responsible for glucuronide conjugates) does not reach adult levels until about 6-8 months of age, although the development of this activity is isoform specific. Activity of sulfotransferases (responsible for sulfate conjugates) seems to develop earlier, although again, it is isoform specific. The activity of some sulfotransferase isoforms may be greater than that of adults during infancy and early childhood (Leeder and Kearns 1997). This conclusion is also supported by data from rat hepatic bioassays in which UGT activities toward phenolic substrates reached adult levels between days 16 and 20 of gestation (Wishart 1978a). Enzymatic activity toward bilirubin is negligible during this gestational period (the “late foetal” group), but surges between gestation day 20 and postnatal day 2 (the “postnatal” group). The differences in fetal and neonatal detoxification systems, compared to the mature organism, may result in a slower elimination of the chlorophenols, which may serve to increase the toxicity of these compounds.

Further discussion of the susceptibility of children is in Section 2.6 Children’s Susceptibility.

2.10 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to chlorophenols. 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 chlorophenols. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice.

2.10.1 Reducing Peak Absorption Following Exposure

Following high-dose oral exposure to chlorophenols, administration of water for dilution may be warranted (Bronstein and Currance 1988). Although Ellenhorn and Barceloux (1988) recommend the use of ipecac/lavage, activated charcoal, and cathartics for gastric contamination from chlorophenols, Bronstein and Currance (1988) recommend against emesis because of possible aspiration into the lungs. This is more important for the liquid chlorophenols than for the solid species.

Specific decontamination procedures for chlorophenols after skin or eye contact are not available. However, general approaches for minimizing absorption can be extrapolated from literature on phenol or pentachlorophenol. After dermal contact, rinsing with water (Gosselin et al. 1984) or washing with soap (Bronstein and Currance 1988) may be the procedures of choice. The case reported by Kintz et al. (1992) in which death occurred in a worker dermally exposed to 2,4-DCP on less than 10% of his body indicated that washing with water may not be sufficient, especially if contaminated clothing is not removed. Attempts to decontaminate phenols with alcohol, vegetable oils, glycerin, or polyethylene glycol, with or without methanol, have met with variable success (Gosselin et al. 1984). After flushing a contaminated eye with water, irrigation is sometimes used. This technique is suggested for adults with an intact lid who have no evidence of edema (Bronstein and Currance 1988). For children, irrigation of each eye with normal saline, using large bore intravenous tubing, is sometimes recommended (Bronstein and Currance 1988). In more advanced cases, the use of proparacaine hydrochloride may follow eye irrigation (Bronstein and Currance 1988).

2.10.2 Reducing Body Burden

The limited experimental data suggest that orally administered chlorophenols are rapidly conjugated and excreted in the urine (see Sections 2.3.3 and 2.3.4). The efficacy of drug therapy to accelerate Phase II

detoxification reactions is not known. For example, supplying substrates for glucuronidation and sulfur conjugation may increase the excretion of the chlorophenols. Based on studies involving pentachlorophenol exposure, the utility of either exchange transfusions or forced diuresis is equivocal (Robson et al. 1969; Young and Haley 1978).

A high intake of ascorbic acid has been shown to reduce accumulation of 2,4-DCP and decrease liquid peroxidation in the liver of guinea pigs compared to animals with low ascorbic acid intake (Derhata et al. 1996).

2.10.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism of toxic action for 2-CP or 4-CP is not known. Although these chemicals may be weak uncouplers of oxidative phosphorylation, inconsistent findings of increased metabolic rate after exposure suggest that this mechanism may not be the mechanism of greatest consequence (Angel and Rogers 1972; Farquharson et al. 1958; Weinbach and Garbus 1965). Convulsive seizures, of unknown origin, are the most characteristic clinical signs of acute overdose (Angel and Rogers 1972; Borzelleca et al. 1985a). Treatment for the prevention of seizures includes the common anticonvulsant sequence of diazepam, phenytoin, and phenobarbital (Bronstein and Currance 1988; Ellenhorn and Barceloux 1988). The use of anticonvulsants on infants and children must be closely monitored to prevent overdosage and toxic effects of drugs.

No methods to directly reduce the adverse effects of chlorophenol-induced stimulation of mitochondrial respiration were located.

2.11 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 chlorophenols 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 chlorophenols.

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.

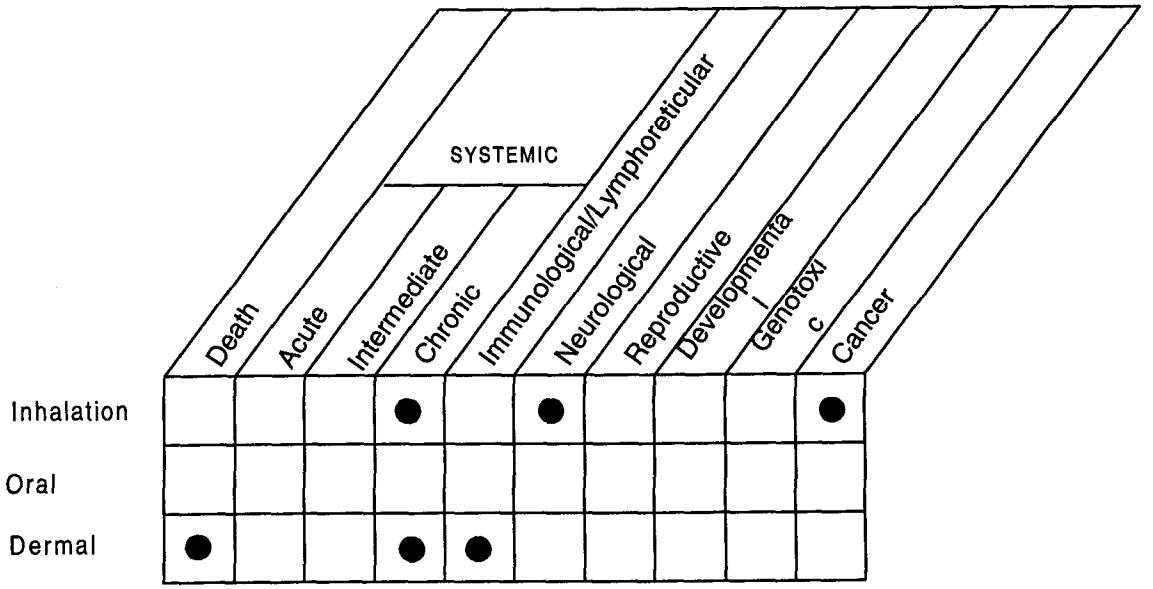
2.11.1 Existing Information on Health Effects of Chlorophenols

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to chlorophenols are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of chlorophenols. 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.

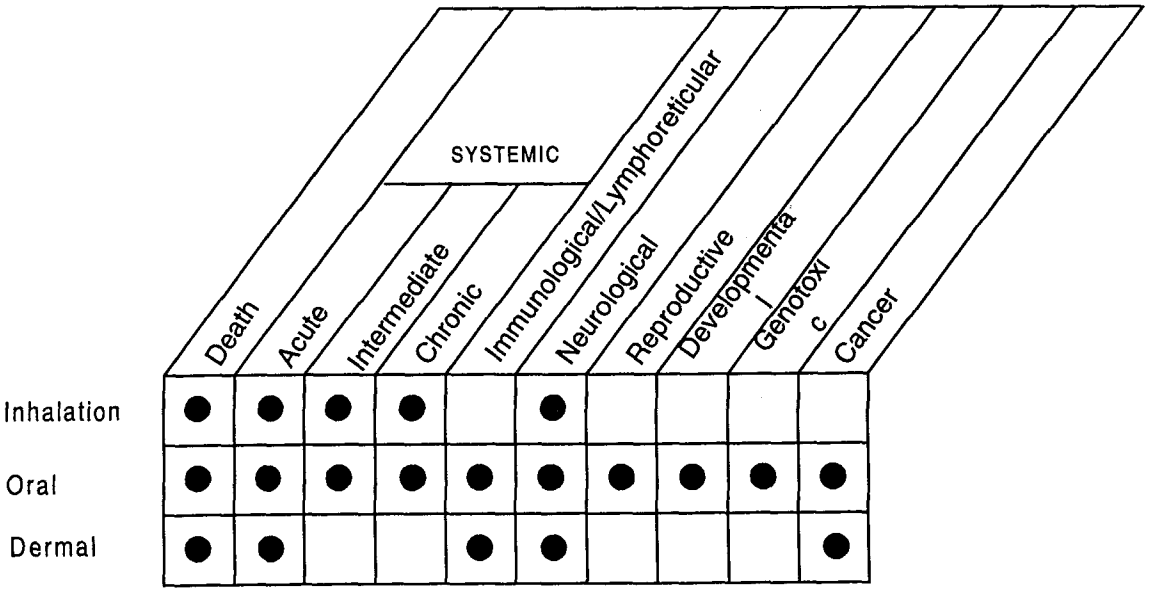
Humans are potentially exposed to chlorophenols occupationally, through municipal solid waste combustion, and as a result of the disinfection of drinking water. The chlorophenol by-products of manufacturing activities may be the greatest single source of concern at NPL hazardous waste sites. Workers in phenoxy pesticide production, wood preservation, dye manufacturing, and alcohol denaturation may be at some risk from chlorophenol exposure. Exposure potential in most of these industries is greater for the higher chlorinated phenols, which, based on the results of animal studies, are more toxic than the dichlorophenols and the monochlorophenols (Borzelleca et al. 1985a). Results of human studies involving exposure to higher chlorophenols suggest that occupational dermal exposure is a more significant concern than inhalation exposure (Kleinman et al. 1986).

Except for the single death following dermal 2,4-DCP exposure (Kintz et al. 1992) no health effects data for humans exposed exclusively to chlorophenols were located. Available occupational data indicate that chemicals involved in the production of phenoxy-based herbicides, and/or the end-use products themselves, may be associated with the development of cancers of the hematopoietic and lymphatic systems (Eriksson et al. 1981; Hardell et al. 1981). Positive results for carcinogenicity do not show a consistent trend across

Figure 2-4. Existing Information on Health Effects of Chlorophenols



Human



Animal

● Existing Studies

worker groups and cannot be specifically associated with a single contaminant or group of contaminants (including trichlorophenols). No epidemiological evidence of adverse health effects associated with drinking chlorophenol-contaminated water was located.

Most of the available animal data, which include several recent, well-conducted studies, have involved the oral route of administration. After acute exposure, the higher chlorophenols, in particular, have effects on basal metabolism that are typical of uncouplers of mitochondrial oxidative phosphorylation. Experimental results suggest that the acute toxicity of tetrachlorophenols is the greatest, followed by the monochlorophenols and then the trichlorophenols, with the dichlorophenols being the least toxic isomers (Borzelleca et al. 1985a). The adverse effects sometimes reported after repeated exposures do not indicate a well-defined toxic syndrome. Intermediate to high chlorophenol doses have been associated with marginal effects on the immune, lymphoreticular, reproductive, and developmental systems, and a range of effects on the liver. Further research to help define the experimental conditions and mechanisms associated with these noncarcinogenic findings, and how they may relate to chlorophenol-exposed humans, is required. 2,4,6-TCP is an animal carcinogen that has produced leukemia in rats and hepatocellular carcinoma and adenomas in mice (NCI 1979). Furthermore, other chlorophenols have tumor promoting capabilities.

2.11.2 Identification of Data Needs

Acute-Duration Exposure. Information from animal studies indicates that most chlorophenols produce lethality in experimental animals following a single-dose oral exposure of 89-5,000 mg/kg (Ahlborg and Larsson 1978; Borzelleca et al. 1985a; Kobayashi et al. 1972; NTP 1989; Vernot et al. 1977). The limited inhalation and dermal data tend to corroborate these findings (Carreon et al. 1980a; Duchosal and Biedermann 1991). The most characteristic clinical sign after lethal or high sublethal doses of monochlorophenols is convulsions (Borzelleca et al. 1985a, 1985b). Physiological changes associated with the uncoupling of oxidative phosphorylation increase with the increasing degree of chlorination (Cascorbi and Ahlers 1989; Farquharson et al. 1958; Izushi et al. 1988; Mitsuda et al. 1963; Narasimhan et al. 1992; Shannon et al. 1991; Stockdale and Selwyn 1971). Following acute oral exposure, the order of toxicity as indicated by LD_{50}s was tetrachlorophenols > monochlorophenols > dichlorophenols > trichlorophenols (Borzelleca et al. 1985a; Deichmann and Mergard 1948). Maternal toxicity, but not fetal toxicity, was observed in rats treated by gavage with 2,4-DCP at 100 mg/kg/day on gestation days 6-15 (Rodwell et al. 1989). No maternal or fetal effects were observed at 25 mg/kg/day. The lowest acute oral LOAEL for the chlorophenols that was identified was 2.58 mg/kg/day for electron microscopic changes in hepatocytes

(foamy cytoplasm, clustering of mitochondria, and endoplasmic reticulum) that were not observed at 1.28 mg/kg/day (Phornchirasilp et al. 1989a). Based on the NOAEL of 1.28 mg/kg/day for liver effects following 4-CP exposure, an acute-duration oral MRL of 0.01 mg/kg/day was calculated for the chlorophenols. Data are insufficient and are needed for the derivation of an acute inhalation MRL for the chlorophenols. Additional experiments to assess dose-response relationships are needed because of reporting deficiencies and methodological differences to obtain data for an inhalation MRL. These data are needed to assess risk to workers exposed during accidental releases. The report of a worker who died after splattering pure 2,4-DCP on portions of his right arm and leg while disposing industrial wastes (Kintz et al. 1992) demonstrates the toxicity of chlorophenols via dermal exposure. More comprehensive dermal toxicity studies analyzing both acute toxicity incidence and localized effects are also needed. Finally, additional studies examining the liver effects following oral exposure to chlorophenols other than 4-CP are needed to confirm that the MRL based on 4-CP exposure is truly protective of liver effects following exposure to these other compounds.

Intermediate-Duration Exposure. Occupational studies have typically involved individuals exposed to chlorophenols for intermediate- or chronic-duration periods. The results of these studies are described under the section Chronic-Duration Exposure and Cancer. Intermediate-duration oral administration of chlorophenols to experimental animals generally produces no effects or marginal effects on systemic, immunological, reproductive, and developmental end points (Bercz et al. 1990; Borzelleca et al. 1985a; Carlson 1978; Exon and Koller 1982, 1983, 1985; Hattula et al. 1981). Immunological effects (a decrease in delayed type hypersensitivity) appears to be the most sensitive target of 2,4-DCP toxicity (Exon and Koller 1985; Exon et al. 1984), and an intermediate oral MRL (0.003 mg/kg/day) based on a NOAEL for immunological effects has been derived for the chlorophenols. Data are insufficient and are needed for the derivation of an intermediate-duration exposure. The liver is the organ most consistently affected by the chlorophenols. Effects noted include enzyme induction (Phornchirasilp et al. 1989a), increased liver weight (Bercz et al. 1990; Exon and Koller 1985), hypertrophy (American Biogenics 1988), and centrilobular degeneration and focal necrosis (Hattula et al. 1981; McCollister et al. 1961). Data on intermediate-duration dermal exposure of chlorophenols in humans or animals are not available and are needed.

Additional studies examining the immunological effects following oral exposure to chlorophenols other than 2,4-DCP are needed to confirm that the intermediate-duration MRL based on 2,4-DCP exposure is truly protective of liver effects following exposure to the other compounds. Mechanistic and toxicokinetic studies may provide useful information about the rate of formation and time course of potential intermediates

associated with chlorophenol-induced hepatotoxicity. Further development of dose-response relationships, with respect to biomarkers of hepatic injury, is needed. These data may provide information about both mechanism of action and potential adverse effects expected at the exposure concentrations associated with NPL sites. Additional experiments to assess dose-response relationship are needed to obtain an intermediate inhalation MRL. Studies focusing on organ function, in addition to histopathological analysis, would be particularly important. Because the higher chlorinated compounds, in particular, contain toxic impurities (particularly dioxins and dibenzofurans), the impurities of each test compound should be minimized since the effects of the contaminants could override the effects from the substance tested. Studies specifically designed to examine the interaction of dioxins and dibenzofurans with chlorophenols should also be completed.

Chronic-Duration Exposure and Cancer. Dermal or inhalation exposure to the chlorophenols used in phenoxy herbicide production may be associated with cancer induction (Eriksson et al. 1981, 1990; Hardell et al. 1981; Hoar et al. 1986). Most investigators, however, have found only weak trends or no evidence of an association (Coggon et al. 1991; Kogevinas et al. 1992; Lynge 1985; Pearce et al. 1988; Smith et al. 1984; Woods et al. 1987). Many of the latter studies included a multinational cohort analysis of workers involved in similar production processes. Current experimental methodology is not sufficiently sensitive to determine those exposure factors, if any, that may be associated with the expression of cancer. Other investigators have observed a possible association between chlorophenol exposure in production workers and the onset of hepatic abnormalities, including porphyria (Bleiberg et al. 1964; Calvert et al. 1992). These results suggest the possibility of biomonitoring individuals living near hazardous waste sites for serological evidence of hepatic dysfunction. No data were located regarding the chronic effects of oral chlorophenol exposure in humans.

Available chronic studies with rats and mice, and evidence of clastogenicity, have indicated that 2,4,6-TCP may produce carcinogenicity in animal models through mechanisms other than direct gene mutation (Armstrong et al. 1993; Jansson and Jansson 1992; NCI 1979). Limited experimental data on mouse skin and orally exposed rats suggest that 2-CP and 2,4-DCP may have tumor promoting capabilities, but are not complete carcinogens (Boutwell and Bosch 1959; Exon and Koller 1985). Additional animal studies designed to determine the conditions under which chlorophenols induce cancer, including supporting evidence for a clastogenic or epigenetic role, are needed. Because of significant information gaps, data are not sufficient to determine a chronic-duration MRL for chlorophenols by either the oral or inhalation route of exposure. Such data should be obtained so that chronic-duration MRLs for chlorophenols can be calculated.

Genotoxicity. There are no human studies on the genotoxicity of the eight chlorophenols. In general, chlorophenols have been negative for mutagenicity in most prokaryotic assays (George et al. 1992; Haworth et al. 1983; Lawlor et al. 1979; Rapson et al 1980; Seuferer et al. 1979; Zeiger et al. 1988). Further mutagenicity studies in these test systems are not needed. Neither 2-CP nor 2,4-DCP induced an increased incidence of SCEs in mouse testicular or bone marrow cells (Borzelleca et al. 1985a). In other eukaryotic tests, 2,4,6-TCP has been associated with structural chromosomal aberrations in both somatic and germ cells (Armstrong et al. 1993; Jansson and Jansson 1992). Evidence of mutational activity in both *in vivo* (Fahrig et al. 1978) and *in vitro* (Fahrig et al. 1978; Hattula and Knuutinen 1985; McGregor et al. 1988) assays is also available for 2,4,6-TCP. The implications of these findings for cancer induction needs further research, including the use of both mammalian cell cultures and additional *in vivo* clastogencity assays in mammals.

Reproductive Toxicity. No occupational or epidemiological studies of potential reproductive effects in exposed individuals are available. Only one animal study comprehensively addresses the reproductive effects of chlorophenols. Blackburn et al. (1986) did not find reproductive effects in male or female rats exposed to 2,4,6-TCP by gavage at doses that caused other systemic effects (e.g., decreased body weight gain). There is limited evidence that 2-CP, 2,4-DCP, and 2,4,6-TCP may reduce litter sizes when administered to rats in drinking water (Exon and Koller 1985). This effect was significant only at $p \leq 0.1$ and was observed at doses that caused other effects (e.g., increased liver weights, decreased delayed-type hypersensitivity). An increase in early embryo loss is suggested by a teratology study of 2,3,4,6-TeCP (RTI 1987). However, the rats were dosed on gestation days 6-15 and not earlier in gestation; thus, further studies regarding the effect of 2,3,4,6- TeCP on pre- and early implantation are needed. No data are available on the reproductive toxicity of chlorophenols after inhalation or dermal exposure in humans or animals.

Developmental Toxicity. Pregnant women may be exposed to chlorophenols occupationally, through the drinking water, or by living near a hazardous waste site. No data are currently available to assess the potential effects of postimplantation exposure on the developing offspring of these women. Results from animal studies showed minor effects occurring at doses that are maternally toxic (Blackburn et al. 1986; Exon and Koller 1985; Rodwell et al. 1989; RTI 1987; Schwetz et al. 1974). Frank teratogenic effects have not been observed following exposure of animals during organogenesis. No data are available on the developmental toxicity of chlorophenols after inhalation or dermal exposure in humans or animals.

Mechanistic studies indicated that cultured hepatocytes ameliorated the adverse developmental effects associated with *in vitro* 4-CP exposure (Oglesby et al. 1992). This finding is apparently attributable to

increased rates of detoxification in the hepatocyte cell cultures. In addition, results from mammalian embryo assay indicate that monochlorophenols are not potent developmental toxicants or teratogens (Mayura et al. 1991). *In vivo* studies involving exposure around the implantation period may help corroborate these *in vitro* data. Studies on developmental effects of postnatal exposure will also be useful.

Immunotoxicity. No experimental data involving the immunotoxic effects of human exposure to chlorophenols are available. Oral studies in rats suggest that a low dose of 2,4-DCP (3 mg/kg/day) is associated with a decreased delayed-type hypersensitivity response and an increased humoral immune response with decreased thymus weights following intermediate exposure (Exon et al. 1984). Both erythroid and myeloid elements of the bone marrow are depleted after oral administration with 500 mg/kg/day of 2,4-DCP for 13 weeks in rats (NTP 1989). Oral administration of other chlorophenols has been associated with elevated spleen weights but not with significant effects on humoral or cell-mediated components (Borzelleca et al. 1985a; Exon and Koller 1983, 1985). The implications of these findings for individuals exposed near NPL hazardous waste sites can only be fully assessed with *in vivo* functional tests of immunocompetence, graft rejection, or immunosurveillance in appropriate animals. Additional animal studies are also needed to provide dose-response and/or threshold information. No data are available on the immunotoxicity of chlorophenols after inhalation exposure in animals. Single dermal exposure of 50 mL of 2,4,5-TCP on one shaved flank of mice indicated 2,4,5-TCP can be a skin sensitizer (Kimber and Weisberger 1991). More data on immunotoxicity of chlorophenols by all the routes of exposure are needed.

Neurotoxicity. Within 20 minutes of being accidentally splashed with 2,4-DCP on his right arm and leg, a worker experienced seizures, collapsed, and died shortly thereafter (Kintz et al. 1992). At single oral doses >300 mg/kg monochlorophenols and dichlorophenols, chlorophenols can produce a variety of neurological effects, including tremors, myoclonic convulsions, a hunched posture, dyspnea, collapse, and coma (Borzelleca et al. 1985a, 1985b; Duchosal and Biedermann 1991; Kobayashi et al. 1972; Phornchirasilp et al. 1989b; Spencer and Williams 1950; Wil Research Laboratories 1982). Convulsions are common after high-dose (intraperitoneal dose of 99 mg/kg) 2-CP administration and apparently are less frequent with increasing halogen substitution on the phenol ring (Angel and Rogers 1972). Other investigators have not observed either clinical or histopathological signs of neurological dysfunction after intermediate-duration exposure to doses up to 1,300 mg/kg/day of 2,4-DCP, trichlorophenols, or tetrachlorophenols (Bercz et al. 1990; NCI 1979; NTP 1989). Acute administration of monochlorophenols has reportedly been associated with hyperactivity and decreased brain weight (Borzelleca et al. 1985a). However, the investigators provided no detailed results, and the conclusions remain questionable. As acute high-dose exposures resulting from

accidents are possible, further studies regarding the dose-response relationship of neurotoxic effects following exposure to chlorophenols are needed. The need is greatest for studies on neurotoxicity following dermal exposure.

Epidemiological and Human Dosimetry Studies. As indicated above, accurate human dosimetry studies may not be possible because environmental and occupational chlorophenols typically exist only in association with other chlorinated organics. Consequently, it would be difficult to ascribe any observed health effect to a single chemical or a single group of isomers. Additional studies in workers, such as sawmill employees, that are exposed specifically to chlorophenols are needed. Careful monitoring of chlorophenol air concentrations and skin exposure combined with kinetic measures of urinary output for specific isomers may provide important correlative data for human dosimetry.

Biomarkers of Exposure and Effect

Exposure. Currently, no specific biomarkers for chlorophenols are known. The presence of chlorophenols or their metabolites in urine is not necessarily diagnostic for chlorophenol exposure because these compounds are also detectable in urine after exposure to other pesticides (Hill et al. 1989; Karapally et al. 1973; Shafik et al. 1973) and hexachlorocyclohexanes (Engst et al. 1976; Koransky et al. 1975). Well-designed animal metabolism studies involving the kinetics of urinary chlorophenol conjugate excretion after exposure to a battery of chlorinated organics are needed to provide data regarding the usefulness of urinary measures as biomarkers of exposure for individuals living near hazardous waste sites.

Effect. No carcinogenic or noncarcinogenic effect in exposed humans has been associated with a specific chlorophenol or a group of chlorophenols. With the possible exceptions of convulsions following monochlorophenol exposure (Angel and Rogers 1972; Borzelleca et al. 1985a, 1985b; Farquharson et al. 1958), clearly defined end points of toxicity in animals are not known. Furthermore, these end points that are associated with chlorophenol exposure are not specific to chlorophenols. When in direct contact with skin and eyes, the chlorophenols demonstrate varying degrees of corrosiveness (Bioassay Systems 1982; Rhodia 1978; Younger Labs 1975). Other effects of chlorophenols, including effects on the immune system (Exon et al. 1984) and reproduction (Exon and Koller 1985), are also not specific to chlorophenols.

Further studies designed to identify specific biomarkers of effects of chlorophenols would facilitate medical surveillance of exposed populations leading to early detection of potentially adverse health effects and possible treatment.

Absorption, Distribution, Metabolism, and Excretion. Studies in sawmill workers indicate that trichlorophenol and tetrachlorophenol are well absorbed during occupational exposure (Fenske et al. 1987; Pekari et al. 1991). The dermal route had a greater absorption potential than the inhalation route. The investigators determined that elimination half-lives were directly proportional to the degree of chlorination for the tri-, tetra-, and pentachlorophenols. Concentrations of 2,4-DCP were measured in the blood, urine, bile, and stomach contents of a worker who collapsed (within 20 minutes) and died shortly after being splashed with pure 2,4-DCP on his right arm and leg (Kintz et al. 1992). Attempts to attain additional data in humans are limited by ethical considerations and by the fact that measurements of chlorophenol levels in the blood and urine of manufacturing workers may not be specific for chlorophenol exposure.

The limited amount of data available from animal oral studies indicates that these chemicals are rapidly absorbed, conjugated to polar metabolites in the liver and kidney, and excreted in the urine (Bahig et al. 1981; Bray et al. 1952a, 1952b; Korte et al. 1978; Spencer and Williams 1950). Absorption also occurs after *in vivo* (Carreon et al. 1980a, 1980b; Hencke and Lockwood 1978) and *in vitro* (Hughes et al. 1993; Huq et al. 1986) dermal application. Rate constants for *in vivo* preparations were not located. Tissue burden is apparently short-lived, with plasma elimination half-lives of approximately 10 minutes after intravenous 2,4-DCP administration (Somani and Khalique 1982), and peak tissue concentrations occurring approximately 30 minutes after intraperitoneal 2,4,6-TCP dosing (Pekari et al. 1986). Plasma protein binding is significant after administration of the higher chlorophenols; in humans, the extent of binding increases with the increasing degree of chlorination (Pekari et al. 1991).

Studies concerning the inhalation absorption and oral absorption of chlorophenols from different media (e.g., water, soil) and the effect of ionization on dermal absorption are needed for estimating exposure at a hazardous waste site.

More systematic information about absorption and elimination kinetics are needed. Furthermore, time series studies using radiolabelled chlorophenols would help identify residence times in individual organs, which may provide insight into potential target organs in human populations.

Semiquinones and quinones may be potentially toxic but short-lived metabolites after oral exposure (Juhl et al. 1991; Phornchirasilp et al. 1989b). The extent and type of Phase II detoxification reactions is apparently species- and isomer-related (Bahig et al. 1981; Bray et al. 1952a, 1952b; Pekari et al. 1986; Somani and Khalique 1982; Spencer and Williams 1950). Broad-based experimentation to determine dose-effect relationships for hepatic adaptive and toxic effects are needed. Part of this experimentation may involve estimation of the rate constants for the formation of both potentially toxic intermediates and Phase II conjugates. Metabolic studies for determining rate differences in conjugate formation between oral, inhalation, and dermal exposure may also suggest route-specific differences in the expression of toxicity.

Comparative Toxicokinetics. Toxicokinetic studies with chlorophenols have been conducted in humans, mice, rats, rabbits, and dogs (Azouz et al. 1953; Bray et al. 1952a, 1952b; Exon and Koller 1982; Fenske et al. 1987; Hattula et al. 1981; Phomchirasilp et al. 1989a; Somani and Khalique 1982; Spencer and Williams 1950). The results of these studies provide a limited profile of toxicokinetics information after oral exposure. These results do not adequately characterize the metabolic rate differences between the various isomers. More comprehensive toxicokinetic studies using radiolabelled isomers administered at several dose levels in two rodent species and one or more nonrodents are needed. These data may be supplemented by hepatic and renal biopsy data and urinary metabolite analysis obtained in exposed individuals.

Methods for Reducing Toxic Effects. The P-448 inducer 3-MC, and possibly other PAHs, apparently increase the Phase 11 conjugation rates of phenolic substrates (Jansen et al. 1992; Wishart 1978a, 1978b). This observation implies that certain chemicals may decrease the body burden of chlorophenols by accelerating the elimination process. Despite this capability, PAH-induced P-448 metabolism may actually increase the extent of hepatic injury through the formation of metabolites capable of undergoing covalent binding (Arrhenius et al. 1977). Research into the development of therapeutic agents that accelerate chlorophenol elimination through Phase II detoxification reactions, but that do not produce bioreactive metabolites (such as semiquinones), may be advisable.

Children's Susceptibility No data are available on the health effects of chlorophenols on exposed children. Since the metabolic enzymes for detoxification may have age dependent expression, there is a need for such data.

There is inadequate experimental evidence to evaluate whether pharmacokinetics of chlorophenols are different in children. There are also limited data to show whether chlorophenols are stored in maternal tissues. There are no direct data on whether chlorophenols cross the placenta or accumulate in breast milk.

There is no experimental evidence to evaluate whether metabolism of chlorophenols or their mechanism of action is different in children. However, in humans, activity of UDP-glucuronosyltransferase (responsible for glucuronide conjugates) does not reach adult levels until about 6-8 months of age, although the development of this activity is isoform specific. Activity of sulfotransferases (responsible for sulfate conjugates) seems to develop earlier, although again, it is isoform specific. The activity of some sulfotransferase isoforms may be greater than that of adults during infancy and early childhood (Leeder and Kearns 1997). It will be helpful to have data on the metabolism and mechanism of action of chlorophenols in children to determine whether children are more vulnerable than adults to the health effects from exposure to chlorophenols. There are no biomarkers of exposure or effect that have been validated in children or adults exposed as children. There are no data to determine whether there are any interactions with other chemicals that are unique to children or whether interactions observed in adults occur in children.

Child health data needs relating to exposure are discussed in 5.8.1 Data Needs: Exposures of Children.

2.11.3 On-going Studies

Dr. Corwin Hansch of Pomona College in California is developing quantitative structure-activity relationships for a variety of chlorinated organics, including the monochlorophenols. The principal end point of concern is teratogenicity in mice and rats. This work is currently being prepared for publication.

No other information regarding on-going research on the health effects of chlorophenols in humans or animals were located.

3. CHEMICAL AND PHYSICAL INFORMATION

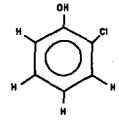
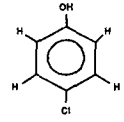
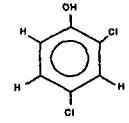
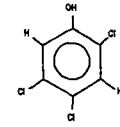
3.1 CHEMICAL IDENTITY

Information regarding the chemical identity of the chlorophenols is located in Table 3-l.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of the chlorophenols is located in Table 3-2. Except for 2-CP, which is a liquid at room temperature, all the chlorophenols discussed in this profile are solids at room temperature.

Table 3-1. Chemical Identity of Chlorophenol Compounds[a]

Characteristic	2-Chlorophenol	4-Chlorophenol	2,4-Dichlorophenol	2,4,5-Trichlorophenol
Synonym(s)	2-CP, 2 chloro-1-hydroxy-benzene, 2 hydroxy-chlorobenzene, *o*-chlorophenol, phenol	4-CP, 4-chloro-1-hydroxy-benzene, 4 hydroxy-chlorobenzene, *p*-chlorophenol, phenol	2,4-DCP, 2,4-dichlorohydroxybenzene	2,4,5-TCP
Registered trade name(s)	Sept-Kleen, Pine-O Disinfect	No data	No data	Preventol I, Collunosol
Chemical formula	C_6H_5ClO	C_6H_5ClO	$C_6H_4Cl_2O$	$C_6H_3Cl_3O$
Chemical structure				
Identification numbers:				
CAS registry	95-57-8	106-48-9	120-83-2	95-95-4
NIOSH RTECS	SK2625000	SK2800000	SR8575000	SN1400000
EPA hazardous waste	UO48	No data	UO51	DO41, FO27
OHM/TADS	8100049	81400051	7217235	8200170
DOT/UN/NA/IMCO shipping	UN 2020 liquid, IMO 6.1, UN 2021 solid	UN 2020 liquid, IMO 6.1, UN 2021 solid	UN 2020 solid, IMO 6.1	UN 2020, NA 2020, IMO 6.1
HSDB	1415	1414	1139	4067
NCI	No data	No data	C55346	C61187

[a]Data from HSDB 1994

CAS = Chemical Abstracts Service; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/International Maritime Dangerous Goods Code; EPA = Environmental Protection Agency; HSDB = Hazardous Substances 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

Table 3-1. Chemical Identity of Chlorophenol Compounds[a] (*continued*)

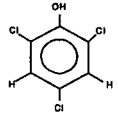
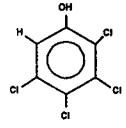
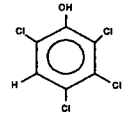
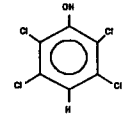
Characteristic	2,4,6-Trichlorophenol	2,3,4,5-Tetrachlorophenol	2,3,4,6-Tetrachlorophenol	2,3,5,6-Tetrachlorophenol
Synonyms	2,4,6-TCP	2,3,4,5-TeCP	2,3,4,6-TeCP	2,3,5,6-TeCP
Registered trade name(s)	Omal, Phenachlor	No data	No data	No data
Chemical formula	$C_6H_3Cl_3O$	$C_6H_2Cl_4O$	$C_6H_2Cl_4O$	$C_6H_2Cl_4O$
Chemical structure				
Identification numbers:				
CAS	88-06-2	4901-51-3	58-90-2	935-95-5
NIOSH RTECS	SN1575000	SM9200000	SM9275000	SM9450000
EPA hazardous waste	DO42, FO27	FO27	FO27	FO27
OHM/TADS	8200171	No data	8200152	No data
DOT/UN/NA/IMCO shipping	UN 2020, NA 2020 solid, IMO 6.1 solid	UN 2020, UN 2021, IMO 6.1	UN 2020 solid, UN 2021 liquid, IMO 6.1	UN 2020 solid, UN 2021 liquid, IMO 6.1
HSDB	4013	6765	1338	6766
NCI	C02904	No data	No data	No data

Table 3-2. Physical and Chemical Properties of Chlorophenol Compounds[a]

Property	2-Chlorophenol	4-Chlorophenol	2,4-Dichlorophenol	2,4,5-Trichlorophenol
Molecular weight	128.56	128.56	163.00	197.46
Color	Light amber	White to pink crystals	White	Gray
Physical state	Liquid	Solid	Solid	Solid
Melting point	9.3°C	43.2–43.7°C	45°C	67°C
Boiling point	174.9°C at 760 mmHg	220°C	210°C	235°C
Density	1.2634	1.2238 at 78°C/4°C	1.383 at 60°C/25°C	1.678 at 25°C/4°C
Odor	Unpleasant, medicinal odor	Medicinal odor	Strong medicinal odor	Strong phenolic odor
Odor threshold:				
Water at 30°C[b]	0.33 µg/L	0.33 µg/L	0.35 µg/L	11 µg/L
Air[c]	0.0189 mg/m^3	0.0189 mg/m^3	1.40 mg/m^3	No data
Solubility:				
Water at 25°C[d]	20,000 ppm	27,000 ppm	4,500 ppm	948 ppm
Organic solvent(s)	Acetone, alcohol, benzene	Alcohol, glycerol, ether, chloroform, fixed and volatile oils, benzene	Ethyl alcohol, carbon tetrachloride, ethyl ether, benzene, chloroform	Acetone, benzene, carbon tetrachloride, ether, denatured alcohol, methanol, liquid petrolatum, toluene
Other solvent(s)	Sodium hydroxide			
pK_a[d]	8.49	8.85	7.68	7.43
Partition coefficients:				
Log K_{ow}[d]	2.17	2.4	3.2	3.72
Log K_{oc}[d]	1.25–3.7	1.2–2.7	2.42–3.98	2.55–3.98
Vapor pressure at 25°C (liquid)[d]	0.99 mmHg	0.23 mmHg	0.14 mmHg	0.05 mmHg
(solid)[d]	0.99 mmHg	0.15 mmHg	0.09 mmHg	0.02 mmHg
Henry's law constant at 25°C[d]	6.8×10^{-6} atm-m^3/mol	9.2×10^{-7} atm-m^3/mol	4.3×10^{-6} atm-m^3/mol	5.1×10^{-6} atm-m^3/mol
Autoignition temperature	No data	No data	No data	No data
Flashpoint	64°C	121°C	114°C	No data
Flammability limits	No data	No data	No data	No data
Conversion factors (ppm to mg/m^3)	2.2	1.1	1.1	No data
Explosive limits	No data	No data	No data	No data

[a]Data from HSDB 1994 except where indicated
[b]From Hoak 1957
[c]From Ruth 1986
[d]From Shiu et al. 1994

Table 3-2. Physical and Chemical Properties of Chlorophenol Compounds[a] (*continued*)

Property	2,4,6-Trichlorophenol	2,3,4,5-Tetrachlorophenol	2,3,4,6-Tetrachlorophenol	2,3,5,6-Tetrachlorophenol
Molecular weight	197.45	231.89	231.89	231.89
Color	Yellow	No data	Light brown	No data
Physical state	Solid	Solid	Solid	Solid
Melting point	69°C	116–117°C	70°C	115°C
Boiling point	246°C	Sublimes	64°C	No data
Density	1.4901	No data	1.83 at 25°C/4°C	No data
Odor	Strong phenolic odor	No data	Strong odor	No data
Odor threshold:				
Water at 30°C[b]	100 µg/L	No data	915 µg/L	No data
Air[c]	No data	No data	No data	No data
Solubility:				
Water at 25°C[d]	434 ppm	166 ppm	183 ppm	100 ppm
Organic Solvent(s)	Acetone, benzene, carbon tetrachloride, diacetone alcohol, methanol, stoddard solvent, touene, turpentine, ether	Alcohol	Acetone, alcohol, benzene, chloroform, ligroin	Benzene
Other Solvent(s)	Hot acetic acid		Hot acetic acid, sodium hydroxide	
pK_a[d]	7.42	6.96	5.38	5.48
Partition coefficients:				
Log K_{ow}[d]	3.69	4.8	4.45	4.9
Log K_{oc}[d]	1.94–3.34	2.9–4.14	3.2–4.21	No data
Vapor pressure at 25°C (liquid)[d]	0.03 mmHg	0.0059 mmHg	0.0059 mmHg	0.0059 mmHg
(solid)[d]	0.0094 mmHg	0.0008 mmHg	0.0021 mmHg	0.0008 mmHg
Henry's law constant at 25°C[d]	5.7×10^{-6} atm-m^3/mol	1.3×10^{-6} atm-m^3/mol	3.6×10^{-6} atm-m^3/mol	2.2×10^{-6} atm-m^3/mol
Autoignition temperature	No data	No data	No data	No data
Flashpoint	No data	No data	No data	No data
Flammability limits	No data	No data	No data	No data
Conversion factors (ppm to mg/m^3)	No data	No data	No data	No data
Explosive limits	No data	No data	No data	No data

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

4.1 PRODUCTION

Table 4-1 lists the facilities in each state that manufacture or process chlorophenol, the intended use, and the range of maximum amounts of chlorophenol that are stored on site. There are currently 4 facilities that produce or process chlorophenols in the United States The data listed in Table 4-1 are derived from the Toxics Release Inventory (TR196 1998). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list.

The chlorinated phenols are manufactured by chlorination of phenol, or for the higher chlorinated phenols, the chlorination of lower chlorinated phenols at high temperatures (WHO 1989). The manufacture of the tetrachlorinated phenols requires a catalyst (e.g., iodine, ferric chloride). 2,4,5-TCP, 2,3,4,5-TeCP, and 2,3,5,6-TeCP have also been produced by the alkaline hydrolysis of hexachlorobenzene (WHO 1989). Both processes of chlorophenol production result in the formation of impurities. The impurities include polychlorinated dibenzo-p-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), polychlorinated phenoxyphenols, polychlorinated diphenyl ethers, polychlorinated benzenes, and polychlorinated biphenyls. Because the higher chlorinated phenols are produced at higher temperature, the contamination of the higher chlorinated phenols is greater than that of the lower chlorinated phenols (WHO 1989).

Recent data about the production of the chlorinated phenols are very limited. The Toxics Release Inventory has grouped all chlorophenols together for 1996 data. The BASF Corp. in Beaumont, Texas is the largest manufacture or processor of chlorophenols with 100,000-999,000 pounds on site (TR1996 1998). 2,3,4,6-TeCP is not produced commercially in the United States (HSDB 1998). Pentachlorophenol, which generally contains about 4% tetrachlorophenols and 0.1% trichlorophenols (Kalliokoski and Kauppinen 1990), is also not produced in the United States (TR1996 1998). Additional data concerning the production of the chlorinated phenols were not available.

4.2 IMPORT/EXPORT

Recent data concerning the import/export of chlorophenols were not available. The latest year for which HSDB (1998) has United States import data on a given chlorophenol is listed below.

Table 4-1. Facilities that Manufacture or Process Chlorophenols

State	Location[a]	Range of Maximum Amounts on Site in Pounds[b]	Activities and Uses[c]
KS	1	10,000 - 99,999	1, 4, 5
MI	1	0 - 99	1, 6, 7
NY	1	100 - 999	7, 11
TX	1	100,000 - 999,999	1, 5, 7

Lindross Source: TRIS96 1998

[a]Lindross Post office state abbreviations used

[b]Lindross Range represents maximum amounts on site reported by facilities in each state

[c]Lindross Activities/Uses:

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

2-CP	1983	33,300 kg
4-CP	1975	33,900 kg
2,4-DCP	1977	500 kg
2,4,5-TCP	1981	216,000 kg
2,4,6-TCP	1980	250 kg

4.3 USE

All the chlorophenols have been used as biocides. The monochlorophenols have been used as antiseptics (HSDB 1998), although in this role they have largely been replaced by other chemicals (WHO 1989). Specifically, 4-CP has been used as a disinfectant for home, hospital, and farm uses (WHO 1989) and as an antiseptic in root canal treatment (Gurney and Lantenschlager 1982). 2,4-DCP has been used for mothproofing and as a miticide (WHO 1989), while the higher chlorophenols have been used as germicides, algicides, and fungicides.

The principal use of the monochlorophenols has been as intermediates for the production of higher chlorinated phenols (WHO 1989). The largest uses for 2,4-DCP and 2,4,5-TCP have also been used as an intermediate, especially in the production of the herbicides 2,4-dichlorophenoxyacetic acid (2,4-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) (WHO 1989). In the United States, 2,4-D is still in use, while 2,4,5-T was taken off the market in 1985. 2,4,6-TCP has been used as an intermediate in the production of higher chlorinated phenols especially 2,3,4,6-TeCP and pentachlorophenol (WHO 1989).

2,4,6-TCP and the tetrachlorophenols have also been used directly as wood preservatives (HSDB 1998). In this role, the tetrachlorophenols are generally used as a mixture and are applied to lumber in an aqueous solution (WHO 1989). Commercial pentachlorophenol, which is more frequently used as a wood preservative, also contains about 4% tetrachlorophenols and 0.1% trichlorophenols (Kalliokoski and Kauppinen 1990). North America and Scandinavia are the main regions of the world where chlorophenols have been used as wood preservatives. The use of these compounds has been banned in Sweden since 1978, and production was banned in Finland in 1984 (Kalliokoski and Kauppinen 1990).

4.4 DISPOSAL

Chlorophenols are listed as toxic substances under Section 313 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Super-fund Amendments and Reauthorization Act (SARA) (EPA 1995). Disposal of wastes containing chlorophenols is controlled by a number of federal regulations (see Chapter 7).

The recommended method of disposing of large amounts of higher chlorinated phenols is incineration, preferably after mixing with another combustible fuel (HSDB 1998). Necessary precautions include the assurance of complete combustion in order to prevent the formation of toxic phosgene gas and the use of an acid scrubber to remove any halo-acids produced upon combustion (Sittig 1985).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

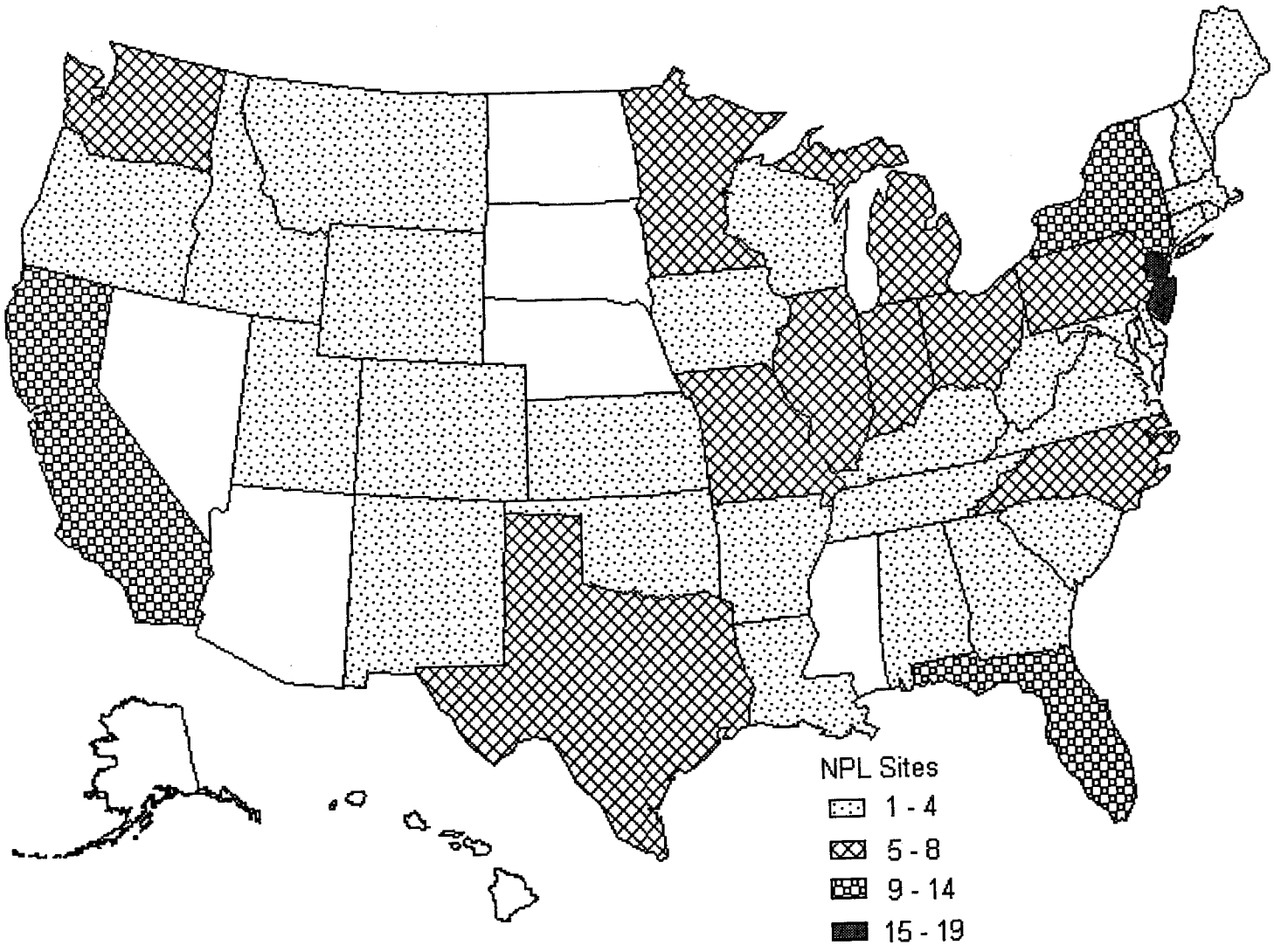
One or more of the eight chlorophenols discussed in the profile has been identified in at least 171 of the 1,467 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL) (HazDat 1998). However, the number of sites evaluated for chlorophenols is not known. The frequency of these sites can be seen in Figure 5-l.

The majority of known environmental releases of chlorophenols were to surface water (Scow et al. 1982). The principal point source of water pollution by chlorophenols is industrial waste discharge; another point discharge is the leaching of chlorophenols from landfills. Chlorophenols enter the atmosphere through volatilization, with mono- and dichlorophenols being the most volatile. The primary nonpoint source pollution of chlorophenols comes from the application of pesticides that are made from chlorophenols and the chlorination of waste water containing phenol.

Once released to the environment, chlorophenols are subject to a series of physical, chemical, and biological transformations. Sorption, volatilization, degradation, and leaching are the primary processes governing their fate and transport. The pH in water and in soil and sediment is a major factor affecting the fate and transport of chlorophenols in these media, since the degree to which the compounds ionize increases with increasing pH. In addition, physiochemical properties of chlorophenols such as water solubility, Henry's law constant, organic carbon sorption coefficient, volatilization rate, and photolysis rate determine transport processes. Important environmental parameters influencing these processes include organic matter content and clay content in soil, sediment, and water, as chlorophenols are in general preferentially adsorbed to these soil constituents. In general, as the number of chlorine molecules increase, there is a reduction in vapor pressure, an increase in boiling point, and a reduction in water solubility of the chlorophenols (Solomon et al. 1994). Therefore, increasing chlorination increases the tendency of these compounds to partition into sediments and lipids and to bioconcentrate. Chlorophenols are subject to abiotic and biotic degradation and transformations. However, compounds containing chlorine in the *meta* positions show greater resistance to microbial attack.

The general population may be exposed to chlorophenols through ingestion of chlorinated drinking water and food contaminated with the compounds and inhalation of contaminated air. Exposure to 4-CP could also occur through its use as a root canal packing. Populations with potentially unusually high exposure to

Figure 5-1. Frequency of Sites with Chlorophenols Contamination*



*Source: HazDat 1998

chlorophenols generally include employees of facilities that manufacture or use chlorophenols and their derivatives and those who live in the vicinity of chlorophenol-containing waste disposal sites and waste incinerators.

5.2 RELEASES TO THE ENVIRONMENT

5.2.1 Air

According to the Toxic Chemical Release Inventory, in 1996, releases of chlorophenols to the air from three large processing facilities were 2148 kg (4,775 pounds) (TRI96 1998). Table 5-l lists amounts released from these facilities. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Both monochlorophenols and 2,4-DCP are volatile, and volatilization may be the major dispersal mechanism of these chemicals into the atmosphere. Trichlorophenols and tetrachlorophenols are slightly volatile. However, only a small fraction (approximately 5%) of chlorophenols (based on 2-CP, 2,4-DCP, and 2,4,6- TCP) are emitted to the atmosphere (Scow et al. 1982). These releases are primarily in vapor form and are principally associated with chlorophenol production and its use in the manufacture of end-use products (Scow et al. 1982).

Releases of chlorophenols to the atmosphere may also occur through the incineration of chlorinated wastes. 2,4-DCP has been detected in atmospheric emissions from the combustion of municipal solid waste, hazardous waste, coal, wood, and 2,4-DCP-based herbicides (Gomez et al. 1988; Junk et al. 1986; Oberg et al. 1989; Paasivirta et al. 1985). Trichlorophenols have been detected in flue gas condensates and fly ash from municipal incinerators (Viau et al. 1984). Di-, tri- and tetrachlorophenols have also been detected in fly ash from wood, oil, and coal-fired power plants at concentrations in the ng/g level (Paasivirta et al. 1985).

Chlorophenols have been detected in air samples collected at 2 of the 1,467 current or former NPL hazardous waste sites (HazDat 1998).

Table 5-1. Releases to the Environment from Facilities that Manufacture or Process Chlorophenols

		Total of reported amounts released in pounds per year[a]						
State[b]	Facilities	Air[c]	Water	Land	Underground Injection	POTW Transfer	Off-site Waste Transfer	Total Environment[d]
KS	1	4,265	0	0	40,154	0	7,500	51,919
MI	1	10	13	0	0	0	0	23
TX	1	500	0	0	73,400	0	4,158	78,058

Source: TRIS96 1998

[a]Data in TRI are maximum amounts released by each facility

[b]Post office state abbreviations used

[c]The sum of fugitive and stack releases are included in releases to air by a given facility

[d]The sum of all releases of the chemical to air, land, and water, and underground injection wells; and transfers off-site by a given facility

POTW = publicly-owned treatment works

5.2.2 Water

According to the Toxic Chemical Release Inventory, in 1996, releases of chlorophenols to the water from three large processing facilities were 6 kg (13 pounds) (TR196 1998). There were no releases of chlorophenols into publicly owned treatment works (POTWs) in 1996 (TR196 1998). Table 5-l lists amounts released from these facilities. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

The majority (85%) of known environmental releases of three chlorophenols (2-CP, 2,4-DCP, and 2,4,6-TCP) were to surface water (Scow et al. 1982). The estimated 1977 water emissions of 2,4-DCP were 741,000 pounds from U.S. production facilities (Scow et al. 1982). Industrial waste discharge is a major point source of water pollution by mono- and dichlorophenols (Krijgsheld and Van der Gen 1986). Monochlorophenol concentrations of between 10-20 μg/L have been released in waste water produced during the manufacture of specialty chemicals (Buikema et al. 1979; Hites et al. 1979), and 5.3 μg/L of 4-CP was detected in a bleaching effluent released to surface water from a straw mill (Folke and Lindgaard-Jorgensen 1985). 2,4-DCP or 2,4,6-TCP were also detected in effluents discharged from industries that manufacture iron and steel, electrical components, photographic equipment/supplies, pharmaceuticals, and organic chemicals/plastics and from paper pulp and paperboard mills (EPA 1981; Paasivirta et al. 1985). Oikari et al. (1985) reported that concentrations of 2,4,6-TCP and 2,3,4,6-TeCP were higher downstream from a pulp and paper mill than upstream from the facility. Free chlorophenols were still present in water 11 km downstream from the mill. However, the release of chlorophenols to water from pulp bleaching mills is being reduced as the use of elemental chlorine for bleaching is being phased out in favor of the use of chlorine dioxide (Solomon et al. 1994). Compared to chlorine, chlorine dioxide bleaching results in the production of fewer chlorophenols, and the chlorophenols that are produced contain fewer chlorine molecules.

Other sources of discharge of chlorophenols into aquatic systems include sewage treatment plants and drinking water treatment, which can result in the chlorination of phenol. In a study of 40 Canadian potable water treatment facilities, 4-CP, 2,4-DCP, and 2,4,6-TCP are the three halogenated phenols found most frequently in samples taken from chlorinated water supplies (Sithole and Williams 1986). The frequency of detection ranged from 1 to 12 out of 40 samples. Mean values were <7 Ng/L and the maximum values <130 Ng/L. 2-CP has also been detected in treated drinking water in the Netherlands (1 μg/L) (Buikema et al.

1979). The maximum monochlorophenol concentrations measured in river water range from 2-6 µg/L (Krijgsheld and van der Gen 1986).

2-CP has been detected in the leachate from a municipal landfill, while 2,4-DCP was found in the leachate from an industrial landfill (Brown and Donnelly 1988). 2-CP was detected in the runoff from 1 of 15 cities, while neither 2,4-DCP nor 2,4,6-TCP were detected in the runoff from 3 cities (Cole et al. 1984). Analysis of groundwater taken from 479 waste disposal sites found that 2,4-DCP was detected at 19 sites, 2-CP at 14 sites, and 2,4,5-TCP at 2 sites, while 2,3,4,6-TeCP was not detected at any of the sites (Plumb 1991).

The detection of 2,4,6-TCP in industrially unpolluted surface water in Sweden at concentrations up to 10 ng/L suggests that this compound can be formed by natural chlorination of humic substances (Grimvall et al. 1991). A laboratory investigation (Hodin et al. 1991) reported that the addition of chloroperoxidase from the fungus *Culduriomyces fumugo***,** hydrogen peroxide, and potassium chloride to bog water (pH adjusted to 3 with 100 mM phosphate) did result in the production of 2,4,6-TCP. Chloroperoxidase could also chlorinate added phenol to form 2-CP and 4-CP. These results suggest that chloroperoxidase-mediated chlorination of natural organic matter does contribute to the levels of chlorophenols (especially 2,4,6-TCP) that are found in surface water.

Chlorophenols have been detected in groundwater and surface water collected at 98 and 25 of the 1,467 current or former NPL hazardous waste sites, respectively (HazDat 1998).

5.2.3 Soil

According to the Toxic Chemical Release Inventory, in 1996, there were no releases of chlorophenols to soil (TRI96 1998); however, an estimated 5,246 kg (11,658 pounds) are disposed of in off site facilities. In addition, about 51,099 kg (113,554 pounds) are disposed of by underground injection. Therefore, manufacturing and processing industries are sources of release in soils surrounding the disposal sites. Table 5-l lists amounts released from these facilities. The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Releases of chlorophenols to soils may occur through several processes such as disposal of manmade wastes (e.g., landfills), atmospheric deposition, and accidental releases (e.g., spills) (Scow et al. 1982). Smith (1985) has found that the herbicide 2,4-dichlorophenoxyacetic acid can be degraded to 2,4-DCP following

soil application. Unspecified trichloro- and tetrachlorophenols have been identified at sites cornposting yard waste and municipal solid waste (Malloy et al. 1993). The investigators (Malloy et al. 1993) suggested that the source was pentachlorophenol on treated wood in chipped form that had been added as a bulking agent. The use of chlorophenols as a wood preservative (predominantly 2,3,4,6-TeCP) has also resulted in the contamination of soil around sawmills where these compounds were used (Kitunen et al. 1985, 1987; Valo et al. 1984).

Chlorophenols have been detected in soil, sediment, and leachate collected at 65, 31, and 12 of the 1,467 current or former NPL hazardous waste sites, respectively (HazDat 1998).

5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

The environmental fate and transport of chlorophenols are controlled by their physical and chemical properties and environmental conditions. As shown in Table 3-2, all chlorophenols are solids at room temperature except 2-CP, which is a liquid. In general, as the number of chlorine molecules increase, there is a reduction in vapor pressure, an increase in boiling point, and a reduction in water solubility (Solomon et al. 1994). Therefore, increasing chlorination increases the tendency of the chlorophenols to partition into sediments and lipids and to bioconcentrate.

The higher vapor pressures of the monochlorophenols suggest that among the chlorophenols, these compounds are most likely to be found in air. Specific data concerning monochlorophenols in air were not identified. The vapor pressures of the chlorophenols suggest that the compounds will not partition from the vapor phase to the particulate phase (Eisenreich et al. 1981). That 2,4-DCP and other chlorophenols do not partition into the particulate phase is supported by the identification of 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, and 2,3,4,6-TeCP in rain but not on rain filters (Leuenberger et al. 1985). This study indicates that gas scavenging rather than particle scavenging is the more important process for removing chlorophenols from the air (Leuenberger et al. 1985). Estimated rain/air partition coefficients at 8°C are 2.2×10^4 for 2,4-DCP and 1.8×10^4 for 2,4,5-TCP and 2,4,6-TCP combined (Leuenberger et al. 1985).

The rate of chemical evaporation from an aqueous solution largely depends on a chemicals vapor pressure and water solubility (Henry's law constant). Among the chlorophenols discussed in this profile, 2-CP has

the highest vapor pressure and, therefore, is mostly likely to evaporate from water (Krijgsheld and Van der Gen 1986). In laboratory studies, evaporation half-lives of 2-CP and 4-CP from water 0.38 cm deep were 1.35-1.6 hours and 12.8-17.4 hours, respectively (Chiou et al. 1980). Since the evaporation rate is inversely related to the depth of water, extrapolation of these data indicates that-2-CP evaporation in water 1 meter deep would require approximately 15 days. The amount of volatilization of 2-CP from fine sandy soil (0.087% organic carbon), applied in spiked municipal waste water, was too small to be directly measured (Piwoni et al. 1986).

Volatilization of 2,4-DCP from water is expected to be slow and, therefore, not a major removal process from surface waters. Using the Henry's law constant, a half-life of 14.8 days was calculated for evaporation from a model river 1 meter deep with a current of 1 meter/second and a wind velocity of 3 meters/second, neglecting adsorption to sediment (Thomas 1982). The biological treatment of waste water containing 2,4-DCP has shown that none of the chemical is removed by stripping (Stover and Kincannon 1983). Volatilization from near-surface soil is also not expected to be a significant removal process.

The Henry's law constants for 2,4,5-TCP (0.0039) and 2,4,6-TCP (0.0043) are similar to 2,4-DCP (0.0033). Therefore, the volatilization of these trichlorophenols should be similar to that of 2,4-DCP. In 2-hour laboratory studies, the volatilization rates of 2,4,6-TCP from water and three soil types were determined by Kilzer et al. (1979). These rates, expressed as the percentage of applied compound per milliliter of water evaporated from humus, loam, sand, and water, were 0.15,0.73, 1.05, and 1.4%, respectively, in the first hour after the addition of 50 ppb 2,4,6-TCP. Similar rates were reported during the second hour. In wind tunnel experiments, Sugiura et al. (1984) estimated a half-life of 48 hours for loss of 2,4,6-TCP from water through volatilization. An estimated 58% of 2,4,6-TCP in a nutrient solution in which tomatoes were grown was lost to the air (from photolysis and/or volatilization) over a period of 30 days (Fragiadakis et al. 1981).

Experimental studies examining the volatilization of tetrachlorophenols were not located. Based on lower Henry's law constants and a greater potential to exist as the dissociated compound in the environment, tetrachlorophenols would be less likely to volatilize from water and soil than the lower chlorinated chlorophenols .

In addition to vapor pressure and solubility, pK_a and log K_{ow} (octanol water partition coefficients) are other important properties which determine the transport and partitioning of chemicals. The lower chlorophenols have higher pK_a values (7.42-8.49). Therefore, in natural waters these compounds will exist primarily as the

undissociated compounds, and adsorption to sediments at a pH of not more than one unit greater than the pK_a can be predicted based on the organiccontent of the sediments and the octanol/water partition coefficient (Schellenberg et al. 1984). In contrast, the pK_a values of the tetrachlorophenols are lower (5.48-6.96) so that at ambient pH values these compounds are present predominantly in the ionized form, and the adsorption to sediemtns will also be dependant on the ionic strength of the wat (Schellenberg et al. 1984).

In general, a chemical will preferentially partition into organic matter if its log K_{ow} is > 1 (Scow et al. 1982). Log K_{ow}s for the chlorophenols are all > 2 (see Table 3-2); therefore, the chlorophenols will all tend to partition into sediments. Despite this prediction, a modeling study completed by Yoshida et al. (1987) suggests that most of the 2,4,6-TCP released to surface waters would remain in the water rather than absorb to sediments. They estimated that in a river receiving daily inputs of the compounds, 72% would be in the water and 28% in the sediment. In a deep, otherwise unpolluted lake, 84% would be in the water and 16% in the sediment. Laboratory sorption experiements with natural sediments containing up to 10% organic matter have been conducted using 2-CP and 2,4-DCP (Isaacson and Frink 1984). Sediment sorption capacity was extensive (up to 0.3 mmol/g), and up to 90% of the adsorption was irreversible.

Chlorophenols are capable of binding to soil organic matter via covalent bond formation, resulting from biologically or chemically catalyzed reactions. In a batch sorption experiment, the binding of 4-CP to soil requires oxygen and soil bioactivity, indicating a biologically mediated oxidative coupling reaction. The addition of hydrogen peroxide, which may be an oxygen source, caused a 4.4 fold increase in 4-CP binding (Bhandari et al. 1996).

As the number of chlorines on phenols increases, sorption of chlorophenols to organic material in soil increases. For example, at two sawmills in Finland where chlorophenol wood preservative (primarily 2,3,4,6-TeCP) was used, soil was contaminated to a depth of 80 to 100 cm to the same extent as at the surface (Valo et al. 1984). As soil depth increased, the concentration of dichlorophenols increased. The investigators attributed this observation to a greater transport of dichlorophenols through the soil and to the relatively increased degradation of the higher chlorinated phenols. An experimental study that examined the movement of 2-CP and 2,4,5-TCP through two soil types (organic carbon 2.1 mg C/g soil or 1.5 mg C/g soil) found that the relative velocity of the chlorophenol through soil into water was 3.5-4 times greater for 2-CP compared to 2,4,5-TCP (Kjeldsen et al. 1990). The chlorophenols moved slowest in the soil with the greatest organic carbon content.

5. POTENTIAL FOR HUMAN EXPOSURE

Chlorophenol groundwater contamination will occur if sufficient quantities of the chemical are present to exceed the sorption capacity of the vadose zone saturated soils (Scow et al. 1982). Contamination is most likely in soils with low organic carbon content or high pH. Once in groundwater, sorption of chlorophenols by the solid aquifer matrix may be estimated based on log K_{ow} and organic carbon content, provided that the organic carbon content exceeds 0.1% and the aquifer pH is not sufficiently high for significant dissociation to occur (Schellenberg et al. 1984; Schwarzenbach and Westall 1985). In a natural gradient tracer test conducted within an unconsolidated aquifer, sorption was not an important factor, compared to dispersion and degradation, in the attenuation of 4-CP concentrations (Sutton and Barker 1985). The authors attributed this finding to the low organic carbon content of the aquifer sand unit, which prevented significant hydrophobic sorption.

The bioaccumulation potential of 2-CP, 4-CP, 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, and 2,3,4,6-TeCP was reviewed by Loehr and Krishnamoorthy (1988). Based on bioconcentration values and log octanol/water partition coefficients, they concluded that all chlorophenols studied had the potential for accumulation in aquatic organisms. Logs of bioconcentration factors ranged from 0.81-2.33 for 2-CP, 1.79-3.28 for 2,4,5-TCP, and 1.95-2.3 for 2,3,4,6-TeCP. Values of bioconcentration factors for 4-CP, 2,4-DCP, and 2,4,6-TCP were predicted mathematically (Veith et al. 1980).

Research on biomagnification of chemical residues within the aquatic food chain indicates that the potential for residue accumulation by fish through food chains is relatively insignificant (<10%) for most compounds when compared to the tissue residues resulting from the bioconcentration process (i.e., direct uptake from water) (Barrows et al. 1980). These data suggest that only those chemicals that are relatively persistent in fish tissues appear to have any potential for significant transfer through food chains (Barrows et al. 1980). A very short tissue half-life of <l day was measured after bluegill sunfish exposure to 2-CP was terminated (Veith et al. 1980). Therefore, due to their relatively low bioconcentration factors (<1,000) and short biological half-lives (<7 days), monochlorophenols will probably not biomagnify within aquatic food chains (Barrows et al. 1980). Data regarding the biomagnification of the higher chlorophenols were not located.

Isensee and Jones (1971) studied the uptake of 2,4-DCP from solution and soil by oats and soybeans. The compound was taken up by the plants, with the concentrations decreasing as the plants matured. At maturity, 2,4-DCP in oat seeds was below detection (<0.001 μg/g) and in soybeans was 0.003 μg/g. Data regarding the uptake of other chlorophenols by plants were not located.

The bioaccumulation of 2,3,4,6-TeCP was examined in earthworms *(Lumbricus rubellus* and *Aporrectodea caliginosa tuberculata)* at a sawmill that had been closed 28 years before sampling (Haimi et al. 1992). At a distance of 5 meters from the dipping basin, 2,3,4,6-TeCP concentrations were 430 and 1,980 μg/g fat in *Lumbricuss* and *Aporrectodea,* respectively, while soil concentrations were 336 μg/g dry soil. The difference between the two species was attributed to greater ingestion of contaminated soil by *Aporrectodea.* Additional data regarding bioaccumulation of chlorophenols in terrestrial organisms was not identified. It is not known whether 2,3,4,6-TeCP biomagnifies up the terrestrial food chain. Based on physical properties (i.e., greatest log octanol water partition coefficient), the tetrachlorophenols, rather than lower chlorinated phenols, would have the greatest potential to biomagnify.

5.3.2 Transformation and Degradation

5.3.2.1 Air

Limited data on the environmental transformations of atmospheric chlorophenols are available. Although chlorophenols absorb primarily in deep ultraviolet, some absorption in the solar visible spectrum is possible because of the overlap between this spectrum and the ultraviolet spectrum (Bunce and Nakai 1989). Bunce and Nakai (1989) found that photolysis and hydroxyl (OH) radical attack were complementary processes for 4 of the chlorophenols. As indicated below, a greater percentage of 2-CP and 4-CP were degraded by hydroxyl attack compared to photolysis, while with increasing chlorination, photolytic degradation increased and hydroxyl attack decreased. Tetrachlorophenols were not tested in this study.

Chlorophenol	Photolytic degradation (% per hour)	Hydroxyl Radical Attack (% per hour)
2-CP	0.024	41
4-CP	0.022	41
2,4-DCP	0.11	11
2,4,5-TCP	2.3	8

5.3.2.2 Water

Both direct photolysis and the reaction of chlorophenols with hydroxyl radicals and singlet oxygen produced by ultraviolet radiation may be important processes of chlorophenol degradation near the water surface. Photolysis of monochlorophenols in water results in dechlorination, with the position of the chlorine on the ring strongly influencing the transformation (Boule 1982). In the molecular form, 2-chlorophenol is

converted into pyrocatechol. However, in the anionic form, it is reduced in a cyclopentadienic acid and dimerizes. For 3-chlorophenol, the photochemical product is resorcinol regardless of the pH. For 4-chlorophenol, hydroquinone is formed along with polyphenolic oligomers (Boule 1982). The photolysis rates of 2-CP in natural waters depends on pH, season, and dissolved organic material (Kawaguchi 1992a, 1992b). In all cases the reaction rate is first order. Based on empirical data, these investigators proposed that direct photolysis of 2-CP may only occur in natural waters at pH between 7 and 9. Indirect photolysis in lake waters was only significant in summer months; in sea waters, indirect photolysis has a more significant role in the spring and fall. Kawaguchi et al. (1992a, 1992b) also found that the dissolved organic matter in pond water does not contribute to indirect photolysis as significantly as a humic acid solution.

The photocatalytic degradation process with titanium dioxide particles has been shown to be feasible for achieving a high degree of removal of 2-chlorophenol in water (Ku et al. 1996), with almost complete disappearance in only a few hours of illumination time. However, the demineralization of reaction intermediates requires a longer time, and was found to be more effective for acidic solutions. Increasing the light intensity would significantly increase the decomposition rate of 2-chlorophenol at pH 3, but not pH 11. The higher removals at acidic conditions may be due to the increased amounts of undissociated 2-chlorophenol species adsorbed on the TiO_2 surface; the TiO_2 acting as a catalyst in the photochemical degradation.

The reaction of hydroxyl radicals with monochloro- and dichlorophenols was studied by Kochany and Bolton (1991) using spin trapping with electron paramagnetic resonance detection of spin adducts. The reaction rate of 4-CP ($3.2/10^{10}$ $M^{-1}s^{-1}$) and 2,4-DCP ($3.8/10^{10}$ $M^{-1}s^{-1}$) with hydroxyl radicals was greater than the reaction rate of 2-CP ($1.92/10^{10}$ $M^{-1}s^{-1}$). The observation that chlorophenols with *meta*-substitution have even slower reaction rates ($1.04/10^{10}$ $M^{-1}s^{-1}$for 3-CP, $0.9/10^{10}$ $M^{-1}s^{-1}$ for 3,5-DCP) indicates that for the monochloro- and dichlorophenols, the location of chlorine rather than the number of chlorines is more important in determining the reaction rate. Higher chlorinated phenols were not examined in this study. Chlorophenols may also be removed via reaction with photochemically produced singlet oxygen in natural waters. The estimated half-life for the reaction of 2,4-DCP at pH 7 and 2,4,6-TCP with singlet oxygen at pH 5.5 under midday sun (assuming a singlet oxygen concentration of $4x10^{-14}$) using experimentally determined rate constants is 62 hours (Scully and Hoigne 1987). The rate of reaction of singlet oxygen with 2,4-DCP and 2,4,6-TCP increased significantly as the solution pH was raised from 5.5 to 9 (Scully and Hoigne 1987). This observation is consistent with a study by Tratnyek and Hoigne (1991) who found that the reaction of phenolate ions with singlet oxygen was about one order of magnitude greater than the reaction of the undissociated chlorophenol. The compounds examined in this

study were 2-CP, 4-CP, 2,4-DCP, and 2,4,6-TCP. Although tetrachlorophenols are most likely to exist as ions in natural waters, it is not known whether the ions react more readily with singlet oxygen than do the undissociated tetrachlorophenol compounds.

Hwang et al. (1986) studied the photolysis and microbial degradation of 4-CP, 2,4-DCP, and 2,4,5-TCP in both estuarine and distilled water. Photolysis was the primary transformation process for 2,4-DCP and 2,4,5-TCP, with the rate of photolysis decreased in the order 2,4,5-TCP, 2,4-DCP, and 4-CP. The rate of photolysis of 2,4-DCP was greater in estuarine compared to distilled water, suggesting a photosensitized reaction, The type of water had no effect on the photolysis of 4-CP and 2,4,5-TCP. Unlike the polychlorinated phenols, microbial degradation was the primary transformation process for 4-CP (Hwang et al. 1986).

There are numerous studies regarding the microbial degradation of chlorophenols in water and sediments (Abrahamsson and Klick 1991; Aly and Faust 1964; Banerjee et al. 1984; Genther et al. 1989; Hwang et al. 1986; Vaishnav and Korthals 1988), as well as numerous studies concerning the degradation of these compounds by sludge (Armenante et al. 1992; Battersby and Wilson 1989; Boyd and Shelton 1984; Liu and Pacepavicius 1990; Tabak et al. 1981). Although as a group chlorophenols are poorly biodegradable and persistent in the environment, several studies have shown that aerobic degradation of chlorophenol congeners is possible (Steiert et al. 1988; Armenante et al. 1992). The aerobic degradation of chlorphenols by microorganisms requires the participation of the enzyme's oxygenases to incorporate atmospheric oxygen into their substrates. For fission of the benzene nucleus, the ring is usually first dihydroxylated by an oxygenase such that two hydroxyl groups are situated either *ortho* or *para* to one another on the ring (Steiert and Crawford 1985). Subsequent ring fission occurs through another oxygenase-catalyzed reaction involving the insertion of dioxygen into the aromatic nucleus. The crucial step in the biodegradation of chlorophenols is the removal of the chlorine substituents. For the catabolism of the lesser substituted phenols (mono- and dichlorophenols), dioxygenase from chlorophenol-degrading bacteria usually opens the dihydroxylated aromatic ring before dechlorination takes place (Steiert and Crawford 1985). With more highly substituted phenols, some of the chlorosubstituents must be removed before ring cleavage since the halogen atoms deactivate the aromatic nucleus to electrophilic attack by dioxygenases.

It has been reported that 4-CP can be partially or completely degraded by several aerobic bacteria such as *Pseudomonas* sp. B13 (Knackmuss 1978) and *Azobactirium sp*. GPl (Wieser 1997). The catabolic degradation routes for mono- or dichlorophenols are known to be *meta*- and modified *ortho*-pathways (Bae et al. 1996). In these pathways, 4-CP is hydroxylated to 4-chlorocatechol which then undergoes intradiol

cleavage before the chloro-substituent is removed. In addition, 4-CP degradation by *Azobactirium ureufaciens* CPR706 was reported via a pathway in which the chloro-substituent of 4-CP was replaced with an incoming hydroxyl group to form hydroquinone (Bae et al. 1996). After 4-CP degradation was completed, the accumulated hydroquinone disappeared from the medium via ring fission forming the 4-hydroxymuconic semialdehyde intermediate. The general observation of these studies is that compounds with a chlorine in the *meta*- and/or *para*- position are the most resistant to degradation (Abrahamsson and Klick 1991). In addition, if the bacteria have not been cultured in the presence of a chlorophenol, they require an adaption period before the compounds can be degraded. For example, degradation of 2,4-DCP was observed in natural water collected from a river following lag times of 2.5 and 8.3 days for 2 separate collections (Banerjee et al. 1984). The rates of degradation of 4-CP, 2,4-CP, and 2,3,4,5-TeCP in river water were 6.5×10^{-6}, 2.3×10^{-6}, and 1.4×10^{-7} moles/hour, respectively (Banerjee et al. 1984). A study by Liu and Pacepavicius (1990) indicates that the position, rather than the number of chlorine atoms, is more important in determining the biodegradation of chlorophenols. The biodegradation of chlorophenols was studied in both aerobic and anaerobic systems using a pentachlorophenol-degrading bacterial culture. The results, shown in Table 5-2, indicate lag time to degradation, and half-life tended to be shorter for compounds with a chlorine in the 4 position and longer for compounds with a chlorine at the 5 position. Anaerobic degradation of the chlorophenols required a longer lag time and the half-lives were longer.

Reductive dehalogenation of chlorinated aromatic compounds whereby chlorines are being replaced by hydrogens occurs extensively under anaerobic conditions (Steiert and Crawford 1985). Anaerobic dehalogenation of 2-chlorophenol, a common intermediate of polychlorophenol degradation, by mixed cultures was reported (Theme1 et al. 1996). Acetate was found to be the major end product, with phenol and benzoate as intermediate products, but CO, was not found to be an end product.

A study of anaerobic degradation of chlorophenols in waste water in an upflow anaerobic sludge blanket reactor indicated that the higher chlorophenols were converted to lower chlorinated compounds via reductive dechlorination reactions (Woods et al. 1989). The rate of these reactions was dependent on the position of the chlorine; chlorines adjacent to the hydroxyl group were preferentially removed, and *meta* chlorines were removed following acclimation, with no evidence for the removal of *para* chlorines. Woods et al. (1989) also found no evidence for the dechlorination of monochlorophenols in this system.

4-chlorophenol was demonstrated to be quickly removed from formulated waste water catalyzed by horseradish peroxidase (Zhang et al. 1997) to form radicals or quinones, which might be subsequently

TABLE 5-2. Aerobic and Anaerobic Biodegradation of Chlorophenols by Pentachlorophenol Adapted Bacteria[a]

Compound	Lag time (hours)		Half-life (hours)	
	Aerobic	Anaerobic	Aerobic	Anaerobic
2-CP	25	250	140	475
4-CP	25	51	88	84
2,4-DCP	0	310	125	430
2,4,5-TCP	300	nd[b]	380	nd[b]
2,4,6-TCP	0	300	120	470
2,3,4,5-TeCP	50	500	165	510
2,3,5,6-TeCP	nd[b]	nd[b]	nd[b]	nd[b]

[a]Data from Liu and Pacepavicius 1990
[b]nd = not degraded after 700 hours of incubation

polymerized to form less soluble large molecules and precipitated from aqueous phase. The flocculant might increase the removal percentage of the pollutant through enhancing the sedimentation of the reaction products The optimum pH for the removal efficiency of chlorophenol was 9.0. The analytical method would, thus, have to quantify both salt and acid forms of the chlorophenol.

5.3.2.3 Sediment and Soil

Chlorophenol isomers undergo biodegradation in soils under aerobic conditions. Aerobic microorganisms that can degrade chlorophenols have been isolated from soil bacterial cultures. *Pseudomonas picketti* DTP0602, which used 2,4,6-TCP as the sole source of carbon and energy, was isolated from mixed cultures of soil bacterial populations that had been acclimatized to 2,4,6-TCP (Kiyohara et al. 1992). This bacterial species dechlorinates the chlorine atom at position 4 of various CPs to yield their corresponding hydroquinones and may involve oxygenation. Two different enzyme systems for hydroxylation at the *ortho* and *para* positions of the phenol ring may be present in this bacterial species. The *para*-hydroxylation system, which may use a monooxygnease, possibly involves the dechlorination of a 4-position chlorine atom of CPs. 2,4,6-Trichlorophenol-4-monooxygenase, a dehalogenating enzyme, was also isolated from TCP-degrading soil bacterium *Azotobacter* sp., strain GPl (Wieser et al. 1997). NADH, flavin adenine dinucleotide, and O_2 are required as cofactors. 2,6-dichlorohydroquinone and Cl^- ions were identified as reaction products. TCP was the best substrate for this enzyme. However, the majority of other chlorophenols converted by the enzyme bear a chloro substituent in the 4-position. 2,6-dichlorophenol, also accepted as a substrate, was hydroxylated in the 4-position to 2,6-dichlorohydroquinone in a nondehalogenating reaction. It was also reported that the addition to the culture medium of a vitamin solution containing biotin, folk acid, pyridoxine hydrochloride, riboflavin, thiamine hydrochloride, niacin, pantothenic acid, cyanocobalamin, p-aminobenzoic acid, and thioctic acid can increase the aerobic degradation and dechlorination of 2-CP and 4-CP by *Pseudomonas picketti* strain LDl culture by 1l-16% (Kafkewitz et al. 1996).

The extent and rate of biodegradation depend on numerous factors, including soil pH, organic carbon content, biomass, and the chlorophenol isomer and its concentration. In neutral clay-loam soil at 20°C under aerobic conditions, 2-CP was degraded the fastest (Baker and Mayfield 1980). Decomposition rates were as follows: 100% of the 2-CP in 1.5 days, 95% of the 2,4,6-TCP in 3 days, 83% of the 4-CP in 20 days, 81% of the 2,4-DCP in 40 days, and 72 and 31% of the 2,4,5-TCP and 2,3,4,5-TeCP, respectively, in 160 days (Baker and Mayfield 1980). Dasappa and Loehr (1991) examined the loss of 2-CP, 4-CP, 2,4 DCP, and 2,4,6-TCP from a laboratory soil microcosm. The loss from soil and the water soluble fraction were examined at two

concentrations for each compound. The loss of chlorophenols from the water soluble fraction was about 1.5 times greater than the loss from soil, and chemical loss was slower at higher initial concentrations. Mineralization of 2,4,5-TCP in soil not previously exposed to chloroorganics has been reported (Matus et al. 1996). The observation of 2,3,4,6-TeCP in soil (157-338 μg/g dry soil) at a sawmill 28 years after it closed provides evidence that this compound can persist in soil. Soil concentrations of 2,3,4,6-TeCP when the mill was closed were not stated. In general, degradation or complete mineralization to carbon dioxide (CO_2) is greater in soils with low organic carbon content (Kjeldsen et al. 1990), slightly alkaline pH (Balfanz and Rehm 1991), increased temperatures (Baker and Mayfield 1980; Baker et al. 1980; Balfanz and Rehm 1991), and increased inoculum concentrations (Balfanz and Rehm 1991).

Microbial degradation of chlorophenols in soil under anaerobic conditions has not been observed consistently. For 2-CP, 4-CP, 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, and 2,3,4,5-TeCP, no statistically significant differences in degradation rates between nonsterile and sterile clay loam soils occurred when both soil samples were incubated under anaerobic conditions (Baker and Mayfield 1980).

In a study of the degradation of halogenated phenols in anoxic marine sediments, the main degradation pathway was progressive dehalogenation with ortho > para > meta. Sediments which had been exposed to effluent water from a paper and pulp mill showed a higher dehalogenation potential (Abrahamsson and Klick 1991).

Another study demonstrated that anaerobic degradation of chlorophenols with an estuarine sediment inoculum was coupled to sulfate reduction, which was the electron sink. The relative rates of degradation were 4-chlorophenol > 3 chlorophenol > 2 chlorophenol, 2,4-dichlorophenol (Haggblom and Young 1990).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

5.4.1 Air

During seven rain events in Portland, Oregon, in 1984, 2,4-DCP was detected in the air in all seven events at an average concentration of 1.5 ng/m^3 (0.23 ppt), combined 2,4,5-TCP and 2,4,6-TCP were detected in 6/7 events at an average concentration of 0.15 ng/m^3 (0.02 ppt), and 2,3,4,6-TeCP was detected in 5/7 events at an average concentration of 0.27 ng/m^3 (0.03 ppt) (Leuenberger et al. 1985). Average concentrations in rain for the seven events were 5.9, 1.1, 1.4, and 20 ng/m^3 (0.89. 0.14,0.17, and 2.1 ppt) for

2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, and 2,3,4,6-TeCP, which were detected in 7/7, 4/7, 5/7, and 7/7 of the events respectively. Additional data regarding ambient levels of chlorophenols in indoor or outdoor air were not identified. However, data on 2-CP levels after the accidental derailment and rupture of a train tanker are available. On the day of the accident, air concentrations ranging from 0.02 to 0.7 mg/m^3 (0.04 to 0.19 ppm) were detected in the immediate vicinity of the spill (Scow et al. 1982). Eighteen days after the spill, air levels were <2 $\mu g/m^3$ (<0.5 ppb). No additional data are available regarding air emissions following accidental releases.

5.4.2 Water

Grimvall et al. (1991) measured 2,4,6-TCP in unpolluted surface waters in remote areas of southern Sweden and in pulp bleaching plant recipient waters, Lake Vattern and the Baltic Sea. Concentrations up to 10 ng 2,4,6-TCP/L were found in unpolluted waters, with concentrations of 2,4,6-TCP in Lake Vattern decreasing from 12 ng/L to 1 ng/L with increasing distance from the bleaching plant. 2,4,6-TCP concentrations in the Baltic Sea were <l ng/L. This study suggests that 2,4,6-TCP can be formed by both industrial and natural chlorination of humic substances, an observation that was confirmed in the laboratory (Haimi et al. 1992).

Analysis of chlorophenol concentrations downstream of paper mills along the Rainy River in Canada and northern Minnesota did not identify 2-CP, 4-CP, 2,4,5-TCP, 2,3,5,6-TeCP, or 2,3,4,5-TeCP using methods with detection limits as low as 50 ng/L (Merriman 1988). In water samples from northern Alberta, Canada, 2-CP was not detected (detection limit 0.005 μg/L), while 2,4-DCP concentrations were <0.002-7.1 μg/L, and 2,4,6-TCP concentrations were <0.002-17 μg/L (Morales et al. 1992). 2,4-DCP, 2,4,6-TCP, and 2,3,4,6-TeCP were identified in water samples from at least one of the three sampling stations. A summary of STORET data of priority pollutants in ambient water (Staples 1985) indicated that 2-CP was detected in 0.2% of 814 samples, 2,4-DCP was detected in 0.4% of 876 samples, and unspecified trichlorophenols were detected in 0.1% of 880 samples. Analysis of runoff from 15 United States cities for 2-CP, 2,4-DCP, and 2,4,6-TCP identified only 2-CP, which was found in samples from only one city (Cole et al. 1984).

Chlorophenols are produced during the chlorination of organic material present in industrial and municipal waste waters. Consequently, several investigators have detected these chemicals downstream of waste water discharge points. Maximum surface water concentrations measured in 13 samples downstream from a chlorinated waste water discharge in the Netherlands were (in μg/L) 0.6 for 2-CP, 2.1 for 4-CP, 0.33 for 2,4-DCP, 0.32 for 2,4,5-TCP, 0.74 for 2,4,6-TCP, 0.02 for 2,3,4,5-TeCP, 0.2 for 2,3,4,6-TeCP, and 0.08 for

2,3,5,6-TeCP (Wegman and van de Broek 1983). Maximum monochlorophenol concentrations of between 2 and 6 μg/L have been measured in European rivers (Krijgsheld and van der Gen 1986).

Chlorination of drinking water at treatment plants can result in detectable levels of chlorophenols if the required precursors are available in the raw water (Krijgsheld and van der Gen 1986). In a study of Canadian potable water treatment facilities conducted in the summer, maximum concentrations of 65, 127, 72, and 148 ng/L of 2-CP, 4-CP, 2,4-CP, and 2,4,6-TCP, respectively, were measured, while 2,3,4,5-TeCP was not detected in the water (Sithole and Williams 1986).

5.4.3 Sediment and Soil

Chlorophenols have been detected in groundwater from waste disposal sites indicating that these compounds can leach through soil (Plumb 1991). 2,4-DCP was detected most frequently, followed by 2,4,6-TCP, 2-CP, and 2,4,5-TCP. 2,3,4,6-TeCP was not detected at any of the 479 sites. It was not reported how much of each chlorophenol was disposed at each site, and soil concentrations at the sites were not reported. 2,4-DCP in the concentration range of 3.2-79.7 μg/L, as well as other organic compounds, has been found in groundwater samples taken near an abandoned creosote waste site in Conroe, Texas (Bedient et al. 1984). It is not clear whether soil samples were analyzed for 2,4-DCP, although soil concentrations of other organic compounds were provided. Kitunen et al. (1985) reported soil concentrations (in mg/kg wet weight) of 2.7- 47.4, 2, 4-DCP; 0.8-15.7, 2, 4, 5-TCP; 7.3-1,258.3, 2, 4, 6-TCP; 231-1,776.4, 2, 3, 4,6-TeCP; and 0.9-2.2, 2, 3, 4, 5-TeCP in soil at an operating sawmill in Finland where chlorophenols (predominantly 2,3,4,6-TeCP) were being used as a wood preservative. The highest concentrations of chlorophenols were found at depths of 5-40 centimeters. Soil concentrations of 157-338 mg 2,3,4,6-TeCP/kg dry soil were found at a sawmill in Finland 28 years after it had closed, indicating that this compound can persist for long periods (Haimi et al. 1992). Soil concentrations of 2,3,4,6-TeCP when the sawmill was in operation were not reported, and soil concentrations of other chlorophenols discussed in this profile were not measured.

A limited amount of data concerning chlorophenol sediment concentrations in areas of known surface water contamination is available. 2-CP and 4-CP were not detected in sediments, while the maximum concentrations of 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, 2,3,4,5-TeCP, 2,3,4,6-TeCP, and 2,3,5,6-TeCP were 10, 15, 3.7, 9.8, 4.9, and 2.8 pg/kg, respectively (Wegman and van de Broek 1983). In the same study, none of the isomers appeared in sediment samples collected from six locations in the vicinity of chemical and industrial waste water effluent discharge points. These findings may be misleading because of the poor sensitivity

(detection limit of 10 μg/kg) of the gas chromatography/electron capture detector (GC/ECD) analytical procedure. No 2-CP, 2,4-DCP, or 2,4,6-TCP was detected in sediment samples from northern Alberta, Canada, where water concentrations of these chlorophenols were low or not detectable (Morales et al. 1992). The limits of detection in sediments were 0.02 μg/g for 2-CP and 0.01 μg/g for 2,4-DCP and 2,4,6-TCP.

5.4.4 Other Environmental Media

The use of the chlorophenoxy herbicides may result in contamination with 2,4-DCP and 2,4,5-TCP. For example, Cook et al. (1983) analyzed the free and acid hydrolyzable residues of 2,4-DCP in millet resulting from treatment with 2,4-dichlorophenoxyacetic acid. The total residues of 2,4-DCP ranged from not detected (<0.02 ppm detection limit) to 0.031 ppm for postemergence and preharvest treatment. Only 15-19% of the 2,4-DCP residues were in the free unaltered form, while the remaining residues were conjugated to sugars and amino acids and converted to the free form by acid hydrolysis.

Few data were found on the levels of chlorophenols in U.S. foods. Most of the data or estimates are for concentrations in fish or shellfish. Based on the EPA (1980a) estimated bioaccumulation factor (BCF) of 150 in the edible portion of fish and assuming ambient water concentration of 30 ppb, tissue concentrations of 4.5 mg 2,4,6-TCP/kg bodyweight in fish were estimated by Scow et al. (1982). The authors stated that the 30 ppb value for water represents a maximum case exposure. 2-CP, 2,4-DCP, and 2,4,6-TCP were not detected in 22 composite samples of fish collected from harbors and tributaries of the Great Lakes (DeVault 1985). 4-CP, 2,4-DCP, and 2,4,6-TCP were not detected (detection limit 0.02 mg/kg) in fish from 13 Lake Michigan tributaries (Camanzo et al. 1987) or in fish from northern Alberta, Canada, (detection limit 0.01 μg/g) (Morales et al. 1992). Fish in the Fraser River estuary downstream from a lumber mill were found to contain chlorophenols including 2,4,5-TCP, 2,4,6-TCP, 2,3,5,6-TeCP, 2,3,4,6-TeCP, and 2,3,4,5-TeCP (Carey et al. 1988). Among the chlorophenols discussed in this profile, 2,3,4,6-TeCP was the most predominant compound, and the highest concentrations (49 ng/g) were found in sculpin, which had concentrations of about 400 times the concentration found in water in the estuary. Trichlorophenol (combined 2,4,5 and 2,4,6 isomers) concentrations of 29-629 ppb (wet weight) were measured in fish livers collected from the Pacific Ocean 6 km northwest of the discharge zone for the Los Angeles County waste water treatment plant by Gossett et al. (1983). Concentrations in edible tissues were not measured.

In addition to environmental contamination of food, another potential source for chlorophenol contamination of food is migration from packaging materials. Shang-Zhi and Stanley (1983) reported levels of

0.1-0.68 ppm 2,4,6-TCP and 0.14-0.55 ppm 2,3,4,6-TeCP in cardboard food containers. Analysis for other chlorophenols was not completed. Shang-Zhi and Stanley (1983) indicated that the source of chlorophenol contamination was polyvinyl acetate and starch adhesives used in carton manufacture.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Oral exposure to chlorophenol-contaminated food and water is the main route of exposure to the general population Water contaminated through chlorination is most likely to contain lower chlorinated phenols, while higher chlorinated phenols are more likely to be found in fish. Exposure to 2,4-DCP through contaminated food may result from the production of 2,4-DCP via degradation/metabolism of 2,4-dichlorophenoxy-based herbicides applied to food crops (Scow et al. 1982; WHO 1989). Although food monitoring data are lacking, exposure to 2,4-DCP through the ingestion of food is expected to be relatively minor. Estimates of total chlorophenol intake reviewed by WHO (1989) ranged from 2.2 μg/person/day assuming contaminated water and fish were the main sources of exposure, to about 10-40 μg/person/day assuming indoor rooms were treated with a chlorophenol preservative.

The identification of chlorophenols in urine and fat of persons not occupationally exposed to chlorophenols confirms general population exposure to these compounds. Analysis of urine from 197 children living near a herbicide manufacturing plant in Arkansas for 2,4-DCP, 2,4,5-TCP, and 2,4,6-TCP, identified these compounds in 27,54, and 11% of the samples, respectively (Hill et al. 1989). The 95th percentile concentrations (in ppb) were 7 for 2,4-DCP, 7 for 2,4,5-TCP, and 4 for 2,4,6-TCP. In the National Health and Nutrition Examination Survey (NHANES II), 2,4,5-TCP was detected (detection limit 5 ppb) in 3.4% of about 6,000 urine samples taken from a representative sample of nonoccupationally exposed persons from 64 communities in the United States during 1976-1980 (Kutz et al. 1992; Murphy et al. 1983). The maximum concentration detected was 56 ppb (Kutz et al. 1992). The investigators warn that because of the considerable variability among the recovery rates over time and between laboratories, the level for 2,4,5-TCP may be underestimated. The average fat concentrations of combined 2,3,4,6-TeCP and 2,3,5,6-TeCP and of 2,3,4,5-TeCP in autopsy specimens were 22 and 6 ng/g respectively in Kingston, Ontario, which is near the Great Lakes, relative to 7 ng/g for 2,3,4,6-TeCP, 2,3,5,6-TeCP, and 2,3,4,5-TeCP in tissue from persons living in Ottawa (Williams et al. 1984). 2,3,4,6-TeCP was detected in 29/46 adipose samples from persons in Finland not occupationally exposed to chlorophenols, while 2,4,6-TCP was detected in only one adipose sample (Mussalo-Rauhamaa et al. 1989). The concentration of 2,3,4,6-TeCP in adipose tissue ranged from

<0.00l (the detection limit) to 0.031 µg/g. 2,3,4,6,-TeCP was also found in 2/13 liver samples, while 2,4,6-TCP was not detected (0.001 µg/g detection limit) in any liver samples.

Occupational exposure to chlorophenol isomers may occur during chemical production and during subsequent use as intermediates in the synthesis of higher chlorinated phenols, phenolic resins, dyes, and drugs (Exon et al. 1984; Krijgsheld and Van der Gen 1986). Exposures result from inhalation and/or dermal contact and are most likely associated with process, storage, or fugitive emissions at chemical manufacturing plants. NOES (1990) estimates that 2,796 workers, principally clinical laboratory technicians at hospitals, are potentially exposed to 4-CP. Chemists comprise the majority of the 975 workers potentially exposed to 2-CP and the 852 workers potentially exposed to 2,4,6-TCP, while janitors; engineers; and furnace, kiln, and oven operators are among the 895 workers potentially exposed to 2,4,5-TCP (NOES 1990). No estimates of the number of workers exposed to the other chlorophenols discussed in this profile were available.

Occupational exposure to chlorophenols may also occur during the incineration of wastes containing chlorinated chemicals (Angerer et al. 1992a, 1993) and through indirect exposure following worker inhalation and subsequent metabolism of chlorobenzene (Kusters and Lauwerys 1990; Yoshida et al. 1986). In a study of 53 municipal waste incinerator workers' urine, concentrations of 2,4-CP and 2,4,5-TCP were small but significantly (p,0.05; nonparametric U-test of Wilcoxon, Mann, and Whitney) greater than the urinary concentrations of these chlorophenols in 248 persons with no known occupational exposure to organic chemicals (Angerer et al. 1992a, 1993). However, 4-CP and combined 2,3,4,6-TeCP and 2,3,5,6-TeCP urine concentrations were small but significantly higher in the control group, which included 88 people from urban communities, than in the incinerator workers. The investigators suggested that the higher 4-CP urine concentrations in the urban population were a result of atmospheric exposure to chlorobenzene, but they did not have an explanation for the higher tetrachlorophenol concentrations (Angerer et al. 1992a). Median and 95 percentile concentrations (µg/g creatinine) of chlorophenols in the urine from the two populations are shown below.

	Waste Incineration (n=53)		Controls (n=248)	
	Median	95%	Median	95%
4-CP	1.2	3.8	1.7	6.6
2,4-DCP/2,5-DCP	10.5	86.6	3.9	46.4
2,4,5-TCP	1.2	3.2	0.8	4.0
2,4,6-TCP	0.9	2.3	0.6	3.7
2,3,4,6-TeCP/2,3,5,6-TeCP	0.3	1.5	1.2	25.6

An industrial hygiene investigation of workers exposed to chlorophenols at a sawmill indicated that dermal exposure was the most important route (Lindroos et al. 1987). The workers were exposed to a wood preservative that contained 80% 2,3,4,6-TeCP, 10-20% 2,4,6-TCP, and 5% pentachlorophenol. Median urinary concentrations of total chlorophenols were 7.8 μmol/L in workers with the skin as the main route of exposure, 1.4 μmol/L in workers with combined inhalation and skin exposure, and 0.9 μmol/L in workers with inhalation as the principal route of exposure.

As with the general population, occupational exposure to chlorophenols can also occur following accidents that result in the release of these chemicals to the environment, such as the previously discussed train derailment. On the day of the accident, 2-CP air concentrations of 0.02-0.7 mg/m^3 (0.004-0.19 ppm) were detected in the immediate vicinity (Scow et al. 1982). Eighteen days after the spill, air concentrations were reduced to <2 μg/m3 (<0.5 ppb). Urine levels in the clean-up workers were 1.98 mg/L approximately 2 months following the spill; however, the pathways, duration, and time of exposure were not recorded, so that the exposure levels cannot be estimated (Scow et al. 1982).

Potential exposure to chlorophenols tends to be limited because of the pronounced odor and taste imparted by the presence of these substances. For example, the odor of 2,4-DCP can be detected in water at 0.35 μg/L (Hoak 1957), and 2,4-DCP can be tasted in water at 8 pg/L (Burttschell et al. 1959). Odor thresholds as low as 0.3-9 15 μg/L in water have also been reported for chlorophenols (Hoak 1957). Although chlorophenols have low odor thresholds in water, 2-CP, 4-CP, 2,4-DCP, and 2,4,6-TCP have been noted to affect the flavor of fish at concentrations of about 2 to 43 times lower than the odor thresholds for these compounds in water (Persson 1984). Data for the other chlorophenols discussed in this profile were not available.

5.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans and briefly considers potential pre-conception exposure to germ cells. Differences from adults in susceptibility to hazardous substances are discussed in 2.6 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, and 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; they put things in their mouths; they may ingest inappropriate things such as dirt or paint chips; they spend more time outdoors. Children also are closer to the ground, and they do not have the judgement of adults in avoiding hazards (NRC 1993).

In a study that analyzed urine samples from 197 children living near a herbicide manufacturing plant in Arkansas for 2,4-DCP, 2,4,5-TCP, and 2,4,6-TCP, these compounds were identified in 27,54, and 11% of the samples, respectively (Hill et al. 1989). The 95th percentile concentrations (in ppb) were 7 for 2,4-DCP, 7 for 2,4,5-TCP, and 4 for 2,4,6-TCP. No measurements have been made of chlorophenols or their metabolite levels in aminiotic fluid, meconium, cord blood, or neonatal blood that indicate prenatal exposure; nor have measurements been made of chlorophenols or metabolite levels in breast milk. However, because of their relative rapid metabolism and excretion in the urine, chlorophenols are not expected to accumulate in maternal tissues.

There are no known unique exposure pathways for children to chlorophenols. However, 4-CP has been used at home as disinfectant, and 2,4-DCP has been used for mothproofing and as a miticide (WHO 1989), while the higher chlorophenols have been used as germicides, algicides, and fungicides. Thus, children may be exposed via accidental ingestion. Because children like to play outdoors and put fingers in their mouths, they may also be exposed via incidental ingestion and dermal contact of contaminated soil. The most likely way that children can be exposed is via drinking water that has beetrdisinfected with chlorine. Exposure to 2,4-DCP through contaminated food may result from the production of 2,4-DCP via degradation of the herbicide 2,4-dichlorophenoxyacetic acid applied to food crops or via ingestion of fish contaminated with TeCP. However, dietary exposure is expected to be minor as chlorophenols generally do not accumulate in animal tissues.

No studies have been found that examine the exposure of children from parents' work clothes, skin, hair, tools, or other objects removed from the workplace. Chlorophenols have been used as biocides. 2,4,6-TCP and the tetrachlorophenols have also been used as wood preservatives. No known information is available at this time concerning exposure from application of wood preservatives, herbicides, and other consumer products and this exposure is unlikely to be significant.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In comparison to members of the general population, workers in certain occupational groups have much greater potential for exposure to high concentrations of chlorophenols (Scow et al. 1982). While quantitative data are not available, workers involved in the production of either chlorophenols or chemicals synthesized from chlorophenols are potentially the most heavily exposed (WHO 1989). Exposure may occur through both inhalation and dermal absorption. Workers in plants that use chlorobenzene are also likely to be heavily exposed to monochlorophenols via the metabolism of inhaled chlorobenzene to monochlorophenols (Kusters and Lauwerys 1990; Ogata et al. 1991; Yoshida et al. 1986). However, most of the inhaled chlorobenzene was metabolized to 4-chlorocatechol rather than chlorophenols, as the average exposed worker excreted three times more 4-chlorocatechol than chlorophenols in the urine (Kustus and Lauwerys 1990; Yoshida et al. 1986) Thus, exposure via metabolism of chlorobenzene is not an important route of exposure.

Workers at sawmills where the higher chlorinated phenols are used as wood preservatives have the highest potential for being exposed to tetrachlorophenols (WHO 1989). The observation of higher urinary concentrations of mixed tetrachlorophenols during hot humid weather when use of protective clothing was minimal (geometric means 196.7 ppm hot humid weather; 98.5 ppm cooler weather) suggests that dermal exposure is an important route of tetrachlorophenol exposure in these workers (Kleinman et al. 1986). The higher volatility of tetrachlorophenols in warmer weather may have also contributed to the higher urinary concentrations of mixed tetrachlorophenols found when the weather was hot. Higher general population exposure may occur through dermal or oral contact with contaminated soils and/or groundwater in the vicinity of disposal or accident sites and through dermal or oral contact with surface waters into which chlorinated effluents have been discharged (Scow et al. 1982). In addition, inhalation and metabolism of chlorobenzene found in urban air can result in higher exposure to monochlorophenols (Angerer et al. 1992b, 1993).

5.8 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 the chlorophenols are 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 the chlorophenols.

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.

5.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties of chlorophenols have been well studied, and reliable values for key parameters for most chlorophenols are available for use in environmental fate and transport models (see Table 3-2). Therefore, further studies of the physical and chemical properties of chlorophenols are not essential at the present time.

Production, Import/Export, Use, Release, and Disposal. 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 Toxics Release Inventory (TRI), which contains this information for 1996, became available in May of 1998. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Chlorophenols have a variety of different uses (HSDB 1998). 2,4-DCP is used as an intermediate in the production of herbicides and the manufacture of compounds used in mothproofing, antiseptics, and seed disinfectants. It is also used to produce miticides and wood preservatives. 4-CP is used as an intermediate in the production of acaricides, rodenticides, and dyes; it is used most commonly as a local antiseptic for dental procedures. 2-CP is used in the production of higher chlorinated phenols, dyestuffs, preservatives, and as a disinfectant/bacteriocide/germicide. It is also used for extracting sulfur and nitrogen compounds from coal. 2,4,5-TCP is used as a fungicide/bactericide; an intermediate in the manufacture of herbicides, hide and leather processing; and in swimming pool and sick-room related surfaces. 2,3,4,6-TeCP is used as a fungicide, pesticide, a slimicide for paper mills, and a preservative. 2,3,4,5-TeCP and 2,3,5,6-TeCP are used primarily as fungicides (HSDB 1998). Chlorophenols are potentially hazardous chemicals and are subject to a variety of regulations (see Chapter 7).

5. POTENTIAL FOR HUMAN EXPOSURE

Data regarding the production methods for the chlorophenols are available; however, data regarding current production and import/export of the chlorophenols are extremely limited (HSDB 1994; Krijgsheld and van de Gen 1986; TR192 1994). No TRI data are currently available (domestic production or environmental release) for the monochlorophenols, 2,4-DCP, or the tetrachlorophenols. General disposal information for chlorophenols is adequately described in the literature. At low concentrations in aqueous media, microbial degradation followed by adsorption on activated charcoal is the common disposal method (WHO 1989).

Environmental Fate. The behavior of chlorophenols in solid and aqueous media depends on numerous physicochemical variables. These chemicals are partitioned to and transported in the air, soil, and water. The pH of soil and water is a major factor controlling their partitioning among the media, their mobility, and their ultimate fate in the environment. These processes are well characterized.

Atmospheric chlorophenols, primarily associated with production processes, are apparently removed by free radical oxidation, photolysis, and both wet and dry deposition (Bunce and Nakai 1989; Scow et al. 1982). More specific data regarding atmospheric dispersion and photochemical reaction rates are needed for occupational settings. Volatilization of the higher chlorinated phenols from water and soil is expected to be a slow process, but there were no experimental data located in the available literature. Experimental data are available pertaining to many of the transformations of chlorophenols in the environment including biodegradation in water, soil, and sediment and photodegradation in water. Confirmation of the estimated slow rate of volatilization in addition to data regarding the overall half-lives for chlorophenols in air are needed to estimate potential inhalation exposure near hazardous waste sites that contain chlorophenols. Data regarding the overall half-life in water and soil are needed to estimate potential oral and dermal exposure to chlorophenols.

Bioavailability from Environmental Media. The observation of systemic effects following inhalation, oral, and dermal exposure indicates that the chlorophenols are readily absorbed (see Chapter 2 for more details). Systematic studies of the bioavailability of the chlorophenols from different media have not been completed. Because the compounds are relatively lipophilic and become adsorbed to soil and sediments, a study of the bioavailability of these compounds from soil relative to water following oral exposure are needed.

5. POTENTIAL FOR HUMAN EXPOSURE

Food Chain Bioaccumulation. Chlorophenols bioconcentrate in aquatic (fish) organisms to a limited extent, with the greatest bioaccumulation (up to 400) observed for the tetrachlorophenols (Carey et al. 1988). The extent of bioconcentration is limited by relatively rapid metabolism and excretion (Veith et al. 1980). Additional data on the bioaccumulation of chlorophenols within both aquatic and terrestrial organisms are needed.

Exposure Levels in Environmental Media. Reliable monitoring data for the levels of chlorophenols in contaminated media at hazardous waste sites are needed so that the information obtained on levels of chlorophenols in the environment can be used in combination with the known body burden of chlorophenols to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. Few data are available concerning the levels of chlorophenols in ambient air or near known sources of atmospheric pollution. Limited monitoring data on chlorophenol levels in surface water are available. Additional monitoring for current data for better characterization of the ambient chlorophenol concentrations in air, surface water, groundwater, soils, and sediment are needed. These data are particularly needed in the vicinity of industrial and municipal chlorinated wastewater discharge points and hazardous waste sites, where individuals may be exposed by oral and/or dermal contact, such that estimates of human intake can be made.

Exposure Levels in Humans. This information is necessary for assessing the need to conduct health studies on these populations. Limited data regarding chlorophenol levels in urine in humans and adipose tissue are currently available. Toxicokinetic data on occupationally and environmentally exposed humans are needed to determine whether there are biomarkers of exposure. Because chlorophenols are metabolites of other chemicals, measurement of these compounds in biological samples (e.g., blood, urine) can provide an estimate of internal dose but may not provide information about the dose of chlorophenols to which individuals were exposed.

This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children No exposure and body burden studies have been conducted on children; therefore, it is not known whether children are different from adults in their weight-adjusted intake of chlorophenols, or if unique exposure pathways for children exist. There is also no monitoring of chlorophenol levels in food (crops, fish), nor in environmental media, following application of herbicides and wood preservatives. Children whose parents work in manufacturing facilities that produce or use

chlorophenols may also potentially be exposed to chlorophenols via parents' work clothes, skin, hair, tools, or other objects removed from the workplace; however, no studies exist on this means of exposure. A take home exposure study may be warranted if such occupational exposure settings are identified. Measurement of chlorophenols and their metabolites in breast milk will also help to determine whether children may be exposed via milk ingestion.

There are no known specific means to decrease exposure, but since children may be more susceptible to chlorophenols, it may be helpful to evaluate methods to do so.

Exposure Registries. No exposure registries for chlorophenols were located. These substances are not currently compounds for which a subregistry has been established in the National Exposure Registry. These substances 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 these substances.

The development of an exposure registry would provide valuable data on exposure levels and frequency. In addition to providing information on exposure levels and duration, a registry would be useful in identifying sources of exposure such as hazardous waste sites and manufacturing and use facilities. Knowledge about exposure levels and sources would be valuable in developing strategies to control unnecessary sources and these exposures. The ability to correlate sources and exposure levels with health effects would be useful in identifying disease conditions that may result from exposure to the chlorophenols.

5.8.2 On-going Studies

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control, will be analyzing human urine samples for 2,4-DCP, 2,4,5TCP, 2,4,6-TCP, 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 measurement of these compounds is being used as a marker of pesticide exposure, rather than just an indication of chlorophenol exposure.

6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting, and/or measuring, and/or monitoring chlorophenols, their metabolites, and other biomarkers of exposure and effect to these isomers. 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 may be included that modify previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

The principal methods used to analyze chlorophenols are gas chromatography with various detectors including flame ionization, electron capture and selected ion monitoring mass spectrometry, and high pressure liquid chromatography. Chlorophenols are highly polar with relatively low vapor pressures, which makes them difficult to measure directly using gas chromatography. To prevent adsorption problems and to improve peak shapes, chlorophenols are usually converted to less polar derivatives before analysis (Hajslova et al. 1988).

6.1 BIOLOGICAL MATERIALS

Methods for analysis of biological materials are summarized in Table 6-1. All methods require that the sample be extracted with an organic solvent. If the extraction of urine is completed under acid conditions, conjugates will be hydrolyzed so that total amounts (free + conjugates) of the various chlorophenols can be measured (Hargesheimer and Coutts 1983). Removal of other organic compounds, using XAD-4 resin (Edgerton et al. 1980; Wright et al. 1981) or a florisil column (Stein and Narang 1984), can improve the detection of chlorophenols. Techniques that require less chromatographic separation are the tandem mass spectrometry (MS/MS) methods described by Yost et al. (1984). These methods, especially the triple-stage quadrupole method, were suggested for rapid screening of a large number of samples. Yost et al. (1984) estimated that to analyze 25 samples by the more standard high-resolution gas chromatography/mass spectrometry method would require 186 hours, while the same number of samples could be analyzed in 27 hours by the triple-stage quadrupole tandem mass spectrometry method.

TABLE 6-1. Analytical Methods for Determining Chlorophenols in Biological Materials

Sample Matrix	Preparation Method	Analytical Method	Sample Detection Limit	Percent Recovery	Reference
Urine	Hydrolyze sample using 70% perchloric acid; extract using diisopropyl ether; evaporate ether phase and dissolve residue in 50:50 acetonitrile/water solution	HPLC-uv/vis	4-CP, 0.2 mg/L	No data	Kusters and Lauwerys 1990
Urine	Hydrolyze sample using concentrated H_2SO_4; add NaOH until pH > 12; extract using methylene chloride; neutralize sample with H_2SO_4; derivatize by adding $NaHCO_3$ followed by acetic anhydride; extract using methylene chloride and concentrate	GC/SIM-MS	2-CP, 4-CP, 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, 2,3,4,6-TeCP, 2,3,4,5-TeCP, 1 pmol/mL	No data	Hargesheimer and Coutts 1983
Urine	Acid hydrolysis extraction, derivatization with acetic acid	GC/ECD	2,4-DCP, 8.3 µg/L; 2,4,5-TCP, 14.8 µg/L; 2,4,6-TCP, 8.5 µg/L; 2,3,4,5-TeCP, 7.1 µg/L; 2,3,4,6-TeCP, 4.9 µg/L	105 100 96 117 106	Angerer et al. 1981
Urine	Acid hydrolysis, elution through XAD-resin with 10% 2-propanol in hexane	GC/ECD	2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, 1 ppb; 2,3,4,5- TeCP, 2,3,4,6-TeCP, 2,3,5,6- TeCP, 2 ppb	2,4-DCP, 70-103; 2,4,5-TCP, 76-94; 2,4,6-TCP, 70-110; 2,3,4,5-TeCP, 74-102; 2,3,4,6-TeCP, 81-102; 2,3,5,6-TeCP, 75-106	Edgerton et al. 1980

TABLE 6-1. Analytical Methods for Determining Chlorophenols in Biological Materials (*continued*)

Sample Matrix	Preparation Method	Analytical Method	Sample Detection Limit	Percent Recovery	Reference
Urine	Acid hydrolysis, extract with diethyl ether, derivatize with diazoethane, sample cleanup with silica gel chromatography	GC/ECD	2,4,5-TCP, 5 ng/mL	Median 62	Kutz et al. 1992
Urine	Distilled with H_2SO_4, extracted with isopropyl ether	GC-FID	2-CP, 1 mg/L; 2,4-DCP, 1 mg/L; 2,4,6-TCP, 1 mg/L; 2,3,5,6-TeCP, 1 mg/L	93-96 99-101 98-102 97-102	Van Roosmalen et al. 1980
Urine	Hydrolysis with H_2SO_4, extract with benzene, derivitization with diazo-ethane, sample cleanup with silica gel chromatography, elution with 80:20 benzene:hexane	GC PCI MS/MS	2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, 1 ppb	2,4-DCP, 80; 2,4,5-TCP, 67; 2,4,6-TCP, 97	Holler et al. 1989
Urine	Acid hydrolysis, elution through XAD-4 resin with 2-propanol-hexane	HPLC/MS	2-CP, 4-CP, 5-25 ppm	No data	Wright et al. 1981
Blood/urine	Samples acidified with HCl and extracted with chloro-form/methanol, chloroform, then hexane	TSQ GC MS/MS	2,4,5-TCP, 0.25 pg/sample	No data	Yost et. 1984
Blood/urine	Samples acidified with HCl and extracted with chloroform/methanol, chloroform, then hexane	MIKES GC MS/MS	2,4,5-TCP, 100 pg/sample	No data	Yost et al. 1984

TABLE 6-1. Analytical Methods for Determining Chlorophenols in Biological Materials (*continued*)

Sample Matrix	Preparation Method	Analytical Method	Sample Detection Limit	Percent Recovery	Reference
Biological tissue	Extract sample with hexane, followed by hexane:ethyl ether (1:1); concentrate organic phase; cleanup on florisil column	GC/ECD	2,4,6-TCP, 2,4-DCP, 2,4,5-TCP, 2,3,4,5-TeCP, 2,3,4,6-TeCP, 4 ng/g fat, 1 ng/g tissue, 0.2 ng/mL blood	86-105	Stein and Narang 1984
Biological tissue	H_2SO_4 extraction of tissue, hydrolysis of conjugates with KOH, extract with diethyl ether, add acetic anhydride to form acetyl derivatives, extract with *n*-hexane	GC/SIM-MS	2,4,6-TCP, 2,3,4,6-TeCP, 0.01 µg/g	80 (minimum recovery of internal 2,4,6-tribromophenol standard)	Mussalo-Rauhamaa et al. 1989
Fish muscle	Add sodium sulfate and ascorbic acid to crushed sample; extract with t-butyl methyl ether/dichloromethane (1:1); concentrate and derivatize using acetic anhydride	GC/SIM-MS	2-CP, 0.01 µg/g	65	Morales et al. 1992

CP = chlorophenol; DCP = dichlorophenol; ECD = electron capture detection; FID = flame ionization detection; GC = gas chromatography; HCl = hydrochloric acid; HPLC = high performance liquid chromatography; H_2SO_4 = sulfuric acid; KOH = potassium hydroxide; MIKES = mass-analyzed ion kinetic energy spectrometry; MS = mass spectrometry; $NaHCO_3$ = sodium bicarbonate; NaOH = sodium hydroxide; PCI = positive chemical ionization; SIM-MS = selected ion monitoring mass spectrometry; TCP = trichlorophenol; TeCP = tetrachlorophenol; TSQ = triple-stage quadrupole tandem mass spectrometry

Edgerton (1981) studied the stability of 2,4,6-TCP and 2,3,5,6-TeCP in human urine and found that the compounds were stable for up to 40 days if frozen at -4°C. A loss of these compounds occurred if the specimens were thawed and refrozen.

6.2 ENVIRONMENTAL SAMPLES

Methods for analysis of environmental samples are summarized in Table 6-2. All methods require extraction of chlorophenols with an organic solvent, and most methods derivatize the chlorophenols before analysis. Samples for chlorophenol determination should be collected into amber glass containers and stored in the refrigerator (APHA 1992). It is also recommended that samples be extracted within 7 days of collection and analyzed within 40 days of extraction. Using gas chromatography with an electron capture detector, Hajslova et al. (1988) compared detection limits and percentage of recovery for 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, and 2,3,5,6-TeCP extracted from water with or without derivatization (acetates, methyl, and pentafluorobenzyl derivatives). All three types of derivatization lowered sample detection limits and increased the percentage of recovery for the tri- and tetrachlorophenols. The detection limit of 2,4-DCP was lowered from 5 to 0.03 mg/L only following derivatization with pentafluorobenzyl bromine, although derivatization decreased recovery from 104 to 85%.

The APHA approved method for analyzing phenols including 2-CP, 2,4-DCP, and 2,4,6-TCP uses gas chromatography and a flame ionization detector (APHA 1992). If there are interfering substances in the sample, APHA (1992) recommends derivitization of the sample with pentafluorobenzyl bromide, followed by clean-up through a silica gel column. Gas chromatography with an electron capture detector is then used to analyze the derivatized chlorophenols.

6.3 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 the chlorophenols 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 the chlorophenols.

TABLE 6-2. Analytical Methods for Determining Chlorophenols in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Wastewater	Acidify and extract sample with methylene chloride; during concentration the extract is exchanged to 2-propanol	GC/FID	2-CP, 0.31 mg/L; 2,4-CP, 0.39 mg/L; 2,4,6-TCP, 0.46 mg/L	No data	APHA 1992 (EPA method 604
Freshwater, seawater, and wastewater	Add 0.5 M Na_2PO_4 buffer solution to sample; add hexane and acetic anhydride and shake	GC/ECD	2,4-DCP, 2 ng/L; 2,4,6-TCP, 2,3,4,6-TeCP, 1 ng/L	99-105	Abrahamsson and Xie 1983
Water	Add ethanol and 2-fluorophenol to groundwater sample and acidify; extract with toluene; separate organic layer and analyze	GC/FID	2,4-DCP, 0.3 ng/sample; 2,4,6-TCP, 0.5 ng/sample	No data	Bengtsson 1985
Water	Acetone, HCl extraction; partition with $NaSO_4$; dry over dichloromethane	GC/ECD	2,4,6-TCP, 1 µg/L; TeCP, 0.5 µg/L	74.8-77.7 46.7-61.4	Woodrow et al. 1986
Water	Adjust sample to pH 11 with 0.1 M NaOH; cleanup on borosilicate column	HPLC/ Dual UV detection	2-CP, 2,4-DCP, 2,4,6-TCP, ng/L range	85 79 95	Alarcon et al. 1987
Water	Add toluene to water sample and shake; separate organic extract, add HFB, shake vigorously and centrifuge; separate toluene phase and analyze	GC/ECD	2,4,6-TCP, 1.1 pg/sample	19.3 (cv)	Bengtsson 1985

TABLE 6-2. Analytical Methods for Determining Chlorophenols in Environmental Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Add acetone and NaOH to sample; extract with hexane; acidify with H_2SO_4; extract with hexane:diethyl ether (1:1) and concentrate	GC/ECD	Free CPs: 2,4-DCP, 5 µg/L; 2,4,5-TCP, 1 µg/L; 2,4,6-TCP, 1 µg/L; 2,3,5,6-TeCP, 2 µg/L	 104 85.3 87.1 70	Hajslova et al. 1988
	Also derivatize above sample by acetylation, methylation, and pentafluorobenzylation		Acetates: 2,4-DCP, 5 µg/L; 2,4,5-TCP, 0.5 µg/L; 2,4,6-TCP, 0.5 µg/L; 2,3,5,6-TeCP, 0.2 µg/L	 92.2 94.2 91.7 76	
			Methyl derivatives: 2,4-DCP, 5 µg/L; 2,4,5-TCP, 0.5 µg/L; 2,4,6-TCP, 0.5 µg/L; 2,3,5,6-TeCP, 0.2 µg/L	 87 91 90 83	
			PFB derivatives: 2,4-DCP, 0.03 µg/L; 2,4,5-TCP, 0.03 µg/L; 2,4,6-TCP, 0.03 µg/L; 2,3,5,6-TeCP, 0.05 µg/L	 85 98.1 87 106	

TABLE 6-2. Analytical Methods for Determining Chlorophenols in Environmental Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Acidify water sample and extract with methylene chloride; separate aqueous layer and add 0.1 M tetrabutyl ammonium chloride; adjust pH to 14 and extract with methylene chloride; combine acidic and basic extracts and analyze	HPLC/Dual UV detection	2-CP, 4.2 ng/sample; 2,4,6-TCP, 12.6 ng/sample	97	Realini 1981
Water	Acidify water sample to pH 1.5 with phosphoric acid; extract with petroleum ether and concentrate organic phase	TLC	2,4,6-TCP, 0.1 µg/L	75-95	Zigler and Phillips 1967
Industrial waste	Lyophilize sample and add dichloromethane; derivatize to carbamates; separate organic phase and concentrate; place extract on or between glass wool plug of glass tubing connected to GC and slowly volatilize	GC/MS	2,4,6-TCP, 10-100 µg/L	No data	Hunt et al. 1985
Sediment	Without pretreatment: Add 0.1 M Na_2CO_3 solution to sample and shake; derivatize sample by adding acetic anhydride; extract with hexane	GC/ECD	2,4,6-TCP, ~0.1 ng/g	94	Xie 1983

TABLE 6-2. Analytical Methods for Determining Chlorophenols in Environmental Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Sediment	Pretreatment hexane extraction to remove neutral and basic impurities for heavily polluted samples; add 0.1 M Na_2CO_3 solution to sample and shake; separate aqueous phase, derivatize with acetic anhydride, and extract with hexane	GC/ECD	2,4-DCP, 2,4,6-TCP, 2,3,4,6-TeCP, ~0.1 ng/g	92	Xie 1983
Soil leachate	Acidify sample and extract with dichloromethane; derivatize with 10% PFC solution in toluene	GC/ECD	2,4,6-TCP, >5 ng/L	73	Buisson et al. 1984
Soil	Add distilled water to soil sample followed by 50% H_2SO_4 and stir; add toluene: methylene chloride (19:1) and reflux; separate organic layer and concentrate	GC/ECD	2,4,6-TCP, µg/g range	98	Narang et al. 1983
Wood dust	Collect dust sample by suction on a membrane filter; extract with diethyl ether	GC/ECD	2,4,6-TCP, 1-4 µg/m^3	No data	Kauppinen and Lindroos 1985
Air	Draw air sample through an impinger containing toluene (at 0°C); derivatize sample by acetylation and extract with hexane	GC/ECD	2,4,6-TCP, 13 µg/m^3	No data	Kauppinen and Lindroos 1985
Air	Collect in toluene in impingers; extract into borax solution	GC/ECD	TCP, TeCP, 2-5 µg/L	No data	Kauppinen and Lindroos 1985

TABLE 6-2. Analytical Methods for Determining Chlorophenols in Environmental Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Spent bleach liquors (bleach plant)	Extract sample continuously with diethyl ether at pH 2 and shake with Na_2CO_3 solution; derivatize with diazomethane and analyze	GC/ECD and GC/MS	2,4,6-TCP, 41 pg/sample	2.6 RSD	Lindstrom and Nordin 1976
Sample formulation	Dissolve sample in acetonitrile and inject into HPLC column	HPLC/ UV detection	2-CP, 2.7 ng/sample; 2,4,6-TCP, 11.3 ng/ sample	0.06 RSD	Buckman et al. 1984

CP = chlorophenol; cv = coefficient of variation; DCP = dichlorophenol; ECD = electron capture detection; FID = flame ionization detection; GC = gas chromatography; HCl = hydrochlororic acid; HFB = heptafluoro butyric anhydride; HPLC = high performance liquid chromatography; H_2SO_4 = sulfuric acid; MS = mass spectrometry; Na_2CO_3 = sodium carbonate; NaOH = sodium hydroxide; Na_2PO_4 = sodium phosphate; $NaSO_4$ = sodium hydroxide; PFB = pentafluoro benzyl bromide; PFC = pentafluoro benzyl chloride; RSD = relative standard deviation; TCP = trichlorophenol; TeCP = tetrachlorophenol; TLC = thin-layer chromatography spectrometry; UV = ultra-violet

6. ANALYTICAL METHODS

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.

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect

Exposure. Analytical methods are available to determine levels of chlorophenols in urine (Angerer et al. 1981; Hargesheimer and Coutts 1983; Kusters and Lauwerys 1990; Van Roosmalan et al. 1980; Wright et al. 1981) and other biological samples, including blood and tissue (Morales et al. 1992; Stein and Narang 1984). Chlorophenols, especially the lower chlorinated compounds, are metabolites of a number of other compounds including pesticides. Therefore, the value of urinary chlorophenols as a measure of exposure to chlorophenols, per se, at hazardous waste sites, where exposure to many compounds can occur, is not clear. Further research on the relationship between low-level exposure and levels of chlorophenols in biological media would be helpful in assessing the risks and health effects of chronic low-level exposure.

Effect. There are no specific markers of the biological effects of chlorophenols. Acute exposure to monochlorophenols results in myelonic convulsions (Angel and Rogers 1972; Borzelleca et al. 1985a, 1985b; Farquharson et al. 1958), and exposure to chlorophenols also results in effects on the immune system (Exon et al. 1984) and on reproduction (Exon and Koller 1985). Further studies are needed to relate levels of chlorophenols in biological media to observed effects. One would doubt that these biological effects (myelonic convulsions) are specific enough to be a food biomarker of effect.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Although there is limited information available about determining levels of chlorophenols in air (Kauppinen and Lindroos 1985), the relatively low vapor pressure of these compounds suggests that, under environmental conditions, exposure through air would be minimal. Sufficient information is available concerning the measurement of the chlorophenols in water (Abrahamsson and Xie 1983; Alarcon et al. 1987; APHA 1992; Bengtsson 1985; Hajslova et al. 1988; Realini 1981; Woodrow et al. 1986; Zigler and Phillips

1967), soil (Buisson et al. 1984; Narang et al. 1983) and sediment (the media of concern for human exposure) (Xie 1983).

Current analytical methods are sensitive enough to measure background levels in environmental media. The precision, accuracy, reliability, and specificity of these methods are sufficiently documented
.

6.3.2 On-going Studies

No on-going studies regarding the development analytical methods for the chlorophenols were identified.

7. REGULATIONS AND ADVISORIES

The international, national, and state regulations and guidelines regarding chlorophenols in air, water, and other media are summarized in Table 7-l. Occupational standards (OSHA) or guidelines (ACGIH) have not been set for any of the eight chlorophenols discussed in this profile.

The chlorophenols as a group have been classified as an IARC group 2B carcinogen (IARC 1987). This classification is based on limited evidence of carcinogenicity in humans exposed during the production of chlorophenoxy herbicides and sufficient animal evidence of carcinogenicity for 2,4,6-TCP. The evidence of carcinogenicity in aimals for 2,4,5-TCP was considered inadequate.

At relatively low concentrations, chlorophenols give water an unpleasant medicinal taste (EPA 1980a). Based on taste thresholds, the EPA has developed ambient water quality criteria. A comparison of the ambient water quality criteria with the health based RfD indicates that a water concentration resulting in the RfD would be well above the taste threshold. For example, drinking two liters of water in a day containing the ambient water quality criteria concentration of 2,4-DCP would result in a dose of 0.009 μg/kg/day relative to the RfD of 3 μg/kg/day.

An acute-duration oral MRL of 0.01 mg/kg/day has been derived for the chlorophenols based on a NOAEL for liver effects in rats identified in the study of 4-CP by Phornchirasilp et al. (1989b). An intermediateduration oral MRL of 0.003 mg/kg/day has been derived for the chlorophenols based on a NOAEL for immunological effects observed in rats following treatment with 2,4-DCP (Exon and Koller 1985; Exon et al. 1984). These MRLs are derived from the chlorophenol with the lowest duration-specific LOAEL and, therefore, should protect against effects following exposure to all chlorophenols as well as exposure to mixtures of chlorophenols, if effects of multiple chlorophenols are additive.

Rather than derive a single RfD for all the chlorophenols, the EPA has derived RfDs for individual compounds for which data were available. The oral RfD for 2-CP is 0.005 mg/kg/day based on a decrease ($p<0.1$) in litter size observed at 50 but not 5 mg/kg/day (Exon and Koller 1982, 1985). The oral RfDs for 2,4-DCP and 2,4,5-TCP are 0.003 mg/kg/day and 0.1 mg/kg/day, respectively (IRIS 1998). These values are based on the same studies and NOAELs as described for the MRLs.

TABLE 7-1. Regulations and Guidelines Applicable to Chlorophenols

Agency	Description	Information	References
INTERNATIONAL			
IARC	Carcinogenic classification chlorophenols	Group 2B[a]	IARC 1987
NATIONAL			
Regulations:			
a. Water:			
EPA OWRS	2,4-DCP General permits under the NPDES Priority pollutant effluent limitations for BAT and NSPS Maximum for 1 day Monthly average shall not exceed	 Yes 112 mg/L 39 mg/L	EPA 1998a (40 CFR 122 Appendix D)
EPA	2-CP Toxic Pollutant	Yes	*EPA 1998b (40 CFR* 401.15)
b. Other			
EPA OERR	Reportable Quantity 2,4,5-TCP, 2,4,6-TCP, 2,3,4,6-TeCP 2-CP, 2,4-DCP	 10 lbs 100 lbs	EPA 1989a (54FR33418)
EPA OSW	Listing as a hazardous waste (2-CP, 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, 2,3,4,5-TeCP, 2,3,4,6-TeCP, 2,3,5,6-TeCP)	Yes	EPA 1988d (53FR13382)
	Listing as a toxic pollutant (2-CP, 2,4-DCP)	Yes	EPA 1998c (40 CFR 401.15)
Guidelines:			
a. Air			
EPA	Cancer Potency Factor 2,4,6-TCP Unit Risk	 3.1×10^{-6} per $\mu g/m^3$	IRIS 1998

TABLE 7-1. Regulations and Guidelines Applicable to Chlorophenols (*continued*)

Agency	Description	Information	References
b. Water			
EPA OWRS	Human Water Quality Criteria		EPA 1980a
	monochlorophenols	0.1 µg/L (organoleptic)	
	2,4-DCP	0.3 µg/L (organoleptic)	
	2,4,5-TCP	1 µg/L (organoleptic)	
	2,3,4,6-TeCP	1 µg/L (organoleptic)	
EPA	Ambient Water Quality Criteria		
	2,4-DCP		EPA 1980b (45FR79318)
	Water and fish	3.09 mg/L	(11/28/80)
	Fish only	3.09 mg/L	
	2,4,5-TCP		EPA 1990c (55FR19986)
	Fresh water		(5/14/89)
	Acute:	100 µg/L	
	Chronic:	63 µg/L	
	Marine		
	Acute:	240 µg/L	
	Chronic:	11 µg/L	
	2,4,6-TCP		EPA 1980b (45FR79318)
	Water and Fish	1.2 µg/L	
	Fish only	3.6 µg/L	
	2,3,4,6-TeCP		EPA 1980b (45FR79318)
	Water and Fish	1 µg/L	(11/28/80)
EPA ODW	Health Advisories[b]		EPA 1996
	2-CP		
	10-kg child		
	1-day	0.5 mg/L	
	10-day	0.5 mg/L	
	Longer term	0.5 mg/L	
	70-kg adult		
	Longer term	2.0 mg/L	
	DWEL	0.2 mg/L	
	Lifetime	0.04 mg/L	
	2,4-DCP		
	10-kg child		
	1-day	0.03 mg/L	
	10-day	0.03 mg/L	
	Longer term	0.03 mg/L	
	70-kg adult		
	Longer term	0.1 mg/L	
	DWEL	0.1 mg/L	
	Lifetime	0.02 mg/L	

TABLE 7-1. Regulations and Guidelines Applicable to Chlorophenols (*continued*)

Agency	Description	Information	References
NAS	SNARL		
	2,4-DCP		NAS 1987
	24-hour	7 mg/L	
	7-day	2 mg/L	
	2,4,6-TCP		NAS 1982
	24-hour	17.5 mg/L	
	7-day	2.5 mg/L	
c. Nonspecific Media			
EPA	Chronic RfD (oral)		IRIS 1998
	2-CP	0.005 mg/kg/day	
	2,4-DCP	0.003 mg/kg/day	
	2,4,5-TCP	0.1 mg/kg/day	
	2,3,4,6-TeCP	0.03 mg/kg/day	
EPA	Carcinogenic classification		
	2,4,6-TCP	Group B2[c]	
DHHS	Carcinogenic classification	Reasonably	NTP 1994
	2,4,6-TCP	anticipated to be a carcinogen	
STATE			
Regulations and Guidelines:			
a. Air	Acceptable ambient air concentration		NATICH 1992
	2-CP		
Texas	(30 minutes)	19.0 $\mu g/m^3$	
	2,4-DCP		
Arizona	(24 hours)	1.6 $\mu g/m^3$	
Florida (Pinella)	(Annual)	3 $\mu g/m^3$	
Michigan	(Annual)	77.0 $\mu g/m^3$	
Texas	(Annual)	53.0 $\mu g/m^3$	
	Trichlorophenols		
Washington (southwest)	(Annual)	0.180 $\mu g/m^3$	
	2,4,5-TCP		
Arizona	(24 hours)	3500 $\mu g/m^3$	
Florida	(Annual)	100 $\mu g/m^3$	
Massachusetts	(Annual)	0.16 $\mu g/m^3$	
Pennsylvania	(1 year)	350 $\mu g/m^3$	
Texas	(Anual)	44 $\mu g/m^3$	

TABLE 7-1. Regulations and Guidelines Applicable to Chlorophenols (*continued*)

Agency	Description	Information	References
	2,4,6-TCP		
Arizona	(Annual)	0.43 µg/m^3	
Florida	(Annual)	0.180 µg/m^3	
Pennsylvania (Philadelphia)	(Annual)	3,500 µg/m^3	
Texas	(30 minutes)	21.0 µg/m^3	
Vermont	(Annual)	0.180 µg/m^3	
	2,3,4,6-TeCP		
Florida	(Annual)	30.0 µg/m^3	
Texas	(Annual)	7.0 µg/m^3	
b. Water	Drinking water quality standards		
Kansas	2-CP	0.1 µg/L	FSTRAC 1990
Kansas	4-CP	0.3 µg/L	
	2,4-DCP		
Arizona		21 µg/L	
Kansas		700 µg/L	
Maine		200 µg/L	
	2,4,5-TCP		
Arizona		700 µg/L	
Kansas		1 µg/L	
	2,4,6-TCP		
Arizona		1.8 µg/L	
Kansas		17 µg/L	
Maine		700 µg/L	
Minnesota		18 µg/L	
New Hampshire		1.87 µg/L	
	2,3,4,6-TeCP		
Kansas		263 µg/L	

[a]Group 2B: Limited evidence for human carcinogenicity.
[b]All health advisories for the chlorophenols listed are in draft status.
[c]Group B2: Probable human carcinogen; sufficient evidence from animal studies

BAT = Best Available Technology; DHHS = Department of Health and Human Services; DWEL = Drinking Water Exposure Level; EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; NAS = National Academy of Science; NPDES = National Pollutant Discharge Elimination System; NSPS = New Source Performance Standards; ODW = Office of Drinking Water; OERR = Office of Emergency and Remedial Response; OSW = Office of Solid Wastes; OWRS = Office of Water Regulations and Standards; RfD = reference dose; SNARL = Suggested No Adverse Response Level

7. REGULATIONS AND ADVISORIES

2,4,6-TCP has been categorized as a group B2 carcinogen (probably human carcinogen) based on leukemias in male rats and hepatocellular adenomas or carcinomas in male mice (NCI 1979), and no RfD has been derived (IRIS 1998). An RfD of 0.03 mg/kg/day has been derived for 2,3,4,6-TeCP based on increased liver weights and hypertrophy observed in rats treated by gavage at 100 but not 25 mg/kg/day (American Biogenics 1988).

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9. GLOSSARY

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

Adsorption Coeffkient (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 (Kd) -- 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.

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.

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.

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.

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.

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 occurred. The terms, as used here, include malformations and variations, altered growth, and in utero death.

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.

Immediately Dangerous to Life or Health (IDLH) -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects.

9. GLOSSARY

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.

In vitro -- Isolated from the living organism and artificially maintained, as in a test tube.

In vivo -- Occurring within the living organism.

Lethal Concentration$_{(Lo)}$ (LC$_{LO}$) -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC$_{50}$) -- 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$_{(LO)}$ (LD$_{LO}$) -- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD$_{50}$) -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT$_{50}$) -- 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 dose 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.

Malformations -- Permanent structural changes that may adversely affect survival, development, or function.

Minimal Risk Level -- An estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

Mutagen -- A substance that causes mutations. A mutation is a change in the genetic material in a body cell. Mutations can lead to birth defects, miscarriages, or cancer.

Neurotoxicity -- The occurrence of adverse effects on the nervous system following exposure to chemical.

No-Observed-Adverse-Effect Level (NOAEL) -- The dose of 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.

9. GLOSSARY

Permissible Exposure Limit (PEL) -- An allowable exposure level in workplace air averaged over an Shour shift.

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 μg/L for water, mg/kg/day for food, and μg/m3 for air).

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 effects during a lifetime. The RfD is operationally derived from the 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.

Reportable Quantity (RQ) -- The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 3 11 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.

Short-Term Exposure Limit (STEL) -- The 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 TLV-TWA may not be exceeded.

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) -- A concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a TWA, as a STEL, or as a CL.

Time-Weighted Average (TWA) -- An allowable exposure concentration averaged over a normal S-hour workday or 40-hour workweek.

Toxic Dose (TD_{50}) -- 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.

Uncertainty Factor (UF) -- A factor used in operationally deriving the RfD 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 LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

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 Super-fund Amendments and Reauthorization Act (SARA) [Pub. L. 99-4991, 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

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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.

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 he 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 agencywide 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.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 4-Chlorophenol- Other chlorophenols - Mixture of chlorophenols
CAS Number: 106-48-9 (4-chlorophenol)
Date: July 1995
Profile Status: Draft 4, pre-public comments
Route: [ ] Inhalation [x] Oral
Duration: [X] Acute [ ] Intermediate [ ] Chronic
Graph Key: 14
Species: Rat

Minimal Risk Level: 0.01 [X] mg/kg/day [ ] ppm

Reference: Phornchirasilp et al. 1989b

Experimental design: (human study details or strain, number of animals per exposure/control groups, sex, dose administration details):

Groups of 4-9 male Sprague-Dawley rats were treated by gavage with 4-CP in corn oil 2 times per day for 2 weeks at doses of 0, 0.32, 0.64, 1.28, 2.58, 5.2, 10.2, and 20.6 mg/kg/day. Liver effects were assessed by the determination of liver weights; microsomal protein levels; cytochrome P-450 activity; and benzphetamine, ethylmorphine, and aminopyrine n-demethylase activities. Electron microscopic examinations of hepatocytes was also completed.

Effects noted in study and corresponding doses:

No significant alterations in relative liver weights were observed. A significant increase in microsomal protein and cytochrome P-450 levels were observed in the 4-CP treated rats. The maximum increase (290% of control) in cytochrome P-450 levels was observed in the 0.64 mg/kg group. Significant increases in the activities of drug-metabolizing enzymes were also observed. Electron microscopic examination revealed foamy cytoplasm and clustering of mitochondria and endoplasmic reticulum in the liver cells of rats exposed to ≥2.58 mg/kg/day. Based on the electron microscopic changes, 2.58 mg/kg/day is considered a LOAEL, and 1.28 mg/kg/day is considered a NOAEL.

Dose and end noint used for MRL derivation:

[x] NOAEL [ ] LOAEL

1.28 mg/kg/day lack of electron microscopic changes in hepatocytes

Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[x] 10 for extrapolation from animals to humans
[x] 10 for human variability

Was a conversion used from nnm in food or water to a mg/body weight dose?
If so, explain: None

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

Other additional studies or uertinent information which lend support? to this MRL:

There are no additional studies that examine liver effects following oral exposure to 4-CP, and studies regarding liver effects of other chlorophenols use higher doses and do not examine hepatocytes with an electron microscope. For example, decreases in microsomal NADPH-cytochrome c reductase activity and P-450 content were observed in rats treated with 2,4,5-TCP but not 2,4,6-TCP at 400 mg/kg/day for 14 days (Carlson 1978). Microscopic examinations were not completed.

Among the chlorophenols examined in the chlorophenol profile (2-CP, 2,4-DCP, 2,4,5-TCP, 2,4,6-TCP, 2,3,4,5-TeCP, 2,3,4,6-TeCP, and 2,3,5,6-TeCP), the acute LOAEL for 4-CP was the lowest LOAEL identified.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: 2,4-Dichlorophenol- Other chlorophenols - Mixture of chlorophenols
CAS Number: 120-83-2 (2,4dichlorophenol)
Date: July 1995
Profile Status: Draft 4, pre-public comments
Route: [ ] Inhalation [x] Oral
Duration: [ ] Acute [x] Intermediate [ ] Chronic
Graph Key: 43
Species: Rat

Minimal Risk Level: 0.003 [x] mg/kg/day [ ] ppm

Reference: Exon et al. 1984; Exon and Koller 1985

Experimental design: (human study details or strain, number of animals per exposure/control groups, sex, dose administration details):

Groups of 10 female Sprague-Dawley rats were exposed to 2,4-DCP (99% pure) in the drinking water at 0,3, 30, or 300 ppm from weaning through breeding at 90 days, parturition, and weaning of pups. Ten randomly selected offspring/groups were then continued on the same treatment regimen as the dams for an additional 10 weeks. IRIS (1994) indicates that doses were calculated by the authors, but the doses are not presented in the papers. To be consistent with IRIS, a 10% drinking water intake factor was used so that estimated 2,4- DCP intakes were 0,0.3,3, and 30 mg/kg/day, at 0,3,30, and 300 ppm**,** respectively.

Effects noted in study and corresnondine doses:

At 30 mg/kg/day, there was a trend for decreased litter sizes (0,9.8±1.3; 30,6.2 ±1.6). Exon and Koller (1985) indicated that this effect was significant at $p \leq 0.1$, but Exon et al. (1984) does not indicate a significant difference. At 30 mg/kg/day significant ($p \leq 0.05$) increases in spleen and liver weights were observed, with no effects on body weight noted. Histological examinations of the liver, spleen, and thymus did not reveal any effects. Examination of immune functions showed a significant ($p < 0.05$) decrease in delayed type hypersensitivity response to bovine serum albumin in Freund's complete adjuvant at 3 and 30 mg/kg/day, with no effect at 0.3 mg/kg/day. Antibody production (in response to keyhole limpet hemocyanin) was significantly increased only at 3 mg/kg/day. No significant effects on phagocytic activity were noted.

Dose and end point used for MRL derivation:

[x] NOAEL [ ] LOAEL

A NOAEL of 0.3 mg/kg/day for a lack of effect on delayed type hypersensitivity was used as the basis of the MRL.

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Uncertainty Factors used in MRL derivation:

[ ] 10 for use of a LOAEL
[X] 10 for extrapolation from animals to humans
[X] 10 for human variability

Was a conversion used from ppm in food or water to a mg/bodv weight dose? Yes.
If so, explain:

A 10% water intake as used in IRIS was used to convert from ppm in water to a mg/kg/day dose.

If an inhalation study in animals, list the conversion factors used in determining human equivalent dose:

Other additional studies or pertinent information which lend support to this MRL:

No other studies of 2,4-DCP examine functional immunological end points. LOAELs identified in other intermediate-duration studies were 500 mg/kg/day, associated with bone marrow hyperplasia in rats fed 2,4-DCP in the diet for 13 weeks (NTP 1989), and 325 mg/kg/day for minimal hepatocellular necrosis in mice fed 2,4-DCP in the diet for 13 weeks (NTP 1989). For chronic exposure, LOAELs of 250 and 820 for reduced body weight in rats and mice were identified (NTP 1989). Therefore, the LOAEL of 3 mg/kg/day for a decrease in delayed type hypersensitivity is the lowest LOAEL, and the MRL is based on the highest NOAEL of 0.3 mg/kg/day. This LOAEL may also be lower than other studies because it is the only study in which 2,4-DCP was administered in water. Unfortunately, there are no studies available to indicate whether there are differences in the absorbed dose following treatment in food relative to water.

2,4-DCP was not carcinogenic in rats or mice (NTP 1989).

An intermediate-duration NOAEL of 0.3 mg/kg/day for increased liver weights at 3 mg/kg/day was also identified by Exon and Koller (1985). Effect levels below the NOAEL of 0.3 mg/kg/day was not identified in intermediate-duration studies of the other chlorophenols.

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

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) 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).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 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 2-1

(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 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) 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 2-1).

(5) Species The test species, whether animal or human, are identified in this column. Section 2.5, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "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.

(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 endpoint 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 8 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 2-1

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^3 or ppm and oral exposure is reported in mg/kg/day.

(16) NOAEL In this example, 18r NOAEL is the critical endpoint 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.

(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.

The Relevance to Public Health section 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 section 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 section. 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 Data Needs section.

SAMPLE

1 → **TABLE 2-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

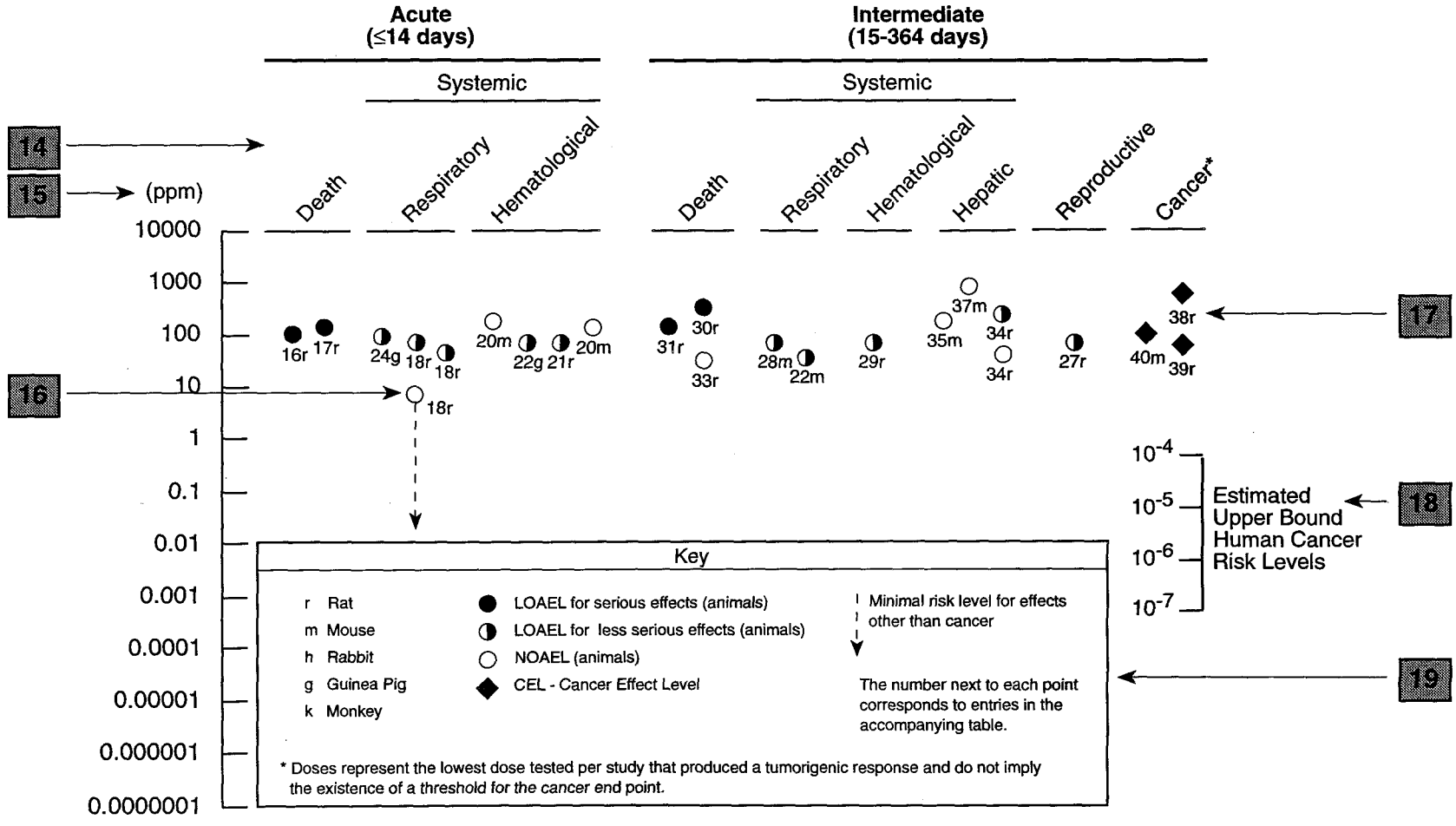
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect) Less serious (ppm)		Reference
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3 [b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					11		
Cancer					↓		
38	Rat	18 mo 5d/wk 7hr/d			20	(CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5d/wk 6hr/d			10	(CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5d/wk 6hr/d			10	(CEL, lung tumors, hemangiosarcomas)	NTP 1982

[a] The number corresponds to entries in Figure 2-1.

12 → [b] by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

13 → **Figure 2-1. Levels of Significant Exposure to [Chemical X] – Inhalation**



Chapter 2 (Section 2.5)

Relevance to Public Health

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 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.8, "Interactions with Other Substances," and 2.9, "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 endpoint 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 endpoint 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.

APPENDIX C

ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F_1	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health

APPENDIX C

IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
Kd	adsorption ratio
kg	kilogram
kkg	metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{Lo}	lethal concentration, low
LC_{50}	lethal concentration, 50% kill
LD_{Lo}	lethal dose, low
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
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
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration

APPENDIX C

PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
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
δ	delta
γ	gamma
μm	micrometer
μg	microgram

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