TOXICOLOGICAL PROFILE FOR HEXACHLOROCYCLOPENTADIENE (HCCPD)

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

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DISCLAIMER

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UPDATE STATEMENT

A Toxicological Profile for HCCPD was released in February 1998. This edition supersedes any previously released draft or final profile.

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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Division of Toxicology/Toxicology Information Branch
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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:

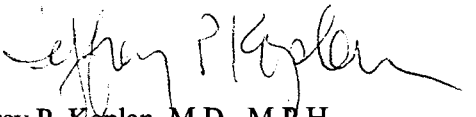
(A) The examination, summary, and interpretation of available toxicologic information and epidemiologic evaluations on a hazardous substance to ascertain the levels of significant human exposure for the substance and the associated acute, subacute, and chronic health effects;

(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.



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*Legislative Background

The toxicological profiles are developed in response to the Superbmd 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 Super-fund). 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 6 1332). 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 FR41280); October 26, 1989 (54 FR 43619); October 17,199O (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 (Chemical X) Affect Children?
Section 1.7 How Can Families Reduce the Risk of Exposure to (Chemical X)?
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

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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-envmed.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-l 856.

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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 HCCPD. The panel consisted of the following members:

1. Dr. Donald Hill, 40 1 Delcris Drive, Birmingham, Alabama;

2. Dr. Donald Morgan Private Consultant, Iowa City, Iowa; and

3. Dr. James Withey, Research Scientist, Environmental & Occupational Toxicology Division, Environmental Health Centre, Ontario, Canada.

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

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

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

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1. PUBLIC HEALTH STATEMENT

This public health statement tells you about hexachlorocyclopentadiene (HCCPD) 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. HCCPD has been found in at least 31 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 HCCPD is found may increase. This information is important because exposure to this substance may harm you and because these sites may be sources of exposure.

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

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

1.1 WHAT IS HCCPD?

HCCPD is a light, lemon-yellow liquid that has a sharp, musty odor. It easily turns from a liquid to a vapor when exposed to air. The vapor looks like a blue haze. This chemical is also called percyclopentadiene, hexachloropentadiene, and hex. Some of its former trade names, still listed in chemical reference documents, are C-56, Graphlox, and HRS 1655.

I. PUBLIC HEALTH STATEMENT

HCCPD is a manufactured chemical and does not occur naturally in the environment. It is made by adding chlorine to cyclopentadiene, or by removing chlorine from octachlorocyclopentane. HCCPD is used to make a group of related pesticides (aldrin, chlordane, dieldrin, endosulfan, endrin, heptachlor, isodrin, mirex, and pentac). Only two of these pesticides, endosulfan and pentac, are currently registered for use in the United States. Thus, your exposure to these compounds is expected to be limited. Endosulfan and pentac are the only two of these pesticides that you can buy in a store. HCCPD is also used to make flame retardants, resins that won't burn, shock-proof plastics, esters, ketones, fluorocarbons, and dyes.

Most of the HCCPD in the environment results from releases during its production and disposal. Releases can also occur as a result of the manufacture, use, and disposal of pesticides made from HCCPD. Most people can smell HCCPD in the air at 30 parts HCCPD per billion (ppb) parts of air. Most people can smell it in water when it is present at 1.4 ppb. The amount of HCCPD that you can taste in water has not been measured and the taste has not been described.

See Chapters 3,4, and 5 for more information on the properties and uses of HCCPD and its presence in the environment.

1.2 WHAT HAPPENS TO HCCPD WHEN IT ENTERS THE ENVIRONMENT?

HCCPD can be released to the air as a vapor during its production and use. However, it does not remain in the air very long since it is usually broken down to other substances by sunlight and by reaction with other chemicals in the air. Half of the HCCPD released to the air is removed in less than one day.

When HCCPD is mixed with water at room temperature, only 2.1 milligrams will dissolve in a liter of water (2 parts per million or 2 ppm). In a stream or small river, the HCCPD near the surface will evaporate to the air. Sunlight on the water will cause HCCPD to change quickly into other chemicals. About half of the HCCPD in the water will be changed to other chemicals by the light in only four minutes.

1. PUBLIC HEALTH STATEMENT

The HCCPD that gets into soil binds to decaying plant and animal matter. If the soil is sandy, the HCCPD can move through the soil and reach the water that is under the ground. When soil that contains HCCPD also contains solvents like gasoline, paint thinners, and acetone, these liquids will help carry the HCCPD through the soil to lakes, rivers, or wells. Bacteria can change HCCPD in the soil to other chemicals, but scientists do not know the nature of these compounds. About half of the HCCPD in the soil will be changed to other chemicals by bacteria in 1-2 weeks.

HCCPD has been known to build up in fish, but only in very small amounts. We do not know if HCCPD accumulates in plants, milk, or animals used for food.

See Chapter 5 for more information on how HCCPD behaves in the environment.

1.3 HOW MIGHT I BE EXPOSED TO HCCPD?

If you live near a hazardous waste site where HCCPD or HCCPD-derived pesticides were disposed, you might be exposed to HCCPD in the air. In one survey, levels ranging from 0.032 to 0.053 ppb were measured in air near a hazardous waste site. HCCPD has not been reported in outdoor air in city, suburban, and rural areas. In most areas, the concentration of HCCPD in the air should be low because this chemical is not widely used.

HCCPD is not commonly found in surface water. In one survey, it was found in less than 0.1% of 854 water samples from various sources. The median concentration of HCCPD was less than 10 ppb in water. HCCPD in not often found in drinking water, so exposure by this route is unlikely. However, it may be formed during chlorination of water containing humic acid.

HCCPD may be present in soils that have recently been treated with the pesticides, endosulfan or pentac, because it is sometimes found as an impurity in these pesticides. The soils near a landfill where these pesticides (including those no longer used, such as aldrin, chlordane, dieldrin, endrin, heptachlor, and isodrin) or waste HCCPD were disposed might also contain HCCPD, but, since it binds to organic matter in soils, it is less likely to be free to affect you.

1. PUBLIC HEALTH STATEMENT

It is highly unlikely that you will be exposed to HCCPD in the foods you eat, although you could be exposed to very small amounts if you catch and eat fish that lived in HCCPD-contaminated water.

The highest exposures to HCCPD are likely to occur in people who are involved in the production or use of HCCPD, who handle pesticides made from it, or who treat wastes that contain it. These people can be exposed by breathing air contaminated with HCCPD, or by skin and eye contact with the vapors or liquid.

Air concentrations ranging from 270 to 970 ppb were reported at a waste water treatment plant after large amounts of the compound were dumped into a city sewage system. Traces of HCCPD were present in waste water at another treatment plant near an industrial facility that used it as a reactant for making pesticides.

See Chapter 5 for more information on how you can be exposed to HCCPD.

1.4 HOW CAN HCCPD ENTER AND LEAVE MY BODY?

There is no information available to tell us what happens to HCCPD once it enters the human body. Based on studies in animals, if you are exposed to HCCPD through food or drinking water, most of the HCCPD you eat or drink will stay bound to the food or water and only a small amount will enter your bloodstream. Thereafter, most of the HCCPD (64-80%) will leave your body in your feces and the rest will leave in your urine.

Animal studies have shown that up to 95% of the HCCPD that is inhaled stays in your windpipe and lungs, and a small amount reaches your liver and kidneys. Inhaled HCCPD, therefore, causes more health effects in people and animals than HCCPD that is ingested (see Section 1.5).

1. PUBLIC HEALTH STATEMENT

If HCCPD touches your skin, it can enter your body. Based on studies in animals, when either pure HCCPD or a solution with 10% HCCPD in mineral oil comes in contact with your skin, a sore can form. The open sore will allow more HCCPD to enter your body.

Most of the HCCPD that enters your body is changed to other chemicals, but those chemicals have not been identified. A small amount of HCCPD remains unchanged. You can find more information on how HCCPD and its breakdown products enter and leave your body in Chapter 2.

1.5 HOW CAN HCCPD 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.

Information on the health effects of HCCPD on people is limited to one incident involving shortterm exposure to HCCPD vapors (0.04-19.2 ppm). Exposure occurred at a waste water treatment plant as a result of an industrial release of HCCPD into the sewage system. This incident showed that the breathing passageways (nose, throat, lungs) in people are very sensitive to HCCPD. You may get a sore throat or have shortness of breath and chest discomfort if you breathe HCCPD at high levels. Your eyes may burn and turn red, and your skin may be irritated. Some people get headaches when they breathe high levels of HCCPD.

1. PUBLIC HEALTH STATEMENT

Your kidneys and liver may show signs that you have been exposed to HCCPD. Some people who were exposed to HCCPD had increased amounts of protein in their urine and increased levels of other compounds in their blood. These are signs that kidney and liver effects may have occurred after exposure to HCCPD. Other people who were exposed did not show these effects.

Bleeding, swelling, and fluid buildup occurred in the lungs of rats, mice, guinea pigs, and rabbits that inhaled small amounts of HCCPD vapors for two weeks under controlled conditions. Severe breathing difficulty was seen in animals exposed to large amounts of HCCPD for a short period of time, and all the animals died during or soon after exposure. In rats, some cells of the lung, windpipe, and nose contained yellow-colored or clear granules after exposure to a very low level (0.01 ppm) of HCCPD in air for a long time. In monkeys, higher levels (0.2 ppm) caused similar changes in those cells.

When rats and rabbits swallowed HCCPD dissolved in corn oil or peanut oil, cells in the lungs, liver, kidney, brain, and heart were harmed and a sore formed in the stomach lining. When the doses were high (261-1,950 milligrams per kilogram of body weight [mg/kg]), most of the animals died after only one dose. There was damage to stomach lining and kidney cells in mice given a low concentration of HCCPD in corn oil by mouth 5 days a week for several months. Because these mice were also exposed to another chemical, hexachlorobutadiene, it is not clear if the cell damage in the kidneys was caused by HCCPD alone.

No information is available on whether HCCPD affects the reproductive organs of people.

No information is available on whether HCCPD causes cancer in people. The Department of Health and Human Services (DHHS) has determined that HCCPD does not cause cancer in rats and mice under the conditions of the study conducted by the National Toxicology Program. The International Agency for Research on Cancer (IARC) has not evaluated HCCPD as a possible cancer-causing chemical. The EPA has determined that HCCPD is not classifiable as to its ability to cause cancer in people.

See Chapter 2 for more information on how HCCPD can affect your health.

I. PUBLIC HEALTH STATEMENT

1.6 HOW CAN HCCPD AFFECT CHILDREN?

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

Children are unlikely to be exposed to HCCPD. There is no information on the effects of exposure to HCCPD in children or in adults who were exposed as children. We do not know whether HCCPD causes birth defects in humans. Studies in animals indicate that exposure to HCCPD does not cause problems during development. HCCPD did not cause birth defects or impair the ability of mice and rabbits to produce offspring. We do not know whether HCCPD can cross the placenta or accumulate in breast milk.

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

If your doctor finds that you have been exposed to significant amounts of HCCPD, he or she can advise you about the potential risk of exposure to the rest of your family. When necessary your doctor may need to ask your state public health department to investigate.

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

If you have been recently exposed to HCCPD, your blood and urine can be tested for its presence. Such tests are not routinely done in a doctor's office because special equipment is needed. Doctors often can collect blood or urine samples and send them to special laboratories to determine if you have been exposed to HCCPD; but these laboratories can't determine how much HCCPD you were exposed to, or whether your health will be affected. Exposure to HCCPD that occurred weeks or months before your test is not likely to be detected in either your blood or urine.

See Chapters 2 and 6 for more information on how HCCPD can be measured in exposed people.

1. PUBLIC HEALTH STATEMENT

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 HCCPD include the following:

To protect workers who may be exposed to HCCPD on the job, the Occupational Safety and Health Administration (OSHA) limits HCCPD exposure to 0.01 ppm in air for an 8-hour workday over a 40-hour workweek. The National Institute for Occupational Safety and Health (NIOSH) suggests the same limit for workplace air.

EPA has recommended guidelines on how much HCCPD can be present in drinking water. The maximum contaminant levels (MCL) and maximum concentration level goal (MCLG) for drinking water are 50 ppb. EPA recommends that exposures in children should not exceed 2 ppm in water

for l0-day periods or no more than 0.7 ppb for up to 7 years. If adults are exposed for more than 7 years, the EPA recommends that exposure levels should not exceed 50 ppb.

HCCPD has been named a hazardous substance by EPA. If quantities equal to or greater than one pound are released to the environment, the National Response Center for the federal government must be told immediately. HCCPD has not been identified as a carcinogen.

See Chapter 7 for more information on state or federal government regulations and guidelines for HCCPD.

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-888-42-ATSDR (l-888-422-8737)
Fax: (404) 639-63 14 or 6324

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

* To order toxicological profiles, contact
National Technical Information Service
5285 Port Royal Road
Springfield, VA 22 16 1
Phone: (800) 553-6847 or (703) 605-6000

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 of the toxicology of HCCPD. 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.

Estimates of exposure levels posing minimal risk to humans (Minimal Risk Levels or MRLs) have been made for HCCPD. 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 199Oe), 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.

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.

2. HEALTH EFFECTS

2.2.1 Inhalation Exposure

2.2.1.1 Death

No studies were located regarding lethality in humans after inhalation exposure to HCCPD.

Short-term inhalation of HCCPD at concentrations that ranged from 0.3 to 66 ppm was lethal to rats, mice, guinea pigs, and rabbits (Rand et al. 1982a; Treon et al. 1955). Duration of exposure and compound concentration affected lethality. With a 15minute exposure to 11.6 ppm HCCPD, 3 of 4 rats, 4 of 5 mice, 2 guinea pigs, and 1 of 3 rabbits survived, but with a 3-hour exposure to 10.0 ppm, all animals died. Males appeared to be more susceptible to HCCPD than females. The LC_{50} (lethal concentration, 50% kill) for male rats exposed to HCCPD for 4 hours was 1.6 ppm, while that for females was 3.5 ppm (Rand et al. 1982a).

Exposures lasting from 30 minutes to 4 hours at concentrations of 17.9-66 ppm were uniformly lethal to rats, mice, guinea pigs, and rabbits (Treon et al. 1955). The number of animals exposed was small (2-5), and a broad range of durations and doses was used. The small group size and variability in individual animal susceptibility must be considered when interpreting the data. With 15minute exposures to a concentration of 18 ppm, 4 rats, 3 of 5 mice, 2 guinea pigs, and none of 3 rabbits survived, but at a concentration of 17.4 ppm for the same period of time, 2 of 3 rats, none of 4 mice, neither of 2 guinea pigs, and 1 of 3 rabbits survived. With 2-week exposures to 0.5 ppm HCCPD, all male rats but only 2 of 10 female rats died (Rand et al. 1982a). When exposures were reduced to 5 days, 3 of 5 males and no females died.

In a 13-week study, all mice exposed to 2 ppm HCCPD for 5 days a week, 6 hours a day died during the first week, while rats exposed to the same concentration survived for up to 3 weeks (NTP 1994). Only 1 of 20 rats survived a 4-week exposure to 1 ppm, while 2 of 20 mice survived up to 5 weeks. Even with the 1 ppm exposure, most animals died during the first or second week. A lower concentration of 0.4 ppm caused the death of 5 of 10 male mice and 2 of 10 female mice during the first and second weeks of exposure. At the lowest concentration tested (0.04 ppm), 2 of 10 male mice and 1 of 10 female mice died. There were no deaths among rats exposed to concentrations of 0.04-0.4 ppm.

2. HEALTH EFFECTS

With an intermediate-duration exposure (6 weeks, 5 days a week, 7 hours a day) to 0.3 ppm, all of 4 rats, all of 5 mice, and 4 of 6 rabbits died, while 2 guinea pigs survived (Treon et al. 1955). The exact time of death for individual animals was not specified. Following 30 weeks of exposure (5 days a week, 7 hours a day) to 0.13 ppm HCCPD, 4 of 5 mice died, but all of 4 rats, 2 guinea pigs, and 3 rabbits survived.

Of the species evaluated, guinea pigs appeared to be the most resistant to compound toxicity, especially during intermediate-duration exposures. When the fatalities were plotted by concentration and duration of exposure for each species, it was possible to draw a single straight line to separate the conditions that were uniformly lethal from those that were not lethal for rats, mice, and rabbits (Treon et al. 1955). Thus, rats, mice, and rabbits exhibited a linear dose/duration response to the toxic and fatal effects of HCCPD. With guinea pigs there were two lines that separated the lethal from the nonlethal conditions. The line for durations of 4 hours or more and concentrations of 3 ppm or less had a lower slope than that for durations of 4 hours or less and concentrations of 3 ppm or more. The authors interpreted this to mean that the guinea pigs adapted to the low level, longer-term exposures to HCCPD. In general, mice appear to be more susceptible to HCCPD toxicity than rats (NTP 1994; Treon et al. 1955).

Survival of male and female rats and male mice chronically exposed to 0.01-0.2 ppm HCCPD was similar to that for controls. Survival was diminished in female mice exposed to 0.2 ppm, but not at lower concentrations (NTP 1994). Ovarian inflammation resulting from infection appeared to be the cause of premature deaths in females. The authors suggest that this may be due to an adverse effect of HCCPD on immune function.

The HCCPD available commercially has a minimum purity of 97%. The purity of the material used by Treon et al. (1955) was 89.5%; thus, it is possible that impurities contributed to the toxicity of HCCPD in this study, especially at the high-exposure concentrations. Impurity concentrations in one 97.4% pure sample of HCCPD included 0.15% tetrachloroethylene, 0.5 1% hexachloro- 1,3-butadiene, 1.73% octachlorocyclopentene, and 0.48% hexachloro-3-cyclopentene-l-one (Abdo et al, 1984). A 98% pure sample contained 0.4% hexachlorobutadiene and 1.5% hexachloro-3-cyclopentene-l-one (NTP 1994). Other impurities that have been reported in HCCPD include hexachlorobenzene, PCBs, and mirex (EPA 1991a; HSDB 1998; WHO 1991). For one report (Treon et al. 1955), all exposure concentrations were adjusted to reflect exposure to HCCPD rather than to the mixture. The purity of the material used by Rand

et al. (1982a) was 97.7% and that used by NTP (1994) was 98% pure; the exposure concentrations were not adjusted to account for compound purity.

LC_{50} values and all reliable LOAEL values for lethality in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2-l. These values indicate that HCCPD is highly toxic to animals when exposures occur through inhalation of vapors.

2.2.1.2 Systemic Effects

No studies were located regarding musculoskeletal, endocrine, or body weight effects in humans after inhalation exposure to HCCPD. Data are available pertaining to respiratory, cardiovascular, gastrointestinal, hematological, hepatic, renal, dermal, or ocular effects. Data are available for all systems in animal studies. The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 2- 1 and plotted in Figure 2- 1.

Respiratory Effects. The available data on respiratory effects of HCCPD in humans are limited to reports of waste water treatment plant workers and clean-up crew members exposed to HCCPD after an industrial release of this material into the sewage system (Kominsky et al. 1980; Morse et al. 1979).

One report of this incident focused on the employees at the waste water treatment plant who were exposed for a period of 3-15 days (Morse et al. 1979). Accidental discharge of HCCPD into a municipal sewer line at a treatment plant exposed sewage workers (125 males, 68 females; average age of 35 years). Seventyfive percent of the workers noticed unusual odors for up to 4 weeks, but particularly during the last 3 days prior to plant closing. An odiferous substance coated bar screens and grit collectors in the primary treatment area. Airborne concentrations were unknown at time of exposure, but 4 days after the plant closed, concentrations ranged from 0.27 to 0.97 ppm in screen and grit chambers. Although large amounts of contamination were found in waste water, exact amounts of contamination were not specified.

The other report considered the adverse health effects reported by the clean-up crew workers who were exposed during the 2-month clean-up period as well as by the waste water treatment workers (154 males, 23 females) (Kominsky et al. 1980). Sewage system contamination of HCCPD dispersed in fuel oil and mixed with sewage created a sticky conglomerate requiring close worker contact with contaminated sewage

Table 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
ACUTE EXPOSURE							
Death							
1	Rat (Sprague-Dawley)	1-2 wk 5 d/wk 6 hr/d				0.5 M (3/5 deaths for 1 wk, 10/10 deaths for 2 wk exposure) 0.5 F (2/10 deaths for 2 wk exposure)	Rand et al. 1982a
2	Rat (Sprague-Dawley)	4 hr				1.6 M (LC50) 3.5 F (LC50)	Rand et al. 1982a
3	Rat	2.5-3.6 hr				2.8 (2/4 animals died)	Treon et al. 1955
4	Rat	5 d 7 hr/d				0.9 (4/4 animals died)	Treon et al. 1955
5	Rat	0.25 hr				11.6 (1/4 animals died)	Treon et al. 1955
6	Mouse	5 d 7 hr/d				0.9 (4/5 animals died)	Treon et al. 1955
7	Mouse	0.25 hr				11.6 (1/5 animals died)	Treon et al. 1955
8	Mouse	2.5-3.6 hr				1.25 (1/5 animals died)	Treon et al. 1955
9	Rabbit	0.25 hr				11.6 (2/3 animals died)	Treon et al. 1955
10	Rabbit	2.5-3.6 hr				1.25 (2/3 rabbits died)	Treon et al. 1955

Table 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
11	Rabbit	5 wk 5 d/wk 7 hr/d					0.3	(4/6 rabbits died)	Treon et al. 1955
12	Gn pig	2.5-3.6 hr					6.4	(1/2 animals died)	Treon et al. 1955
13	Gn pig	5 d 7 hr/d					1.4	(1/2 animals died)	Treon et al. 1955
	Systemic								
14	Rat (Sprague-Dawley)	1-2 wk 5 d/wk 6 hr/d	Resp	0.11	0.5	(lung weight increased 13-14%; bronchial and olfactory epithelial changes)			Rand et al. 1982a
			Cardio	0.5					
			Hemato	0.11	0.5	(WBC reduced; red blood cell, packed cell volume, and hemoglobin increased)			
			Hepatic	0.5					
			Renal	0.5					
			Bd Wt	0.11 M 0.5 F	0.5 M	(~10% reduced body weight)			

Table 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL			Reference
					Less serious (ppm)	Serious (ppm)		
15	Rat	2.5-3.6 hr	Resp			1.25	(hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio			1.25	(diffuse degeneration of the heart)	
			Hepatic			1.25	(diffuse degeneration of the liver)	
			Renal			1.25	(diffuse degeneration of the kidney)	
			Endocr			1.25	(diffuse degeneration of the adrenals)	
16	Rat	0.25 hr	Resp			11.6	(hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio			11.6	(diffuse degeneration of the heart)	
			Hepatic			11.6	(diffuse degeneration of the liver)	
			Renal			11.6	(diffuse degeneration of the kidneys)	
			Endocr			11.6	(diffuse degeneration of the adrenals)	
17	Rat	4 hr	Resp			65.9	(respiratory distress, hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio			65.9	(diffuse degeneration of the heart)	
			Hepatic			65.9	(diffuse degeneration of the liver)	
			Renal			65.9	(diffuse degeneration of the kidneys)	
			Endocr			65.9	(diffuse degeneration of the adrenals)	

Table 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)		Reference
18	Rat	5 d 7 hr/d	Resp			0.3	(increased respiration; hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio			0.3	(diffuse degeneration of the heart)	
			Hepatic			0.3	(diffuse degeneration of the liver)	
			Renal			0.3	(diffuse degeneration of the kidneys)	
			Endocr			0.3	(diffuse degeneration of the adrenal glands)	
19	Mouse	0.25 hr	Resp			11.6	(hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio			11.6	(diffuse degeneration of the heart)	
			Hepatic			11.6	(diffuse degeneration of the liver)	
			Renal			11.6	(diffuse degeneration of the kidney)	
			Endocr			11.6	(diffuse degeneration of the adrenals)	
20	Rabbit	2.5-3.6 hr	Resp			1.25	(hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio			1.25	(diffuse degeneration of the heart)	
			Hepatic			1.25	(diffuse degeneration of the liver)	
			Renal			1.25	(diffuse degeneration of the kidneys)	
			Endocr			1.25	(diffuse degeneration of the adrenals)	

Table 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)		Reference
21	Rabbit	0.25 hr	Resp			11.6	(hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio			11.6	(diffuse degeneration of the heart)	
			Hepatic			11.6	(diffuse degeneration of the liver)	
			Renal			11.6	(diffuse degeneration of the kidneys)	
			Endocr			11.6	(diffuse degeneration of the adrenals)	
22	Rabbit	7 hr	Resp			1.3	(hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio			1.3	(diffuse degeneration of the heart)	
			Hepatic			1.3	(diffuse degeneration of the liver)	
			Renal			1.3	(diffuse degeneration of the kidneys)	
			Endocr			1.3	(diffuse degeneration of the adrenals)	
23	Gn pig	2.5-3.6 hr	Resp			1.25	(hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio			1.25	(diffuse degeneration of the heart)	
			Hepatic			1.25	(diffuse degeneration of the kidney)	
			Renal			1.25	(diffuse degeneration of the kidneys)	
			Endocr			1.25	(diffuse degeneration of the adrenal glands)	

Table 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)		Reference
24	Gn pig	0.25 hr	Resp			11.6	(hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio			11.6	(diffuse degeneration of the heart)	
			Hepatic			11.6	(diffuse degeneration of the liver)	
			Renal			11.6	(diffuse degeneration of the kidneys)	
			Endocr			11.6	(diffuse degeneration of the adrenals)	
25	Gn pig	4 hr	Resp			65.9	(hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio			65.9	(diffuse degeneration of the heart)	
			Hepatic			65.9	(diffuse degeneration of the liver)	
			Renal			65.9	(diffuse degeneration of the kidneys)	
			Endocr			65.9	(diffuse degeneration of the adrenals)	
Neurological								
26	Rat	1-2 wk 5 d/wk 6 hr/d		0.5				Rand et al. 1982a
27	Rat	0.25 hr				11.6	(diffuse degeneration of the brain)	Treon et al. 1955
28	Mouse	7 hr				1.3	(diffuse degeneration of the brain)	Treon et al. 1955

Table 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)		Reference
29	Mouse	5 d 7 hr/d				0.3	(diffuse degeneration of the brain)	Treon et al. 1955
30	Mouse	0.25 hr				11.6	(diffuse degeneration of the brain)	Treon et al. 1955
31	Rabbit	0.25 hr				11.6	(diffuse degeneration of the brain)	Treon et al. 1955
32	Gn pig	0.25 hr				11.6	(diffuse degeneration of the brain)	Treon et al. 1955
INTERMEDIATE EXPOSURE								
Death								
33	Rat (Fischer- 344)	2-4 wk 5 d/wk 6 hr/d				1	(10/10 males and 10/10 females died)	NTP 1994
34	Rat	4 wk 5 d/wk 7 hr/d				0.3	(4/4 animals died)	Treon et al. 1955
35	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d				0.04	(20% [2/10] mortality in males, 10% [1/10] mortality in females)	NTP 1994
36	Mouse	30 wk 5 d/wk 7 hr/d				0.13	(4/5 died)	Treon et al. 1955

Table 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
37	Gn pig	4 wk 5 d/wk 7 hr/d					0.3	(5/5 animals died)	Treon et al. 1955
	Systemic								
38	Human	10 wk	Resp	7.1			19.2	(mucous membrane irritation, sinus congestion, dyspnea, chest discomfort in 1 individual)	Kominsky et al. 1980
			Gastro	7.1	19.2	(nausea in 1 individual)			
			Hemato	19.2					
			Hepatic			(elevated values for 4 liver enzymes in some workers)			
			Dermal		0.04	(skin irritation in 4 individuals)			
			Ocular		0.04	(eye irritation in 4 individuals)			
39	Monkey	13 wk 5 d/wk 6 hr/d	Resp	0.2					Rand et al. 1982a
			Cardio	0.2					
			Gastro	0.2					
			Hemato	0.2					
			Hepatic	0.2					
			Renal	0.2					
			Bd Wt	0.2					
40	Monkey	14 wk 5 d/wk 6 hr/d	Resp	0.2					Rand et al. 1982b

Table 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Less serious	LOAEL Serious (ppm)	Reference
41	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d	Hemato	0.04	0.4	(increased mean and packred cell volume; and red blood cell increased hemoglobin; decreased reticulocytes)		NTP 1994
			Hepatic	0.04	2	(increased aspartate aminotransferase)		
			Renal	0.04	0.4	(decreased urinary creatinine and volume)		
42	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d	Resp	0.15	0.4	(inflammation and necrosis of the bronchi and bronchioles; increased lung weight in males)		NTP 1994
			Cardio	2				
			Gastro	2				
			Hemato	0.15	0.4	(increased hemoglobin and hematocrit)		
			Musc/skel	2				
			Hepatic	2				
			Renal	2				
			Endocr	2		(absence of effects on adrenal, thyroid parathyroid, and pituitary glands)		
			Bd Wt		0.04	(decreased weight gain - 11%)		

Table 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
43	Rat (Sprague-Dawley)	13 wk 5 d/wk 6 hr/d	Resp	0.2					Rand et al. 1982a
			Cardio	0.2					
			Gastro	0.2					
			Hemato		0.01	(increased hemoglobin, red blood cell count, mean corpuscular hemoglobin concentration in males)			
			Hepatic	0.2					
			Renal	0.2					
44	Rat (Sprague-Dawley)	14 wk 5 d/wk 6 hr/d	Resp	0.2[b]					Rand et al. 1982b
45	Rat	30 wk 5 d/wk 7 hr/d	Resp				0.13	(pneumonia)	Treon et al. 1955
			Cardio	0.13					
			Hepatic		0.13	(slight degenerative changes)			
			Renal			(slight degenerative changes)			
			Bd Wt	0.13					

Table 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)		Reference
46	Rat	6 wk 5 d/wk 7 hr/d	Resp			0.3	(pulmonary edema and hyperemia)	Treon et al. 1955
			Cardio			0.3	(degenerative changes in the heart)	
			Hepatic			0.3	(degenerative changes in the liver)	
			Renal			0.3	(degenerative changes in the kidneys)	
			Endocr			0.3	(degenerative changes in the adrenal gland)	
47	Mouse (B6C3F1)	33 wk 5 d/wk 6 hr/d	Resp		0.2 M		(pigmentation of the nose, trachea, and lungs)	NTP 1994
			Bd Wt	0.2 M				
48	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d	Resp	0.15	0.4		(metaplasia of larynx or trachea; focal supprative inflammation of the nose)	NTP 1994
			Cardio	0.4				
			Gastro	0.4				
			Hemato	0.4				
			Musc/skel	0.4				
			Hepatic	0.4				
			Renal	0.4				
			Bd Wt	0.04	0.15		(decreased mean final body weight gain in males - 16%)	
49	Mouse (B6C3F1)	26 wk 5 d/wk 6 hr/d	Resp		0.5 M		(pigmentation of the epithelium of the nose, trachea, and lung)	NTP 1994
			Bd Wt	0.5 M				

Table 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
50	Mouse (B6C3F1)	42 wk 5 d/wk 6 hr/d	Resp		0.5 M	(pigmentation of the epithelium of the nose, trachea, and lungs)			NTP 1994
			Bd Wt		0.5 M	(decreased body weight gain during exposure when compared to controls; recovery during the post- exposure period)			
51	Mouse	30 wk 5 d/wk 7 hr/d	Resp				0.13	(pulmonary edema and bronchitis)	Treon et al. 1955
			Hepatic		0.13	(slight degenerative changes)			
			Renal		0.13	(slight degenerative changes)			
			Bd Wt	0.13					
52	Rabbit	6 wk 5 d/wk 7 hr/d	Resp				0.3	(hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio				0.3	(diffuse degeneration of the heart)	
			Hepatic				0.3	(diffuse degeneration of the liver)	
			Renal				0.3	(diffuse degeneration of the kidneys)	
			Endocr				0.3	(diffuse degeneration of the adrenals)	

Table 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
53	Rabbit	30 wk 5 d/wk 7 hr/d	Resp	0.13					Treon et al. 1955
			Cardio	0.13					
			Hepatic		0.13	(slight degenerative changes)			
			Renal		0.13	(slight degenerative changes)			
			Bd Wt	0.13					
54	Gn pig	6 wk 5 d/wk 7 hr/d	Resp				0.3	(hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio				0.3	(degenerative changes in the heart)	
			Hepatic				0.3	(degenerative changes in the liver)	
			Renal				0.3	(degenerative changes in the kidneys)	
			Endocr				0.3	(degenerative changes in the adrenals)	
55	Gn pig	30 wk 5 d/wk 7 hr/d	Resp				0.13	(pneumonia)	Treon et al. 1955
			Cardio	0.13					
			Hepatic		0.13	(slight degenerative change)			
			Renal		0.13	(slight degenerative change)			
			Bd Wt	0.13					

Table 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
56	Gn pig	6 wk 5 d/wk 7 hr/d	Resp				0.3	(pulmonary edema and hyperemia)	Treon et al. 1955
			Cardio				0.3	(diffuse degeneration of the heart)	
			Hepatic				0.3	(diffuse degeneration of the liver)	
			Renal				0.3	(diffuse degeneration of the kidneys)	
			Endocr				0.3	(diffuse degeneration of the adrenals)	
	Neurological								
57	Human	10 wk		7.1	19.2	(fatigue in one individual)			Kominsky et al. 1980
58	Monkey	13 wk 5 d/wk 6 hr/d		0.2					Rand et al. 1982a
59	Rat (Fischer- 344)	13 wk 5 d/wk 6 hr/d		0.15	0.4	(listless)			NTP 1994
60	Rat (Sprague-Dawley)	13 wk 5 d/wk 6 hr/d		0.2					Rand et al. 1982a
61	Rat	30 wk 5 d/wk 7 hr/d		0.13					Treon et al. 1955

Table 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)		LOAEL Serious (ppm)		Reference
62	Rat	6 wk 5 d/wk 7 hr/d					0.3	(degenerative changes in the brain)	Treon et al. 1955
63	Mouse (B6C3F1)	13 wk 5 d/wk 6 hr/d		0.15	0.4	(listless)			NTP 1994
64	Mouse	30 wk 5 d/wk 7 hr/d					0.13	(degenerative changes in the brain)	Treon et al. 1955
65	Rabbit	30 wk 5 d/wk 7 hr/d		0.13					Treon et al. 1955
66	Rabbit	6 wk 5 d/wk 7 hr/d					0.3	(diffuse degenerative changes in the brain)	Treon et al. 1955
67	Gn pig	6 wk 5 d/wk 7 hr/d					0.3	(diffuse degeneration of the brain)	Treon et al. 1955
68	Gn pig	6 wk 5 d/wk 7 hr/d					0.3	(degenerative changes in the brain)	Treon et al. 1955
69	Gn pig	30 wk 5 d/wk 7 hr/d		0.13					Treon et al. 1955

Table 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
CHRONIC EXPOSURE							
Death							
70	Mouse (B6C3F1)	103-104 wk 5 d/wk 6 hr/d				0.2 (death in 57% of females)	NTP 1994
Systemic							
71	Rat (Fischer- 344)	103-104 wk 5 d/wk 6 hr/d	Resp		0.01[c] (pigmentation of mucosa of the nose and lung)		NTP 1994
			Cardio	0.2			
			Gastro	0.2			
			Musc/skel	0.2			
			Hepatic	0.2			
			Renal	0.2			
			Endocr	0.2			
			Bd Wt	0.2			
72	Mouse (B6C3F1)	66 wk 5 d/wk 6 hr/d	Resp		0.2 M (pigmentation of the epithelium of the nose, trachea, and lung)		NTP 1994
			Bd Wt	0.2 M			
73	Mouse (B6C3F1)	103-104 wk 5 d/wk 6 hr/d	Resp		0.01 (pigmentation of mucosa of nose and trachea)		NTP 1994
			Cardio	0.2			
			Gastro	0.2			
			Musc/skel	0.2			
			Hepatic	0.2			
			Renal	0.2			
			Endocr	0.2			
			Bd Wt	0.2			

Table 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (continued)

Key to figure[a]	Species/ (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL Less serious (ppm)	LOAEL Serious (ppm)	Reference
	Neurological						
74	Mouse (B6C3F1)	103-104 wk 5 d/wk 6 hr/d		0.2			NTP 1994
	Reproductive						
75	Mouse (B6C3F1)	103-104 wk 5 d/wk 6 hr/d		0.01	0.05	(supprative inflammation of the ovaries)	NTP 1994

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

[b]Used to derive an intermediate-duration inhalation minimal risk level (MRL) of 0.01 ppm based on a $NOAEL_{HEC}$ of 0.39 ppm; concentration divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration inhalation MRL of 0.02 ppb (0.0002 ppm) based on a $LOAEL_{HEC}$ of 0.02 ppm; concentration divided by an uncertainty factor of 90 (3 for a minimally adverse LOAEL, 3 for extrapolation from animals to humans, and 10 for human variability).

Cardio = cardiovascular; d = day(s); F = female; Gastro = gastrointestinal; Gn Pig = guinea pig; HEC = human equivalency concentration; Hemato = hematological; hr = hour(s); LC_{50} = lethal concentration, 50% kill; LOAEL = lowest-observable-adverse-effect level; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observable-adverse-effect level; NS = not specified; Resp = respiratory; WBC = white blood cells; wk = week(s)

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

Acute (≤14 days)

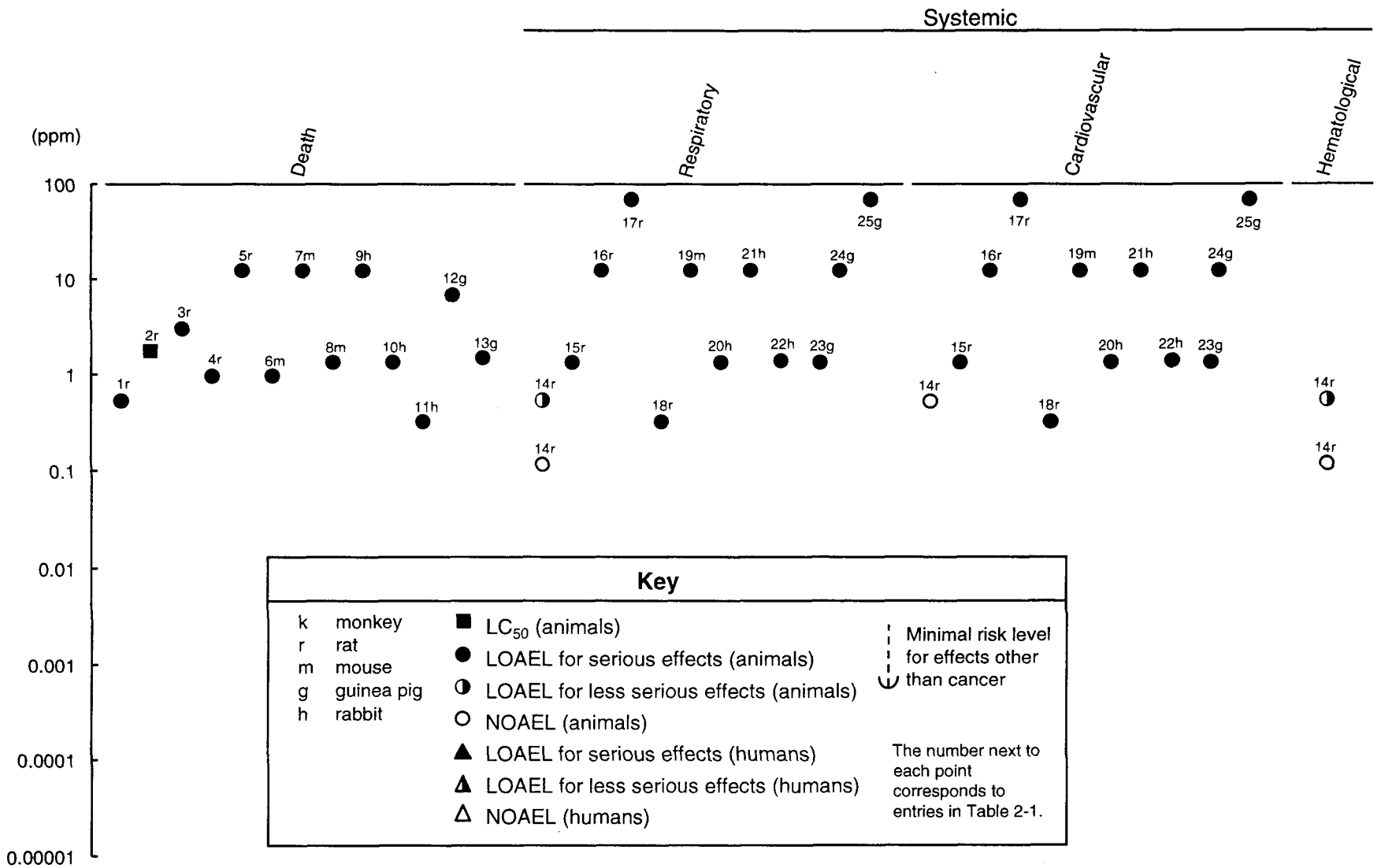


Figure 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (cont.)

Acute (≤14 days)

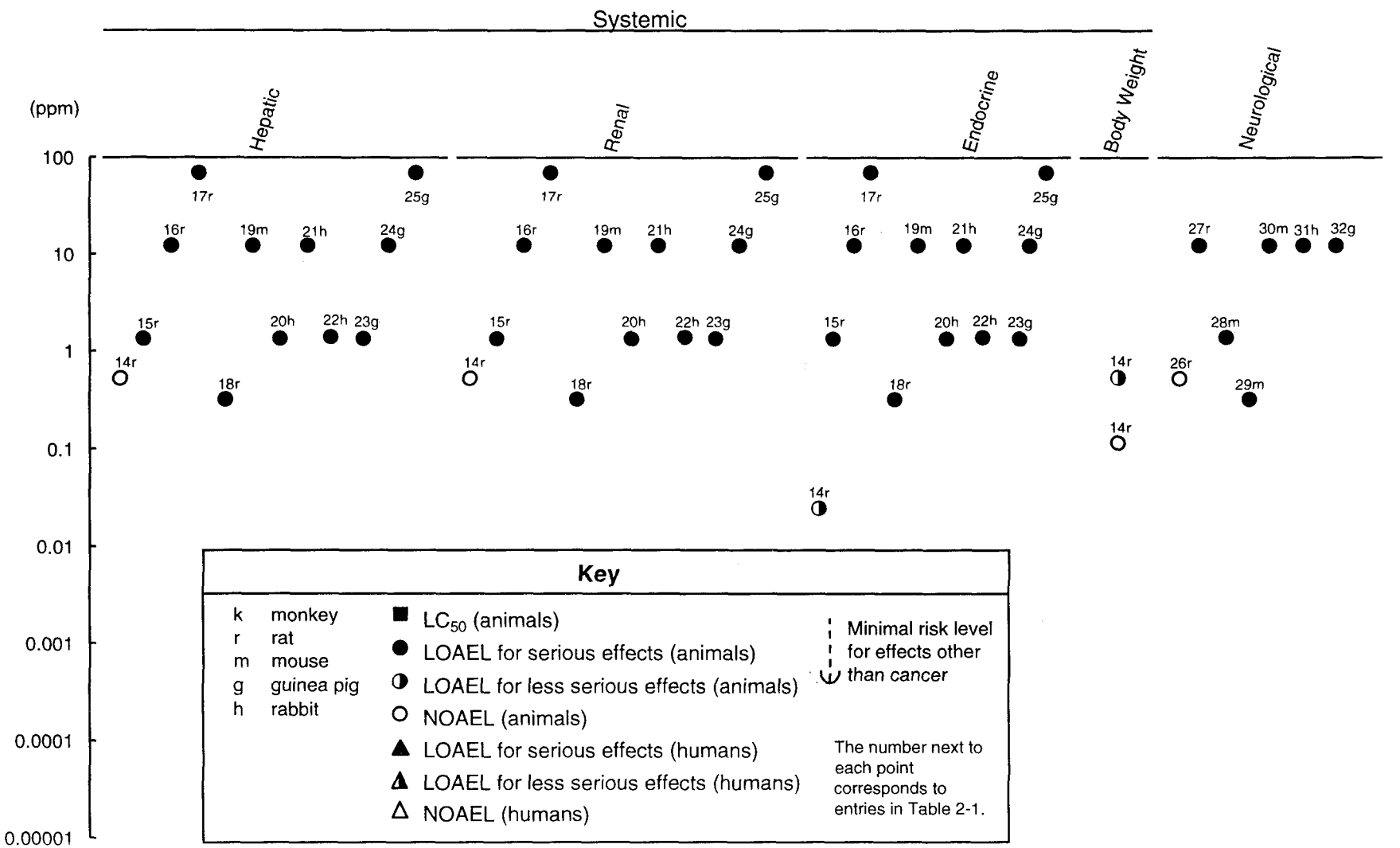


Figure 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (cont.)

Intermediate (15-364 days)

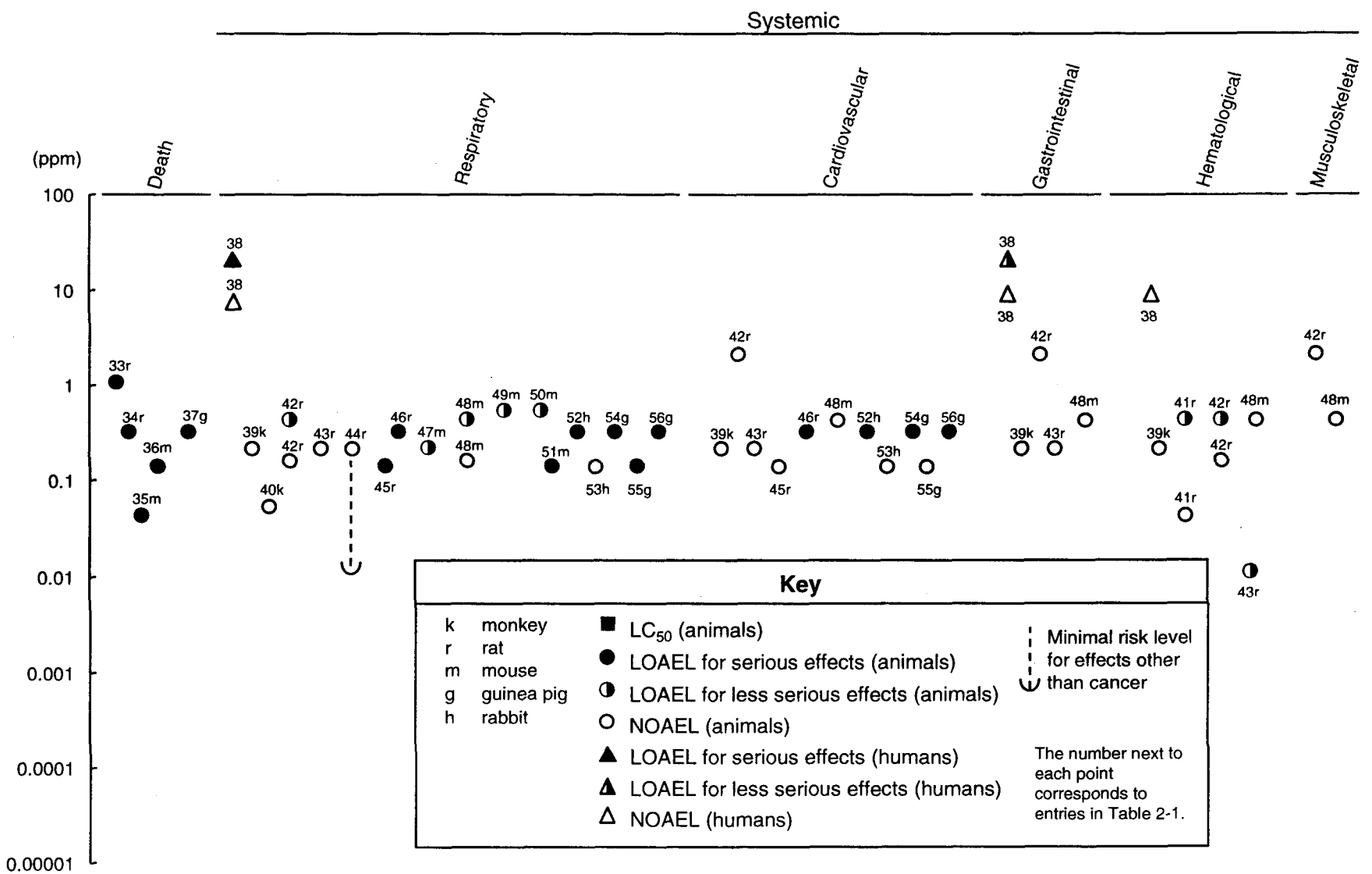


Figure 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (cont.)

Intermediate (15-364 days)

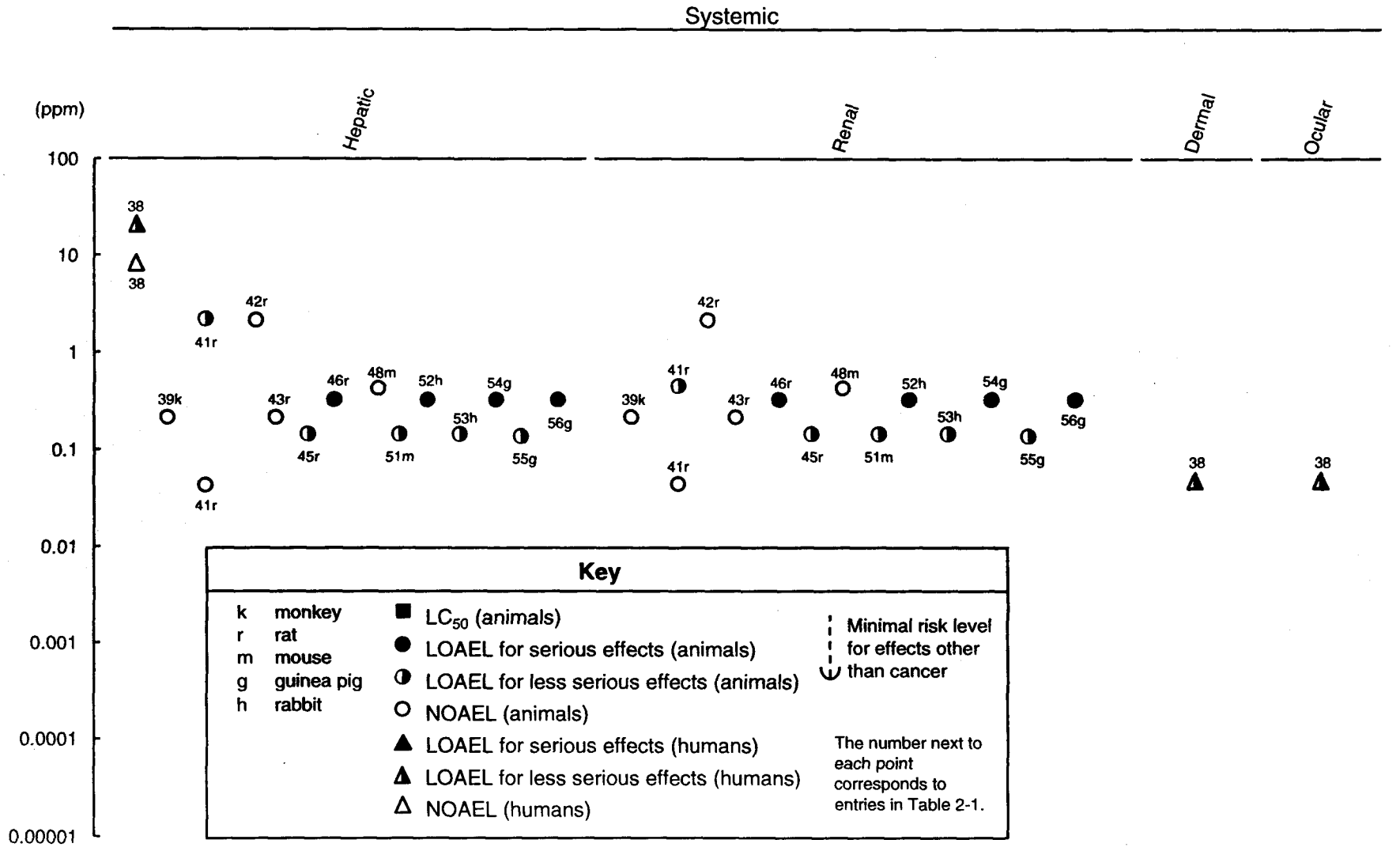


Figure 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (cont.)

Intermediate (15-364 days)

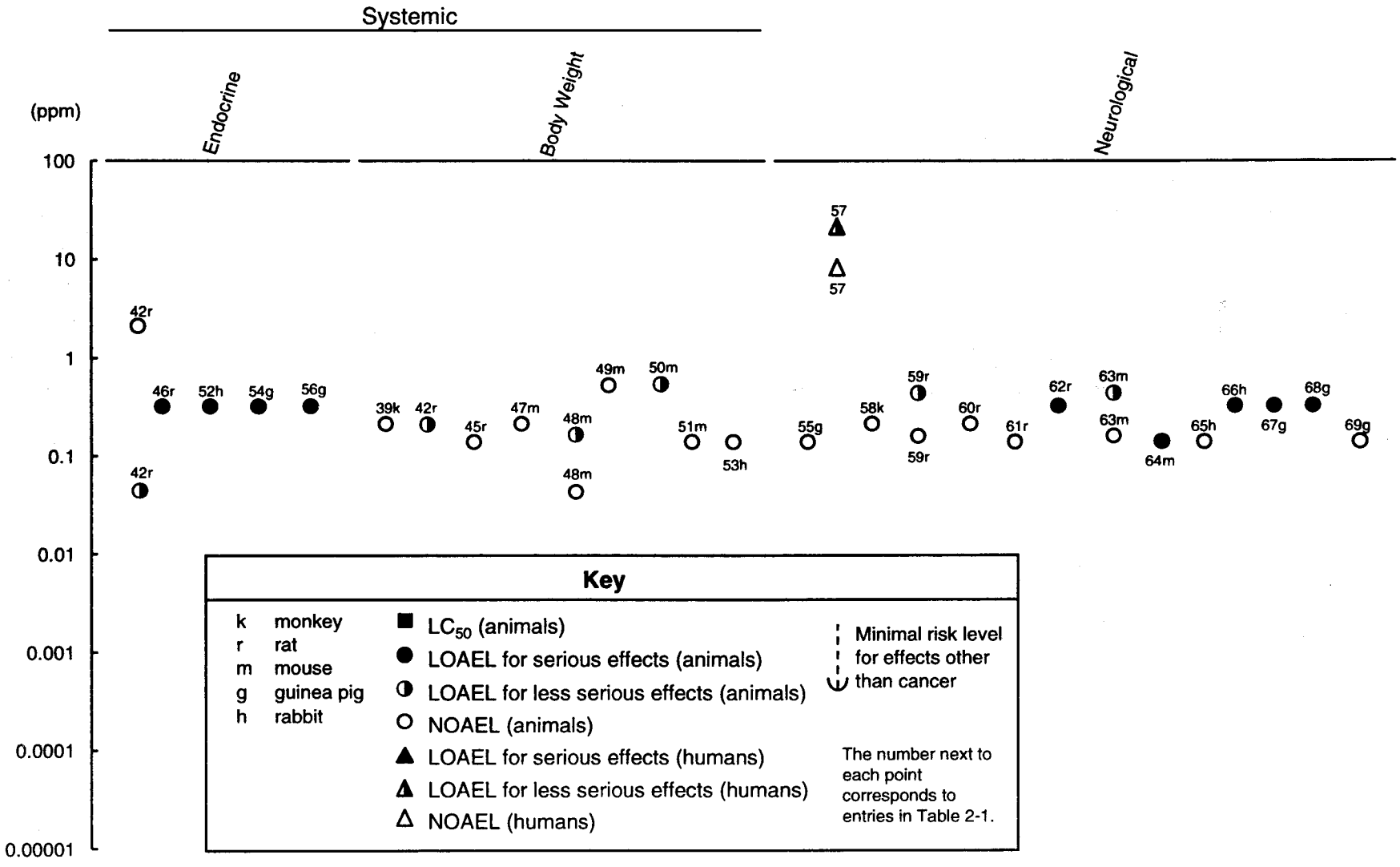
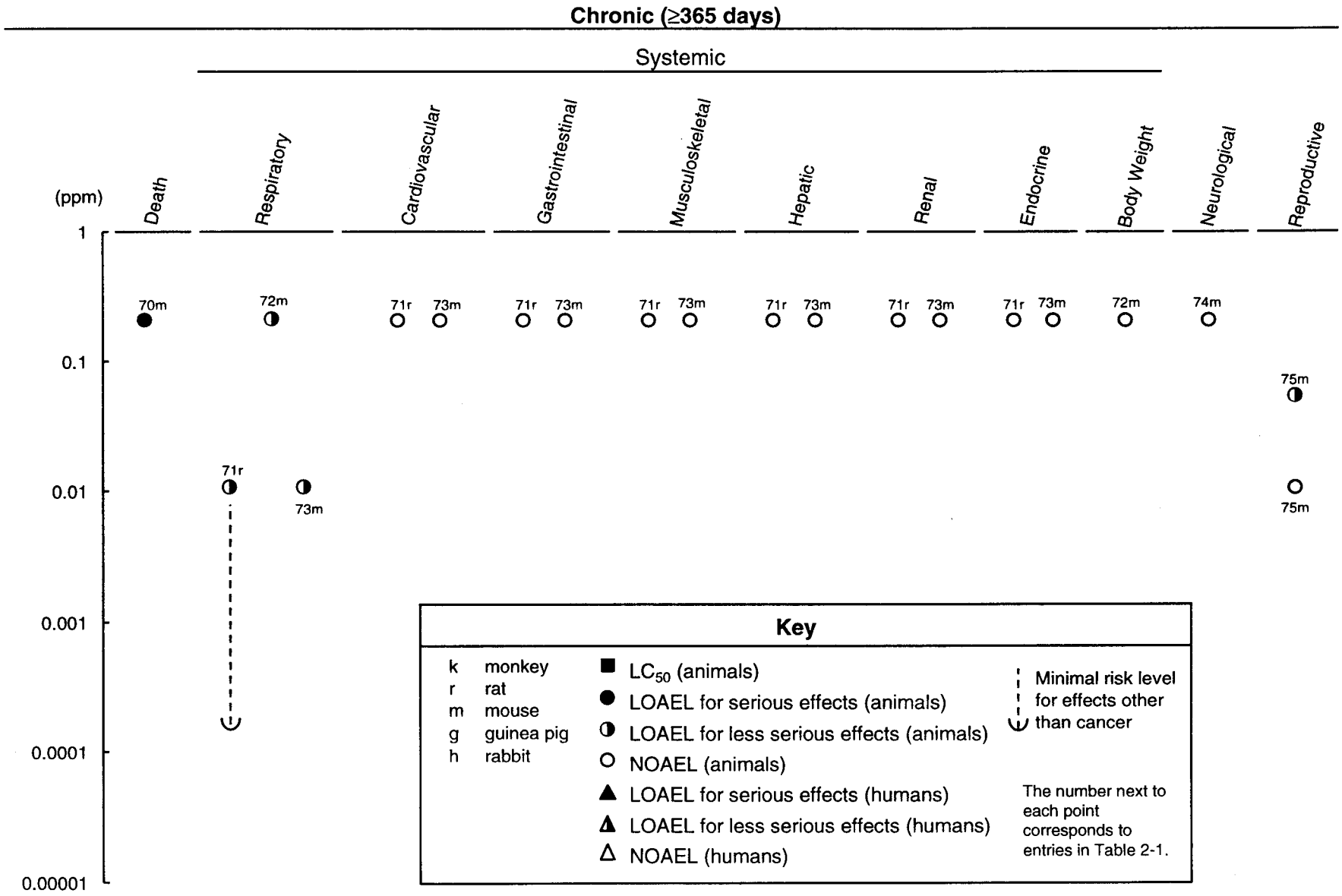


Figure 2-1. Levels of Significant Exposure to Hexachlorocyclopentadiene - Inhalation (cont.)



during scraping, shoveling, and high pressure water cleaning operations in Louisville, Kentucky (Kominsky et al. 1980). Epidemiological evidence suggests that material entered as early as March 14, 1977, when there were concurrent above-background level increases in detection of an objectionable odor and in symptoms. On March 26, 1977, four employees used steam to attempt to remove an odiferous, highly viscous and sticky substance from the bar screens and gut collection systems. Although airborne concentration at the time of exposure was unknown, HCCPD concentrations in screen and grid chambers ranged from 0.270 to 0.97 ppm on April 2, 1977 (4 days after plant closing). This initial attempt at removal produced a blue haze, which permeated the primary treatment area and caused about 20 workers to seek medical attention. On the next day, following a heavy rain, operating personnel observed a blue haze hovering over grit collection channels and noted an objectionable odor throughout the primary treatment area. The plant was closed on March 29, 1977 (15 days after an odor had been first noticed), when analysis showed waste water to be contaminated with HCCPD at an unspecified level. Workers' symptoms were determined by physical examination, blood and urine analyses, and by a review of medical records for employees seen by the plant physician from about April 15 to May 15, 1977; one questionnaire was administered to 145 employees on April 1-2, 1977, by the Center for Disease Control (CDC), and a second questionnaire was administered to 177 employees by the National Institute for Occupational Safety and Health (NIOSH).

Maximum atmospheric concentrations for the treatment plant workers were unknown, but were most likely greater than 0.97 ppm. This was the maximum concentration measured 4 days after compound identification (Morse et al. 1979). Small amounts of octachlorocyclopentene and other chlorinated cyclohydrocarbons were also contaminants of the waste water. Cleanup crew members were equipped with personal protective equipment and had minimum or no direct exposure to HCCPD. The maximum concentration recorded during cleanup was 19.2 ppm. Two cleanup crew members were exposed to the HCCPD for at least one brief period without protective gear. Seven other workers were exposed for brief periods with half-face respirators (Kominsky et al. 1980).

Symptoms of tracheobronchial irritation were reported by the treatment plant workers early in the exposure paradigm. These symptoms were recounted by 39 of 145 employees who responded to a questionnaire shortly after the exposure incident and in 16 or 177 employees who responded to a follow-up questionnaire 6 weeks later. Chest X-rays of 28 exposed workers were normal. Tests of pulmonary function were normal in a subset of 22 workers from this group (Kominsky et al. 1980). The date of testing was not specified. Minor respiratory complaints included sore throats, coughs, chest discomfort, and difficulty in

breathing. Because all the workers knew that exposure to a noxious substance had occurred, it is possible that some symptoms were psychosomatic. One cleanup crew worker also reported respiratory difficulty when exposed for a few seconds to 19.2 ppm HCCPD without protective equipment (Kominsky et al. 1980). Chest discomfort persisted for several days in this individual.

Headaches were reported by 45% of 145 individuals after exposure to HCCPD at a waste water treatment plant for 3-15 days. Six weeks later, 18% of 177 questionnaire respondents were still experiencing headaches (Morse et al. 1979). These headaches may have been secondary to sinus irritation and congestion.

Animals exposed to HCCPD vapors exhibited labored breathing and gasping during acute (≤ 1 hour) exposures at concentrations greater than 41.6 ppm (Treon et al. 1955). All animals exposed to these concentrations of HCCPD died as a result of the exposure. Lung tissues, when examined, displayed inflammation, hemorrhagic lesions, edema, and necrosis of the bronchi. In some cases the walls of the alveoli became coated with a hyaline or fibroid membrane. Where lung injury was severe, there was a proliferation of fibrous tissue into the bronchi and alveoli (Treon et al. 1955). Hyperemia and edema of the lungs were seen in all the rats, mice, rabbits, and guinea pigs acutely exposed to HCCPD at concentrations of 0.3-66 ppm. These effects were more severe in those animals that died from exposure than those that did not.

Exposures to 0.5 ppm (6 hours a day, 5 days a week) for l-2 weeks resulted in inflammation, hyperplasia, and epithelial erosion in the lungs, but recovery was apparent 2 weeks after exposure ceased in those animals that survived treatment (Rand et al. 1982a). Similar lesions were present in the lungs, bronchi, larynx, and nasal passages of rats and mice exposed to 1 and 2 ppm HCCPD for < l-5 weeks (their survival time) (NTP 1994). During exposure, the rats displayed respiratory distress with mouth breathing and increased respiratory rate. Some rats, particularly males, had lesions of the lungs with 13-week exposures to 0.4 ppm HCCPD. Absolute and relative lung weights were increased in females and significantly increased in males. Squamous metaplasia of the larynx and trachea was found in mice exposed to concentrations of 0.15 and 0.4 ppm (NTP 1994). Lesions were not present in the lungs of rats exposed to 0.15 ppm HCCPD or mice exposed to 0.4 ppm. Exposure to a concentration of 0.13 ppm for 30 weeks (6 hours a day, 5 days a week) caused pulmonary edema in mice and was associated with pneumonia in some rats and guinea pigs (Treon et al. 1955). Comparable effects were not seen in rabbits (Treon et al. 1955).

2. HEALTH EFFECTS

Pulmonary function tests performed on 6 monkeys after 7 and 13 weeks of exposure to concentrations of 0.01-0.2 ppm HCCPD showed all parameters remained within the normal range (Rand et al. 1982a). However, monkeys are more resistant to pulmonary irritants than rats (Rand et al. 1982b), most likely due to the differences in airway diameters; therefore, the lack of an HCCPD effect on lung function in this species is not surprising.

Even under exposure conditions where no overt lung damage was apparent (Rand et al. 1982a), changes were present in rat Clara cells when they were examined by electron microscopy (Rand et al. 1982b). Exposure to 0.01-0.2 ppm HCCPD for 14 weeks (6 hours a day, 5 days a week) caused a significant doserelated incidence of rod-shaped, electron-lucent inclusions in the Clara cells. One monkey exposed to 0.2 ppm displayed comparable cell inclusions under parallel exposure conditions (Rand et al. 1982b). There is no evidence that these minor changes in cell structure may have caused impaired oxygen transport across the lung epithelium (see Section 2.2.1.2).

Chronic exposure of rats and mice to 0.01-0.2 ppm HCCPD for 2 years (6 hours/day, 5 days/week) caused the accumulation of a granular yellow-brown pigment in the lung, nasal, and tracheal epithelium (NTP 1994). The pigmentation appeared in the noses of 80% of the male and female rats exposed to 0.01 ppm for 15 months and 80% of those exposed for 2 years. The severity and incidence of the lesions increased with dose. Pigmentation of the lungs was present in 98-100% of the male and female rats exposed to 0.2 ppm for 2 years. The lungs of no male rats were affected at the 0.01 ppm concentration and only 2 of 50 were affected at the 0.05 ppm concentration. However, 50% of the female rats had pigmentation of the lungs with exposure to 0.01 ppm, and 86% with exposure to 0.05 ppm. The situation was very similar in mice. A concentration of 0.01 ppm caused nasal pigmentation in 80% or more of the animals and exposure to 0.2 ppm caused lung pigmentation in a higher percentage of the animals.

In order to examine the progression and permanence of pigmentation, NTP (1994) conducted stop exposure studies in male mice. These studies were designed to measure the relative effects of dose and duration on the pigment formation. In these studies, a concentration of 0.2 ppm (6 hours/day, 5 days/week) was used for 26 or 42 weeks. The animals were allowed to complete their lifespan without additional exposures. Pigmentation of the respiratory tract (nose, trachea, and/or lungs) was seen in all animals and did not disappear when exposure ceased. A comparison of the data for different durations and different exposure

concentrations showed that both concentration and duration of exposure had an effect on the amount of pigmentation.

The human and animal data indicate that the linings of the respiratory passages and the lungs are very susceptible to damage from low concentrations of HCCPD following inhalation exposure. The irritating effects of HCCPD on the lungs and nasal passages were evidenced by mouth breathing and shallow, labored respiration. Inflammation of the tissues was followed by necrosis, exfoliation, and hemorrhage. Tissue repair was often fibrous in appearance. Long-term exposure to very low levels of HCCPD (0.01 ppm, 6 hours/day, 5 days/week) produced granular yellow-brown pigmentation of the epithelium of the nose, trachea, larynx, and lungs. In animals, the inflammation of the trachea and lungs did not appear to occur unless the product of the concentration and duration was greater than 20 or 21 ppm-weeks (NTP 1994).

Cardiovascular Effects. Elevated lactic dehydrogenase (LDH) levels were detected in blood samples from 11 of 41 workers examined after a 3-15-day exposure to HCCPD at a waste water treatment plant, but not in blood samples evaluated 3 weeks later (Morse et al. 1979). LDH values were elevated in only one of 97 members of the cleanup crew, but aspartate amino-transferase (AST) values were elevated in 12 cleanup crew members and seemed to be related to the HCCPD exposure (Kominsky et al. 1980). Elevated LDH and AST values can be indicative of damage to the heart muscle as well as the liver. Therefore, without some evidence of impaired cardiac function, it is not possible to conclude that there was damage to the heart based on enzyme levels alone.

In animals acutely exposed to HCCPD (0.3-66 ppm) for varying periods of time (15 minutes to 2 weeks of intermittent exposure), diffuse degenerative changes were noted in the heart (Treon et al. 1955). These degenerative changes may have been the result of autolysis in deceased animals. In another study, there were no effects on rat heart weights or tissue histopathology with exposures to 0.022-0.5 ppm (6 hours a day, 5 days a week) after either 1 or 2 weeks, and there were no changes in the levels of serum AST (Rand et al. 1982a).

Intermediate-duration (13-week) exposure of female rats and mice of both sexes to 0.01-0.4 ppm HCCPD had no effect on heart tissues, heart weight, or serum LDH and AST values (NTP 1994; Rand et al. 1982a). Relative heart weights were increased in male rats with exposure to 0.4 ppm but not with the

lower concentrations tested. Diffuse degenerative changes in the heart were seen in rats, mice, guinea pigs, and rabbits exposed to 0.3 ppm HCCPD for 6 weeks or 0.13 ppm for 30 weeks (Treon et al. 1955).

There were no effects on the histopathology of the heart tissues of rats or mice in the NTP (1994) bioassay for HCCPD where doses of 0.01-0.2 ppm were evaluated. Thus, there is no clear evidence that HCCPD has an adverse effect on the cardiovascular system with any duration of exposure or dose level.

Gastrointestinal Effects. Waste water treatment plant workers exposed to HCCPD for 3-15 days due to a large industrial release complained of nausea (22%) and abdominal cramps (Kominsky et al. 1980; Morse et al. 1979). One member of the cleanup crew who was exposed to 19.2 ppm for several seconds without protective equipment experienced nausea several minutes after the exposure (Kominsky et al. 1980).

No microscopic changes were seen in the stomach, esophagus, or intestines of rats, mice, or monkeys exposed to 0.01-0.4 ppm HCCPD for 13 weeks (6 hours a day, 5 days a week) (NTP 1994; Rand et al. 1982a), or in chronic-duration studies of rats and mice using exposure concentrations of 0.01-0.2 ppm (NTP 1994). The gastrointestinal tract is apparently not vulnerable to damage from exposure to HCCPD inhaled vapors.

Hematological Effects. No changes in blood counts were observed in workers exposed to HCCPD at a waste water treatment plant after an industrial discharge of the material into the sewage system (Kominsky et al. 1980).

Significant increases in hemoglobin, red blood cell count, and packed cell volume resulted from acuteduration exposures of rats to 0.5 ppm HCCPD for one or 2 weeks (Rand et al. 1982a). Intermediate-duration (13-week) exposure of males to 0.01 ppm and 0.2 ppm and exposure of females to 0.05 and 0.2 ppm HCCPD resulted in increased hemoglobin and hematocrit values (Rand et al. 1982a). These minor variances in hematological parameters were believed to be a consequence of hemorrhagic lesions in the lungs and not a direct influence of HCCPD on hematopoiesis or red cell turnover.

In rats exposed to 0.4 ppm HCCPD, 6 hours/day, 5 days/week for 13 weeks, there was also a statistically significant increase in packed cell volume, hemoglobin, and erythrocytes, but these values were not increased in all groups of animals evaluated (NTP 1994). Absolute and relative lung weights showed a

statistically significant increase in males, but not females, and lung effects were more severe in males than in females. Thus, it may be that the hematological effects in males reflect a compensatory response to lung damage as was suggested by Rand et al. (1982a), even though NTP scientists judged that the effects were not compound-related. Mean cell hemoglobin concentration was the only hematological parameter affected in male and female mice (NTP 1994).

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans after inhalation exposure to HCCPD.

There were no observed effects in mice or rats on bone or bone marrow histopathology with either 13-week or 2-year studies (NTP 1994). The intermediate-duration studies used doses of 0.04-0.4 ppm HCCPD and the chronic-duration studies used doses of 0.01-0.2 ppm.

Hepatic Effects. Elevated LDH levels were detected in blood samples from 11 of 41 workers examined shortly after exposure to HCCPD at a waste water treatment plant, but not in blood samples evaluated 3 weeks later (Morse et al. 1979). Exposure occurred over a 3-15-day period as a result of an industrial discharge of HCCPD. LDH values were elevated in only one of 97 members of the cleanup crew, but AST values were elevated in 12; alkaline phosphatase (AP) in 5; and bilirubin in one (Kominsky et al. 1980). For eight of the cleanup crew members, these biochemical parameters were abnormal on more than one occasion and, in some cases, were temporarily related to exposure conditions.

Relative to a group of 35 controls, 73 male operators employed for an average of 8.2 years (range 0.5-23 years) in a plant producing chlorinated hydrocarbons, including HCCPD, showed no evidence of hepatotoxicity (Boogaard et al. 1993). The tests included measurement of alanine and aspartate aminotransferases, alkaline phosphatase, total bilirubin, γ-glutamyltranspeptidase, lactate dehydrogenase, and total bile acids.

In animals, mild to moderate hepatic tissue degeneration was a common manifestation of acute-duration inhalation exposures to 0.3-66 ppm for 15 minutes to 2 weeks, and to intermediate-duration exposures to 0.3 ppm for 6 weeks, and 0.13 ppm for 30 weeks. Hepatic damage was more pronounced in the animals that died than in those that survived and, thus, may have been, at least partially, the result of autolysis (Treon et al. 1955).

2. HEALTH EFFECTS

Liver weights of rats were significantly reduced (8-9%) in females receiving doses of 0.11 and 0.5 ppm HCCPD for 1 or 2 weeks and 3-E% in males receiving doses of 0.01-0.2 ppm, 6 hours/day, 5 days/week for 13 weeks (Rand et al. 1982a). On the other hand, biochemical parameters, LDH, AST, AP, and ALT levels were not influenced by inhalation exposure to 0.01-0.5 ppm HCCPD for 1-13 weeks (Rand et al. 1982a). There were no changes in liver weights or tissue histopathology with intermediate-duration exposure of rats or mice to concentrations of 0.04-0.4 ppm HCCPD or chronic-duration exposures to 0.01-0.2 ppm (NTP 1994). The 13-week intermediate-duration exposure also had no dose-related effects on liver enzymes (ALT, AST, and LDH). These data suggest that HCCPD has some minimal effects on the liver enzymes in rats and mice at low concentrations and may cause necrotic lesions at high concentrations.

Renal Effects. Urine samples were collected from 41 workers exposed for 3-15 days to HCCPD at a waste water treatment plant as the result of an industrial release of this material into the sewage system (Morse et al. 1979). Proteinuria was identified in 6 of 41 workers immediately after exposure but not 3 weeks later. Urinalysis parameters were normal in the cleanup crew workers (Kominsky et al. 1980).

Relative to a group of 35 controls, 73 male operators employed for an average of 8.2 years (range 0.5-23 years) in a plant producing chlorinated hydrocarbons, including HCCPD, showed no evidence of damage to the renal tubules (Boogaard et al. 1993). The tests included measurement of urinary alanine aminopeptidase, N-acetyl-β-D-glucosaminidase, and retinol binding protein. Although total urinary protein concentrations did not differ between the two groups, urinary albumin was significantly higher in the exposed group. The difference, however, was not related to time of employment, and there was no difference in urinary albumin concentration in workers involved in the manufacture of HCCPD and those involved in the preparation of other chlorinated hydrocarbon. Thus, the effect was not considered to be due to the damage to the glomerulus caused by exposure to HCCPD.

Inhalation exposure of HCCPD caused renal tubular necrosis in rats, mice, guinea pigs, and rabbits with acute-duration exposure to concentrations of 0.3-66 ppm for 15 minutes to 2 weeks (7 hours/day, 5 days/week) and to intermediate-duration exposure to 0.3 ppm for 6 weeks and 0.13 ppm for 30 weeks, also for 7 hours/day, 5 days/week (Treon et al. 1955). No tissue damage was seen in rats exposed to 0.01-0.5 ppm for up to 13 weeks, although there was a slight reduction (10-l 1%) in average kidney weights in males and females receiving 0.5 ppm for 2 weeks and in males receiving 0.01-0.5 ppm for up to 13 weeks (Rand et al. 1982a).

2. HEALTH EFFECTS

Exposure of male rats to 0.01-0.2 ppm and female rats to 0.05-0.2 ppm for 15 months was associated with an increase in urine specific gravity (NTP 1994). The urine volume was reduced in the females exposed to 0.2 ppm. In companion studies of mice, the specific gravity was increased in the males with the 0.05 and 0.2 ppm exposures and the volume was increased in females exposed to the 0.2 ppm concentration. These findings suggest some deficit in renal function, but there were no observable changes in the tissues to suggest kidney damage, and no changes in kidney weights. Although the data are not completely consistent, HCCPD may affect the kidney, especially with acute, high-concentration exposures or more moderate long-term exposures.

Endocrine Effects. No reports of changes in human endocrine parameters or organs after inhalation exposure to HCCPD were found.

There were degenerative changes in the adrenal glands of rats, mice, guinea pigs, and rabbits after acuteduration exposures to concentrations of 0.3-66 ppm for periods of 15 minutes to 2 weeks. Similar changes occurred with intermediate-duration exposures to 0.3 ppm for 6 weeks, and 0.13 ppm for 30 weeks (Treon et al. 1955). These changes may have been the result of tissue autolysis in moribund animals.

The weights of the adrenal glands were significantly reduced in rats exposed to 0.5 ppm for 5-10 days (Rand et al. 1982a). The significance of the observation cannot be assessed quantitatively in the absence of measurements of hormone products. There were no histopathological changes in the adrenal glands of rats or mice with 13-week exposures to 0.04-0.4 ppm for 2 years (NTP 1994).

Dermal Effects. Skin irritation was one of the symptoms reported by plant workers (21%) and cleanup crew members exposed to HCCPD (>0.97 ppm) at a waste water treatment plant as a result of an industrial release of HCCPD into the sewage system (Kominsky et al. 1980; Morse et al. 1979).

Skin irritation in humans and animals are more likely a consequence of the direct action of HCCPD vapors on the skin rather than a systemic effect due to exposure to HCCPD through the lungs, and is discussed further in Section 2.2.3.

2. HEALTH EFFECTS

Body Weight Effects. No reports of weight loss in humans after inhalation exposure to HCCPD were found.

Rats exposed to 0.22 ppm HCCPD for 10 days did not gain weight at the same rate as the controls; at an exposure concentration of 0.5 ppm, the animals lost weight (Rand et al. 1982a). Once exposure ceased, the weight gain returned to normal, although the treated animals weighed less than the controls. Weight gains were decreased approximately 10% in male rats exposed to 0.04 ppm and greater, 16% in male mice exposed to 0.15 ppm, and 28% in male mice exposed to 0.4 ppm for 13 weeks, but not in females at any dose tested (NTP 1994).

Other Systemic Effects. No studies were located regarding other systemic effects in humans after inhalation exposure to HCCPD.

Rats exposed to 0.22 ppm HCCPD for 10 days ate less food than control animals (Rand et al. 1982a).

2.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans after inhalation exposure to HCCPD.

There were no histopathological changes in the spleens, thymus, or lymph nodes of rats or mice exposed to 0.04-0.4 ppm HCCPD for 13 weeks (NTP 1994; Rand et al. 1982a) or to 0.01-0.2 ppm for 2 years (NTP 1994). No studies were located that evaluated a broad range of immunological parameters; therefore, a reliable NOAEL cannot be identified for this end point.

2.2.1.4 Neurological Effects

Headaches were reported by 45% of 145 individuals after exposure to HCCPD at a waste water treatment plant for 3-15 days. Six weeks later, 18% of 177 questionnaire respondents were still experiencing headaches (Morse et al. 1979).

Some rats, mice, guinea pigs, and rabbits exposed to high concentrations of HCCPD (>41.6 ppm) by acute-duration inhalation experienced tremors (Treon et al. 1955). Rats and mice exposed to concentrations of 0.4-2 ppm HCCPD were described as listless after l-3 weeks of exposure for 6

hours/day, 5 days/week (NTP 1994). The higher the HCCPD concentration, the sooner the listlessness was noted.

The brain tissues of all rats, mice, guinea pigs, and rabbits that died due to HCCPD exposure showed diffuse degenerative changes with both acute- and intermediate-duration exposures (Treon et al. 1955). These changes may have been the result of tissue autolysis. There were no histopathological changes in the brains of rats at a dose of 0.5 ppm for l-2 weeks or in the brains of rats, mice, and monkeys at doses of 0.04-0.4 ppm for 13 weeks (NTP 1994; Rand et al, 1982a). No other indications of effects on the nervous system were noted.

The highest NOAEL values and all LOAEL values from each reliable study of neurological effects for each species and duration category are recorded in Table 2- 1 and plotted in Figure 2- 1. Although the data are minimal, HCCPD vapors do appear to cause headaches in humans and some symptoms associated with impaired function of the nervous system in animals were evident.

2.2.1.5 Reproductive Effects

No studies were located regarding reproductive effects in humans after inhalation exposure to HCCPD.

In animals, there were no treatment-related histopathological lesions of the male reproductive organs (testes, prostate, seminal vesicle) or of the female reproductive organs (ovaries, uterus) in rats, mice, or monkeys exposed to vapors of HCCPD *at* concentrations up to 0.4 ppm for 13 weeks (NTP 1994; Rand et al. 1982a). However, lifetime exposure of female mice to 0.05 or 0.2 ppm resulted in inflammation and infection of the ovaries (NTP 1994). These infections were hypothesized to have shortened the lifespan of the afflicted animals. NTP (1994) suggested that the infections were caused by *Klebsiella* because this species has caused similar problems in mice during other NTP studies. It is not possible to identify a NOAEL for this end point or to reach any conclusions regarding the potential for HCCPD to cause reproductive effects, because studies evaluating a broad range of reproductive parameters related to reproductive function and success have not been conducted.

2.2.1.6 Developmental Effects

No studies were located regarding developmental effects in humans or animals after inhalation exposure to HCCPD.

2.2.1.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans after inhalation exposure to HCCPD.

Male or female mice exposed to 0.01-0.2 ppm HCCPD for 13 weeks did not have an increase in reticulocyte micronuclei (NTP 1994). This indicates that HCCPD does not act as a clastogen causing chromosome breaks. Other genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

No studies were located regarding cancer in humans after inhalation exposure to HCCPD.
There were no statistically significant increases in tumor incidence in rats or mice exposed to atmospheric concentrations of 0.01-0.2 ppm HCCPD for 6 hours/day, 5 days/week for 2 years (NTP 1994). The incidence of alveolar/bronchiolar carcinomas was significantly increased in male mice exposed to 0.5 ppm HCCPD for 26 or 42 weeks, but was within the historical range for the laboratory and, thus, was not definitely compound-related. There was a slight increase in the incidence of adenomas of the pituitary pars distalis in male rats and in thyroid follicle cell adenomas in female mice, but NTP did not consider these tumors to be related to HCCPD administration. On the basis of these data, the U.S. Department of Health and Human Services (DHHS) has determined that HCCPD is not a carcinogen in either male or female rats or mice (NTP 1994).

2.2.2 Oral Exposure

2.2.2.1 Death

No studies were located regarding lethality in humans after oral exposure to HCCPD.

2. HEALTH EFFECTS

HCCPD is moderately toxic to animals by the oral route of exposure. The LD_{50} (lethal dose, 50% kill) was 471 mg/kg administered in 5% peanut oil in a gavage study in male rats (Treon et al. 1955) and 584 mg/kg (in corn oil) for a group of male and female rats (IRDC 1972). There was a dose-response trend for the number of deaths per group with doses ranging from 261 to 1,344 mg/kg in male rats (Treon et al. 1955). The full dose range was not evaluated in the females. A dose of 877 mg/kg was lethal to over 90% of the males and females tested. The material tested was 93.3% pure; therefore, impurities could have contributed to the toxicity observed in this study, especially at the high exposure concentrations. Impurity concentrations in one 97.4% pure sample of HCCPD included 0.15% tetrachloroethylene, 0.5 1% hexachloro-1,3-butadiene, 1.73% octachlorocyclopentene, and 0.48% hexachloro-3-cyclopentene- l-one (Abdo et al. 1984). A 98% pure sample contained 0.4% hexachlorobutadiene and 1.5% hexachloro-3-cyclopentene-l-one (NTP 1994). Other impurities that have been reported in HCCPD include hexachlorobenzene, PCBs, and mirex (EPA 199la; HSDB 1998; WHO 1991). All exposure concentrations were adjusted to reflect exposure to HCCPD rather than the mixture for the Treon et al. 1955) results.

With repeated administration of HCCPD (purity 97.4% in corn oil) to rats, doses of 150 mg/kg/day caused mortality in 7 of 10 males and 5 of 10 females (Abdo et al. 1984). A low number of animal deaths (l-3) occurred in all lower dose groups including controls, but the increase in mortality was not dose-related.

Data on species other than the rat are more limited. A dose of 877 mg/kg administered in 5% peanut oil killed all of 3 exposed rabbits while a dose of 579 mg/kg killed only 1 and all survived a dose of 392 mg/kg (Treon et al. 1955). On the other hand, several rabbits (exact number not identified) did not survive 13 days of treatment (during pregnancy) with 75 mg!kg/day HCCPD in cottonseed oil (Murray et al. 1980). With intermediate-duration exposure, mice appeared to be less sensitive to HCCPD in corn oil than rats (Abdo et al. 1984). There were no deaths with 13-week exposures to 150 mg/kg/day, but all males and 3 females died during the first 2 weeks of exposure to doses of 300 mg/kg/day. On the other hand, in rats, 7 males and 5 females died with exposure to 150 mg!kg/day and 3 males and 3 females with exposure to 75 mg/kg/day. This is the reverse of the situation observed after inhalation exposure where mice were more sensitive than rats (Abdo et *al.* 1984). NTP (1994) hypothesized that the sensitivity of mice to inhalation exposure was the result of HCCPD-induced inflammation of the breathing passages and the narrower diameter of the air passages in mice.

2. HEALTH EFFECTS

An LD_{50} value and all reliable LOAEL values for lethality in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2. Rats appear to be more sensitive to HCCPD than mice and rabbits, and males more sensitive than females via the oral route.

2.2.2.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, or other systemic effects in humans or hematological musculoskeletal, dermal, or ocular effects in animals after oral exposure to HCCPD. Respiratory, cardiovascular, gastrointestinal, hepatic, renal, endocrine and body weight effects were observed in animals and are discussed below. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

Respiratory Effects. Single doses of 261-1,959 mg/kg administered in 5% peanut oil caused labored breathing in rats and rabbits (Treon et al. 1955). Upon death or sacrifice, the lung tissues were hyperemic and edematous in animals given doses of 261 mg/kg/day or greater. Evidence of extensive hemorrhage of the lungs was reported in rats that received a single non-lethal dose of HCCPD (exact dose not specified; 96% pure) when the animals were sacrificed 21 days after dosing (Lawrence and Dorough 1982). On the other hand, there were no gross or histopathological changes in the lungs of rats exposed to doses of 75 and 150 mg/kg/day or in mice exposed to 150 and 300 mg/kg/day in corn oil for 13 weeks (Abdo et al. 1984). These differences in results may be due to gavage procedures. Lung damage may be more severe when inhalation of volatilized HCCPD occurs during dosing.

Cardiovascular Effects. Single doses of 261-1,959 mg/kg administered in 5% peanut oil caused degenerative changes in the hearts of rats and rabbits (Treon et al. 1955) but there were no gross or histopathological changes in the hearts of rats exposed to doses of 75 and 150 mg/kg/day or mice exposed to 150 and 300 mg/kg/day in corn oil for 13 weeks (Abdo et al. 1984). The changes seen in the study by Treon et al. (1955) may have been the result of tissue autolysis in moribund animals.

Table 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene - Oral

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL			Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
	ACUTE EXPOSURE							
	Death							
1	Rat	once				584	(LD_{50})	IRDC 1972
2	Rat	once				261 M	(LD_{Lo} in males)	Treon et al. 1955
						471 M	(LD_{50} in males)	
3	Mouse (B6C3F1)	1-2 wk 5 d/wk 1x/d				300 M	(100% mortality)	Abdo et al. 1984
						300 F	(30% mortality)	
4	Rabbit (New Zealand)	13 d Gd 6-18 1x/d				75 F	(increased maternal death during pregnancy)	Murray et al. 1980
5	Rabbit	once				579 F	(1/3 rabbits died)	Treon et al. 1955
	Systemic							
6	Rat	once	Resp			261 F	(pulmonary hyperemia and edema, retarded respiration rate)	Treon et al. 1955
			Cardio			261 F	(degenerative changes in heart)	
			Gastro			261 F	(diarrhea, necrotizing gastritis)	
			Hepatic			261 F	(liver degeneration and necrosis)	
			Renal			261 F	(renal tubular necrosis)	
			Endocr			261 F	(degenerative changes in adrenal glands)	

Table 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
7	Rabbit (New Zealand)	13 d Gd 6-18 1x/d	Bd Wt		75 F (unspecified decreased maternal body weight)		Murray et al. 1980
8	Rabbit	once	Resp			579 F (hyperemia and edema of the lungs)	Treon et al. 1955
			Cardio			579 F (degenerative changes in the heart)	
			Gastro			579 F (diarrhea)	
			Hepatic			579 F (degenerative changes)	
			Renal			579 F (necrosis of tubular epithelia)	
			Endocr			579 F (degenerative changes in the adrenal glands)	
	Neurological						
9	Rat	once			261 F (lethargy)	579 F (degenerative changes in brain)	Treon et al. 1955
10	Rabbit	once			168 F (lethargy)	579 F (degenerative changes in brain)	Treon et al. 1955
	Developmental						
11	Mouse (CD-1)	5 d Gd 8-12 1x/d		45			Chernoff and Kavlock 1982
12	Mouse	5 d Gd 8-12 1x/d		45			Gray and Kavlock 1984
13	Mouse	5 d Gd 8-12		45			Gray et al. 1986

Table 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
14	Mouse	10 d Gd 6-15 1x/d		75			Murray et al. 1980
15	Rabbit (New Zealand)	13 d Gd 6-18 1x/d		75			Murray et al. 1980
	INTERMEDIATE EXPOSURE						
	Death						
16	Rat (Fischer- 344)	13 wk 5 d/wk 1x/d				75 (death in 10% of males)	Abdo et al. 1984
	Systemic						
17	Rat (Fischer- 344)	13 wk 5 d/wk 1x/d	Resp	150			Abdo et al. 1984
			Cardio	150			
			Gastro	10	19 (forestomach epithelial hyperplasia)		
			Hemato	150			
			Hepatic	150			
			Renal	19[b]	38 (nephrosis)		
			Bd Wt	19 M 38 F		38 M (body weight gain reduced 75 F 21% in males; 28% in females)	

Table 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference
18	Mouse (B6C3F1)	13 wk 5 d/wk 1x/d	Resp	300			Abdo et al. 1984
			Cardio	300			
			Gastro	19	38 (focal inflammation, hyperplasia of fore-stomach)		
			Hepatic	300			
			Renal	38	75 (nephrosis)		
			Endocr	300			
			Bd Wt	75 M 75 F		150 M (reduced body weight 39%) 150 F (reduced body weight 21%)	
	Immunological/Lymphoreticular						
19	Mouse (B6C3F1)	13 wk 5 d/wk 1x/d		300			Abdo et al. 1984
	Neurological						
20	Rat (Fischer- 344)	13 wk 5 d/wk 1x/d		150			Abdo et al. 1984
21	Mouse (B6C3F1)	13 wk 5 d/wk 1x/d		300			Abdo et al. 1984

Table 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene - Oral (continued)

Key to figure[a]	Species/ (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference
					Less Serious (mg/kg/day)	Serious (mg/kg/day)	
	Reproductive						
22	Mouse (B6C3F1)	13 wk 5 d/wk 1x/d		300			Abdo et al. 1984

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

[b]Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.1 mg/kg/day; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Cardio = cardiovascular; d = day(s); F = female (G) = gavage; Gastro = gastrointestinal; Gd = gestational day (s); (GO) = gavage in oil; Hemato = hematological; LD_{50} = lethal dose, 50% kill; LD_{Lo} = lethal dose, low; LOAEL = lowest-observable-adverse-effect level; M = male; NOAEL = no-observable-adverse-effect level; Resp = respiratory; wk = week(s); x = times

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

Acute (≤14 days)

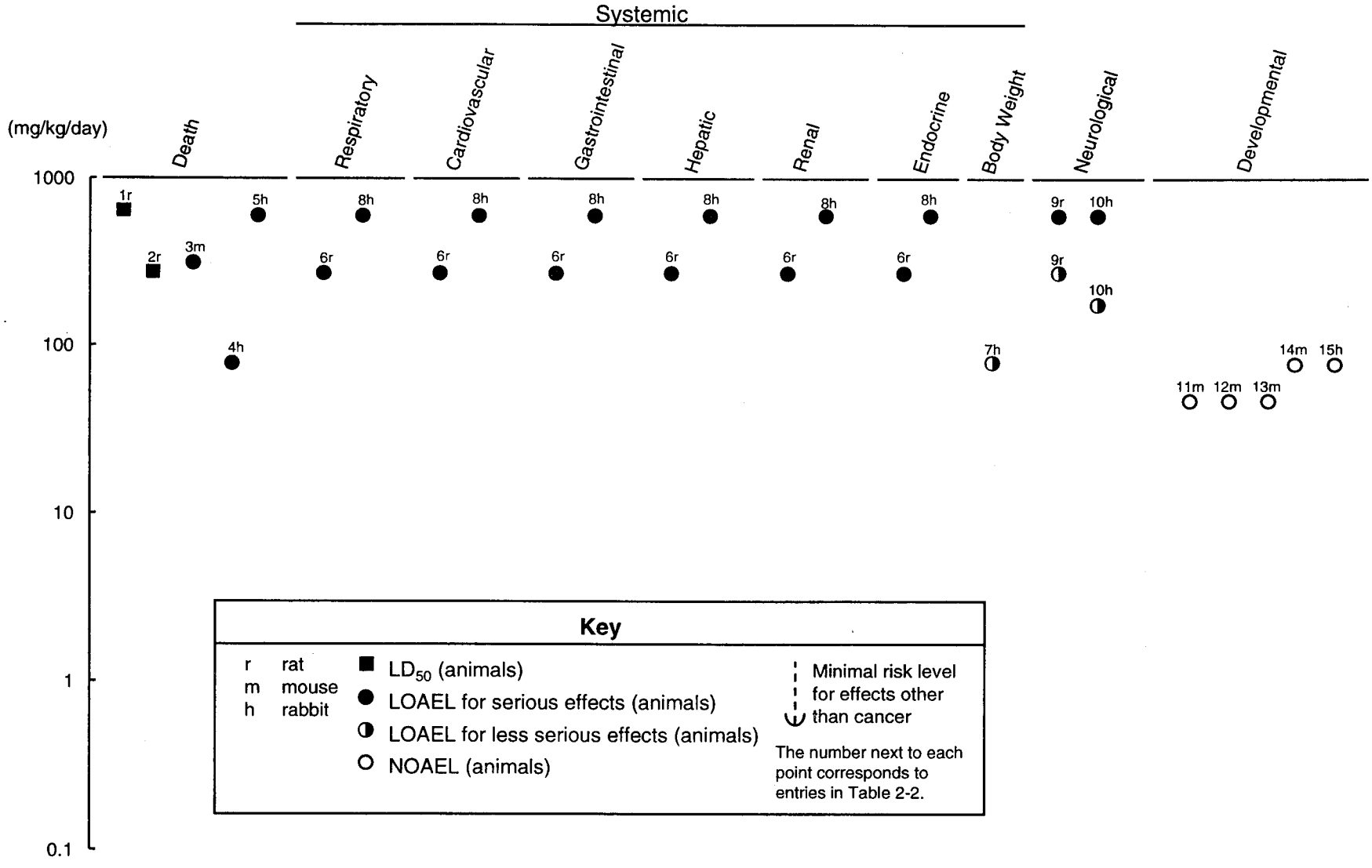
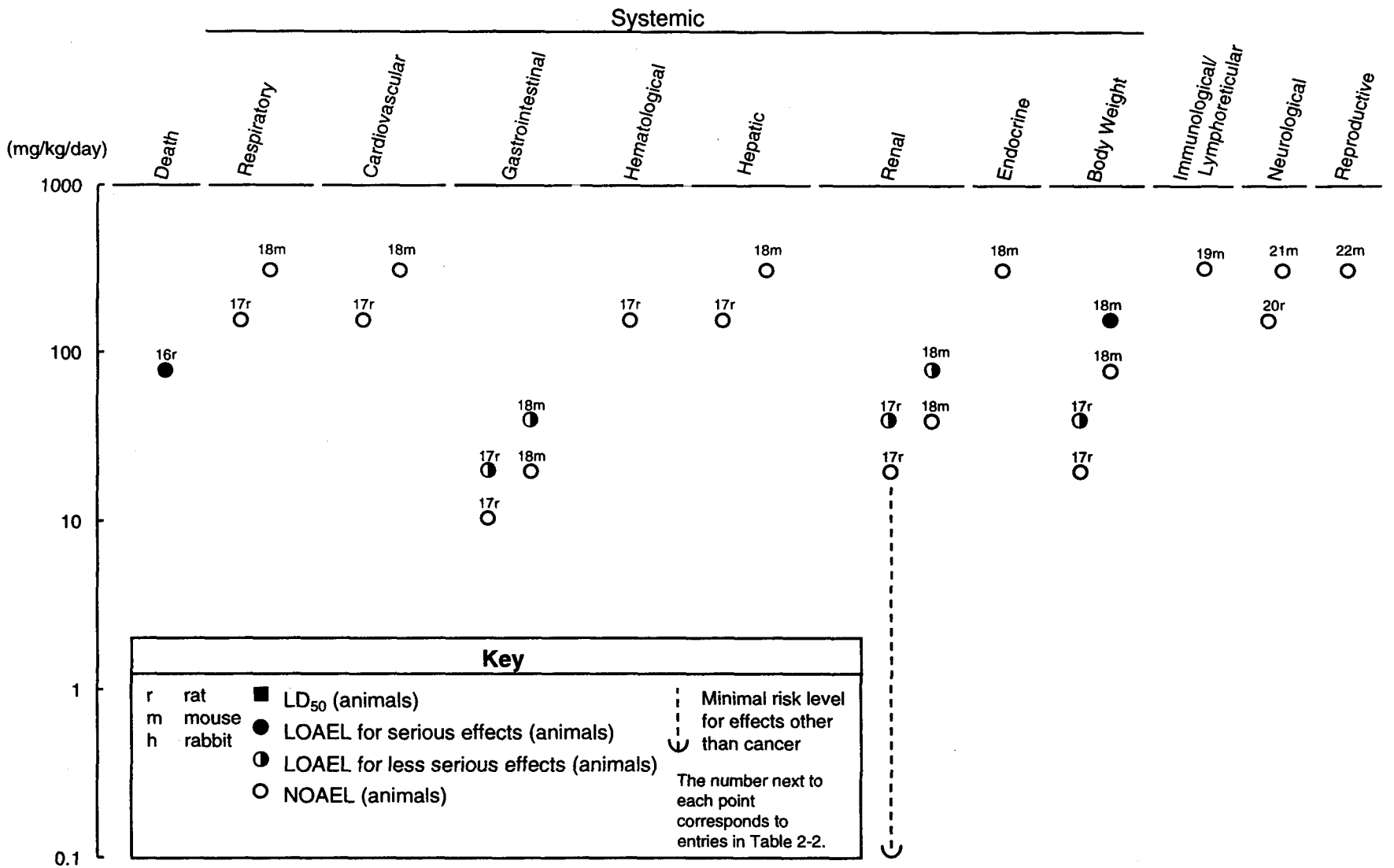


Figure 2-2. Levels of Significant Exposure to Hexachlorocyclopentadiene - Oral (cont.)

Intermediate (15-364 days)



2. HEALTH EFFECTS

Gastrointestinal Effects. Rats and rabbits experienced diarrhea following single oral doses of HCCPD (93.3% purity in peanut oil); the exact doses associated with the diarrhea were not specified. In some rats given an oral dose of 261-1,959 mg/kg, acute necrotic lesions of the forestomach were noted (Treon et al. 1955). After 13-week exposures to HCCPD administered in corn oil, inflammation and epithelial hyperplasia of the forestomach were present in female rats given doses of 19 mg/kg/day and greater, and in males with doses of 38 mg/kg/day and greater (Abdo et al. 1984). The severity of the lesions was directly related to dose. No effects were seen in either sex with a dose of 10 mg/kg/day. A similar pattern was seen in mice with inflammation and hyperplasia at doses of 38 mg/kg/day or greater (Abdo et al. 1984). The location of lesion suggests that they result from direct contact of the tissues with HCCPD during dosing.

Hepatic Effects. High acute oral doses of HCCPD (261-1,959 mg/kg administered in 5% peanut oil) were associated with liver necrosis and tissue degeneration in rats; doses of 579 and 877 mg/kg had the same effects in rabbits (Treon et al. 1955). However there were no changes in liver weights or histopathological changes in the livers of rats exposed to doses of 75 and 150 mg/kg/day, or of mice exposed to 150 and 300 mg/kg/day in corn oil for 13 weeks (Abdo et al. 1984). These differences in effects may reflect the ability of the liver to detoxify the lower, but not the higher, concentrations of HCCPD or tissue autolysis in animals killed through exposure.

Renal Effects. The kidneys also appear to be a target tissue for HCCPD toxicity. Degenerative lesions in the tubules resulted from single-dose exposures administered in 5% peanut oil of 261-l ,959 mg/kg in rats and 579-877 mg/kg in rabbits (Treon et al. 1955). Lesions were also noted in the terminal sections of the proximal tubules of the kidney cortex in rats given 38-150 mg/kg/day HCCPD and mice (female) given 70-300 mg/kg/day in corn oil for 13 weeks (Abdo et al. 1984). There were changes in epithelial cell structure. Brown granular pigment debris protruded into the lumen. Tubular necrosis was present in 70% of the male mice receiving the 300 mg/kg/day d ose, but this lesion was morphologically distinct from that seen in the other animals. It should be noted that hexachlorobutadiene was present as an impurity (0.5%) in the HCCPD used for this study. Since hexachlorobutadiene is a renal toxin, it may have contributed to the lesions observed, particularly those at the highest dose. No effects on the kidney tubules were apparent in rats with doses of 19 mg/kg/day or in mice with doses of 38 mg/kg/day (Abdo et al. 1984).

2. HEALTH EFFECTS

Endocrine Effects. No effects on endocrine tissues were reported for humans exposed to HCCPD by the oral route.

Degenerative changes in the adrenal tissues resulted from exposure to single doses of 261-l ,959 mg/kg HCCPD in rats and doses of 579 and 877 mg/kg administered in 5% peanut oil in rabbits (Treon et al. 1955). These changes may have resulted from tissue autolysis. In a 13-week study using exposure of up to 150 mg!kgIday in rats and 300 mg/kg in mice administered in corn oil, there were no reported histopathological changes in the adrenals of either species (Abdo et al. 1984).

Body Weight Effects. Maternal weight loss was observed in rabbits administered 75 mg/kg/day in cottonseed oil on gestation days 6-18 in a teratogenic study. The magnitude of the weight loss was not reported (Murray et al. 1980). Male and female rats and mice experienced dose-related diminished weight gains when compared to controls after exposure to HCCPD in corn oil for 13 weeks (Abdo et al. 1984). Male rats were affected more than females and rats more than mice. Body weights in male rats were reduced 21-58% at dose levels of 38 mg/kg/day or greater. In females, comparable weights were reduced 28-36%, but weight loss first occurred in the 75 mg/kg/day or greater dose groups. Body weights in male mice were reduced 39% at dose levels of 150 mg/kg/day. No data were provided for the 300 mg/kg/day dose group (highest dose tested) because all the males died. In females, comparable weights were reduced 21-44% in the 150 mg/kg/day or greater dose groups. No effect on weight gain was noted in rats at a dose of 19 mg/kg/day or in mice at a dose of 75 mg/kg/day.

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological and lymphoreticular effects in humans or animals after oral exposure to HCCPD.

2.2.2.4 Neurological Effects

No studies were located regarding neurological effects in humans after oral exposure to HCCPD.

Rats exposed to single doses administered in 5% peanut oil of 168-1,959 mg/kg HCCPD and rabbits exposed to 168-877 mg/kg were described as lethargic in the period immediately after exposure (Treon et al. 1955). During postmortem examination of tissues, degenerative lesions of the brain were observed in

the rats and rabbits that succumbed to exposure and also in the rats that survived. No histopathological lesions of the brain were noted in rats exposed to 150 mg/kg/day or mice exposed to 300 mg/kg/day in corn oil for 13 weeks (Abdo et al. 1984). The data suggest that brain lesions occur only with exposures to high oral doses of HCCPD.

All LOAEL values from each reliable study of 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 the reproductive effects in humans after oral exposure to HCCPD. Animal studies demonstrated HCCPD did not cause treatment-related effects on the testes, seminal vesicle, prostate, airwaves, and uterus in rats exposed to concentrations up to 150 mg/kg/day or in mice up to 300 mg/kg/day in corn oil for 13 weeks (Abdo et al. 1984). A multigeneration study evaluating a wide range of parameters regarding reproductive function and success has not been conducted. Accordingly, a reliable NOAEL value cannot be determined for this end point.

2.2.2.6 Developmental Effects

No studies were located regarding the developmental effects in humans after oral exposure to HCCPD

In animals, studies of the developmental toxicity of HCCPD have been limited to screening tests that evaluated effects following exposure during gestation. HCCPD was not embryotoxic, fetotoxic, or teratogenic in mice exposed to the compound at dose levels up to 75 mg/kg/day in cottonseed oil during gestation days 6-15 or in rabbits at corresponding doses during gestation days 6-18 (Murray et al. 1980). It should be noted that the compound was not maternally toxic in mice, but weight loss was noted in rabbits, and there were some rabbits that died (number not specified).

Mice that received HCCPD (45 mg/kg/day in corn oil) during gestation days 8-12 did not show developmental effects (Chernoff and Kavlock 1982). When offspring of mice that were administered HCCPD (45 mg/kg/day in corn oil) during gestation days 8-12 were evaluated over a 250-day postnatal

period (including through puberty and breeding), there were no adverse effects on postnatal viability, growth, locomotor activity, or reproductive function (Gray and Kavlock 1984; Gray et al. 1986).

The highest NOAEL values for developmental effects in each species and 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 the genotoxic effects in humans after oral exposure to HCCPD.

Data on animals are limited to a study evaluating dominant lethality in mice (Litton Bionetics 1978b). HCCPD did not induce genetic damage in germ cells in male mice exposed to doses up to 1 mg/kg for 5 days. Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding cancer in humans or animals after oral exposure to HCCPD.

2.2.3 Dermal Exposure

2.2.3.1 Death

No studies were located regarding lethality in humans after dermal exposure to HCCPD.

Dermal doses of 569 mg/kg and greater in 10% Ultrasene were lethal to rabbits when applied to a shaved area encircling the trunk and covered by a rubber sleeve for 24 hours (Treon et al. 1955). The higher the dose, the shorter the survival time for the animals. None of the animals died with a dermal application of a 401 mg/kg dose, although one was in poor condition and probably would have died naturally if it had not been sacrificed at 21 days. In a separate study, a dermal dose of 200 mg/kg led to the death of 2 male rabbits exposed for 24 hours. HCCPD was nonlethal in guinea pigs and monkeys when 0.05 mL of solutions of up to 90% HCCPD in mineral oil were applied to the skin (Treon et al. 1955).

2. HEALTH EFFECTS

When an unspecified quantity of HCCPD was placed in the conjunctival sac of the right eye of 5 rabbits for only 5 minutes and then washed away, the quantity of material absorbed was lethal to all the animals within 9 days (IRDC 1972).

The LOAEL values for lethality in rabbits after acute-duration dermal exposure to HCCPD are recorded in Table 2-3.

2.2.3.2 Systemic Effects

No studies were located regarding respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, body weight or other systemic effects in humans after dermal exposures to HCCPD.

There are no data for gastrointestinal, hematological, and musculoskeletal effects in animals. Data are available for respiratory, cardiovascular, hepatic, renal, endocrine dermal, ocular, and body weight effects after dermal exposure to HCCPD in animals. These effects are discussed below. The highest NOAEL values and all reliable LOAEL values for systemic effects in each species and duration category are recorded in Table 2-3.

Respiratory Effects. Workers were exposed to HCCPD vapors for 3-15 days at a waste water treatment plant as a result of an inadvertent industrial release (Kominsky et al. 1980; Morse et al. 1979). Complaints included nasal irritation, and sinus congestion. These effects were more likely a consequence of the direct action of the HCCPD vapor on the mucous membranes, rather than systemic effects due to exposure to HCCPD through the lungs.

The lungs of rabbits that were dermally exposed to HCCPD (93.3% pure) were congested with blood and fluid (Treon et al. 1955). Some studies were conducted using the undiluted compound. Others were conducted using 10% (v/v) in Ultrasene. The exact doses associated with these effects cannot be determined because the authors did not directly correlate descriptions of effects with specific doses. It is presumed that the lung effects were seen in all exposed animals at doses of 401-5,719 mg/kg/day. The HCCPD was applied to a shaved area of skin encircling the trunk that was covered by a rubber sleeve for 24 hours, limiting any opportunity for inhalation exposure.

Table 2-3. Levels of Significant Exposure to Hexachlorocyclopentadiene - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL Less Serious		LOAEL Serious		Reference
ACUTE EXPOSURE								
Death								
Rabbit	once 4 hr					365 mg/kg	(3/6 rabbits died)	IRDC 1972
Rabbit	once					200 M mg/kg	(2/2 died within 14 days)	IRDC 1972
Rabbit	once 24 hr					84 mg/kg	(all animals died within 6 days)	IRDC 1972
Rabbit	once 5 min					84 mg/kg	(all animals died within 9 days)	IRDC 1972
Rabbit	once 24 hr					569 mg/kg	(1/3 died)	Treon et al. 1955
Systemic								
Human	3-15 d	Dermal		0.97	(irritation of skin)			Kominsky et al. 1980
		Ocular		0.97	(irritation of eyes)			
Monkey	3 d 1x/d	Dermal				1 mg/cm	(skin irritation and necrosis)	Treon et al. 1955
Monkey	once	Dermal	1.6 mg	3.2 mg	(skin discoloration and irritation)			Treon et al. 1955
Rat	4 hr	Ocular		65.9 ppm	(eye irritation)			Treon et al. 1955
Rat	2.5-3.6 hr	Ocular		1.25 ppm	(eye irritation)			Treon et al. 1955

Table 2-3. Levels of Significant Exposure to Hexachlorocyclopentadiene - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL			Reference
				Less Serious		Serious	
Rat	0.25 hr	Ocular		11.6 ppm	(eye irritation)		Treon et al. 1955
Rat	5 d 7 hr/d	Ocular		0.3 ppm	(irritation of eyelids)		Treon et al. 1955
Mouse	0.25 hr	Ocular		17.4 ppm	(eye irritation)		Treon et al. 1955
Rabbit	once	Dermal		200 mg/kg	(dermal irritation and discoloration)		IRDC 1972
		Bd Wt	2000 M	200 F mg/kg	(weight loss - amount not specified)		
Rabbit	0.25 hr	Ocular		11.6 ppm	(eye irritation)		Treon et al. 1955
Rabbit	2.5-3.6 hr	Ocular		1.25 ppm	(eye irritation)		Treon et al. 1955
Gn pig	2.5-3.6 hr	Ocular		1.25 ppm	(eye irritation)		Treon et al. 1955
Gn pig	once	Dermal	0.8 mg	31.7 mg	(skin discoloration and irritation)		Treon et al. 1955
Gn pig	0.25 hr	Ocular		11.6 ppm	(eye irritation)		Treon et al. 1955
Neurological							
Rabbit	once 4 hr			365 mg/kg	(ataxia and hypoactivity)		IRDC 1972

Table 2-3. Levels of Significant Exposure to Hexachlorocyclopentadiene - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL Less Serious	LOAEL Serious	Reference
INTERMEDIATE EXPOSURE						
Systemic						
Monkey	13 wk 5 d/wk 6 hr/d	Ocular	0.2 ppm			Rand et al. 1982a
Rat (Sprague-Dawley)	13 wk 5 d/wk 6 hr/d	Ocular	0.2 ppm			Rand et al. 1982a
Rat	6 wk 5 d/wk 7 hr/d	Ocular		0.3 ppm	(irritation of eyes and mucous membranes)	Treon et al. 1955
Rat	30 wk 5 d/wk 7 hr/d	Bd Wt	0.13 ppm			Treon et al. 1955
Mouse	30 wk 5 d/wk 7 hr/d	Ocular	0.13 ppm			Treon et al. 1955
Rabbit	6 wk 5 d/wk 7 hr/d	Ocular		0.3 ppm	(eye irritation during exposure)	Treon et al. 1955
Rabbit	30 wk 5 d/wk 7 hr/d	Ocular	0.13 ppm			Treon et al. 1955
Gn pig	6 wk 5 d/wk 7 hr/d	Ocular		0.3 ppm	(eye irritation)	Treon et al. 1955

Table 2-3. Levels of Significant Exposure to Hexachlorocyclopentadiene - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL	LOAEL		Reference
				Less Serious	Serious	
Gn pig	30 wk 5 d/wk 7 hr/d	Ocular	0.13 ppm			Treon et al. 1955

d = day(s); Gn Pig = guinea pig; hr = hour(s); LOAEL = lowest-observable-adverse-effect level; min = minute(s); NOAEL = no-observable-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x = times

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Nasal irritation, accompanied by nasal discharge and nasal lesions, was also observed in animals exposed to HCCPD vapors (IRDC 1972; Rand et al. 1982a; Treon et al. 1955). Contact of the vapors with the olfactory membranes most likely contributed to these effects. At vapor concentrations of 41.6 ppm or higher there was sneezing, mucus discharge from the nose, and salivation in rats, mice, guinea pigs, and rabbits (Treon et al. 1955). These signs were manifested almost immediately. Irritation of the mucous membranes took several minutes to appear with exposure concentrations of 11.1 or 12.4 ppm, but it took several hours to appear when the exposure concentration s were 0.9 or 1.4 ppm (Treon et al. 1955). Necrotizing or suppurative inflammation of the nasal passages was present in rats and mice after exposure to 0.4 ppm HCCPD for 13 weeks or 0.2 ppm for 2 years (NTP 1994).

Cardiovascular Effects. Rabbits exposed to single dermal doses of 569-5,919 mg/kg and greater displayed degenerative changes in the heart as determined by gross necropsy (Treon et al. 1955). This may have been the result of tissue autolysis.

Hepatic Effects. Rabbits exposed to single dermal doses of 401-5,719 mg/kg displayed necrosis of the liver as determined by gross necropsy (Treon et al. 1955). Degenerative changes persisted even 21 days after the exposure period in the animals that survived exposure.

Renal Effects. Rabbits exposed to single dermal doses of 401-5,719 mg/kg displayed degeneration and necrosis of the kidney tubules as determined by gross necropsy (Treon et al. 1955). These changes were still apparent 21 days after exposure period when the animals that survived the exposure period were sacrificed.

Endocrine Effects. No reports of endocrine effects in humans after dermal exposure to HCCPD were found.

Rabbits that were dermally exposed to HCCPD (401-5,719 mg/kg) had degenerative changes of the adrenal glands that were still apparent in survivors 21 days after exposure (Treon et al. 1955).

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Dermal Effects. Workers were exposed to HCCPD vapors for 3-15 days at a waste water treatment plant as a result of an inadvertent industrial release (Kominsky et al. 1980; Morse et al. 1979). Dermal complaints included skin irritation. These effects were more likely a consequence of the direct action of the HCCPD vapor on the skin, rather than systemic effects due to exposure to HCCPD through the lungs.

Brief periods of exposure to 19.2 ppm HCCPD for several seconds by one cleanup crew worker using no protective equipment at a waste water treatment plant caused skin irritation of the face and neck (Kominsky et al. 1980). Three workers wearing half-face protectors complained of skin irritation after exposure to 7.1 ppm for several seconds. Another four workers also reported skin irritation.

HCCPD in either its pure form or in solution appears to have a pronounced effect upon the epidermis based on results in guinea pigs, monkeys, and rabbits (Treon et al. 1955). At lesion-forming doses the skin became discolored (purple-colored) and inflamed; ulceration and fissuring of the surface followed (IRDC 1972; Treon et al. 1955). Eventually the ulcerated area became encrusted. If the animal did not die, the lesions healed with time. In one monkey, the lesion site was still hairless and scarred 13 months after exposure (Treon et al. 1955).

Ocular Effects. Brief periods of exposure to 19.2 ppm HCCPD for several seconds by one cleanup crew worker using no protective equipment at a waste water treatment plant caused lacrimation (Kominsky et al. 1980). Three workers wearing half-face protectors complained of lacrimation and soreness around the eyes after exposure to 7.1 ppm for several seconds.

Eye irritation was one of the major symptoms reported by humans exposed to HCCPD vapors for 3-15 days at a waste water treatment plant as a result of an inadvertent industrial release (Kominsky et al. 1980; Morse et al. 1979). From the 145 individuals who responded to a questionnaire immediately after exposure occurred, 86% complained of eye problems; in a follow-up questionnaire 6 weeks later, 16% of 177 respondents were still experiencing ocular irritation. Tearing and redness of the eyes were present in five individuals on the day of exposure.

Eye irritation accompanied by lacrimation was also observed in animals exposed to HCCPD vapors (IRDC 1972; Rand et al. 1982a; Treon et al. 1955). Contact of the vapors with the eye most likely contributed to these effects. At vapor concentrations of 41.6 ppm or higher the eyes were closed. There was reddening of

the eyelids and tearing in rats, mice, guinea pigs, and rabbits (Treon et al. 1955). These signs were manifested almost irnrnediately.

Unexpectedly, there were no reports of ocular irritation in the intermediate- or chronic-duration studies of HCCPD conducted by NTP (1994). When an unidentified amount of HCCPD was placed in the right conjunctival eye sac for only 5 minutes, it caused severe eye irritation (IRDC 1972). When the material was left in place for 24 hours, it caused corrosion of the tissues as well (IRDC 1972).

Body Weight Effects. No reports of body weight effects in humans after dermal exposure to HCCPD were found.

Weight loss occurred in rabbits even with a nonlethal dose (IRDC 1972; Treon et al. 1955).

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals after dermal exposure to HCCPD.

2.2.3.4 Neurological Effects

No studies were located regarding neurological effects in humans after dermal exposure to HCCPD.

Rabbits exposed to single dermal doses of HCCPD (401-5,719 mg/kg) displayed degenerative changes in the brain as determined by gross necropsy (Treon et al. 1955). These changes were still apparent 21 days after exposure in survivors. Exposure to 856 mg applied to the shaved shin of rabbits was accompanied by ataxia, hypoactivity, and a depressed breathing pattern (IRDC 1972).

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No studies were located regarding the following health effects in humans or animals after dermal exposure to HCCPD.

2.2.3.5 Reproductive Effects

2.2.3.6 Developmental Effects

2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.3.8 Cancer

No studies were located regarding carcinogenic effects in humans or animals after dermal exposure to HCCPD.

2.3 TOXICOKINETICS

Absorption of HCCPD occurs throughout the lungs, gastrointestinal tract, and skin based on both toxicokinetic data and the occurrence of toxic effects in animals exposed through these routes (Dorough and Ranieri 1984; El Darreer et al. 1983; Lawrence and Dorough 1981, 1982; Mendenhale 1977; Treon et al. 1955). The low levels of labeled HCCPD in the blood after oral dosing, when compared to inhalation dosing, may be evidence of poor gastrointestinal absorption due to binding to the gastrointestinal contents. Absorbed HCCPD is distributed to the liver, kidneys, and lungs. There is some tendency for this material to distribute to in adipose tissues. Distribution in rats differs from that in mice. The highest concentrations are found in the kidneys of rats and the livers of mice.

There have been no studies of the metabolism of HCCPD. Four to five radiolabeled compounds were isolated in extracts from the urine of exposed rats and seven from fecal matter, but these compounds were not identified (Dorough and Ranieri 1984). There was negligible degradation to carbon dioxide. Since HCCPD has a strong tendency to participate in cycloaddition reactions, it is possible that some of the materials excreted in the urine are the products of HCCPD reaction with cellular or extracellular biomolecules. Some of the fecal metabolites may be formed by the result of interaction with intestinal microbes.

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Absorbed HCCPD and/or its products are excreted principally via the kidneys; some material is also excreted in the bile. Unabsorbed material is removed with the fecal matter; some appears to remain free, and some is bound to the fecal solids.

2.3.1 Absorption

No data were located regarding absorption of HCCPD in humans by any exposure route. In rats, the route of exposure appears to have a significant effect on absorption. The low levels of radiolabel from ^{14}C-HCCPD in the blood after oral dosing, as compared to the intravenous and inhalation routes, may be evidence of poor gastrointestinal absorption.

2.3.1.1 Inhalation Exposure

Rats absorbed and retained an average of 83.9% of the radioactivity associated with the inhaled labeled compound during a l-hour exposure period (Lawrence and Dorough 1981). Retention increased to 95.2% after 2 hours (Lawrence and Dorough 1982).

2.3.1.2 Oral Exposure

The route of exposure appears to have a significant effect on absorption. The low levels of ^{14}C in the blood and tissues after oral dosing of rats with ^{14}C-HCCPD and the relatively large amount in the feces suggest that HCCPD is poorly absorbed from the gastrointestinal tract (Dorough and Ranieri 1984; Lawrence and Dorough 1982; Mehendale 1977; Yu and Atallah 1981). Estimates of absorption range from 25 to 40% (Dorough and Ranieri 1984; Lawrence and Dorough 1982; Mehendale 1977). In one study, a portion of the ingested HCCPD reacted with the contents of the gastrointestinal tract and was not available for absorption. When HCCPD was added to the contents of a rat's stomach, only 50% of what was added could be extracted with hexane. The unextractable HCCPD was found in both the liquid and solid fractions of the stomach contents (Lawrence and Dorough 1982).

The dosing medium may have an effect on the amount of HCCPD absorbed. In the work by Treon et al. (1955), the dosing vehicle was peanut oil. In the study by Abdo et al. (1984), corn oil was used. These two oils differ in their degree of unsaturation and, thus, in the number of double bonds that are potential reaction sites for HCCPD. If HCCPD reacted with double bonds in fatty acids, it would be less

bioavailable from the more unsaturated fat (corn oil). The LD_{50} for HCCPD in peanut oil was 471 mg/kg in male rats (Treon et al. 19.55) while the LD_{50} for HCCPD in corn oil was 630 mg/kg (IRDC 1972), suggesting that there is a slight difference in bioavailability.

2.3.1.3 Dermal Exposure

No studies were located regarding absorption of HCCPD in humans or animals after dermal exposure. However, absorption through both skin and ocular membranes does occur in amounts leading to effects on target tissues (liver and kidney) and sometimes death (IRDC 1972; Treon et al. 1955).

2.3.2 Distribution

No studies were located regarding the distribution of HCCPD in human tissue after any route of exposure.

In rats and mice, liver and kidney tissues are sites of HCCPD distribution with all routes of compound administration. In rats, higher levels accumulate in the kidneys than in the liver. In mice, the situation is reversed. When dosing occurs by the inhalation route, there is a high concentration of material in the lungs. The brain and fat have very low concentrations of HCCPD label, suggesting that the metabolites of this material are not lipid soluble.

2.3.2.1 Inhalation Exposure

The site of uptake, like the trachea and lungs of rats showed the highest concentration of ^{14}C-radiolabel 72 hours after inhalation exposure to a dose of 0.024 mg/kg labeled HCCPD. The concentration in the trachea was 107 ng/g and the concentration in the lungs was 7 1.5 rig/g (Lawrence and Dorough 1981, 1982). The concentration of ^{14}C in the kidneys (29.5 ng/g) was 8 times that in the liver (3.6 ng/g). Fat tissue was not a site of retention following inhalation of HCCPD. Only 11.4% of the administered dose was found in the tissues at 72 hours; 2% was found in the lungs and 7.8 % in the carcass.

Little or no radioactivity was present in the fat tissue or in the brain of rats 6 and 72 hours after exposure to ^{14}C-HCCPD (El Dareer et al. 1983). The largest percentage of the total dose remained in the lungs and kidneys at both 6 and 72 hours after exposure. The amount of ^{14}C-HCCPD in the lungs decreased from 4.5 to 1.6% in 66 hours and that in the kidneys decreased from 3.6 to 1.7%. At 72 hours, about 20% of the

radiolabel in the kidneys was unextractable, indicating some binding to tissues; the remainder was water soluble. In the lungs, 47% was unextractable and 53% was water soluble (El Dareer et al. 1983).

2.3.2.2 Oral Exposure

When rats were given a single dose of 25 mg/kg [^{14}C]HCCPD in corn oil, the concentration of radioactivity in blood rose slowly, reaching its maximum level at 4 hours (Yu and Atallah 1981). Blood levels were then relatively stable over the next 4 hours. The tissues were analyzed for the presence of label from HCCPD between 8 and 120 hours after compound administration. At both 8 and 24 hours, the highest concentration of label was in the kidneys. The liver contained 30-40% of the amount in the kidneys (Yu and Atallah 1981). Moderate amounts were present in the blood, lungs, adipose deposits, and gonads. At the end of 8 hours, the amount of label recovered from the carcass was 41%, the digestive system contained 36.3%, and the remaining tissues contained 4.1%. Similar results were found at the end of 24 hours when single doses of 2.5 or 25 mg/kg were administered in corn oil (Dorough and Ranieri 1984). The affinity of the gonadal tissue differed for males and females. The concentration in the ovaries peaked at 24 hours at 11.6 ppm with a 25 mg/kg dose, and was 0.98 ppm at the end of 3 days. The concentration in the testes was not determined at 24 hours, but was 0.32 ppm at the end of 3 days, one-third the concentration in the ovaries at that time.

When doses of 17.7 or 25 mg/kg were given to rats and the tissue metabolites were monitored after 72 hours, the amount (% of dose) in the kidneys was about twice that in the liver with the 25 mg/kg dose; the concentrations in the liver and kidneys were roughly equal for the 17.7 mg/kg dose (Yu and Atallah 1981). For both doses, 12-13% of the label that remained in the tissues at 72 hours was present in the adipose tissue.

The tissue distribution in mice differs from that in rats. In mice, the highest concentration of radiolabel from a single dose of 2.5 or 25 mg/kg was found in the liver rather than the kidneys (Dorough and Ranieri 1984). The amount in the kidneys was between 33 and 50% of that in the liver. The adipose tissues and gonads contained moderate concentrations of the radiolabel and the muscle and brain, low concentrations. As with the rats, the mouse ovaries had a higher affinity for HCCPD than the testes as demonstrated by the concentrations of label 3 days after compound administration.

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In both rats and mice, the tissue distribution pattern for radioactivity derived from [^{14}C]HCCPD was similar for single doses and multiple doses (0.06, 0.3, or 1.5 mg/kg/day in the diet for 30 days). For rats in the high-dose group, the concentration of label in the kidneys increased rapidly, reaching homeostasis at a concentration of about 7 ppm in about 10 days (Dorough and Ranieri 1984). The concentrations in the fat and ovaries also increased rapidly, reaching about 4 ppm for the fat and about 3 ppm for the ovaries. Steady state was reached in 10 days for the ovaries, but not until about 20 days for the fat tissues. The concentration in the liver reached steady state near the end of the 30-day treatment period and was roughly 50% of the value for the kidneys. Low levels of label were found in muscle (0.5 ppm) and brain (0.3 ppm). Once exposure ceased, tissue levels decreased quickly in the first 20 days post-treatment for all tissues except the fat. For both brain and muscle, the tissue concentration remained stable for the last 20 days of observation.

In mice, the concentration of label in the liver increased rapidly, reaching homeostasis at about 5 ppm in 7 days with a dose of 4.2 mg/kg/day (Dorough and Ranieri 1984). The concentration in the fat and ovaries also increased rapidly and was nearly equivalent to that in the liver. Steady state was reached by about 20 days for the ovaries (3 ppm) and fat (5 ppm). The concentration in the kidneys was about 50% of that in the liver. Low levels of label were found in muscle (0.8 ppm) and brain (0.2 ppm). Once exposure ceased, tissue levels decreased quickly in the first 10 post-treatment days for all tissues except the fat. For both brain and muscle, the tissue concentration remained stable for the last 20 days of observation.

2.3.2.3 Dermal Exposure

No studies were located regarding distribution of HCCPD in the tissues of humans or animals after dermal exposure.

2.3.2.4 Other Effects

Seventy-two hours after an intravenous dose of 0.59 mg/kg ^{14}C-HCCPD in Emulphore EL-620 and ethanol:water, 1: 1:4 (v/v), 39.0% remained in the tissues of rats. The following levels of ^{14}C-HCCPD label were observed: liver 13.9%, kidneys 1.2%, tail section 1.4% (site of injection), intestine 0.7%, lungs 0.3%, brain 0.l%, skin (ears) <0.l%, remaining carcass 18.4%, and blood 2.9% (El Dareer et al. 1983). Since an elevated level of ^{14}C-HCCPD label remained in the blood at 72 hours, the highest concentrations of

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^{14}C-HCCPD label in the liver and kidney after intravenous administration may be due to the added presence of blood in those tissues.

In a separate study, there was little difference in the percentage of radiolabel that was recovered 24 or 48 hours after 0.7 mg/kg HCCPD was administered intravenously in Emulphor® EL-620 (Yu and Atallah 1981). At 24 hours, 37% of the label was recovered and at 48 hours, 38% was recovered. The amount in the blood at 24 hours (15%) was less than that at 48 hours (26%). The kidneys contained 2-3% of the dose at both times and the liver contained about 5%. The amount in fat at 24 hours (1.2%) was greater than that at 48 hours (0.2%). The lungs contained 0.7-0.8% of the label.

Oral preexposure of rats to HCCPD at 0.05 mg/kg/day for 3 days increased the concentration of HCCPD in the kidneys from a challenge intravenous dose of ^{14}C-HCCPD. The hepatic concentration, biliary excretion, and blood decay curves appeared to be unaltered by preexposure to HCCPD (Mehendale 1977).

2.3.3 Metabolism

No studies were located concerning the metabolism of HCCPD in humans. Complete oxidation of this material is apparently limited, based on the small amount of radiolabel that is excreted as carbon dioxide (<1%) after exposure to ^{14}C-HCCPD in rats by the oral, inhalation, and intravenous routes (El Dareer et al. 1983).

Based on the levels of radioactivity in the blood following intravenous administration, [^{14}C]HCCPD was rapidly metabolized and distributed to blood, liver, kidneys, and lungs before being distributed to the peripheral tissues (Yu and Atallah 198 1). There is some metabolism of HCCPD by bacteria in the gastrointestinal tract (Yu and Atallah 1981).

When rat urine was extracted with a mixture of hexane and cyclohexanol, approximately 70% of the radiolabel from HCCPD dissolved in the organic phase (Mehendale 1977). Thin layer chromatography (TLC) of this extract suggested the presence of four labeled compounds in the urine; these compounds were not identified. Most of the HCCPD urinary metabolites or derivatives were considered to be nonpolar.

In a different study, ethyl acetate extraction of acidified urine recovered 33% of the radiolabel. When the aqueous phase was refluxed for 30 minutes and re-extracted with ethyl acetate, an additional 10% of the

radiolabel was recovered (Yu and Atallah 198 1). The urinary extracts were chromatogrammed using silica gel plates and a relatively nonpolar solvent (toluene/acetone/acetic acid, 75:20:5); 5 fractions were identified. Most of the material was polar, as indicated by the fact that Rf values were low. An additional 36% of the label was water soluble. These results indicate that urinary metabolites or derivatives are predominantly polar rather than nonpolar and are not in agreement with those of Mehendale (1977).

Identification of the chromatogram fractions using mass spectroscopy (MS) was not possible due to the presence of coextractives, several compounds in one fraction, and the polar nature of the metabolites (Yu and Atallah 1981). One major fraction was purified by high pressure liquid chromatography (HPLC). Based on its elution, this compound did not correspond to either HCCPD or any of four HCCPD potential metabolites (hexachloro-2-cyclopentanone, hexachloro-3-cyclopentanone, hexachloro-indone, or octachloro-3a,4,7,7a-tetrahydro-4,7-methanoindene- 1,8-dione).

Using TLC and a toluene/acetone/acetic acid solvent system, fecal matter was found to contain seven radioactive fractions (Yu and Atallah 1981). None of these fractions corresponded with the four potential metabolites listed above. With the fecal matter, only 10.6% of the label was recovered in an ethyl acetate extract, and 6.8% was relatively polar, based on its movement in the solvent system. Another 32% of the label was extracted from the fecal matter after refluxing with acid. A portion of the fecal label (21%) was found as unextractable solids and 25% was water soluble. In a separate rat study, 20% of the fecal label was extracted in benzene after continuous feeding of 0.06 or 0.3 mg/kg/day HCCPD in the diet for 30 days, but only 7-12% was extracted with a dose of 1.5 mg/kg/day (Dorough and Ranieri 1984).

The affinity that HCCPD (or its products) has for the Clara cells in the lungs and the production of electron-lucent granules in these cells after inhalation exposure situations (Rand et al. 1982b) suggests that HCCPD may interact with the microsomes in rats and monkeys to form a metabolite (possibly a free radical) that binds to secretory molecules and changes their ability to be transported from the cell. When the granular pigments that are found in the lungs and nasal passages after long-term inhalation exposure to HCCPD were stained with reagents to detect mucopolysaccarides, mucoproteins, carbohydrates, iron, reducing substances, and acid fast substances, all tests were negative except those for reducing substances (NTP 1994). These results support the classification of the pigment as lipofuscin or ceroid material (substances that are formed through free-radical-induced crosslinking of cellular lipids. These results do not confirm the presence of either of these complexes.

It is also possible that HCCPD rather than a metabolite could react directly with cellular alkenes in a spontaneous Diels-Alder cycloaddition reaction. The occurrence of such a non-enzymatic reaction could explain why HCCPD causes effects at the point of contact for all exposure routes. It also explains the tissue-binding properties of HCCPD.

2.3.4 Elimination and Excretion

No data were identified for excretion of HCCPD by humans after any route of exposure. Based on animal data, the route of exposure appears to have a significant effect on elimination and retention. In rats, inhaled ^{14}C-HCCPD was primarily excreted by the kidneys, and the oral dose was primarily eliminated in the feces. These differences may be attributable to the poor absorption from the gastrointestinal tract (El Dareer et al. 1983; Lawrence and Dorough 1981).

2.3.4.1 Inhalation Exposure

Inhaled ^{14}C-HCCPD was excreted primarily in the urine (33.1%) of rats with a smaller percentage eliminated in the feces (23.1%) 72 hours after dosing (Lawrence and Dorough 1981, 1982). Most of the radiolabel was eliminated in the first 24 hours; only 70% of the radiolabel was recovered.

Higher values for rat urinary and fecal excretion were obtained after inhalation exposures that resulted in absorbed doses of 1.3-1.8 mg/kg HCCPD (El Dareer et al. 1983). The urine contained 41% of the label after 6 hours and 40% after 72 hours. The label in the feces entered the gastrointestinal tract with the bile. Only about 1% of the label was exhaled as carbon dioxide, indicating that the pulmonary route is not a major route of excretion as suggested by Mehendele (1977).

2.3.4.2 Oral Exposure

The amount of radiolabel found in rat urine in a 72-hour period after single oral doses of 2.5-61 mg/kg ranged from 13 to 35% and the amount in the feces ranged from 64 to 80% (Dorough and Ranieri 1984; El Dareer et al. 1983; Lawrence and Dorough 1982; Yu and Atallah 1981). In each case, most of the label was excreted in the first 24 hours. About 16-18% of the radiolabel entered the fecal matter with the bile (Dorough and Ranieri 1984; Lawrence and Dorough 1981). Less than 1% of HCCPD was metabolized to carbon dioxide; there were trace amounts that were exhaled as volatiles other than carbon dioxide (≤0.3%)

(El Dareer et al. 1983). In mice, the urine contained 15% of the dose after 72 hours and the feces contained 74% following a dose of 25 mg/kg HCCPD dissolved in corn oil (Dorough and Ranieri 1984).

When HCCPD was given to rats at doses of 0.06, 0.3, or 1.5 mg/kg/day in feed for 30 days, urinary excretion of label ranged from 5 to 9% at the end of the exposure period and fecal excretion ranged from 62 to 69% (Dorough and Ranieri 1984). When mice were fed 0.2,0.8, or 4.2 mg/kg/day under the same study conditions, urinary excretion ranged from 7 to 12% and fecal excretion ranged from 54 to 68%.

In one study, some of the HCCPD in the feces was volatile and was considered to be unmetabolized (El Dareer et al. 1983). In another study, some of the fecal label was bound to insoluble matter (Yu and Atallah 1981). Fecal microbes appear to metabolize HCCPD rather rapidly. The half-life for degradation of HCCPD in a spiked fecal homogenate was 6.2 hours in the presence of mercuric chloride and 1.6 hours in the absence of mercuric chloride (Yu and Atallah 1981). Mercuric chloride is a bacterial inhibitor and, thus, minimized microbial metabolism when it is present in the medium.

2.3.4.3 Dermal Exposure

No studies were located regarding excretion of HCCPD by humans or animals after dermal exposure.

2.3.4.4 Other Exposure

Data are available from two studies that evaluated the excretion of radiolabel from ^{14}C-HCCPD after intravenous dosing. When a dose of 0.01 mgkg in dimethylsulfoxide or a 10:4:1: mixture of saline, propylene glycol, and ethanol was given to rats, 22% was excreted in the urine and 3 1% in the feces over 72 hours (Lawrence and Dorough 1982). A total of 85% of the label was recovered. With a 0.59 mg/kg in emulphor, ethanol, water (1:1:4) intravenous dose, rats excreted 16% in the urine and 34% in the feces (El Dareer et al. 1983). A very small amount of label (0.02%) was excreted as exhaled carbon dioxide and other volatiles.

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 and Krishnan 1994; Andersen et al. 1987). 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 substancespecific 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 HCCPD 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.

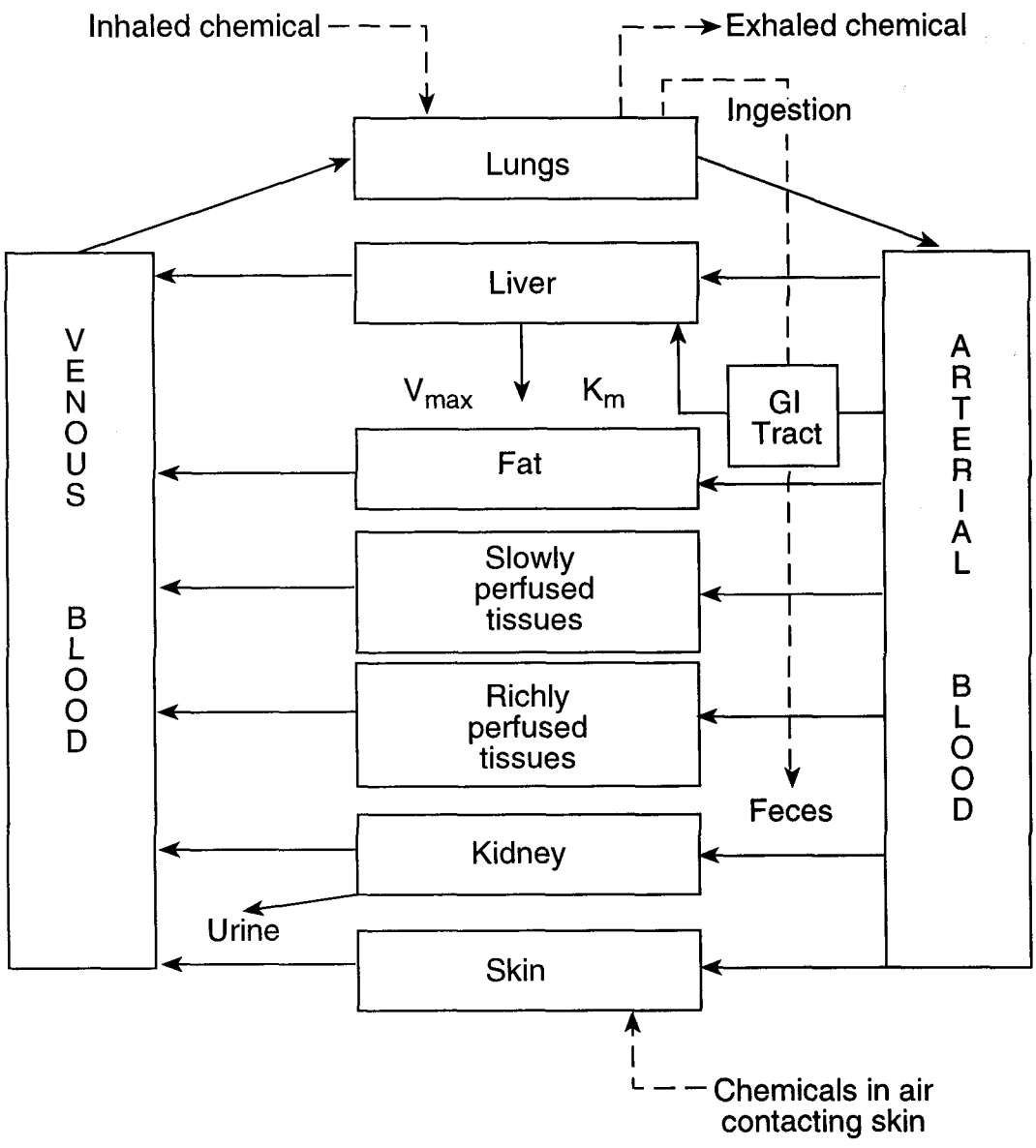
No PBPK models for HCCPD were found in the literature. The existing kinetic data (see Section 2.3) are insufficient for developing a model.

2.4 MECHANISMS OF ACTION

Little information was located regarding the mechanism of action of HCCPD. It can be postulated, however, that some of its toxic properties are a consequence of its reactivity in Diels-Alder reactions where a conjugated diene combines with a substituted or unsubstituted alkene (a dienophile) in a cycloaddition reaction (EPA 1991a; Morrison and Boyd 1983). Biological tissues contain a large number of potential reactants for cycloaddition reactions (quinones, sterols, 2-alkenoic acids, unsaturated fatty acids, and unsaturated fatty acid derivatives). HCCPD can also undergo addition and substitution reactions (EPA 199la) or be oxidized by way of the mixed function oxidase system (Rand et al. 1982b).

The attack of HCCPD on tissues can be regarded as a 2-phase phenomenon. Primary lesions are formed by direct contact of the material with exposed tissues (nasal passages, lungs, forestomach, and skin) (Abdo et al. 1984; Rand et al. 1982a ;Treon et al. 1955). These lesions can be hypothesized to result from reactions of HCCPD or one of its metabolites with epithelial cells impairing function and resulting in cell death. Once exposure ceases, new cells replace the damaged ones, and slow recovery begins (Rand et al.

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



Source: adapted from Krishnan et al. 1994

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

1982a; Treon et al. 1955). Secondary lesions form at sites distant from the point of contact when systemic circulation carries unreacted HCCPD or a metabolite to lungs, liver, kidney, heart, brain, and adrenals. These tissues may become targets for HCCPD by virtue of their physiological function (liver and kidney) or the tendency for their cell products or membrane components to react with HCCPD or an HCCPD metabolite (lung, adrenal).

There are minor changes in Clara cells of the lung epithelium in rats and monkeys when exposure occurs by the inhalation route (Rand et al. 1982b). Electron-lucent inclusions become apparent in the affected cells. There, inclusions could represent the reaction products of HCCPD or a microsomal metabolite with the carbon double bonds in phospholipids, prostaglandins, eicosanoids, and other molecules within the lung tissues. Alternatively, the changes in the lung could be the result of free radical modification of the cellular molecules that form the yellow-brown pigment found in the epithelial cells of the respiratory tract after long-term exposure (NTP 1994). Clara cells have particularly rich concentrations of microsomes and enzymes of the mixed function oxidase system.

Effects of HCCPD on the brain may also be a reflection of the reaction of either HCCPD or a metabolite with brain lipids. Degenerative brain effects were not seen in rats exposed to low inhalation concentrations of up to 0.2 ppm (6 hours a day, 5 days a week) for 13 weeks (Rand et al. 1982a), but they were seen with acute exposure to higher dose (Treon et al. 1955). At low exposure levels, the reactivity of HCCPD makes it unlikely that reactive species would be present in the blood at high enough concentrations to cause significant change in a secondary site such as the brain, but at higher doses, transport of reactive material across the blood-brain barrier is possible.

The effects of HCCPD on the adrenal glands (Rand et al. 1982a; Treon et al. 1955) may be a reflection of its ability to combine with the unsaturated carbons in sterols produced by this gland. The hydroxyl functional group of a sterol is on a carbon adjacent to the double bond and can activate that bond to cycloaddition reactions. Such reactions would require exposure to large doses of HCCPD so that reactive material would reach the adrenal gland.

2. HEALTH EFFECTS

2.5 RELEVANCE TO PUBLIC HEALTH

Overview.

HCCPD is a highly volatile, reactive liquid that has entered the environment primarily as a result of its use in the manufacture of pesticides and flame-retardant chemicals. In recent years, limited use of pesticides synthesized from HCCPD has decreased the possibility of exposure to pesticide residues among most members of the population. Exposure to materials at hazardous waste sites is still possible.

Some data pertaining to human exposures to HCCPD (100-200 people) come from an incident where waste water treatment plant workers and clean-up crews members were exposed after an industrial discharge. Irritation of the eyes, skin, and breathing passages were the primary complaints of those exposed. Less frequently, there were complaints of nausea and headaches. Issues relevant to children are explicitly discussed in Section 2.6, Children's Susceptibility, and Section 5.6, Exposures of Children.

Animal studies confirm the observation that HCCPD vapors irritate the eyes and breathing passages. In addition, the hmg epithelium is damaged by HCCPD contact, leading to edema, hemorrhage, and fibrosis. The extent of damage is related to the dose. Even doses that cause no histopathological changes that can be seen under the light microscope cause ultrastructural changes in Clara cells that are visible by electron microscopy, and accumulation of granular pigmented material in the epithelial cells of the nose, trachea, and lungs.

High oral and dermal doses also cause lung damage in exposed animals. At least a portion of the damage observed may be the result of inhalation of HCCPD vapors during dosing and thereby may not be due to systemic toxicity. The effective doses for inhalation exposures are lower than those for oral and dermal exposures. Reaction of HCCPD with the contents of the gastrointestinal tract or the cellular constituents of the epidermis seems to limit oral and dermal uptake.

Liquid HCCPD causes lesions at the point of tissue contact with oral and dermal dosing. Lesions form in the rat forestomach when HCCPD is administered by gavage. When administered dermally, lesions form at the point of skin contact.

2. HEALTH EFFECTS

Other target tissues for HCCPD, based on animal studies, are the kidneys, liver, ovaries, adrenals, brain, and heart. Damage to the kidney tubules was seen with intermediate-duration oral doses of 38 mg/kg/day in rats and 70 mg/kg/day in mice, and tubular necrosis was apparent in rats, mice, guinea pigs, and rabbits acutely exposed to concentrations as low as 0.3 ppm and intermediate-duration exposures as low as 0.13 ppm. Effects on the liver (minimal weight changes) are not definitive at low doses. Lesions appeared in the liver, brain, adrenals, and heart with high doses and, in mice, ovarian inflammation was associated with chronic exposure to low doses of HCCPD.

HCCPD appears to have no histological effects on the male reproductive organs of rats and mice. There have been no reproductive studies of HCCPD to determine if it affects fertility and embryogenesis. Studies in mice and rabbits indicate that HCCPD is not developmentally toxic at doses of up to 45 mg/kg/day.

Minimal Risk Levels for HCCPB

Inhalation MRLs

- An MRL of 0.01 ppm has been derived for intermediate-duration inhalation exposure (15-364 days) to HCCPD .

This MRL was calculated using a LOAEL of 0.2 ppm based on structural effects on the bronchial epithelial cells of rats (Rand et al. 1982b). Electron microscopic examination revealed a statistically significant increase in the mean number of electron-lucent inclusions in the Clara cells at a concentration of 0.01 ppm or greater. The importance of this finding is not clear; nevertheless, it does show that the pulmonary lining can be affected. Clara cells are nonciliated cells that line the terminal bronchioles and contribute materials to the extracellular lining of the peripheral airways. In addition, they contain mixed function oxidases that are active in detoxifying inhaled contaminants. Thus, Clara cells are biomarkers of exposure, and not effect.

Since HCCPD is a category 1 gas, a $NOAEL_{HEC}$ was calculated. An RGDR of 1.95 was calculated using the surface area of the entire respiratory tract. An uncertainty factor of 30 (3 for extrapolation from humans to animals using a $NOAEL_{HEC}$ and 10 for human variability) was used in the calculation of the MRL. Exposure concentrations were not normalized over time due to the high reactivity of HCCPD and its

tendency to form lesions on directly exposed tissues. The chemical exerts a direct contact effect, and the effects are concentration- rather than time-dependent.

- An MRL of 0.2 ppb has been derived for chronic-duration (365 days or more) inhalation exposure to HCCPD.

This MRL was derived from the NTP (1994) bioassay where yellow-brown granular pigmentation of the nasal epithelium, trachea, and/or bronchioles was noted in rats after 15 months or 2 years of exposure to concentrations of 0.01-0.2 ppm HCCPD for 6 hours a day, 5 days a week. In all cases, the nasal tissues were affected to a greater extent than the lungs or trachea, suggesting that pigment formation was an *in situ* reaction resulting from the contact of the vapor with the mucosa, which increases the half-life of some mucosal components. The survival of the exposed animals did not differ from the controls, suggesting that the pigment had, at best, a minimal effect on organ function. Since HCCPD is a category 1 gas, a $LOAEL_{HEC}$ was calculated. An RGDR of 2.4 was calculated using the surface area of the entire respiratory tract. An uncertainty factor of 90 (3 for minimally adverse cellular changes, 3 for extrapolation from humans to animals using a $LOAEL_{HEC}$ and 10 for human variability) was used in the calculation of the MRL. Exposure concentrations were not normalized over time due to the high reactivity of HCCPD and its tendency to form lesions on contact with exposed tissues. The chemical exerts a direct contact effect, and the effects are concentration- rather than time-dependent.

An MRL was not derived for acute-duration inhalation exposure. An acute-duration exposure study was available for workers in a sewage treatment plant who were exposed to HCCPD as a result of a large industrial release (Kominsky et al. 1980; Morse et al. 1979). Workers experienced breathing difficulties and tracheobronchial irritation as well as sore throat and chest discomfort. Exposure duration was presumed to be from 3 to 5 days. Concentrations to which the workers were exposed could not be firmly established. Because exposure duration or concentration could not be determined with certainty, these data are not adequate for deriving an acute MRL. ACGIH also adopted the 0.01 ppm (0.01 mg/m^3) exposure limit for HCCPD (ACGIH 1998).

HCCPD caused inflammation and hyperplasia in nasal and lung epithelium in rats exposed to a concentration of 0.5 ppm (highest concentration) for 5 days and allowed to recover for 21 days, but no effects were seen at concentrations of 0.1 I ppm or less for up to 10 days of exposure except for a marginal reduction in liver weight and a slight decrease in body weight (Rand et al. 1982a). The usefulness of these

data are limited due to a high mortality in the high-dose group. Three of the 5 exposed males died either during the 5-day exposure period or during the 2 l-day recovery period. The resulting MRL calculated from this study would be lower than the intermediate-duration inhalation MRL calculated from Rand et al. (1982a) (see above). Therefore, the calculated intermediate-duration inhalation MRL is protective of acute exposures.

Oral MRLs.

- An MRL of 0.1 mg/kg/day has been derived for intermediate-duration (15-364 days) oral exposure to HCCPD.

This MRL was calculated using a NOAEL of 19 mg/kg/day based on the absence of renal lesions in rats exposed to HCCPD for 13 weeks, 5 days/week (Abdo et al. 1984). Lesions were seen in the terminal sections of the proximal tubules at a LOAEL of 38 mg/kg/day. Doses were normalized to account for a 5 days a week exposure and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) was applied. A NOAEL of 10 mg/kg/day and a LOAEL of 19 mg/kg/day were observed for epithelial hyperplasia and inflammation of the forestomach in female rats. However, humans lack an anatomical equivalent to the rat forestomach. Accordingly, the NOAEL of 10 mg/kg/day for this end point was not used as the basis for the MRL.

No data were located on effects of acute-duration oral exposure in humans or animals except single highdose exposures (261-1,959 mg/kg/day) in rats that resulted in death (IRDC 1972; Treon et al. 1955). An acute MRL for this exposure route has not been derived.

No data were located on the effects of chronic-duration oral exposure in humans or animals. A chronic MRL for this exposure route has not been derived.

Death. No studies were located regarding lethality in humans after exposure to HCCPD. HCCPD was lethal to animals by all exposure routes (Abdo et al. 1984; NTP 1994; Rand et al. 1982a; Treon et al. 1955). Compound concentrations, duration, and route of exposure influenced lethality. Exposure by the inhalation route appeared to be most toxic (NTP 1994; Rand et al. 1982a; Treon et al. 1955); oral exposure is less toxic because HCCPD binds to the contents of the gastrointestinal tract (Abdo et al. 1984; Lawrence and Dorough 1982). Mice seem to be more susceptible to death than rats following inhalation

exposure to HCCPD (NTP 1994; Treon et al. 1955) while rats are more susceptible than mice when exposure is oral (Abdo et al. 1984). The small diameter of the air passages, which become even narrower as the result of HCCPD-induced inflammation, may explain the high incidence of death in mice with inhalation exposure. Guinea pigs are less likely to be affected than rats, mice, and rabbits, and appear to have an adaptive response to intermediate-duration, low-dose exposures (Treon et al. 1955). Adaptive responses were not apparent in rats, mice, and rabbits. The lowest lethal concentration for oral exposures was 0.04 ppm in mice (NTP 1994) and 75 mg/kg/day in rats (Abdo et al. 1984). Exposure to 0.2 ppm for 2 years decreased the longevity of female mice (NTP 1994).

Animal data suggest that HCCPD could be lethal to humans if there were a sudden release of a large amount of vapor from a drum or other vessel at a hazardous waste site resulting in acute exposures to a high concentration. The odor, appearance, and irritating effects of the vapors on the eyes and nose (Kominsky et al. 1980; Morse et al. 1979) would alert the victim to the presence of a noxious substance. The toxicity of HCCPD makes the use of protective equipment advisable at any site where contact with this material is possible.

Systemic Effects.

All systems appear to be vul,nerable to HCCPD toxicity with the exception of the musculoskeletal and hematological systems. The musculoskeletal system has not been thoroughly evaluated in any of the studies of HCCPD toxicity.

Respiratory Effects. The lungs are vulnerable to HCCPD after exposure by every route. In humans acutely exposed to concentrations of greater than 0.97 ppm (100-200 people, exact concentration not known) as the result of an industrial discharge, respiratory complaints (tracheobronchial irritation and discomfort, sore throats, cough, chest discomfort, and breathing difficulty) were reported (Kominsky et al. 1980; Morse et al. 1979). Pulmonary function tests and chest X-rays were normal for those individuals examined (Kominsky et al. 1980). When one individual was exposed to 19.2 ppm for several seconds, he experienced shortness of breath and chest discomfort (Kominsky et al. 1980). Respiratory irritation was reported by workers and cleanup crew members exposed to HCCPD at a waste water treatment plant (Kominsky et al. 1980). Exposed individuals complained of nasal irritation and sinus congestion. These effects were more likely a consequence of the direct action of the HCCPD vapor on the mucus membranes than systemic effects due to exposure through the lungs.

2. HEALTH EFFECTS

Nasal irritation accompanied by nasal discharge was observed in animals exposed to HCCPD vapors (Rand et al. 1982a; Treon et al. 1955). Nasal lesions caused by concentrations of 0.022-0.5 ppm HCCPD over a 5-10-day period healed within 3 weeks (Rand et al. 1982a). In animals, concentrations of less than 0.9 ppm HCCPD for durations of 2 days or less, or a concentration of 0.13 ppm for up to 30 weeks caused no overt symptoms of respiratory distress (Treon et al. 1955). However, at higher concentrations, breathing patterns became irregular and the animals were gasping for breath. Even under conditions where there were no apparent effects on respiration, the tissues of the bronchi and alveoli were inflamed, hyperemic, and edematous (Treon et al. 1955). The higher exposure concentration, the more severe the tissue inflammation. A yellow-brown pigment was found in the nasal cavity, lungs, and/or trachea of all rats and mice exposed to concentrations of 0.01-0.2 ppm for 15-24 months (NTP 1994). A hyaline or fibrinoid membrane and proliferation of fibrous tissue into the bronchus, bronchiole, and alveoli appeared with the most severe lung necrosis (Treon et al. 1955).

Under exposure conditions where there were no apparent histopathological effects (0.01 ppm for 14 weeks), electron microscopy of the Clara cells of the alveolar epithelium of rats revealed electron-lucent granules. These same inclusions were seen in one monkey exposed to 0.2 ppm for 14 weeks (Rand et al. 1982b). Additional research will be necessary to determine if these inclusions are associated with impaired cell function and to evaluate the influence of species differences in respiration rates and Clara cell structure on the occurrence of granules. The increased values for hemoglobin concentration and hematocrit observed after 12 weeks in male rats exposed to 0.01 ppm HCCPD, females exposed to 0.05 ppm, and males and females exposed to 0.2 ppm (Rand et al. 1982a) provide some support for impaired lung function. Some rats exposed to 0.4 ppm for 13 weeks also had increased hemoglobin and hematocrit values (NTP 1994). These changes could reflect a compensatory physiological response to impaired oxygen transfer across the alveolar membranes.

Sudden releases of HCCPD vapors from containers at hazardous waste sites pose the greatest risk to people who live in these areas. If there were a release of HCCPD into the air at or near a hazardous waste site, it is highly likely that some effects on the respiratory system would be experienced by exposed individuals, even with low exposure concentrations. Low-level exposure concentrations (1-19.2 ppm) can cause respiratory irritation within seconds or minutes, although this effect was observed in only one exposed person (Kominsky et al. 1980; Morse et al. 1979). Direct contact with HCCPD vapors would be likely to cause damage. It is important for workers at sites that may contain HCCPD to use proper protective equipment.

2. HEALTH EFFECTS

Cardiovascular Effects. There are minimal data from human HCCPD exposure situations that relate to the cardiovascular system. In several humans, the levels of LDH and AST were elevated (Kominsky et al. 1980; Morse et al. 1979). These enzymes can be released to the systemic circulation following damage to the heart muscle or liver. However, because these enzymes are not exclusively associated with heart damage, their presence cannot be regarded as evidence that HCCPD has a direct effect on the heart in the absence of other tests of heart function.

Diffuse degeneration of the heart muscle was seen in animals after inhalation, oral, and dermal exposures (Treon et al. 1955). The amount of tissue damage was directly related to the dose and may have been at least partly due to tissue autolysis. Tissue damage was seen in rats at concentrations of 0.3 ppm and greater for inhalation exposures and 26 mg/kg and greater for oral exposures. The doses associated with tissue damage were not specified for dermal exposures (Treon et al. 1955). There was no histopathological examination of the tissues and no testing for cardiac function in this study. There were no histopathological changes in the hearts of rats or mice exposed to concentrations of 0.04-0.4 ppm for 13 weeks or 0.01-0.2 ppm for 2 years (NTP 1994). There was an increase in relative heart weight in male rats exposed to 0.4 ppm, but not in male rats at lower doses (0.04 and 0.15 ppm). Female rats and mice of both sexes were not affected.

Although the data from the NTP (1994) studies indicate that the risk is minimal at low doses, it is premature to draw any conclusions concerning the potential for cardiovascular damage resulting from human exposure to HCCPD in the environment.

Gastrointestinal Effects. Humans exposed to HCCPD through inhalation had some complaints of nausea and abdominal cramps (Morse et al. 1979). No other gastrointestinal symptoms were reported. Rats given single oral doses of 261-1,959 mg/kg had diarrhea (Treon et al. 1955), but this effect was not reported for inhalation exposure to concentrations of 0.04-2 ppm for up to 13 weeks (NTP 1994) or oral doses of up to 150 mg/kg/day in rats and 300 mg/kg/day in mice (Abdo et al. 1984). With single doses of 261 mg/kg and with daily doses of 10 mg/kg for 13 weeks, inflammation, hyperplasia, and necrotic lesions appeared in the forestomach of rats (Abdo et al. 1984; Treon et al. 1955). There were no observable effects on the stomach lining in rats at doses of 19 mg/kg/day or less (Abdo et al. 1984). It is possible that erosion of the gastrointestinal epithelium might occur as a result of contact exposure to HCCPD through contaminated drinking water or foods. However, humans do not have a forestomach and, thus, may not respond to HCCPD exposure in the same manner as rats. In addition, it is unlikely that exposure of this kind would

occur. No histopathological changes were seen in the esophagus, stomach, or intestines of rats and mice that were exposed to 0.01-0.2 ppm HCCPD vapors over a 2-year period (NTP 1994).

Hematological Effects. The only effects of HCCPD on hematological parameters (slightly elevated packed red cell volumes, hemoglobin concentration, and erythrocyte count) were seen in animals (NTP 1994; Rand et al. 1982a). These effects were a compensatory response to hemorrhagic damage to the lungs following inhalation exposure rather than direct effects on hematopoiesis (Rand et al. 1982a). No hematological effects were observed in animals when exposure occurred by the oral or dermal route. Exposure of humans to HCCPD at hazardous waste sites is unlikely to cause hematological effects unless there is hemorrhagic damage to the lung.

Hepatic Effects. Elevated values for LDH, AST, ALT, and/or AP were seen in a small number (about 18) of the 145 waste water treatment workers and 97 clean-up crew members after exposure to HCCPD at a sewage treatment plant. These enzymes were not elevated in blood samples taken three or more weeks after the initial samples (Kominsky et al. 1980; Morse et al. 1979). For eight of the cleanup crew members, these biochemical indices of possible liver damage were abnormal in more than one blood sample (Kominsky et al. 1980).

In animals, mild to moderate liver damage was a common manifestation of exposure to HCCPD by all routes in the studies by Treon et al. (1955). Exposure concentrations ranged from 0.13 to 66 pm and exposure durations ranged from 15 minutes to 30 weeks for inhalation conditions. For the oral route, single doses of 168-1,959 mg/kg were given, and for the dermal route, single doses of 401-5,719 mg/kg were used. These changes may have been the result of autolysis of tissues following death. Liver weights were slightly reduced with inhalation exposures of 0.01-0.5 ppm for 5 days to 13 weeks (Rand et al. 1982a), but not with 13-week inhalation of 0.04-0.4 ppm HCCPD vapors by rats or mice (NTP 1994) or oral exposures of up to 150 mg/kg/day for 13 weeks in rats and up to 300 mg/kg/day in mice (Abdo et al. 1984). The biochemical parameters, LDH, AST, ALT, and AP were not influenced by inhalation exposure to 0.01-0.5 ppm HCCPD (Rand et al. 1982a). It is not clear whether or not exposure to HCCPD could have an impact on liver function in individuals exposed to this substance at hazardous waste sites. Available evidence indicates that the risks of hepatic damage are minimal.

2. HEALTH EFFECTS

Renal Effects. Urine samples were collected from workers and cleanup crew members exposed to HCCPD at a waste water treatment plant. Proteinuria was the only abnormality seen; it was identified in six workers immediately after exposure, but not 3 weeks later (Morse et al. 1979).

Inhalation, oral, and dermal exposure to HCCPD caused renal tubular necrosis in animals (Treon et al. 1955). Inhalation exposure concentrations ranged from 0.13 to 66 pm and durations ranged from 15 minutes to 30 weeks. For oral exposures, single doses of 168-1,958 mg/kg were given and for dermal exposures, the doses were 40 l-5,719 mg/kg.

No kidney damage was seen in rats or mice exposed by inhalation to 0.01-0.4 ppm for 13 weeks (NTP 1994; Rand et al. 1982a), or to 0.01-0.2 ppm for 2 years (NTP 1994). However, 15-month exposures to 0.01-0.2 ppm were associated with an increase in volume and/or specific gravity in the urine in both rats and mice (NTP 1994).

Lesions were located in the terminal sections of the proximal tubules of the kidney cortex of rats given 38-150 mg/kg/day HCCPD and female mice given 75-300 mg/kg/day by gavage for 13 weeks (Abdo et al. 1984). There were changes in renal epithelial cell structure, and brown granular pigment debris protruded into the lumen of the kidney tubules.

Based on animal data, chronic exposure to HCCPD from a hazardous waste site might result in impaired kidney function due to changes in tubules.

Dermal Effects. Dermal irritation was a symptom reported by workers and cleanup crew members exposed to HCCPD at a waste water treatment plant (Kominsky et al. 1980). Exposed individuals complained of skin irritation. These effects were more likely a consequence of the direct action of the HCCPD vapor on the skin than systemic effects due to exposure through the lungs.

If there were a release of HCCPD into the air at or near a hazardous waste site, it is highly likely that some effects on the skin would be experienced by exposed individuals even with low exposure concentrations. Direct contact with liquid HCCPD would be likely to cause chemical burns and ulceration. It is important for workers at sites that may contain HCCPD to use proper protective equipment.

2. HEALTH EFFECTS

Ocular Effects. Eye irritation was one of the major symptoms reported by workers and cleanup crew members exposed to HCCPD at a waste water treatment plant (Kominsky et al. 1980; Morse et al. 1979). From the 145 individuals who responded to a questionnaire immediately after the exposure incident, 59% complained of eye problems; in a follow-up questionnaire 6 weeks later, 9% of 177 respondents were still experiencing ocular irritation. Eye irritation occurred with exposure concentration as low as 0.009 ppm (Kominsky et al. 1980). These effects were more likely a consequence of the direct action of the HCCPD vapor on the mucus membranes than systemic effects due to exposure through the lungs.

Eye irritation accompanied by lacrimation was observed in animals exposed to HCCPD vapors (Rand et al. 1982a; Treon et al. 1955). Nasal lesions caused by concentrations of 0.022-0.5 ppm HCCPD over a 5-10-day period healed within 3 weeks (Rand et al. 1982a).

If there were a release of HCCPD into the air at or near a hazardous waste site, it is possible that some effects on the eyes would be experienced by exposed individuals even with low exposure concentrations. It is important for workers at sites that may contain HCCPD to use proper protective equipment.

Other Systemic Effects. No studies were located regarding other systemic effects in humans after inhalation exposure to HCCPD.

Rats exposed to HCCPD vapors (0.5 ppm) for 10 days ate less food than controls and they also lost weight. At lower doses (0.022 and 0.01 ppm), the weight gain was diminished (Rand et al. 1982a). Decreases in weight gain were also noted in male rates and male mice with 13-week inhalation exposure to 0.4 ppm HCCPD (NTP 1994) and with oral exposures to 38 mg/kg/day in rats and 75 mg/kg/day in mice (Abdo et al. 1984).

There were degenerative changes in the adrenal glands of rats, mice, guinea pigs, and rabbits after inhalation, oral, and dermal exposures to HCCPD (Treon et al. 1955). The weights of the adrenal glands were also significantly reduced in rats exposed to 0.5 ppm for 10 days (Rand et al. 1982a). However, no changes in the histopathology of the adrenal glands were seen with 13-week exposures of rats and mice to 0.04-0.4 ppm or lifetime exposures to 0.01-0.2 ppm (NTP 1994). Adrenal function was not monitored in any of the studies of HCCPD toxicity.

2. HEALTH EFFECTS

Immunological and Lymphoreticular Effects. There are no human data to indicate that HCCPD affects the immunological system; in the animal studies that have been conducted, there were no histopathological effects on the spleen or thymus (NTP 1994; Rand et al. 1982a). No data were identified from a study designed to monitor immunological response to xenobiotic materials.

Neurological Effects. Exposure to HCCPD vapors was associated with headaches in 45% of 145 individuals who responded to a questionnaire after being exposed at a waste water treatment plant (Morse et al. 1979). As much as 6 weeks later, 18% of 177 respondents were still experiencing headaches. Tremors were noted in animals acutely exposed to HCCPD vapor concentrations of 41.6 ppm or greater (Treon et al. 1955). Rats exposed to concentrations of 0.4-2 ppm were described as listless after l-3 weeks of exposure (NTP 1994). The higher the dose, the sooner the listlessness was noted. It must be remembered that these same doses were also lethal. Thus, the listless behavior could well have been a symptom of impending death rather than HCCPD neurotoxicity. Scattered degenerative brain lesions were seen following acute- and intermediate-duration doses of 0.13 ppm or more, or acute oral doses of 579 mg/kg/day or more. With dermal exposure, the doses associated with effects on the brain were not specified (Treon et al. 1955).

Based on these data, individuals could get headaches if they are exposed to HCCPD at a hazardous waste site where vapors are released into the air.

Reproductive Effects. No studies were located regarding reproductive effects in humans after inhalation, oral, or dermal exposure. Limited data suggest that HCCPD did not adversely affect reproductive organs in rats exposed to vapors of HCCPD (up to 0.5 ppm) or in rats or mice after oral exposure to 150 or 300 mg/kg/day (Abdo et al. 1984). A lack of adverse effects on male reproduction has been confirmed in a dominant lethal test in mice (Litton Bionetics 1978b). Fertility index, implantation/pregnancy, and average resorption/pregnancy in females mated to treated males were comparable to untreated controls. Although this test is used primarily to assess mutagenic potential, it can be used as supplemental data in the overall assessment of the reproductive potential of chemical contaminants.

No multi-generational reproduction studies evaluating reproductive function and success have been located. However, maternal toxicity was associated with oral exposure to 75 mg/kg/day in cottonseed oil during

gestation (Murray et al. 1980). Thus, reproductive toxicity potential of HCCPD cannot be established with certainty.

Long-term exposure of female mice to HCCPD was associated with an increased incidence of suppurative ovarian inflammation which was hypothesized to be caused by a *Klebsiella* infection in the NTP mouse colony (NTP 1994). Studies of HCCPD distribution in both rats and mice showed that the concentrations in the ovaries were relatively high. Changes in cell chemistry resulting from the presence of HCCPD may help to explain why exposure was associated with an increased risk for infection.

Developmental Effects. Acute-duration oral studies in animals suggest that HCCPD is not developmentally toxic in offspring of mice and rabbits administered doses of 75 mg/kg/day (Murray et al. 1980). Further, there appeared to be no effects on postnatal development with exposure to 45 mg/kg/day in mice evaluated for up to 250 days (Gray and Kavlock 1984; Gray et al. 1986). Based on these considerations, HCCPD does not seem likely to pose significant risk to human development.

Genotoxic Effects. No studies were located regarding the genotoxic effects of HCCPD in humans after inhalation, oral, or dermal exposure. In *in vivo* tests, HCCPD did not induce dominant lethals in mice following oral exposure or recessive lethal mutations in *Drosophila* (Table 2-4). The absence of gene mutation and chromosomal aberrations suggests that HCCPD does not cause significant genetic damage in humans at low exposure concentrations. For the most part, *in vitro* tests employing bacterial assays or mammalian cell cultures were negative, with two exceptions (Table 2-5). Results were positive in one bacterial assay evaluating DNA damage potential (Matsui et al. 1989). Because other genotoxic end points were negative and the carcinogenic potential of HCCPD is not confirmed, the importance of a positive response in the DNA assay is not clear. It should be further noted that other studies evaluating the same end point are not available. Thus, the reproducibility of this response has not been determined. In a second assay that evaluated Chinese hamster ovary cells, HCCPD caused sister chromatid exchanges (SCE) and chromosomal aberrations with and without metabolic activation (NTP 1994). It should be noted that there was no clear dose-response relationship in the SCE assay. Further, a sufficient number of cells were not scored for chromosomal aberrations at the highest dose tested due to high cytotoxicity of HCCPD. Accordingly, the overall importance of the positive response for chromosomal aberrations is reduced. For these reasons, it is difficult to speculate regarding the potential for HCCPD to induce DNA damage and chromosomal aberrations in humans.

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

Species (test system)	End point	Results	Reference
Mammalian cells:			
Mouse/micronucleus assay	Chromosomal aberrations	–	NTP 1994
Mouse/dominant lethal assay	Chromosomal aberrations	–	Litton Bionetics 1978b
Eukaryotic organisms:			
Insect			
Drosophila/sex-linked recessive lethal assay	Gene mutation	–	Mason et al. 1992
Drosophila/sex-linked recessive lethal assay	Gene mutation	–	NTP 1994

– = negative result; + = positive result

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

Species (test system)	End point	Result: With activation	Result: Without activation	Reference
Prokaryotic organisms:				
Salmonella typhimurium TA 1535, TA 1538	Gene mutation	–	No data	Greim et al. 1977
S. typhimurium TA 100, TA 1535, TA 1537, TA 998	Gene mutation	–	–	NTP 1994
S. typhimurium TA 1535, TA 1537, TA 98, 100	Gene mutation	–	–	Haworth et al. 1983
Escherichia coli K12	Gene mutation	–	No data	Greim et al. 1977
E. coli K12	Gene mutation	–	–	Goggelman et al. 1978
Bacillus subtilis Rec - assay	DNA damage	+	+	Matsui et al. 1989
Mammalian cells:				
Mouse/L5178Y/Lymphoma assay	Gene mutation	–	–	Litton Bionetics 1978a
Chinese hamster ovary cells	Sister chromatid exchanges	+	+	NTP 1994
Chinese hamster ovary cells	Chromosomal aberrations	+	+	NTP 1994

– = negative results; + = positive results

Cancer. There were no data from studies in humans pertaining to the carcinogenicity of HCCPD. NTP conducted 2-year bioassays of HCCPD in mice and rats, and concluded that it is not a carcinogen in either species (NTP 1994). Although the incidence of alveolar/bronchiolar carcinomas was significantly increased in male mice exposed to 0.5 ppm HCCPD for 26 or 42 weeks, the incidence was within the historical range for the laboratory and was not seen in animals exposed to 0.2 ppm for 2 years. There was also a slight increase in the incidence of adenomas of the pituitary pars distalis in male rats and thyroid follicle cell adenomas in female mice, but these tumors were not considered to be compound-related.

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 the developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on the developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and

Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic-metabolizing enzymes have distinctive developmental patterns, and at various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults; sometimes unique enzymes may exist at particular developmental stages (Komori 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in the newborn who has a low glomerular filtration rate and has not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer 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).

There are no data describing the health effects, developmental or otherwise, of HCCPD in children. It is unlikely that children will be directly exposed to HCCPD. Nor are there any data describing the health effects of HCCPD in immature animals, except for prenatal developmental studies. HCCPD was not embryotoxic, fetotoxic, or teratogenic in mice exposed to the compound at oral dose levels up to 75 mg/kg/day during gestation days 6-15 or in rabbits at corresponding doses during gestation days 6-18 (Murray et al. 1980). It should be noted that the compound was not maternally toxic in mice, but weight loss was noted in rabbits and some rabbits died. Mice that received oral doses of HCCPD (45 mg/kg/day) during gestation days 8-12 did not show developmental effects (Chernoff and Kavlock 1982). When offspring of mice that were administered oral doses of HCCPD (45 mg/kg/day) during gestation days 8-12 were evaluated over a 250-day postnatal period (including the period through puberty and breeding), there were no adverse effects on postnatal viability, growth, locomotor activity, and reproductive function (Gray and Kavlock 1984; Gray et al. 1986). There is no information on whether HCCPD can cross the placenta or accumulate in breast milk either in animals or humans.

2. HEALTH EFFECTS

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 (NAWNRC 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 HCCPD 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 HCCPD are discussed in Section 2.7.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organisms 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 HCCPD

There are no specific biomarkers for HCCPD except the compound itself. Studies with the radiolabeled compound indicate that HCCPD and several metabolites are excreted in the urine and feces (Dorough and Ranieri 1984; El Dareer et al. 1983; Lawrence and Dorough 1981, 1982; Yu and Atallah 1981). The metabolites have not yet been identified and have only been classified as polar and nonpolar. HCCPD can also be identified in blood.

2.7.2 Biomarkers Used to Characterize Effects Caused by HCCPD

Evaluation of humans exposed to HCCPD did not identify any unique adverse health effects (Kominsky et al. 1980; Morse et al. 1979). Minimal-to-mild abnormalities in liver function tests (LDH, AST, ALT, AP, bilirubin) were observed in a small percentage of waste water treatment plant workers exposed to sewage contaminated with HCCPD (Kominsky et al. 1980; Morse et al. 1979). However, many other xenobiotic reports of compounds, as well as several physiological conditions, can cause increased levels of these enzymes. Initial reports of compound-induced proteinuria following HCCPD exposure could not be confirmed (Morse et al. 1979). Urinary porphyrin excretion in a group of 40 industrial workers exposed to HCCPD was found to be an unsuitable parameter for monitoring long-term exposure (Nagelsmit et al. 1979) because the values for the exposed individuals were not significantly different from those for controls.

In studies of rats, mice, guinea pigs, rabbits, and monkeys using the inhalation, oral, and dermal routes of exposure, adverse effects were seen in the lungs, liver, kidneys, and stomach (Treon et al. 1955). Following long-term inhalation exposure, a yellow-brown pigment formed in the epithelium of the nose, trachea, and lungs with vapor concentrations as low as 0.01 ppm (NTP 1994). The presence of pigment in the epithelial cells of the nose would be a useful biomarker for long-term exposure. Inhalation exposure to HCCPD also caused the appearance of electron-lucent granules in lung epithelial Clara cells. The Clara cell changes are not appropriate biomarkers of effects because undesirable invasive procedures would be necessary to obtain tissue specimens for analysis.

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Studies of Japanese quail dosed with 100-300 mg/kg/day HCCPD for 15 days showed no macroscopic or microscopic fluorescence of porphyrins in the intestines, intestinal contents, liver, or kidneys (Nagelsmit et al. 1979). Quail were used as test animals because they are highly sensitive to porphyrinogenic chlorinated xenobiotics.

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

2.8 INTERACTIONS WITH OTHER CHEMICALS

No data were located pertaining to interactions of HCCPD with other compounds. Based on the chemical properties of this material, interactions with materials that provide reactive alkene functional groups, especially those with an electron withdrawing substituent on the carbons adjacent to the double bond, are expected. Interactions with these materials preceding exposure would be expected to reduce HCCPD concentration.

In one oral exposure study, the sample HCCPD contained 0.5% hexachlorobutadiene as an impurity (Abdo et al. 1984). Because hexachlorobutadiene is also a renal toxin, the authors postulated that the renal lesions seen in the male mice at the highest dose (300 mg/kg) were due to the combined effects of both compounds.

2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to HCCPD than will most persons exposed to the same level of HCCPD in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters may result in reduced detoxification or excretion of HCCPD, or compromised function of target organs affected by HCCPD. Populations who are at greater risk due to their unusually high exposure to HCCPD are discussed in Section 5.6, Populations With Potentially High Exposure.

People with preexisting lung, kidney, or liver damage may be more at risk than the general population in the event of HCCPD exposure because of compromised organ function. Asthmatics are probably also likely to be more affected. In two studies of human exposure to HCCPD in the workplace, respiratory

symptoms predominated (Kominsky et al. 1980; Morse et al. 1979). There was also transient elevation of serum enzyme levels (e.g., LDH, AST, ASL, and AP) and proteinuria, suggesting potential effects of HCCPD on the liver and kidneys (Morse et al. 1979). Animal studies have confirmed the potential respiratory, renal, and hepatic toxicity of HCCPD. Animal studies also suggest that males are generally more susceptible to HCCPD toxicity than females (Abdo et al. 1984; NTP 1994; Rand et al. 1982a).

2.10 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to HCCPD. 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 HCCPD. 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

Humans may be exposed to HCCPD by inhalation, ingestion, or dermal contact. Exposure may be prevented by wearing respiratory protection, protective clothing, and gloves. Inhalation and ingestion have been associated with lung, liver, and kidney damage in animals (Abdo et al. 1984; Rand et al. 1982a, 1982b), although comparable data do not exist for humans. Several methods can be used to reduce absorption and thereby reduce the severity of the lesions.

If inhalation of HCCPD has occurred, it is recommended that patient be removed to fresh air. Humidified supplemental oxygen (100%) may be administered as required (HSDB 1998).

In cases of ingestion, measures are usually taken to limit gastrointestinal absorption and accelerate excretion. If patients have ingested small amounts of HCCPD, milk or water may be administered to dilute the ingested compound if the patient can swallow and has good gag reflex (Bronstein and Currance 1988; Stutz and Janusz 1988). In cases where substantial amounts of the compound have been ingested, vomiting may be induced if the patient is alert and not at risk of convulsing. Syrup of ipecac may be used for this purpose; however, it is most effective if administered within 30 minutes of ingestion (HSDB 1998). Gastric aspiration and lavage are recommended to empty the stomach of patients with severe respiratory distress or for those that are unconscious. Measures must be taken to prevent aspiration of gastric contents

into the lungs. Administration of activated charcoal to absorb the HCCPD and saline cathartics to speed fecal excretion are other measures which may be employed following ingestion of HCCPD.

In order to reduce absorption of HCCPD through the skin, areas of the skin that have come in contact with the compound should be washed thoroughly with soap and water. If the compound is splashed into the eyes, irrigation with large amounts of water for at least 15 minutes is recommended (Bronstein and Currance 1988; HSDB 1998; Stutz and Janusz 1988).

2.10.2 Reducing Body Burden

HCCPD that is absorbed in the body is distributed to the lung, liver, and kidney (Lawrence and Dorough 198 1). Although the major routes of elimination are the urine and feces, the disparity between elimination and retention as a function of route is not fully understood. It should be noted that the metabolic fate and the identity of metabolites have not been fully characterized: In the absence of data, it is difficult to speculate on methods for reducing HCCPD in body tissues. Considering the reactivity of HCCPD, it is unlikely that dialysis or hemoperfusion would be effective in reducing body burden.

2.10.3 Interfering with the Mechanism of Action for Toxic Effects

The primary effects associated with exposure to HCCPD are in the lung, kidney, liver, and stomach. The mechanism of toxicity for these effects is not well understood, but may involve binding of the HCCPD with cell constituents which leads to cell death. The lack of data on metabolic fate of the compound and mechanism of action for these effects precludes any speculation regarding methods that would reduce toxic effects. Administration of natural products containing dieneophiles may be a possible method of interfering with the mechanism of action in the gastrointestinal tract.

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 HCCPD 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 HCCPD.

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.

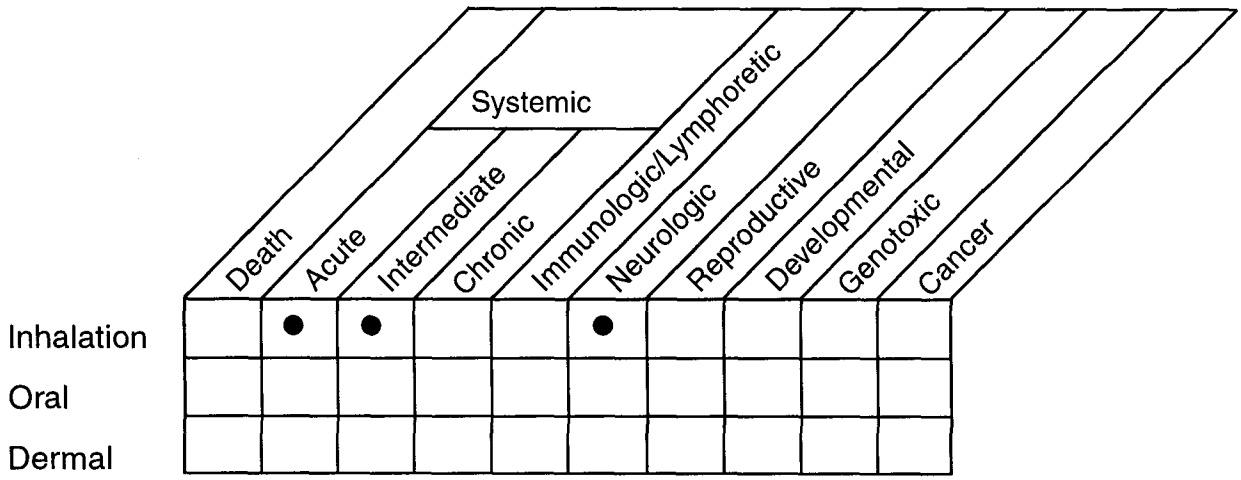
2.11.1 Existing Information on Health Effects of HCCPD

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to HCCPD are summarized in Figure 2-4. The purpose of this figure is to illustrate the existing information concerning the health effects of HCCPD. 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 1989b), 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.

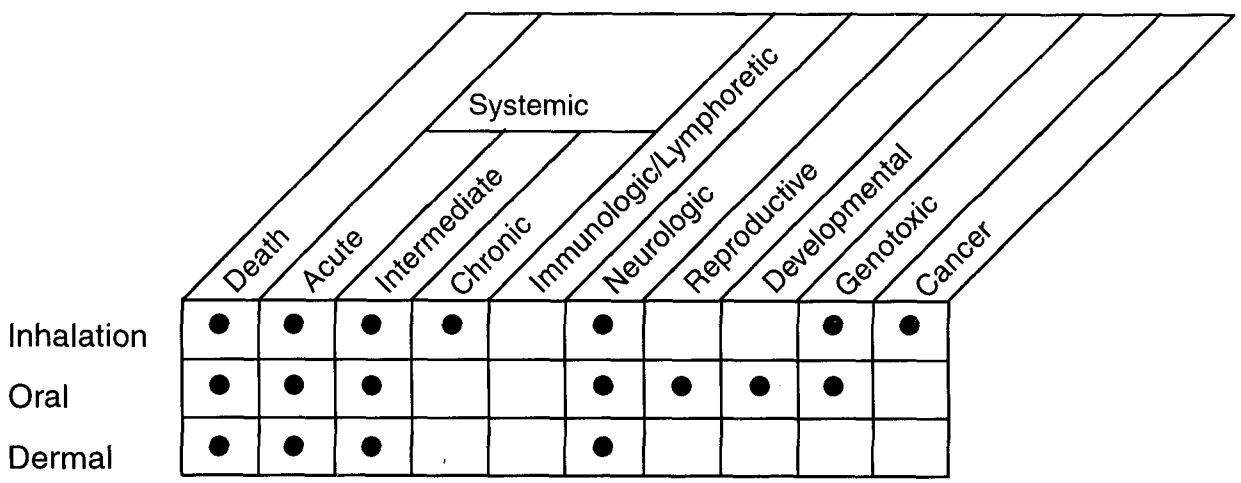
As indicated in Figure 2-4, there are very few studies available on the health effects of HCCPD in humans. No studies were located regarding oral exposure. There are several reports of the effects of acute- or intermediate-duration inhalation and dermal exposure in the workplace (Kominsky et al. 1980; Morse et al. 1979). For the most part, these reports focused on systemic (respiratory, cardiovascular, gastrointestinal, hepatic, renal, dermal, and ocular) and neurological effects. Effects of HCCPD on human development, reproduction, genotoxicity, and cancer incidence have not been evaluated, although there have been studies of cancer incidence among workers involved in the manufacture of pesticides prepared from HCCPD (Shindell and Ulrich 1986; Wang and MacMahon 1979).

More data are available in animals and include studies by the inhalation, oral, and dermal routes of exposure. These exposure routes have focused on lethality and systemic effects (respiratory, cardiovascular, gastrointestinal, hepatic, renal, dermal, and ocular). There has been minimal evaluation of

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



Human



Animal

● Existing Studies

neurological and immunological effects. There are data available on the histopathological effects of HCCPD on the spleen, thymus, and reproductive organs after inhalation and oral exposure. It should be noted that effects on reproductive functions have not been evaluated. There are studies in animals on the effects of HCCPD on development after oral exposure, but not after inhalation or dermal exposure. The carcinogenic potential of HCCPD has been studied in rats and mice using the inhalation route of exposure.

2.11.2 Identification of Data Needs

Acute-Duration Exposure. In humans involved with the cleanup of HCCPD at a waste water treatment plant, an exposure concentration as low as 0.009 ppm caused symptoms of eye irritation, and exposure to 19.2 ppm for only a few seconds affected respiration (Kominsky et al. 1980; Morse et al. 1979). Thus, acute human exposures are a concern when there are environmental releases of HCCPD.

Single-dose exposures to HCCPD were evaluated in several animal species using all three routes of administration (Treon et al. 1955). The doses used for the oral and dermal routes were lethal in most instances and caused substantial damage to the lungs, liver, kidney, brain, and adrenals in all cases. A broader range of doses was tested by the inhalation route. There were substantial effects on most of the same tissues. Based on the data from single-dose exposures, the inhalation route seems to cause the most profound physiological effects. Some effects on blood parameters, body weight, and liver and kidney weight occur with lo-day exposures to 0.5 ppm for 6 hours per day (Rand et al. 1982a). Additional testing of acute inhalation exposure situations in animals in order to detect subtle cellular changes that accompany low-dose, short-term exposures is justified because human exposures to a sudden release of HCCPD vapors from a container at or near hazardous waste sites during cleanup would be very serious.

Intermediate-Duration Exposure. There are no well-conducted studies of intermediate-duration exposure of humans to HCCPD by any route. There are well conducted oral and inhalation intermediateduration studies of HCCPD in animals but no studies using the dermal route. One kinetic study in mice (Dorough and Ranieri 1984) provides some information on the distribution of HCCPD and its metabolites after oral administration. Rats displayed minimal but significant decreases in liver weight after 13 weeks at the lowest vapor concentration tests (0.01 ppm) and in kidney weight (males only) at the highest concentration tested (0.2 ppm) (Rand et al. 1982a). Comparable effects were not observed in the liver with doses of up to 0.4 ppm. A concentration of 0.2 ppm caused a significant increase in the presence of electron-lucent granules in Clara cells from rat lungs; monkey lungs were also affected at 0.2 ppm (Rand

et al. 1982b). The data from this study were used to develop the intermediate-duration inhalation MRL of 2.0 ppb for HCCPD.

A NOAEL of 10 mg/kg/day in rats was identified in a 13-week oral study (Abdo et al. 1984). The LOAEL in this study was 19 mg/kg/day based on hyperplasia of the forestomach, a site that is lacking in humans. Accordingly, the NOAEL of 10 mg/kg/day for forestomach hyperplasia was not selected for use in deriving an MRL. However, nephrosis was present in both mice and rats at higher dose levels. The NOAEL of 19 mg/kg/day for nephrotic lesions in rats was used to derive an intermediate-duration oral MRL of 0.1 mg/kg/day from the study by Abdo et al. (1984). Additional research evaluating intermediate-duration exposures is not recommended at this time.

Chronic-Duration Exposure and Cancer. There are no human studies of chronic-duration exposure to HCCPD or of the tumorigenic effects of this compound. Long-term inhalation studies in animals have been conducted, but the oral and dermal routes have not been studied. There are no available pharmacokinetic data for chronic exposure by any route. There were no effects noted after chronic inhalation exposures except for the changes in the epithelium of the respiratory tract (NTP 1994). A yellow-brown pigment formed in the mucosal epithelium of the nose, trachea, and lungs; hyperplasia was noted in the nose; and there was squamous metaplasia of the larynx in female rats. A critical burden of 20-21 ppm-weeks appeared to be necessary for tissue pigmentation. The occurrence of pigmentation in nasal passages at a LOAEL of 0.01 ppm was used to derive an MRL for chronic-duration inhalation exposure of 0.03 ppb. Because there are differences in the effects of HCCPD after inhalation and oral exposures, a long-term study using the oral route, with emphasis on defects in kidney function and possible ulceration of the stomach lining, may be justified. HCCPD was determined to be noncarcinogenic in rats and mice on the basis of the NTP (1994) bioassay. Occupational exposure data are limited to parameters other than carcinogenicity (Kominsky et al. 1980; Morse et al. 1979). However, in light of the results of the NTP (1994) bioassay, no additional studies of the carcinogenic potential of HCCPD are recommended at this time.

Genotoxicity. HCCPD has been tested in several in vitro and in vitro test systems to determine the compounds ability to cause gene mutation (Greim et al. 1977; Haworth et al. 1983; Litton Bionetics 1978a; Mason et al. 1992; NTP 1994), DNA damage (Matsui et al. 1989), and chromosomal aberrations (Litton Bionetics 1978b; NTP 1994). Because HCCPD appears to lack genotoxic potential in several test

systems evaluating different end points, additional testing is not needed at this time. Although HCCPD is highly cytotoxic, potential human exposures are likely to fall within the concentration ranges already tested.

Reproductive Toxicity. No studies were located regarding the effects of HCCPD on human reproduction. Acute- and intermediate-duration inhalation exposure in rats, mice, and monkeys (NTP 1994; Rand et al. 19821 Rand et al. 1982a) and intermediate-duration oral exposure in rats and mice (Abdo et al. 1984) did not reveal effects on either male or female reproductive organs. Ovarian inflammation was observed in female rats and mice after long-term inhalation exposure, but this may have been due to bacterial infection (NTP 1994). One kinetic study suggests that after a single oral exposure in mice, the testes appeared to have a lower affinity for HCCPD than the ovaries (Dorough and Ranieri 1984). In the absence of information of the effect of the compound on reproductive function, occupational exposure studies and one-generation studies in animals by the inhalation, oral, and dermal routes would be useful in judging whether reproductive toxicity is an area of concern in humans following exposure to HCCPD.

Developmental Toxicity. The effects of HCCPD have been studied on development (up to 2.50 days of age) after oral exposure in mice (Gray et al. 1986; Gray and Kavlock 1984) and rabbits (Murray et al. 1980). The compound did not cause adverse effects on development, even at doses that were maternally toxic (75 mg/kg/day) (Murray et al. 1980). It should also be noted that systemic effects (kidney lesions) have been seen at lower doses (19 mg/kg/day) (Abdo et al. 1984) than those employed in oral developmental studies (45 and 75 mg/kg/day). Based on these considerations and the fact that the compound is not readily absorbed orally, additional testing by this route may not be useful at this time. On the other hand, HCCPD can be absorbed more readily after inhalation contact. No information on developmental toxicity is available by this route, nor is there any kinetic information that supports HCCPD's potential for developmental toxicity. Because environmental exposure to HCCPD may occur in humans at hazardous waste sites, additional animal studies by the inhalation route would enhance our understanding of the potential effects of the compound on human development.

Immunotoxicity. There have been no studies of the immunotoxicity of HCCPD by any exposure route. This compound does not appear to have effects on the spleen or thymus after inhalation or oral exposure, but there are many aspects of immunotoxicity that have not been evaluated (Abdo et al. 1984; NTP 1994; Rand et al. 1982a). A well conducted study of the immunotoxicity of this compound after inhalation exposure is needed. There is no information to suggest that the potential of HCCPD to cause immune effects would be route- or species-specific.

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Neurotoxicity. Inhalation exposure to HCCPD for 3-15 days was associated with complaints of headaches in workers in a waste water treatment plant (Morse et al. 1979). High-concentration acuteduration inhalation exposures (>41.6 ppm) in animals caused tremors (Treon et al. 1955), and longer-term exposures were associated with lethargy (NTP 1994). Diffuse degeneration of the brain was seen in animals following inhalation, oral, and dermal exposures (Treon et al. 1955). Accordingly, detailed investigation of the brain lesions that are observed with HCCPD exposure is justified. Additional neurotoxicity studies evaluating functional end points after inhalation exposure that might be relevant to the occupational setting are needed. In addition, attention should be paid to the effects of HCCPD on unsaturated brain lipids and neurotransmitter derivatives of the aromatic amino acids. These molecules have the potential to react with this conjugated diene. There is no information to suggest that the potential of HCCPD to cause neurological effects would be route- or species-specific.

Epidemiological and Human Dosimetry Studies. No epidemiological studies of HCCPD exposure in humans were identified. This material is a reactant in the manufacture of a number of pesticides (aldrin, dieldrin, chlordane, and heptachlor). The toxicity of these pesticides makes it difficult to evaluate occupational exposure to the HCCPD in workers that manufacture or use these pesticides. There would be problems differentiating the effects of the pesticides from the effects of HCCPD. HCCPD is also used in the manufacture of flame-retardant materials. An epidemiological study of lung, liver, and kidney function in workers who made or used any low-toxicity HCCPD-based, flame-retardant materials would be helpful in establishing cause/effect relationships and in future monitoring of individuals living near hazardous waste sites by possible identifying biomarkers of exposure or effect.

Biomarkers of Exposure and Effect.

Exposure. HCCPD and some unknown metabolites have been excreted in the urine and feces of humans and rats, but only HCCPD is useful as a biomarker because none of the urinary or fecal metabolites have been identified (Dorough and Ranieri 1984; Elia et al. 1983; Mehendale 1977; Yu and Atallah 1981). HCCPD can also be measured in the blood (DeLeon et al. 1980a). No data were located regarding the fate of the chlorine from HCCPD. If isotopic labeling experiments were to identify a unique chlorine-containing metabolite, it might be possible to use extraction from urine and analysis for total organic halogen (TOX) as a biomarker of exposure.

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Effect. Inadequate information is available at the present time regarding biomarkers of effect for acuteand intermediate-duration exposures to HCCPD. Additional tests of liver and renal function in workers exposed to HCCPD would be useful (Kominsky et al. 1980; Morse et al. 1979). With a larger database on HCCPD-associated changes in liver enzymes such as LDH, AST, ALT, AP, and glutamyltransferase (GGT) following HCCPD exposure it might be possible to use these enzymes as biomarkers of effect. The presence of yellow-brown granular pigment in the nasal epithelium appears to be a biomarker for chronic inhalation exposure (NTP 1994).

Absorption, Distribution, Metabolism, and Excretion. Little is known concerning the mechanism of HCCPD absorption or the mechanism of compound metabolism. Data on distribution to tissues in rats demonstrate that absorption occurs through the inhalation, oral, and dermal exposure routes (El Dareer et al. 1983; Lawrence and Dorough 1981,1982). The liver, kidneys, lungs, fat, and ovaries contain the highest amount of label (Dorough and Ranieri 1984; El Dareer et al. 1983; Yu and Atallah 198 1). HCCPD and/or unidentified HCCPD metabolites are excreted in urine, fecal matter, and bile. The metabolites that were extracted and separated by TLC appeared to be largely polar. It has been hypothesized that when exposure occurs by the oral route, much of the HCCPD binds to the contents of the gastrointestinal tract or is metabolized by intestinal microbes and is excreted with fecal matter (Lawrence and Dorough 1982; Yu and Atallah 1981). Additional studies to identify the metabolites of HCCPD are a priority in further understanding HCCPD toxicity. From this information, a metabolic scheme could be constructed. Additional research on the ability of HCCPD to bind to natural products would be helpful in understanding metabolism and for use in developing mitigation measures. Studies using labeled chlorine rather than labeled carbon would also be valuable in elucidating the toxicokinetic properties of HCCPD.

Comparative Toxicokinetics. There is some evidence that there are species differences in toxicity. Monkeys and guinea pigs are less susceptible to inhalation toxicity than rats, mice, and rabbits (Rand et al. 1982a, 1982b; Treon et al. 1955). Rats are more susceptible to oral toxicity than mice (Abdo et al. 1984) and mice are more susceptible to inhalation toxicity than rats (NTP 1994; Treon et al. 19.55). Males appear to be more sensitive than females (Abdo et al. 1984; Rand et al. 1982a).

Before additional studies of comparative toxicokinetics are conducted, it is important to establish the mechanism of toxicity for the most sensitive response. An understanding of the mechanism will make it possible to evaluate the contribution that anatomical and physiological species differences make to the observed differences in HCCPD toxicity. Differences in the diameters of the bronchioles may be the

critical factor in respiratory toxicity. Regardless, there is a need for a well-conducted pharmacokinetic study of HCCPD.

Methods for Reducing Toxic Effects. There are no compound-specific methods for reducing toxic effects. The mitigation measures suggested are general procedures that apply to inhalation and oral toxins as a group and are not unique to HCCPD (Bronstein and Currance 1988; HSDB 1998; Stutz and Janusz 1988). Before research efforts are devoted to compound-specific mitigation techniques, more must be learned concerning the mechanism of toxicity. The toxicity of HCCPD and the lack of compound-specific methods for mitigating toxicity make it important to use proper protective equipment in any situation where HCCPD exposure is possible.

Children's Susceptibility. Data needs relating to developmental effects are discussed above under Developmental Toxicity. There are no data describing the effects of HCCPD exposure either on children or postnatal animals. As pointed out in Chapter 5, there are still hazardous waste scenarios that could result in children's exposure. Should that occur, information on the kinetics of HCCPD in children, and how it differs from that in adults, would be useful. In addition, information on lung and liver toxicity and ocular sensitivity would help define children's susceptibility; these organs are known to be targets in either adult animals or humans.

Studies in animals on the effect of prenatal exposure to HCCPD on postnatal survival and growth suggest that HCCPD has little effect on these parameters (Chernoff and Kavlock 1983; Gray and Kavlock 1984; Gray et al. 1986). The studies that exist are primarily extended screening studies. Pharmacokinetic information, including distribution and metabolism, for the developing human or animal is also lacking, especially information on whether HCCPD or its metabolites cross the placenta or are excreted in breast milk. Since HCCPD appears to target the liver, kidney, and the central nervous system, and since these systems undergo further development in the infant and young child, additional information in these areas would aid in determining whether HCCPD presents a unique risk to children.

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

2.11.3 Ongoing Studies

No ongoing studies of HCCPD were identified.

3. CHEMICAL AND PHYSICAL INFORMATION

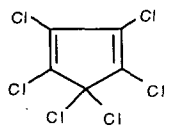
3.1 CHEMICAL IDENTITY

Hexachlorocyclopentadiene (HCCPD) is a yellow to yellow-green dense oily liquid with a pungent odor. It is used as an intermediate in the manufacture of pesticides, flame-retardant materials, and some plastics. Information regarding the chemical identity of HCCPD is located in Table 3- 1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

HCCPD is slightly soluble in water and will react slowly with water to form hydrochloric acid (HSDB 1998). It is a corrosive chemical, and contact can burn the eyes and skin. While HCCPD itself does not burn, it may decompose upon heating to produce toxic fumes (HSDB 1998). Information regarding the physical and chemical properties of HCCPD is located in Table 3-2.

Table 3-1. Chemical Identity of HCCPD

Characteristic	Information	Reference
Chemical name	Hexachlorocyclopentadiene	HSDB 1998
Synonym(s)	HCCPD; 1,3-cyclopentadiene; 1,2,3,4,5,5-hexachloro-; hex; perchlorocyclopentadiene	HSDB 1998
Registered trade name(s)	C-56; graphlox; HRS 1655	
Chemical formula	C_5Cl_6	HSDB 1998
Chemical structure		Verschueren 1983
Identification numbers:		
CAS registry	77-47-4	HSDB 1998
NIOSH RTECS	GY1225000	HSDB 1998
EPA hazardous waste	U130	HSDB 1998
OHM/TADS	7800117	HSDB 1998
DOT/UN/NA/IMCO shipping	UN2646 IMCO 6.1	HSDB 1998
HSDB	4011	HSDB 1998
NCI	C55607	HSDB 1998

CAS = Chemical Abstracts Service; DOT/UN/NA/IMO = Dept. 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 3-2. Physical and Chemical Properties of HCCPD

Property	Information	Reference
Molecular weight	272.77	Weast 1989
Color	Lemon yellow/yellow-green	EPA 1991a
Physical state	Liquid	EPA 1991a
Melting point	-9 °C	Weast 1989
Boiling point at 753 mm Hg	239 °C	Weast 1989
Density at 25 °C	1.7019 g/mL	Weast 1989
Odor	Pungent	EPA 1991a
Odor threshold:		
Water	0.0014–0.0074 mg/L	Amoore and Hautala 1983; Verschueren 1983
Air	0.03 ppm (0.34 mg/m^3) 1.5–3.3 mg/m^3	Amoore and Hautala 1983 Ruth 1986
Solubility:		
Water at 25 °C	2.1 mg/L 1.03–1.25 mg/L	EPA 1991a WHO 1991
Organic solvents	Miscible in acetone carbon tetrachloride, methanol, hexane	ACGIH 1992
Partition coefficients:		
Log K_{ow}	4.0–5.04	Mabey et al 1982; Wolfe et al. 1982
Log K_{oc}	3.68–4.08	Mabey et al. 1982; Wolfe et al. 1982
Vapor pressure at 25 °C	0.08 mm Hg	Verschueren 1983
Henry's law constant at 24.8 °C	2.7x10^{-2} atm-m^3/mol	Wolfe et al. 1982
Autoignition temperature	No data	
Flashpoint	No data	
Flammability limits	No data	
Conversion factors:	1 ppm = 11.3 mg/m^3; 1 mg/m^3 = 0.088 ppm	WHO 1991
Explosive limits	No data	

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.1 PRODUCTION

HCCPD may be produced commercially by chlorination of cyclopentadiene or dechlorination of octachlorocyclopentene. In the chlorination process, cyclopentadiene is mixed with alkaline hypochlorite and HCCPD is recovered by fractional distillation. The maximum yield of product is about 75%, with impurities including lower chlorinated cyclopentadienes. The dechlorination process involves thermal dechlorination of octachlorocyclopentene at 470-480 °C and yields a product of greater than 90% purity. Technical grade HCCPD usually contains impurities, which may include hexachlorobenzene, octachloropentene, hexachlorobutadiene, tetrachloroethylene, hexachloro-3-cyclopentane- 1 -one, PCBs, and mirex, depending on the production method used. The commercial product currently available has a minimum purity of 97% (Abdo et al. 1984; EPA 1991a; HSDB 1998; WHO 1991).

The only current commercial producer of HCCPD is the Velsicol Chemical Company in Memphis, TN (SRI 1997). Because current production of HCCPD is limited to one producer, information on the current production volume of HCCPD is not available (EPA 1984b, 1991a). Estimates of past production, based on production volumes of chlorinated cyclodiene pesticides, indicate that production volume for HCCPD was about 50 million pounds per year (22,680 metric tons per year) in the early 1970s and dropped to 8-15 million pounds per year (3,600-6,800 metric tons per year) in the late 1970s due to regulatory restrictions on the use of many of the organochlorine pesticides using HCCPD as a chemical intermediate (EPA 1984b, 1991a; Lu et al. 1975; Nubbe et al. 1995). HCCPD was a key intermediate in the production of chlorinated cyclodiene pesticides, including aldrin, dieldrin, endrin, chlordane, heptachlor, kepone, endosulfan, pentac, isodrin, and mirex (EPA 1984b). Only two of these pesticides, endosulfan and pentac are currently registered for use in the United States. It was estimated that 8,300 metric tons (18 million pounds) of HCCPD were produced in 1983 (EPA 1984b, 1991a; SRI 1992). No more recent information on production volumes was located.

Table 4-l lists the facilities in each state that manufacture or process HCCPD, the intended use, and the range of maximum amounts of HCCPD that are stored on site. The data listed in Table 4-l 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.

Table 4-1. Facilities That Manufacture or Process HCCPD

FACILITY	LOCATION [a]	RANGE OF MAXIMUM AMOUNTS ON SITE IN POUNDS	ACTIVITIES AND USES
OCCIDENTAL CHEMICAL CORP.	NIAGARA FALLS , NY	100,000 - 999,999	REACTANT
MORTON INTL. INC.	WEST ALEXANDRIA , OH	10,000 - 99,999	REACTANT
VELSICOL CHEMICAL CORP.	MEMPHIS , TN	1,000,000 - 9,999,999	PRODUCE , ON-SITE USE/PROCESSING , SALE/DISTRIBUTION , REACTANT
BASF CORP.	BEAUMONT , TX	10,000 - 99,999	REACTANT

Source: TRI96 1998

[a] Post Office state abbreviations used

4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

4.2 IMPORT/EXPORT

No information on historic or current import or export volumes of HCCPD was located.

4.3 USE

The principal end use for HCCPD is as a key intermediate in the production of chlorinated cyclodiene pesticides, including aldrin, dieldrin, endrin, chlordane, heptachlor, kepone, endosulfan, pentac, isodrin, and mirex. Technical grade chlordane, for example, has been reported to contain impurities of HCCPD up to 1% (Dorough and Ranierei 1984; Lu et al. 1975). Rand et al. (1982a) also reported that HCCPD was present as a contaminant in several cyclodiene pesticides at concentrations of up to 1%. It is also used as an intermediate in the manufacture of flame retardants such as Dechlorane Plus and chlorendic anhydride and, to a lesser extent, in the manufacture of nonflammable resins, polyester resins, pharmaceuticals, unbreakable plastics, acids, esters, ketones, fluorocarbons, and dyes. It has previously been used as a biocide (Bell et al. 1980; Cole 1954; EPA 1984b, 1991a; HSDB 1998; Stevens 1979; Verschueren 1983; WHO 1991).

4.4 DISPOSAL

HCCPD and waste containing HCCPD are classified as hazardous wastes by EPA. Generators of waste containing this contaminant must conform to EPA regulations for treatment, storage, and disposal (see Chapter 7, Regulations and Advisories). HCCPD is a potential candidate for fluidized bed incineration at a temperature range of 450-980 °C and residence times of seconds for liquids and gases, and longer for solids. It is also a potential candidate for rotary kiln incineration at a temperature range of 820-l ,600 °C and residence times of seconds for liquids and gases, and hours for solids. HCCPD is also a candidate for liquid injection incineration at a temperature range of 650-1,600 °C and a residence time of 0.1-2 seconds (EPA 198 1 b). Rotary kiln or fluidized bed incineration methods are acceptable disposal methods for these wastes. HCCPD can be incinerated after mixing with a combustible fuel; however, this mixture should be completely combusted to prevent the formation of phosgene, and an acid scrubber is necessary to remove the halogen acids produced (HSBD 1998; IRPTC 1985; WHO 1991).

HCCPD can also be buried in specially designated chemical landfills. However, HCCPD should not be disposed of in the same area of a landfill as organic solvents to prevent potential migration (leaching) of

HCCPD from the disposal site into groundwater (Chou and Griffin 1983; Chou et al. 1981; WHO 1991). Deep well underground injection may also be used as a disposal method (HSDB 1998; WHO 1991). In 1996, 250 pounds (0.1 metric tons) were released from manufacturing and processing facilities via underground injection (TR196 1998).

According to the TRI, about 45,000 pounds (20.4 metric tons) and 56,882 pounds (25.8 metric tons) of HCCPD were transferred off-site to landfills and/or to treatment and disposal facilities in 1990 and 1996, respectively (see Section 5.2) (TR190 1992; TR196 1998). In addition, about 900 pounds (0.4 metric tons) and 1,580 pounds (0.7 metric tons) were discharged to publicly owned treatment works (POTWs) in 1990 and 1996, respectively (TR190 1992; TR196 1998).

5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

HCCPD is an anthropogenic chemical that is released to the atmosphere primarily by emissions from industrial manufacturing and processing facilities and to a lesser extent from the use of products such as chlorinated cyclodiene pesticides that may contain small amounts of HCCPD. Treatment and disposal of HCCPD-containing wastes also contribute to environmental concentrations. HCCPD tends to volatilize readily to the atmosphere from other media and to adsorb strongly to soils and sediments. HCCPD reacts readily with hydroxyl and nitrate radicals and can be rapidly degraded by photolysis (EPA 1984b; Grosjean and Williams 1992). The atmospheric residence time for this chemical is less than one day (EPA 1984b; Grosjean and Williams 1992). Bioconcentration of HCCPD occurs to a very small extent (EPA 1989a; Spehar et al. 1979). Biomagnification through the food chain is unlikely to occur because HCCPD degrades rapidly by photolysis in less than 1 day (Butz et al. 1982; Chou et al. 1987; Podowski and Khan 1996; Wolfe et al. 1982) and by hydrolysis, half-life values of 5 days or less have been reported for aquatic environments (Podowski and Khan 1996; Wolfe et al. 1982). Photolysis and hydrolysis are the most important environmental fate processes, however, biodegradation also occurs in water, soil, and sediment.

Exposure of the general population, including children, to HCCPD is insignificant (EPA 199 1 a). Human exposure to HCCPD occurs primarily in occupational settings (Boogaard et al. 1993; Kominsky et al. 1980; Morse et al. 1979). Individuals in the general population who live in the vicinity of industrial facilities or hazardous waste sites where contamination has been detected may be exposed to potentially higher levels of HCCPD. A unique exposure route that may exist for young children involves hand-mouth activity if they play in or around HCCPD-contaminated soil or sediment in the vicinity of production facilities or hazardous waste sites. However, monitoring data are insufficient to estimate potential exposure levels in children or adults at these sites.

According to the Toxic Chemical Release Inventory, in 1996, a total of 66,678 pounds of HCCPD was released to the environment from 4 large processing facilities (TR196 1998). Of the total environmental releases, 7,966 pounds were released to air, 250 pounds were released via underground injection, 1,580 pounds were released to POTWs, and 56,882 pounds were transferred off-site for disposal.

5. POTENTIAL FOR HUMAN EXPOSURE

HCCPD has been identified in at least 31 of 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 HCCPD is not known. The frequency of these sites within the United States can be seen in Figure 5-l. Of these sites, all 31 are located in the contiguous United States.

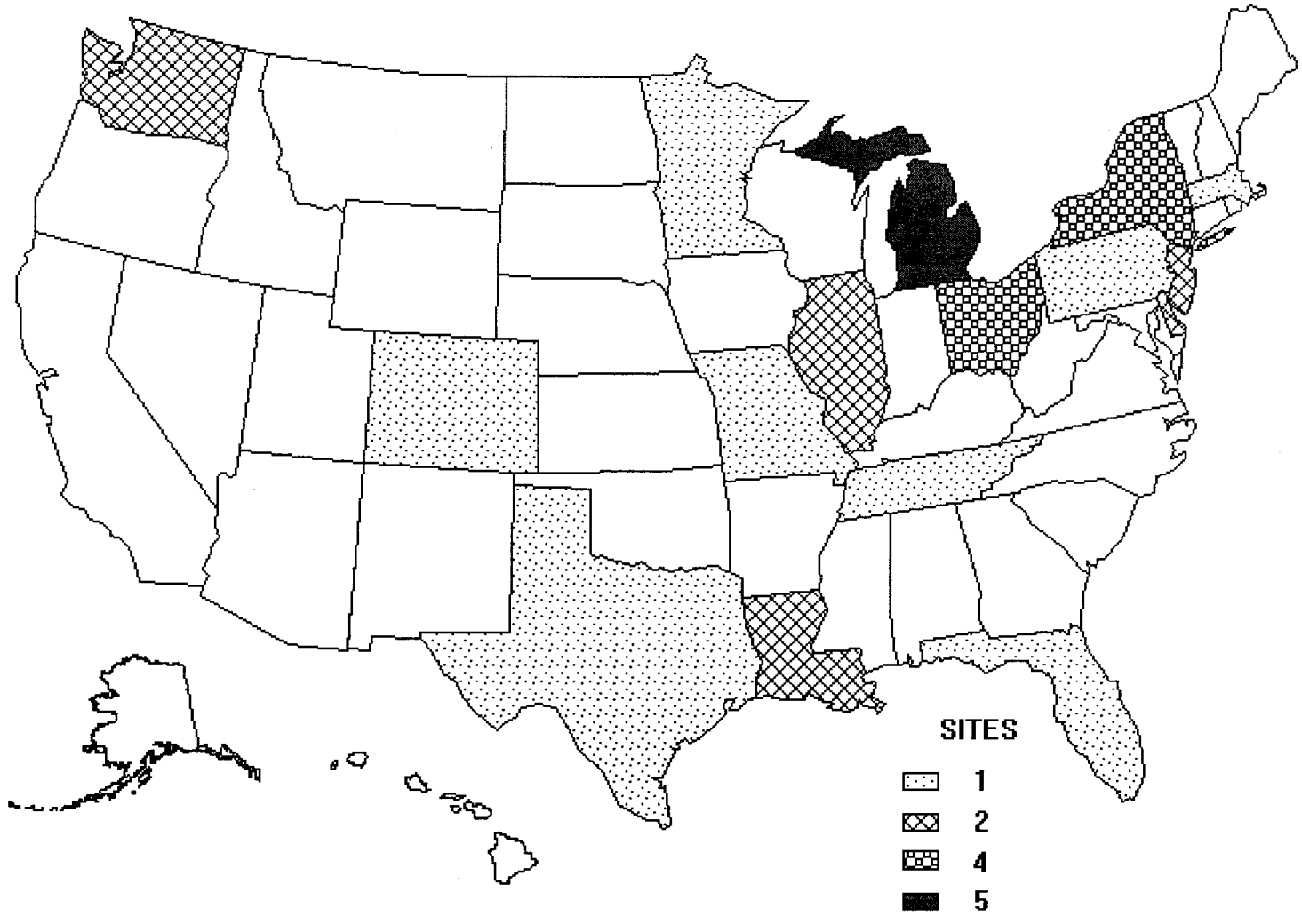
5.2 RELEASES TO THE ENVIRONMENT

According to the Toxic Chemical Release Inventory, in 1996, a total of 66,678 pounds of HCCPD was released to the environment from 4 large processing facilities (TRI96 1998). Table 5- 1 lists amounts released from these facilities. Of the total environmental releases, 7,966 pounds were released to air, 250 pounds were released via underground injection, 1,580 pounds were released to publicly owned treatment works (POTWs), and 56,882 pounds were transferred off-site for disposal. The TRI data should be used with caution because only certain types of facilities are required to report. This is not a exhaustive list. Manufacturing and processing facilities are required to report information to the Toxics Release Inventory only if they employ 10 or more full-time employees; if their facility is classified under Standard Industrial Classification (SIC) codes 20 through 39; and if their facility produces, imports, or processes 25,000 or more pounds of any TRI chemical or otherwise uses more than 10,000 pounds of a TRI chemical in a calendar year (EPA 1997c).

5.2.1 Air

The major sources of HCCPD releases to the air are from its production, processing, and use as a chemical intermediate (EPA 1980a, 1984b, 199 la). Releases may also occur from waste water treatment facilities, hazardous waste sites, and from the application and disposal of products such as chlorinated cyclodiene pesticides that may contain small amounts of HCCPD (Clark et al. 1982; Elia et al. 1983; EPA 1984b; Kominsky et al. 1980). In May 1977, HCCPD was detected at 56 ppb in air samples collected from a hazardous waste site in Montague, Michigan (EPA 1980a). An emission rate of 0.26 grams HCCPD per hour was reported at an abandoned hazardous waste site in Michigan (EPA 1984b). At this rate, emissions from this site would amount to about 5 pounds per year. In the United States, releases of HCCPD during 1978 were estimated to be approximately 60,000 pounds: 94% originated from manufacturing and 6% was due to its use (Anderson 1983). This compound has also been identified as a combustion product in emissions from a waste incinerator (Junk and Ford 1980).

Figure 5-1. Frequency of NPL Sites with HCCPD Contamination



Derived from HazDat 1998

Table 5-1. Releases to the Environment from Facilities That Manufacture or Process HCCPD

			Reported amounts released in pounds per year [a]						
STATE [b]	CITY	FACILITY	AIR [c]	WATER	LAND	UNDER-GROUND INJECTION	POTW TRANSFER	OFF-SITE WASTE TRANSFER	TOTAL ENVIRONMENT [d]
NY	NIAGARA FALLS	OCCIDENTAL CHEMICAL CORP.	920	0	0	0	4	5,010	5,934
OH	WEST ALEXANDRIA	MORTON INTL. INC.	63	0	0	0	0	1,130	1,193
TN	MEMPHIS	VELSICOL CHEMICAL CORP.	6,973	0	0	0	1,576	46,207	54,756
TX	BEAUMONT	BASF CORP.	10	0	0	250	0	4,535	4,795
		TOTALS	7,966	0	0	250	1,580	56,882	66,678

Source: TRI96 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. POTENTIAL FOR HUMAN EXPOSURE

Estimated releases of 7,966 pounds (3.6 metric tons) of HCCPD to the atmosphere from 4 domestic manufacturing and processing facilities in 1996 accounted for 12% of the estimated environmental releases (TR196 1998). These releases are summarized in Table 5-1. The TRI data should be used with caution because only certain types of facilities are required to report (EPA 1997c). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the Toxics Release Inventory only if they employ 10 or more full-time employees; if their facility is classified under Standard Industrial Classification (SIC) codes 20 through 39; and if their facility produces, imports, or processes 25,000 or more pounds of any TRI chemical or otherwise uses more than 10,000 pounds of a TRI chemical in a calendar year (EPA 1997c).

HCCPD has been identified in air samples collected at 2 of the 31 NPL hazardous waste sites where it was detected in some environmental media (HazDat 1998).

5.2.2 Water

Releases of HCCPD to water may occur during production, processing, and disposal of the chemical. In the past, concentrations of HCCPD in waste water from a production plant ranged from 0.156 to 18 mg/L (156-18,000 ppb) (EPA 1980a). HCCPD measurements were taken from the effluent stream of the Memphis North Sewage Treatment Plant from February to July 1982. Monthly average HCCPD concentrations in the effluent stream of this sewage treatment plant located near a production facility (Velsicol Chemical Corporation plant) ranged from 0.15 to 0.61 ppb μg/L), with a maximum concentration of 1.80 ppb (EPA 1984b). More recently, Nubbe et al. (1995) reported that a concentration of HCCPD around 100 mg/L (100,000 ppb) was in the range of concentrations that were typical of an aqueous HCCPD waste stream from a commercial production facility.

HCCPD was detectable in 0.9% of 1,228 effluent samples reported in the Storage and Retrieval (STORET) database maintained by EPA from 1980 to 1982 (Staples et al. 1985). The median concentration for all samples was less than 10 μg/L (ppb). In a recent study of chlorinated organic chemicals associated with industries along the Passaic River in New Jersey, Shear et al. (1996) reported that HCCPD was associated with the following industries: metal finishing, plastics, inorganic chemicals, electroplating, and steam electric power production. However, no quantitative information on the concentrations of HCCPD in the Passaic River or in industrial effluents were presented for this compound.

5. POTENTIAL FOR HUMAN EXPOSURE

In 1996, no HCCPD was reported discharged to water from the four manufacturing and processing facilities in the United States (TR196 1998). However, 1,580 pounds (0.7 metric tons) of HCCPD representing 2.4% of all environmental releases were transferred to POTWs, and a portion of these releases may eventually have been discharged to surface water (TR196 1998). These releases are summarized in Table 5- 1. The TRI data should be used with caution because only certain types of facilities are required to report (EPA 1997~). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the Toxics Release Inventory only if they employ 10 or more full-time employees; if their facility is classified under Standard Industrial Classification (SIC) codes 20 through 39; and if their facility produces, imports, or processes 25,000 or more pounds of any TRI chemical or otherwise uses more than 10,000 pounds of a TRI chemical in a calendar year (EPA 1997c).

In May 1977, HCCPD was also detected at 17 mg/L (17,000 ppb) in the aqueous discharge collected from a hazardous waste site in Montague, Michigan (EPA 1980a). HCCPD has been identified in surface water and groundwater samples collected at 7 and 15 of the 3 1 NPL hazardous waste sites, respectively, where it was detected in some environmental media (HazDat 1998).

5.2.3 Soil

HCCPD can be released to soil and sediment directly from manufacturing and processing facilities. HCCPD has been identified in the soil and river sediments downstream from a Virginia manufacturing plant, even after pesticide production at the plant was discontinued (EPA 1980a). Historically, HCCPD may have been released during application of several of the chlorinated cyclodiene pesticides. For example, chlordane has been reported to contain up to 1% HCCPD in the technical grade (Dorough and Ranieri 1984; Lu et al. 1975). Since the use of most of these chlorinated cyclodiene pesticides containing HCCPD as an impurity has been banned or restricted in the United States by the EPA, direct deposition on soil currently should be minimal with the possible exception of disposal at waste sites, accidental spills, and disposal by illegal methods (EPA 1984b). Deposition of volatilized HCCPD from air to soil is also not expected to be significant (see Section 5.3.1).

As shown in Table 5-1, in 1996, no HCCPD was reported discharged to soil from the four manufacturing and processing facilities in the United States (TR196 1998). However, 250 pounds (0.1 metric tons) accounting for 0.37% of the total environmental releases were released to soil via underground injection. This is not an exhaustive list. The TRI data should be used with caution because only certain types of

facilities are required to report (EPA 1997c). Manufacturing and processing facilities are required to report information to the Toxics Release Inventory only if they employ 10 or more full-time employees; if their facility is classified under Standard Industrial Classification (SIC) codes 20 through 39; and if their facility produces, imports, or processes 25,000 or more pounds of any TRI chemical or otherwise uses more than 10,000 pounds of a TRI chemical in a calendar year (EPA 1997c).

HCCPD has been identified in soil and sediment samples collected at 16 and 8 of the 31 NPL hazardous waste sites, respectively, where it was detected in some environmental media (HazDat 1998).

5.3 ENVIRONMENTAL FATE

In general, HCCPD is not persistent in air, water, or soil. Volatilization, photolysis, hydrolysis and biodegradation are key processes influencing the environmental fate and transformation of HCCPD (EPA 1984b).

5.3.1 Transport and Partitioning

Because HCCPD has a vapor pressure of 0.063 mm Hg at 25 °C (see Table 3-2), when released to the atmosphere, it will exist almost entirely in the vapor phase (Eisenreich et al. 1981). Detection of HCCPD in ambient air downwind (distance not reported) of a hazardous waste site indicates that atmospheric transport of HCCPD may occur (EPA 1984b). However, transported distance will be limited by the high reactivity of the chemical in the atmosphere (see Section 5.3.2.1). No data were located on deposition of HCCPD from air to water or soil, but deposition would probably be limited by the chemical's high reactivity. The relatively low water solubility of HCCPD suggests that there is little potential for washout in precipitation.

HCCPD released to water or soil may volatilize into the air or adsorb onto soil and sediment particles. Volatilization is most likely to occur from moving water bodies, with estimated removal of about 15% of the HCCPD in a turbid river compared with less than 5% removal from a lake or pond (Callahan et al. 1979). The volatilization rate from aquatic systems depends on specific conditions, including adsorption to sediments, pH of the medium, and air flow rate (Kilzer et al. 1979). In a laboratory study, 5.87% of ^{14}C-HCCPD per mL of evaporated water volatilized during the first hour (Kilzer et al. 1979). Data from the same study indicated that volatilization is much lower from soils. The volatilization rate of HCCPD

was expressed as the percentage of applied radioactivity per mL of evaporated water; for sand, loam, and humus soils, rates were 0.83, 0.33, and 0.14%, respectively, for the first hour and 0.23, 0.11, and 0.05%, respectively, for the second hour. Volatilization was highest from the sand and lowest from the humus. Volatilization was greater in soils with low organic content (Kilzer et al. 1979). In another study, the rate of volatilization of HCCPD from Maury silt loam soils was measured. Following the application of 100 mg of 14C-HCCPD to soil, the cumulative evaporation of HCCPD and its nonpolar metabolites (pentaand tetrachlorocyclopentadiene) on days 1, 2, 3, 5, 7, and 14 were 9.3, 10.2, 10.6, 10.8, 11.0 and 11.2%, respectively. The results indicate that HCCPD evaporation to air occurred mainly during the first day following application and was probably associated with the soil surface only (EPA 1984b).

HCCPD is readily adsorbed by soils and sediments (Chou and Griffin 1983; Chou et al. 198 1; Wolfe et al. 1982). Results of adsorption studies with nine different soil types indicate that adsorption capacity for HCCPD increases with increases in the total organic carbon (TOC) content of the soil (Chou and Griffin 1983; Chou et al. 1981). HCCPD was significantly more mobile in low TOC soils. Under the study conditions, HCCPD was fairly immobile in all soils when leached with tap water, landfill leachate, and caustic brine solution, but was highly mobile when the leaching agent was an organic solvent, such as acetone, methanol, or dioxane. Only 0.0005% of the HCCPD spiked into loamy sand was leached with tap water. Thus, the authors cautioned that to decrease the risk of migration of HCCPD from landfills into groundwater, wastes containing this chemical should not be disposed of in the same landfill location as organic solvents. The mechanisms of attenuation in soil materials were not reported. In another study, an average of about 68% of an applied dose of HCCPD was adsorbed to a flooded soil (EPA 1984b).

In aquatic environments, partitioning of HCCPD to sediments is likely. The soil adsorption properties of compounds such as HCCPD can be predicted from their soil organic carbon-water partition coefficients (K_{OC}). Kenaga (1980) examined the adsorption properties of 100 chemicals and concluded that compounds with K_{OC} values >l000 are tightly bound to soil components and are immobile in soils. Accordingly, the K_{OC} value is useful as an indicator of potential soil leachability of the chemical. Because K_{OC} values for HCCPD ranged from 4,786 to 12,023 (Mabey et al. 1982; Wolfe et al. 1982), the compound will tend to be tightly bound to soil and sediment particles. In a computer simulation of the fate of HCCPD in four different aquatic systems, the major portion of the chemical (86-99%) was predicted to be distributed to the sediments (Wolfe et al. 1982). The transport and partitioning data presented were consistent with the measured log K_{OW} of 5.04 (28 °C), and the experimental Henry's law constant of $2.7x10^{-2}$ atm-m^3/mol (Mabey et al. 1982; Wolfe et al. 1982).

5. POTENTIAL FOR HUMAN EXPOSURE

The reported log K_{OW} of 5.04 (Wolfe et al. 1982) indicates that bioconcentration of HCCPD could be substantial. However, data indicate that HCCPD does not bioconcentrate, bioaccumulate, or biomagnify in the food chain to a substantial degree (Lu et al. 1975; Podowski and Khan 1984; Podowski et al. 1991; Spehar et al. 1979; Wolfe et al. 1982), primarily because it is rapidly degraded in air, water, and soil and because it is metabolized in aquatic organisms. Podowski and Khan (1984) studied elimination, metabolism, and tissue distribution of HCCPD injected intraperitoneally into goldfish and concluded that the goldfish eliminate HCCPD both rapidly and linearly. Fish were injected with 39.6 μg of ^{14}C-HCCPD and analyzed 3 days later. Of the 97% of the labeled dose recovered, 19% was eliminated by the fish, 47% was extractable in an organic solvent (little of the labeled material could be identified as HCCPD, which indicated that biotransformation had occurred); 11% was water soluble metabolites; and 20% was unextractable. None of the metabolites were identified. A biphasic elimination of HCCPD was observed; rapid at first, followed by a slower phase. Based on a study of goldfish injected with ^{14}C -HCCPD, the elimination of HCCPD occurs in multiple stages, with a reported half-life in the organism of 7 days and predicted clearance of 90 and 95% of the chemical after 162 and 211 days, respectively (Podowski et al. 1991).

In a model ecosystem, a moderate potential for bioaccumulation of HCCPD was reported (Lu et al. 1975). The model ecosystem consisted of 50 sorghum (*Sorghum vulgare*) plants (3-4 inches tall) in the terrestrial portion; 10 snails (*Physa sp.*), 30 water fleas (*Daphnia magna*), filamentous green algae *(Oedogonium cardiacum)* and a plankton culture were added to the aquatic portion. The sorghum plants were treated topically with 5 mg of ^{14}C-HCCPD in acetone to simulate a terrestrial application of 1 lb/acre (1.1 kg/ha). Ten early-fifth-instar caterpillar larvae *(Estigmene acrea*) were placed on the plants. The insects consumed most of the treated plant surface within 3-4 days. The feces, leaf grass, and the larvae themselves contaminated the moist sand, permitting distribution of the labeled metabolites by water throughout the ecosystem. After 26 days, 300 mosquito larvae *(Culex pipiens quinquefasciatus)* were added to the ecosystem, and on day 30, three mosquitofish *(Gambusia affinis)* were added. The experiment was terminated after 33 days, and the various parameters were analyzed. The ecological magnification (EM) values reported were 340 for algae, 929 for snails, 1,634 for mosquitoes, and 448 for fish. However, biomagnification of HCCPD from algae to snails was 4.8, and from mosquito larvae to fish was 0.48, both of which were not substantial.

A measured bioconcentration factor (BCF) of less than 11 was reported in fathead minnows (Spehar et al. 1979). After adjustment of the BCF for lipid content, the weighted average BCF for the edible portion of

freshwater and estuarine aquatic organisms was calculated and found to be 4.34 (EPA 1980a). The available data on bioconcentration are currently under review by EPA, but this value will be used until the review is completed (EPA 1989a).

5.3.2 Transformation and Degradation

HCCPD is not persistent in air, water or soil. Photolysis, hydrolysis, and biodegradation are key processes influencing the environmental transformation and degradation of HCCPD (EPA 1984b).

5.3.2.1 Air

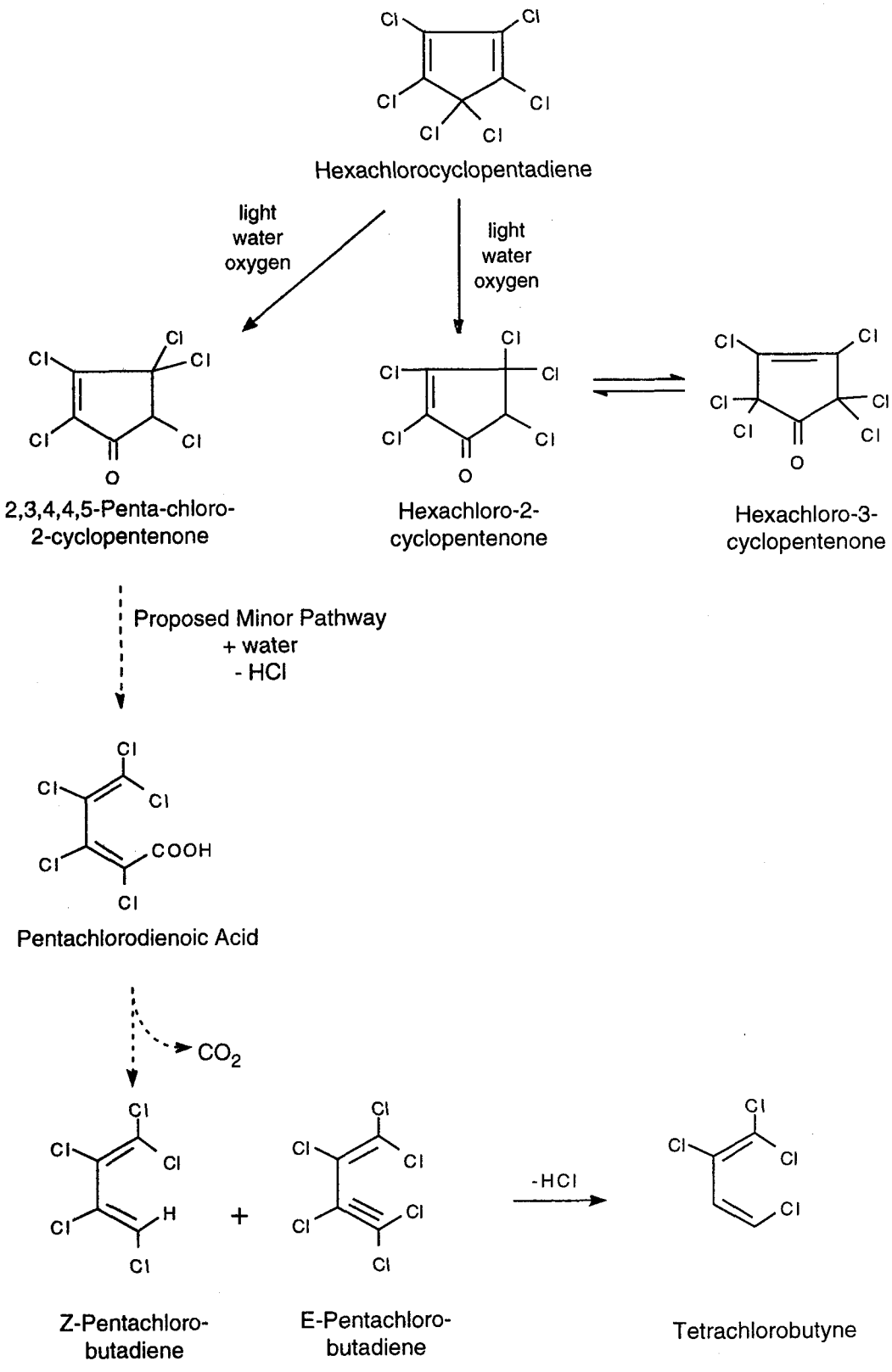
Although no measured values for HCCPD reactions in air were located, the chemical is expected to react rapidly with hydroxyl and nitrate radicals and ozone, and to be degraded rapidly by photolysis. Estimates of reaction rates with hydroxyl and nitrate radicals and ozone are available. Based on estimated reaction rates of the chemical with hydroxyl radicals and ozone of $59x10^{-12}$ and $8x10^{-18}$ cm^3 $molecule^{-1}$ sec^{-1}, respectively, the tropospheric residence time was estimated to be 5 hours (Cuppitt 1980). Recent estimates of the reaction rates with hydroxyl and nitrate radicals are $9.0x10^{-11}$ cm^3 $molecule^{-1}$ sec^{-1} and $2.14x10^{-12}$, cm^3 $molecule^{-1}$ sec^{-1}, respectively, based on structure-activity relationships (Grosjean and Williams 1992). Based on the estimated reaction rate and an atmospheric concentration of 10^6 OH molecule/cm3, the halflife of HCCPD in air is estimated to be less than 1 day (Grosjean and Williams 1992).

Since HCCPD is known to photolyze rapidly (half-life ~10 minutes) in water (Atallah et al. 1981; Butz et al. 1982; Wolfe et al. 1982), atmospheric photolysis is also expected (EPA 1984b). In addition, HCCPD absorbs light in the solar spectral region (EPA 1984b). However, no estimate of the reaction rate for atmospheric photolysis was located.

5.3.2.2 Water

Degradative processes for removal of HCCPD from water include photolysis, hydrolysis, and biodegradation. In shallow or flowing waters, photolysis is the predominant fate process; in deeper waters hydrolysis and biodegradation may be more important environmental fate processes (EPA 1984b).
The major pathways for transformation of HCCPD in water are shown in Figure 5-2.

Figure 5-2. Transformation of HCCPD



5. POTENTIAL FOR HUMAN EXPOSURE

HCCPD photolyses rapidly in water when exposed to sunlight or a mercury-vapor light source (Butz et al. 1982; Chou et al. 1987; Wolfe et al. 1982). The half-life values ranged from less than 2 minutes (Wolfe et al. 1982) to 4 minutes in natural sunlight (Chou et al. 1987) and less than 1.03 minutes when irradiated with a mercury-vapor light source (Butz et al. 1982). More recently, Podowski and Khan (1996) reported that HCCPD was photolyzed rapidly as a solution in acetone (half-life, <1 day) to apolar, polar, and hydrophilic products. The 15-day photolysis mixture contained no HCCPD. The reported photodegradation products included three primary products (2,3,4,4,5-pentachloro-2-cyclopentenone, hexachloro-2-cyclopentenone, and hexachloro-3-cyclopentenone) and three secondary products (pentachloro-cis-2,4-pentadienoic acid, Z- and E-pentachlorobutadiene, and tetrachlorobutyne (Chou et al. 1987). Dimerization of 2,3,4,4,5-pentachloro-2-cyclopentenone to form higher molecular weight compounds such as hexachloro-indenone may be a minor degradation pathway. This indicates that degradation of HCCPD in water does not always produce lower molecular weight, less toxic products (Butz et al. 1982; Chou et al. 1987). Pentachlorocyclopentenone has been reported to be the primary photolysis product by Butz et al. (1982) and the dimerization has been proposed as an artifact. However, more recent work by Podowski and Khan (1996) reject the idea that the dimer is an artifact as they could not produce the dimer compound by injecting pentachlorocyclopentenone into the GC at 190 °C. The authors also reported that the dimer, with a proposed molecular formula of C_9 C_{18} 0, was not mirex or chlordecone as judged by its GC behavior, indicating that HCCPD may not form at least the latter stable chemicals.

Hydrolysis of HCCPD in water occurs much more slowly than photolysis. In a study of the transformation pathways of HCCPD in aquatic systems, the reported average hydrolysis rate constant over a pH range of 3-10 was 1.5×10^{-6} sec^{-1} at 30 °C (Wolfe et al. 1982), which corresponds to a half-life of 5.35 days (EPA 1984b). More recently, Podowski and Khan (1996) reported that the time it took for HCCPD to reach 50, 10, and 5% of its initial concentration in water (7 ppb) was 4, 27, and 40 days, respectively.

Wolfe et al. (1982) found hydrolysis of HCCPD to be independent of pH over a range of pH 3-10. The rate of hydrolysis at neutral pH and 30 “C corresponded to a half-life (first order kinetics) of 5.45 days. The rate of hydrolysis was temperature dependent, with the half-life estimated to be 3.3, 1.7, and 0.6 days at 30, 40, and 50 °C, respectively. The addition of 0.5 molar NaCl did not affect the hydrolysis rate, suggesting that the rate constant was also applicable to marine environments. Addition of natural sediments sufficient to adsorb up to 92% of the HCCPD caused the rate constant to vary by less than a

factor of 2. Wolfe et al. (1982) therefore concluded that sorption to sediments would not significantly affect the rate of hydrolysis.

Some changes in hydrolysis rate did occur with changes in pH (EPA 1984b). The stability of ^{14}C-HCCPD in water at pH 3, 6, 9, and 12 at 25 and 45 °C was studied under dark conditions. HCCPD was relatively unstable at alkaline pH. At 25°C, the half-lives were 11.4, 11.4, 6 and 0.1 days at pH 3, 6, 9, and 12, respectively. At 45 °C, the half-lives were 9.2, 10.6 and 4.4 days at pH 3, 6, and 9, respectively. The above data indicate that at neutral pH, the hydrolysis half-life is from 3-l 1 days compared with a much more rapid photolytic half-life of < 10 minutes.

HCCPD also reacts with ozone in ozonated waters (Yao and Haag 1991). The measured rate constant for the consumption of the compound was 90 moles^{-1} second-‘, indicating that HCCPD will react significantly (greater than 10% conversion) with ozone at typical treatment conditions of 1 ppm ozone for 10 minutes (Yao and Haag 1991).

Biodegradation of HCCPD occurs in water under laboratory conditions. In a static laboratory culture, 100% of HCCPD was lost within 7 days from both 5 mg/L (ppm) and 10 mg/L (ppm) solutions (Tabak et al. 198 1). Volatilization was not reported to occur under the test conditions. However, in an evaluation of the potential for biodegradation as a spill-cleanup technique, HCCPD was reported not to be directly accessible to microorganisms in aquatic media (Thuma et al. 1983). The reported degradation of HCCPD ranged from 16 to 40% after 7 days, and from 35 to 60% after 14 days. Addition of methanol as a solubilizer increased the rate of biodegradation in 3 of 7 test cultures, with degradation up to 76%. Atallah et al. (1981) conducted an aqueous aerobic biodegradation study to determine whether and at what rate, HCCPD can be degraded to CO_2. The inoculum was a mixed acclimated culture containing secondary municipal waste effluent and several strains of *Pseudomonas putida.* HCCPD labeled with ^{14}C was the sole source of carbon in the study with the exception of trace levels of vitamins. Total removal of ^{14}C, primarily as volatile organics, was >80% in the first day in both uninoculated and inoculated media, although removal was slightly higher in inoculated media. $^{14}C0_2$ was released from both media, indicating that CO_2 was a product of hydrolysis as well as biodegradation. These studies show that HCCPD can be degraded in aquatic media under laboratory conditions. However, another study of the fate of HCCPD found biodegradation to be a relatively unimportant process in aquatic systems, based on the observation that there was no detectable difference in hydrolysis rates between sterile and nonsterile studies and measured numbers of microorganisms (Wolfe et al. 1982).

5.3.2.3 Sediment and Soil

Degradation of HCCPD occurs via both abiotic and biotic degradation processes in both sterile and nonsterile soil systems. Limited information shows that degradation rates are faster under nonsterile aerobic and anaerobic conditions, indicating that biodegradation has a role in the degradation process (EPA 1984b; Tabak et al. 1981). Potential exists for significant losses via photolysis of HCCPD on soil surfaces, while in moist soils hydrolysis may also occur. The relative importance of each process is difficult to assess and is dependent on site specific physical, chemical, and biological conditions (EPA 1984b).

The metabolism of HCCPD by soil microbial populations is an important process in its environmental degradation. Soil degradation is rapid under nonsterile aerobic and anaerobic conditions. In one study, several types of treatments and soil pHs were used to determine if the biodegradation of HCCPD in Maury loam soil was biologically and/or chemically mediated (EPA 1984b). Soils were incubated in glass flasks covered with perforated aluminum foil and maintained in the laboratory, presumably exposed to ambient lighting. When ^{14}C-HCCPD was applied to nonsterile soil at 1 ppm, only 6% was recovered as nonpolar material (either HCCPD or nonpolar degradation products) 7 days after treatment, and 72% was polar and unextractable material. By comparison, in autoclaved soil (control), 36% of the applied dose was recovered as nonpolar material and only 33% was recovered as polar and unextractable material. The degradation of HCCPD under anaerobic (flooded) conditions occurred at a slightly faster rate than under aerobic conditions (EPA 1984b). However, no single, flooded control was used to determine the effects of hydrolysis which could have accounted for the observed difference in this treatment.

A study was undertaken to examine the feasibility of using selected pure cultures of organisms (strains not identified) to biodegrade spills of hazardous chemical including HCCPD. Twenty-three of the test strains were found to remove 2 to 76% of the HCCPD from the aqueous culture medium within 14 days and 7 of the 23 strains degraded more than 33% of the HCCPD in 14 days (EPA 1984b).

5. POTENTIAL FOR HUMAN EXPOSURE

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of human exposure to HCCPD depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of HCCPD in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on HCCPD levels monitored in the environment, it should also be noted that the amount of chemical identified analytically is not necessarily equivalent to the amount that is bioavailable. The analytical methods available for monitoring HCCPD in a variety of environmental media are detailed in Chapter 6 (Analytical Methods).

5.4.1 Air

Because HCCPD is readily degraded in the atmosphere (see Section 5.3.2. l), it is not expected to be detected frequently in ambient outdoor air, and data from few monitoring studies were located. HCCPD was detected in indoor air at levels ranging from 0.06 to 0.10 pg/m3 (0.0053-0.0089 ppb) in 3 of 5 Tennessee homes where a contaminated groundwater supply was used as a source of potable water. The groundwater supply was contaminated with leachate from a pesticide waste dump operated by the Velsicol Corporation near Memphis, Tennessee (Clark et al. 1982).

HCCPD was also detected in air samples collected in June 1978 at the Memphis North Treatment Plant, the POTW that handled wastewater from the pesticide manufacturer (Clark et al. 1982; Elia et al. 1983). Concentrations of HCCPD ranged from 0.03 to 39 $\mu g/m^3$ (Elia et al. 1983). HCCPD also was detected in ambient outdoor air near a hazardous waste site at concentrations ranging from 0.032 to 0.053 ppb (0.36-0.59 $\mu g/m^3$) (EPA 1984b).

In May 1977, HCCPD was detected at 56 ppb in air samples collected from a hazardous waste site in Montague, Michigan (EPA 1980a). An emission rate of 0.26 grams HCCPD per hour was reported at an abandoned hazardous waste site in Michigan (EPA 1984b). HCCPD has been identified in air samples collected at 2 of the 3 1 NPL hazardous waste sites where it was detected in some environmental media (HazDat 1998).

5. POTENTIAL FOR HUMAN EXPOSURE

5.4.2 Water

HCCPD is rarely found in drinking water, surface water, or groundwater. HCCPD was tentatively identified in 1 of 16 samples of Philadelphia drinking water samplgd during 1976 (Suffet et al. 1980). HCCPD was also detected at a median concentration of 0.05 μg/L (ppb) (range, trace to 2.2 ug/L) in private wells used for drinking water by residents in the Toone-Teague area of Hardeman County, Tennessee (Clark et al. 1982). The source of the well water contamination was leachate from a pesticide waste dump site. HCCPD was detected in treated drinking water samples in Ottawa, Canada, at concentrations ranging from 57 to 110 ng/L (0.057-0.11 ppb), but was not detected (<50 ng/L [<050 ppb]) in raw water (Benoit and Williams 1981). Chlorination of the drinking water may be the source of the HCCPD, since the chemical reportedly formed during chlorination of a humic acid solution (Meier et al. 1985).

Data reported in the STORET database indicate that the chemical was detectable in only 0.1% of 854 surface water samples (Staples et al. 1985). The median concentration for all samples was less than 10 μg/L (10 ppb). HCCPD was also detected in Lake Ontario water, but not in water samples from Lakes Erie, Michigan, or Superior (Great Lakes Water Quality Board 1983).

In a recent study of chlorinated organic chemicals associated with industries along the Passaic River in New Jersey, Shear et al. (1996) reported that HCCPD was associated with metal finishing, plastics, inorganic chemicals, electroplating, and steam electric power production facilities. However, no quantitative information and concentrations of HCCPD in the Passaic River were presented for this compound.

HCCPD was detected in leachate from a hazardous waste site (Hauser and Bromberg 1982). HCCPD also has been identified in surface water and groundwater samples collected at 7 and 15 of the 31 NPL hazardous waste sites, respectively, where it was detected in some environmental media (HazDat 1998).

5.4.3 Sediment and Soil

No data were located documenting HCCPD concentrations in soil or sediments. HCCPD was not detectable in any of 344 sediment analyses reported in the STORET database (Staples et al. 1985). The median detection limit was 500 μg/kg (ppb).

5. POTENTIAL FOR HUMAN EXPOSURE

HCCPD has been identified in soil and sediment samples collected at 16 and 8 of the 3 1 NPL hazardous waste sites, respectively, where it was detected in some environmental media (HazDat 1998).

5.4.4 Other Environmental Media

HCCPD was qualitatively detected in fish samples collected from waters near one industrial source (a pesticide manufacturing plant in Michigan (Spehar et al. 1977). However, the chemical was not detected in any of the 116 fish samples reported in the STORET database (Staples et al. 1985), nor was it detected in fish samples from waters near other industrial sources (EPA 1984b) or from 14 Lake Michigan tributaries (Camanzo et al. 1987). HCCPD was qualitatively identified in fish collected from the Great Lakes and major watersheds to the Great Lakes during 1979 in 28 whole fish composite samples (7% positive detections; however, no detection limits were reported) (Kuehl and Leonard 1983). No recent information was located on detection of HCCPD in any commercially available fish or shellfish species, and no information was located on detection of HCCPD in raw or prepared foods.

In a study of the semiconductor industry, Bauer et al. (1995) reported detecting HCCPD at a concentration of 1.26 mg/kg (ppm) in waste oil samples collected from vacuum pump oils contaminated from aluminum plasma etching processes.

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Exposure of the general population to HCCPD is extremely low (EPA 1991a). The chemical has not been frequently detected in any environmental medium. However, this may be due to analytical difficulties (see Section 6.2). Ambient air is the most likely source of HCCPD for exposed individuals in the general population. Nevertheless, due to the high reactivity of HCCPD, it is unlikely to remain in air or in other environmental media for extended periods.

Occupational exposure to HCCPD is mainly by inhalation, but dermal exposure may also occur. NIOSH estimated that 1,427 workers were potentially exposed to HCCPD in 1980, and the Velsicol Chemical Company of Memphis, Tennessee, estimated that about 157 employees are potentially exposed to HCCPD at their facility (EPA 1991a). Monitoring data indicate that workplace air concentrations of HCCPD ranged from 0.001 to 2.0337 ppm (0.0113-22.98 mg/m^3 check) in 1982 at various locations in industrial facilities producing or using HCCPD (EPA 1984b). The &hour time-weighted average (TWA)

concentrations ranged from 0.0003 to 0.035 ppm (0.0034-0.396 mg/m^3 check). In those areas of the facility where exposure to HCCPD is possible, respirators are required and are worn (EPA 1984b).

Exposure to HCCPD has been determined for operators employed in a chemical plant producing chlorinated hydrocarbons, including HCCPD, for an average of 8.2 years (range, 0.5-23 years) (Boogaard et al. 1993). Exposures, calculated as mean airborne concentrations over an &hour time-weighted average, occasionally exceeded 0.11 mg/m^3 and were higher during maintenance stops than during routine operation of the plant.

The Occupational Safety and Health Administration (OSHA) has not set a Permissible Exposure Limit (PEL) for HCCPD in the workplace (OSHA 1974). The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a threshold limit value/TWA (TLV/TWA) of 0.1 mg/m^3 (0.01 ppm) for occupational exposures (ACGIH 1998). The recommended exposure limit for occupational exposure (TWA) set by the National Institute for Occupational Safety and Health (NIOSH) is 0.1 mg/m^3 (0.01 ppm) based on a 10-hour average workday (NIOSH 1997).

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 Section 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).

From the preceding sections of the profile, it is apparent that information on the exposure of children to HCCPD is non-existent.

5. POTENTIAL FOR HUMAN EXPOSURE

No measurements of HCCPD or its metabolite levels in amniotic fluid, meconium, cord blood, or neonatal blood that would indicate prenatal exposure have been made. HCCPD is a lipophilic compound, so there should be no significant barrier to its crossing the placenta. In addition, no information was located on measurements of HCCPD in breast milk that might result in post-natal exposure of an infant. Because HCCPD is a lipophilic molecule, its passage into breast milk is also possible and could result in exposure of breast-fed infants.

HCCPD is currently found as only a small component of two pesticides (endosulfan and Pentac), and neither of these pesticides is used in the home. There is no information on HCCPD concentrations in infant and toddler foods, baby formula, or prepared foods for infants and children.

Children may receive higher doses of pesticides such as HCCPD from dermal exposures if they play on soil in contaminated areas such as a production facility or hazardous waste sites (Youngren et al. 1991). In addition, children may receive potentially higher oral doses from intentionally ingesting dirt containing HCCPD, from accidentally ingesting dirt by putting their hands in their mouths while playing in contaminated areas, or from putting contaminated toys or other objects in their mouths. Because HCCPD is relatively immobile in soil and soil is a temporary reservoir for HCCPD in the environment, these behaviors could be a source of HCCPD exposure for children. Although the bioavailability of HCCPD from the ingested soil particles via intestinal absorption in humans is not known, the gastrointestinal absorption of even free HCCPD is limited (see Section 2.3.1 for further details).

Occupational exposures appears to constitute the only documented source of human exposure to HCCPD (Boogaard et al. 1993; Kominsky et al. 1980; Morse et al. 1979). Occupational exposure to HCCPD is mainly by inhalation of contaminated air (Boogaard et al. 1993; EPA 1984b, 1991 a), so it is unlikely that workers would inadvertantly bring home HCCPD on their hair or clothing.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

In addition to those individuals who are occupationally exposed to HCCPD during its production and processing (see Section 5.5), several other groups within the general population may receive potentially higher inhalation exposures. These groups include individuals working in waste water treatment plants or living or working near manufacturing and processing facilities or near hazardous waste sites where HCCPD has been detected in some environmental media. Air concentrations in the treatment areas of a waste water treatment plant were reported to range from 270 to 970 ppb (3,050-10,960 $\mu g/m^3$) (Morse et

al. 1979). However, these concentrations resulted from an incident in which large quantities of HCCPD were dumped into a municipal sewage system in Kentucky.

Individuals living in the vicinity of manufacturing or processing facilities or hazardous waste sites are most likely to be exposed to higher concentrations of HCCPD in the air; however, for workers at disposal sites, dermal contact with HCCPD may also occur during remediation activities. Individuals who consume groundwater from HCCPD-contaminated wells as their primary drinking water supply may also be exposed to higher concentrations of HCCPD than the general population.

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 HCCPD 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 HCCPD.

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 HCCPD are sufficiently well characterized for most properties to allow estimation of its environmental fate (Amoore and Hautala 1983; EPA 1991a; Mabey et al. 1982; Ruth 1986; Verschueren 1983; Weast 1989; Wolfe et al. 1982). However, information on the autoignition temperature, flashpoint, flammability limits, and explosive limits would be helpful.

5. POTENTIAL FOR HUMAN EXPOSURE

Production, Import/Export, Use, Release, and Disposal. HCCPD is manufactured by one facility (SRI International 1997; USITC 1991). However, recent production volume and import/export information are not available. More current information on import and export volumes of the chemical ant on uses of this compound would be helpful, as would additional information on the current registered uses of the chlorinated cyclodiene pesticides in which HCCPD is present as an impurity. Current comprehensive information on disposal volumes and methods are also needed. This information would be useful in assessing current exposure of workers and the general population to HCCPD.

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.

Environmental Fate. The environmental fate of HCCPD has been well described (Chou and Griffin 1983; Chou et al. 1981; EPA 1984b; Wolfe et al. 1982). The chemical is highly reactive and degrades readily in environmental media. However, further research on the metabolic, degradation, and reactive products would help in assessing the impact of HCCPD on the environment and humans. It is not likely that exposure of the general public is of concern. Nevertheless, because it appears to migrate at a higher rate in soil in the presence of other organic chemicals (Chou and Griffin 1983; Chou et al. 1981), additional studies might be useful to assess the potential for leaching of this chemical from soils at hazardous waste c sites into groundwater.

Bioavailability from Environmental Media. The occurrence of toxic effects in animals following inhalation, oral, and dermal exposures to HCCPD demonstrates that it is bioavailable from the media used in these studies (air, corn oil, peanut oil, and Ultrasene) (Abdo et al. 1984; Treon et al. 1955). Bioavailability from the gastrointestinal tract appears to be limited, presumably due to binding of HCCPD to intestinal contents (El Dareer et al. 1983). No data were available concerning bioavailability of HCCPD from soil or sediments. Research on the nature of the HCCPD interactions with soils, sediments, and food materials would help in evaluating the risk posed by contamination at hazardous waste sites.

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Food Chain Bioaccumulation. Bioaccumulation and biomagnification of HCCPD are not expected to be substantial in the food chain, since the chemical is rapidly metabolized in aquatic organisms (Lu et al. 1975; Podowski and Khan 1984; Podowski et al. 1991; Spehar et al. 1979; Wolfe et al. 1982). HCCPD has only rarely been detected in edible aquatic species (Camanzo et al. 1987; EPA 1984b). On this basis, it does not appear that exposure of humans by this route is of concern, and further research in this area does not seem to be a high priority.

Exposure Levels in Environmental Media. HCCPD is infrequently detected in environmental media (EPA 1984b, 1991a; Staples et al. 1985). This may be due to difficulties in analysis (see Section 6.2) and/or its rapid degradation in air, water, and soil. Insufficient data are available to estimate exposure levels in drinking water, food, or air (EPA 199Oc), but exposure of the general population to HCCPD from these sources is not expected to be significant. However, exposure in the workplace and in the vicinity of hazardous waste sites may occur at levels that could be of concern. Additional monitoring data for various inhalation exposure situations would be useful for determining occupational exposure and exposures of individuals in the general population living near manufacturing and processing facilities or near hazardous waste sites where HCCPD has been detected.

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

Exposure Levels in Humans. Detection of HCCPD in urine of waste water treatment plant workers indicates occupational exposures to this chemical (Elia et al. 1983). However, since HCCPD is rapidly metabolized *in vivo*, it was not possible to directly associate urine levels with environmental concentrations. Additional information on exposure levels in humans would be helpful. This information is necessary for assessing the need to conduct health studies on these populations.

Exposures of Children. A unique exposure route that potentially exists for children involves intentional ingestion and hand-mouth activity associated with young children. Exposure may arise if these behaviors occur in children who play in or around contaminated soil or sediment (e.g., hazardous waste sites). HCCPD has been detected in both soil and sediment collected at some NPL hazardous waste sites (HazDat 1998). As soil is at least a short-term reservoir of HCCPD in the environment, additional studies

of the transfer of HCCPD via both oral and dermal routes of exposure in children are warranted as are studies of the bioavailability of the chemical from soil and sediment. Quantitative information is also needed to determine the concentrations of HCCPD in air associated with hazardous waste sites.

Current information on whether children are different in their weight-adjusted intake of HCCPD via inhalation, oral, or dermal exposures was not located. A study should be conducted to determine if there are any HCCPD residues in breast milk, especially in women residing in areas in proximity to production facilities and hazardous waste sites. This information would be useful in determining which exposure pathway is most important for children. Since exposure to HCCPD is likely to be negligible in members of the general population, exposure and body burden studies for children would be helpful especially in those children living in proximity to production facilities or hazardous waste sites.

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

5.8.2 Ongoing Studies

No additional information was located on current studies that would fill existing data needs for HCCPD (FEDRIP 1998).

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

6.1 BIOLOGICAL SAMPLES

Few methods are available for measuring HCCPD in biological materials. Representative examples of analytical methods for HCCPD in biological samples are summarized in Table 6- 1.

Determination of HCCPD involves two steps, sample preparation and sample analysis. Prior to analysis, HCCPD must be separated from the biological sample matrix and prepared for introduction into the analytical instrument. Separation is usually effected by extraction with an organic solvent or a mixture of solvents such as hexane, acetonitrile, toluene/acetonitrile, petroleum ether, or hexane/methylene chloride (DeLeon et al. 1980a; EPA 1984b, 1991a; Gill et al. 1996). Clean-up procedures such as fractionation using solid-phase extraction (SPE) materials may be required for some biological matrices (Gill et al. 1996).

Gas chromatography (GC) is the most common method for detecting and measuring HCCPD in biological materials (DeLeon et al. 1980a; EPA 1984b, 199 la). The chromatograph separates complex mixtures of organics and allows individual compounds to be identified and quantified by a detector. Because of its sensitivity, the electron capture detector (ECD) has often been used to identify HCCPD. Mass spectrometry (MS) can provide compound identification and has been used to provide confirmation of GC/ECD results. Modern GUMS techniques provide sensitivity comparable to GC/ECD (DeLeon et al.

Table 6-1. Analytical Methods for Determining HCCPD in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Blood	Extraction with toluene/acetonitrile	Capillary column GC/ECD; GC/MS	50 ng/mL	28.8–54.5	DeLeon et al. 1980a
Blood	Extraction with hexane/dichloromethane: SPE fractionation	Capillary column GC/MSD or ECD	low ppb	47–50	Gill et al. 1996
Urine	Acidify with hydrochloric acid; extraction with petroleum ether	Capillary column GC/ECD; GC/MS	10 ng/mL	35–51.8	DeLeon et al. 1980a

ECD = electron capture detector; GC = gas chromatography; MS = mass spectrometry; MSD = mass selective detector; SPE = solid-phase extraction

1980a; Gill et al. 1996). Current methods provide adequate recovery (~50%) and sensitivity (low ppb range) for the measurement of HCCPD in blood (DelLeon et al. 1980a; Gill et al. 1996).

Accurate analysis of HCCPD in biological samples is complicated by the tendency of the chemical to degrade during storage. It was reported that up to 3 1% of HCCPD in a urine sample containing 10 ppb of the chemical could be degraded when the sample was stored overnight in a cooler. Degradation may also occur when sample extracts are concentrated (EPA 1984b).

6.2 ENVIRONMENTAL SAMPLES

Methods are available for the determination of HCCPD in most important environmental matrices. Representative methods for quantifying HCCPD in each of these media are summarized in Table 6-2. Validated methods, approved by agencies and organizations such as EPA, the American Society for Testing and Materials (ASTM), APHA, and NIOSH, are available for air, water, and solid waste matrices. These methods for analysis of air, drinking water, waste water, and soil/sediment samples are included in Table 6-2. Many of the methods published by APHA (1995) for water are equivalent to the EPA methods.

Most environmental analyses have been performed using multiresidue methods involving solvent extraction of the analytes from the sample matrix, clean-up to remove interfering compounds, and determination by GC with ECD or MS.

HCCPD in workplace air or ambient air is sampled by pulling a volume of air through a sorbent trap. The adsorbent is extracted with solvent, then analyzed by GCYECD (Boyd et al. 1981; EPA 1988a; NIOSH 1994). Recovery, where reported is good (80-99.7%). Detection limits depend upon the volume of air sampled; detection limits in the low ppb range can be achieved (Boyd et al. 1981; EPA 1988a; NIOSH 1994).

HCCPD is usually extracted from water with organic solvents for analysis (Eichelberger et al. 1983; EPA 1982a, 1984a, 1989b, 1995c). Newer methods utilize adsorption onto cartridges or disks with subsequent solvent desorption (EPA 1995c). Analysis is by capillary column GC/ECD (EPA 1989b) or GUMS (Eichelberger et al. 1983; EPA 1995c). Where GC/ECD is used, confirmation using a second dissimilar column or GUMS is recommended (EPA 1995c). Recovery for these methods is good (≥70%) and precision, where reported, is also good (>15% RSD). Detection limits are in the low ppb to ppt range.

Table 6-2. Analytical Methods for Determining HCCPD in Environmental Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Workplace air	Collection on sorbent tubes; extraction with hexane	GC/ECD	5 ppb[a]	99.7	NIOSH 1994
Workplace air	Collection on solid sorbent; extraction with hexane	GC/ECD	25 ng	>80	Boyd et al. 1981
Air	Collection on PUF; extraction with ether/hexane	GC/ECD	No data	No data	EPA 1988a
Drinking water	Extraction with hexane	Capillary column GC/ECD	0.13 µg/L	69–191	EPA 1989b (Method 505)
Drinking water	Extraction through LSE disk or cartridge; elution with solvent	Capillary column GC/MS	0.072–0.16 µg/L	84–86	EPA 1995c (Method 525.2)
Drinking water	Extraction with methylene chloride or hexane	GC/MS	50 ng/L	79–88	Benoit and Williams 1981
Drinking water	Solvent extraction	capillary column GC/ECD; confirmation using dissimilar column or GC/MS	0.016–0.018 µg/L	98–103	EPA 1995c (Method 551.1)
Water	Extraction with methylene chloride; exchange to hexane	GC/ECD	No data	No data	EPA 1982a (Method 612)
Water	Extraction with methylene chloride	GC/MS	No data	No data	APHA 1992 (Method 6410B)
Water	Extraction with methylene chloride	Capillary column GC/MS	1–10 µg/L	38	Eichelberger et al. 1983 (EPA Method 625, 625.1)
Water	Isotope dilution; acid/base extraction with methylene chloride	GC/MS	10 µg/L	No data	EPA 1984a (Method 1625)

Table 6-2. Analytical Methods for Determining HCCPD in Environmental Samples (continued)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water; soil; wastes	Extraction with methylene chloride; exchange to hexane	Dual capillary column GC/ECD; GC/MS	240 ng/L[b]	30–32	EPA 1996d (Method 8121)
Water; soil; wastes	Automated Soxhlet extraction	Capillary column GC/MS	10 µg/L (ground water); 660 µg/L (soil; sediment)	19	EPA 1996d (Method 8270C)
Soils	Microwave-assisted extraction	Capillary column GC/MSD	No data	27	Lopez-Avila and Benedicto 1996
Food (fish, milk, butter, corn oil)	Extraction with acetonitrile; clean-up using Florisil	GC/ECD	No data	≥80	Yurawecz and Puma 1986

[a] Based on 5-L air sample. Estimated detection limit is 5 ng/sample.
[b] Method detection limit (MDL) in reagent water. Estimated quantitation limits for other matrices are 10 MDL in groundwater; 670–10,000 MDL in soil, and 100,000 MDL in nonaqueous wastes.

ECD = electron capture detection; FID = flame ionization detector; GC = gas chromatography; LSE = liquid-solid extraction; MS = mass spectrometry; MSD = mass selective detector; PUF = polyurethane foam

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Soxhlet extraction is used most commonly to extract HCCPD from solid matrices such as soils, sediments and solid wastes (EPA 1996d, 1996e). The extracts are analyzed by capillary column GUECD (EPA 1996d) or GUMS (EPA 1996d, 1996e; Lopez-Avila and Benedict0 1996). Recovery is poor (19-30%); detection limits are in the ppb range (EPA 1996d, 1996e; Lopez-Avila and Benedict0 1996).

Accurate determination of HCCPD in environmental samples is also complicated by the susceptibility of the chemical to photochemical and thermal decomposition (EPA 1991b). HCCPD decomposes rapidly upon exposure to light (see Section 5.3.2) and, therefore, samples to be analyzed for this chemical must be stored protected from light (Benoit and Williams 198 1). Thermal decomposition may occur in the inlet of the gas chromatograph (APHA 1992). HCCPD also reacts chemically in acetone solution (APHA 1992). Degradation may occur during storage processing (Eichelberger et al. 1983). Thus, recovery of HCCPD is sometimes low (see Table 6-2) and some methods used for semivolatile compounds are considered inappropriate for quantification of this chemical (APHA 1992; Otson and Williams 1981).

6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA 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 HCCPD is available. Where adequate information is not available, ATSDR, in conjunction with 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 HCCPD.

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 or eliminate 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. ANALYTICAL METHODS

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Methods for extracting and identifying HCCPD from urine and blood using GC or GUMS have been developed (DeLeon et al. 1980a; Gill et al. 1996). However, in spiked samples, compound recovery was low (approximately 50%). HCCPD metabolites have been identified in rat urine and feces after exposure to HCCPD, but the metabolites were not characterized (Dorough and Ranieri 1984; Mehendale 1977; Yu and Atallah 1981). Metabolites seem to be predominantly polar. Research efforts to identify HCCPD metabolites and/or reaction products in blood, urine, fecal matter, and tissues could help to identify stable derivatives that could be used as biomarkers of exposure.

Inhalation exposure to HCCPD causes the appearance of electron-lucent granules in the Clara cells in the epithelial lining of the lungs at exposure concentrations as low as 0.01 ppm (Rand et al. 1982b). Although these cellular changes might be used as a biomarker of effect, obtaining tissues for analysis would involve invasive procedures. Thus, Clara cell changes are not recommended as a suitable biomarker of effect. Additional research concerning the mechanism of toxicity is needed in order to identify suitable biomarkers of effect.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. Analytical methods are available to detect and quantify HCCPD in air, water, soil, wastes, and food (APHA 1992; Benoit and Williams 1981; Boyd et al. 1981; Eichelberger et al. 1983; EPA 1982a, 1984a, 1988a, 1995, 1996d, 1996e; Lopez-Avila and Benedicto 1996; NIOSH 1994; Yurawecz and Puma 1986). Air is the medium of most concern for human exposure to this chemical. Exposure may also occur from water, especially in the vicinity of hazardous waste sites or industrial sources. The existing analytical methods can provide determinations for HCCPD at levels sufficiently low to meet regulatory requirements (Boyd et al. 1981; EPA 1989b, 1991b; NIOSH 1985). However, its tendency to photochemical and thermal degradation and chemical reactivity in some solvents limits the accuracy of analyses of this chemical in all media. Improved methods of extraction and analysis that minimize these reactions would enhance recovery of HCCPD from environmental samples and provide a better estimate of environmental levels, especially in drinking water and soil at hazardous waste sites. In addition, methods to measure degradation products of HCCPD in environmental samples would be useful to determine the environmental impact of this chemical.

6.3.2 Ongoing Studies

No reports of ongoing studies were located.

7. REGULATIONS AND ADVISORIES

Because of its potential to cause adverse health effects in exposed people, various international, national, and state agencies regulate HCCPD as a toxic or hazardous substance and have established standards, guidelines, and advisories for its manufacture, use, and disposal. Some of the major regulations regarding HCCPD in air, water, and other media are summarized in Table 7- 1.

An inhalation MRL of 0.01 ppm for intermediate-duration exposure was calculated based on a LOAEL of 0.2 ppm from a 14-week study by Rand et al. (1982b) that examined structural changes in the Clara cells of the lung epithelium in rats exposed to HCCPD. The critical effect was the appearance of electron-lucent granules in the Clara cells of the exposed animals.

A chronic-duration inhalation MRL of 0.2 ppb was calculated from a LOAEL of 0.01 ppm for the formation of yellowish-brown pigmentation of the nasal/tracheal and/or bronchial epithelium of male and female rats in the study by NTP (1994).

The EPA has calculated a chronic oral Reference Dose (RfD) of 0.007 mg/kg/day for HCCPD. Hyperplasia and focal inflammation of the forestomach were the critical effects (IRIS 1997). The EPA has not determined a reference concentration (RfC) for chronic inhalation exposures using HCCPD (IRIS 1997)

ATSDR has calculated an oral MRL for intermediate-duration exposures of 0.1 mg/kg/day using the same study and end point used in the derivation of the EPA RfD (Abdo et al. 1984).

The EPA has determined that HCCPD is not classifiable as to its human carcinogenicity because there is inadequate supporting data from human studies and no data from animal studies. Therefore, HCCPD has been assigned to cancer group D (IRIS 1997). The American Conference of Governmental Industrial Hygienists (ACGIH) also finds HCCPD to be “not classifiable as a human carcinogen.” ACGIH has assigned HCCPD to the cancer category A4, which indicates that there is cause for concern about its carcinogenicity but a conclusive assessment cannot be made from the available data (ACGIH 1998). The National Toxicology Program (NTP) of the U.S. Department of Health and Human Services and the

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International Agency for Research on Cancer (IARC) have not evaluated HCCPD for human carcinogenicity.

To protect workers against the adverse health effects that could result from exposure to chemicals, the Occupational Safety and Health Administration (OSHA) has promulgated permissible exposure limits (PELs) for more than 400 hazardous or toxic substances commonly found in the workplace (OSHA 1989). An employer must ensure that an employee's exposure to an OSHA-regulated substance in any 8-hour work shift of a 40-hour week does not exceed an 8-hour time-weighted average (TWA) determined for the substance (OSHA 1974). On January 18, 1989, OSHA promulgated a final rule that provided more protective PELs for approximately 376 toxic substances (OSHA 1989). Of the 428 substances considered in the rule, 164 substances, including HCCPD, had not been previously regulated by OSHA (OSHA 1989). The primary basis for setting a new limit for HCCPD was to avoid sensory irritations (e.g., eye irritation and intolerable odor) that had been associated with exposures to the substance (OSHA 1989). OSHA established an 8-hour TWA limit of 0.01 ppm for HCCPD. The new PEL was 10 times lower than the level associated with systemic damage and pulmonary irritation in animal exposure studies (OSHA 1989). Although OSHA set the new PEL so that employee risks of intense eye and pulmonary irritation and multiple organ damage would be reduced, all limits set in the 1989 promulgation were revoked in July 1992 by the 1lth Circuit Court of Appeals (OSHA 1993). On March 23, 1993, OSHA resumed enforcing the air contaminant exposure limits that were in effect prior to the issuance of the new limits in 1989 (i.e., OSHA 1974 PELs). The Agency later published in the June *30,* 1993, *Federal Register* a final rule announcing the revocation of the 1989 exposure limits (OSHA 1993). Because OSHA had not established a PEL for HCCPD prior to the 1989 promulgation, there is no current PEL for HCCPD. However, the National Institute for Occupational Safety and Health (NIOSH) and approximately 25 states have adopted the 0.01 ppm (0.1 mg/m^3) exposure limit for HCCPD set by OSHA in 1989 (NIOSH 1992, 1997; OSHA 1993). ACGIH also adopted the 0.01 ppm (0.1 mg/m3) exposure limit for HCCPD (ACGIH 1998).

HCCPD has been designated as a hazardous substance pursuant to the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) of 1980 (EPA 1995a) and as an extremely hazardous substance under Section 3 13 of Title III of the Superfund Amendments and Reauthorization Act (SARA) of 1986 (EPA 1996f). The statutory sources for designating HCCPD as a CERCLA hazardous waste are sections 31 l(b)(4) and 307(a) of the Clean Water Act (CWA) and section 3001 of the Resource Conservation and Recovery Act (RCRA) (EPA 1995a). The owners and operators of facilities that have HCCPD on their sites are required to immediately report releases of HCCPD to any environmental media,

if the amount released exceeds the established “reportable quantity” of 10 pounds (4.54 kg) (EPA 1995a). Title III of SARA is also known as the Emergency Planning and Community Right-to-Know Act (EPCRA) of 1986. As a chemical subject to the emergency planning and release reporting requirements of EPCRA, owners and operators of certain facilities that have HCCPD on their sites in amounts exceeding the “threshold planning quantity” of 100 pounds must develop a program that addresses implementing emergency response plans and notifying the public of accidental releases (EPA1996c, 1996f).

Table 7-1. Regulations and Guidelines Applicable to HCCPD

Agency	Description	Information	Reference
INTERNATIONAL			
WHO	Drinking Water Guideline Values	None	WHO 1996
IARC	Cancer Classification	None	IARC 1987
NATIONAL			
a. Air:			
OSHA	PEL -TWA	None	29 CFR 1910.1000 OSHA 1974
	Newly promulgated PEL; later vacated	0.01 ppm	54 FR 2464 OSHA 1989 58 FR 35338 OSHA 1993
U.S. Congress	National Emission Standards for Hazardous Air Pollutants (NESHAPs)	Yes	Clean Air Act Amendments, Title III U.S. Congress 1990
b. Water:			
EPA OW	Maximum Contaminant Level (MCL)	0.05 mg/L	40 CFR 141 EPA 1995e
	EPA Administered Permit Program National pollutant discharge elimination system (NPDES)	Yes	40 CFR 122 EPA 1995d
	Designation of Hazardous Substances List of hazardous substance	Yes	40 CFR 116 EPA 1989e
	Determination of Reportable Quantities for Hazardous Waste	10 pounds (4.54 kg)	40 CFR 117.3 EPA 1995b
c. Other:			
EPA OERR	Designation, Reportable Quantities, and Notification	10 pounds	40 CFR 302.4 EPA 1995a
	Emergency Planning and Notification Extremely hazardous substances and their threshold	10 pounds	40 CFR 355 EPA 1996f
EPA OSW	Identification and Listing of Hazardous Waste Hazardous waste constituents	Yes	40 CFR 261 EPA 1997a
	Land Disposal Restrictions (LDRs) Prohibitions on storage and surface disposed wastes regulated in the LDRs	Yes	40 CFR 268.32 and Appendix VII EPA 1996b
	Universal treatment standards	Wastewater 0.057 mg/L Nonwastewater 2.4 mg/L	40 CFR 268.48 EPA 1997b

Table 7-1. Regulations and Guidelines Applicable to HCCPD (continued)

Agency	Description	Information	Reference
NATIONAL (cont.)			
	Standards for the Management of Hazardous Waste and Specific Types of Hazardous Waste Facilities Health-based [concentration] limits for exclusion of waste-derived residues	0.2 mg/kg	40 CFR 266 EPA 1993
EPA OTS	Toxic Chemical Release Reporting: Community Right-to-Know	Yes	40 CFR 372.65 EPA 1997
	Health and Safety Data Reporting Rule	Yes	40 CFR 716.120 EPA 1996c
Guidelines:			
a. Air:			
ACGIH	Threshold Limit Value/Time-weighted average	0.01 ppm (0.1 mg/m^3)	ACGIH 1998
NIOSH	Recommended Exposure Limit/Time-weighted average	0.01 ppm (0.1 mg/m^3)	NIOSH 1997
b. Water:			
EPA OW	Maximum Contaminant Level Goals (MCLGs)	0.05 mg/L	40 CFR 141 EPA 1995e
	Effluent Guidelines and Standards	Yes	40 CFR 401a EPA 1981
c. Other			
EPA	RfD (oral)	7x10^{-3} mg/kg/day	IRIS 1997
	Carcinogenic Classification	Group D[a]	IRIS 1997
ACGIH	Carcinogenic Classification	Group A4[b]	ACGIH 1998
STATE			
Regulations and Guidelines			
a. Air:	Acceptable ambient air concentrations		NATICH 1992
AZ	1-hour	2.5 µg/m^3	
	24-hour	0.79 µg/m^3	
CT	8-hour	2 µg/m^3	
FL (Fort Lauderdale)	8-hour	0.001 mg/m^3	
FL (Pinella.)	8-hour	1 µg/m^3	
	24-hour	0.24 µg/m^3	
	Annual	5.0 µg/m^3	
FL (Tampa)	8-hour	0.001 mg/m^3	
IN	8-hour	0.5 µg/m^3	

Table 7-1. Regulations and Guidelines Applicable to HCCPD (continued)

Agency	Description	Information	Reference
STATE (cont.)			
IN (Indianapolis)	8-hour	0.5 µg/m^3	
MA	24-hour	0.006 µg/m^3	
	Annual	0.01 µg/m^3	
NC	1-hour	0.01 mg/m^3	
	24-hour	0.0006 mg/m^3	
NC (Forsyth County)	1-hour	0.01 mg/m^3	
	24-hour	0.0006 mg/m^3	
ND	8-hour	0.0011 mg/m^3	
NV	8-hour	0.002 mg/m^3	
NY	Annual	0.33 µg/m^3	
OK	24-hour	1 µg/m^3	
SC	24-hour	0.5 µg/m^3	
TX	30-minute	1.1 µg/m^3	
	Annual	0.11 µg/m^3	
VA	24-hour	1.8 µg/m^3	
WA-SWEST	24-hour	0.3 µg/m^3	
b. Water	Drinking Water Guidelines and Standards		
ME	Guideline	50 µg/L	FSTRAC 1995

[a] Group D not classifiable as to its human carcinogenicity.
[b] Group A4 substances exhibit cause for concern as to their human carcinogenicity, however, a conclusive assessment cannot be made from existing data.

ACGIH = American Conference of Governmental Industrial Hygienists; CFR = Code of Federal Regulations; EPA = Environmental Protection Agency; FR = Federal Register; FSTRAC = Federal-State Toxicology and Risk Analysis Committee; MCL = Maximum Contaminant Level; NATICH = National Air Toxics Information Clearinghouse; NIOSH = National Institute for Occupational Safety and Health; NPDES = National Pollutant Discharge Elimination System; OERR = Office of Emergency and Remedial Response; OSHA = Occupational Safety and Health Administration; OSW = Office of Solid Wastes; OTS = Office of Toxic Substances; OW = Office of Water; PEL = Permissible Exposure Limit; REL = Recommended Exposure Limit; RfD = Reference Dose

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9. GLOSSARY

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

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

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

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

Adsorption Ratio (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.

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

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

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

Biomarkers–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.

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

Carcinogen – A chemical capable of inducing cancer.

Case-Control Study-A type of epidemiological study which examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-controlled study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without outcome.

Case Report-describes a single individual with a particular disease or exposure. These may suggest some potential topics for scientific research but are not actual research studies.

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Case Series-describes the experience of a small number of individuals with the same disease or exposure. These may suggest potential topics for scientific research but are not actual research studies.

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.

Cohort Study-A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome. At least one exposed group is compared to one unexposed group.

Cross-sectional Study-A type of epidemiological study of a group or groups which examines the relationship between exposure and outcome to a chemical or to chemicals at one point in time.

Data Needs-substance-specific informational needs that if met would reduce the uncertainties of human health assessment.

Developmental Toxicity-The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship-the quantitative relationship between the amount of exposure to a toxicant and the incidence of the adverse effects.

Embryotoxicity and Fetotoxicity- Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the insult occurs. The terms, as used here, include malformations and variations, altered growth, and in utero death.

Environmental Protection Agency (EPA) Health Advisory-An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials. Epidemiology-refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Genotoxicity-a specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life-a measure of rate for the time required to eliminate one half of a quantity of a chemical from the body or environmental media.

9. GLOSSARY

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

Incidence-The ratio of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure-Exposure to a chemical for a duration of 15-364 days, as specified in the Toxicological Profiles.

Immunological Effects-are functional changes in the immune response.

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 has been reported to have caused death in humans or animals.

Lethal Dose $_{(LO)}$ (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 exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects-represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

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

Minimal Risk Level (MRL) -An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

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Modifying Factor (MF)-A value (greater than zero) that is applied to the derivation of a minimal risk level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity-State of being diseased; morbidity rate is the incidence or prevalence of disease in a specific population.

Mortality-Death; mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen-A substance that causes mutations. A mutation is a change in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy-The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

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

No-Observed-Adverse-Effect Level (NOAEL)-The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Effects may be produced at this dose, but they are not considered to be adverse.

Octanol-Water Partition Coeffkient (K_{OW})-The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio-a means of measuring the association between an exposure (such as toxic substances and a disease or condition) which represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio of greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed.

Organophosphate or Organophosphorus Compound-a phosphorus containing organic compound and especially a pesticide that acts by inhibiting cholinesterase.

Permissible Exposure Limit (PEL)-An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an &hour shift of a 40 hour workweek. Pesticide-general classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics-is the science of quantitatively predicting the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism and excretion of chemicals by the body.

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Pharmacokinetic Model-is a set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments which, in general, do not represent real, identifiable anatomic regions of the body whereby the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model-is a type of physiologically-based dose-response model which quantitatively describes the relationship between target tissue dose and toxic end points. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model-is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information: tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates and, possibly membrane permeabilities. The models also utilize biochemical information such as air/blood partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence-The number of cases of a disease or condition in a population at one point in time.

Prospective Study-a type of cohort study in which the pertinent observations are made on events occurring after the start of the study. A group is followed over time.

q_1*-The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q_1 * can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually μg/L for water, mg/kg/day for food, and $\mu g/m^3$ for air).

Recommended Exposure Limit (REL)-A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentrations for up to a lo-hour workday during a 40-hour workweek.

Reference Concentration (RfC)-An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation reference concentration is for continuous inhalation exposures and is appropriately expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)--An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the No-Observed-Adverse-Effect Level (NOAEL- from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

9. GLOSSARY

Reportable Quantity (RQ)-The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 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.

Retrospective Study-A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to casual factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk-the possibility or chance that some adverse effect will result from a given exposure to a chemical.

Risk Factor-An aspect of personal behavior or lifestyle, an environmental exposure, or an inborn or inherited characteristic, that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio-The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed.

Short-Term Exposure Limit (STEL)-The American Conference of Governmental Industrial Hygienists (ACGIH) maximum concentration to which workers can be exposed for up to 15 min continually. No more than four excursions are allowed per day, and there must be at least 60 min between exposure periods. The daily Threshold Limit Value - Time Weighted Average (TLV-TWA) may not be exceeded.

Target Organ Toxicity-This term covers a broad range of adverse effects on target *organs* or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen-A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)-An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which most workers can be exposed without adverse effect. The TLV may be expressed as a Time Weighted Average (TWA), as a Short-Term Exposure Limit (STEL), or as a ceiling limit (CL).

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

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Toxic Dose$_{(50)}$ (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.

9. GLOSSARY

Toxicokinetic-The study of the absorption, distribution and elimination of toxic compounds in the living organism.

Uncertainty Factor (UF)-A factor used in operationally deriving the Minimal Risk Level (MRL) or Reference Dose (RfD) or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using Lowest-Observed-Adverse-Effect Level (LOAEL) data rather than No-Observed-Adverse-Effect Level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of one can be used; however a reduced UJ? of three may be used on a case-by-case basis, three being the approximate logarithmic average of 10and 1.

Xenobiotic-any chemical that is foreign to the biological system.

APPENDIX A
ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99-4991, 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 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.

APPENDIX A

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and 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.

MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical name(s): Hexachlorocyclopentadiene
CAS number(s): 77-47-4
Date: January 15, 1999
Profile status: Final Draft
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 44
Species: rat

MRL: 0.01 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: Rand GM, Nees PO, Calo CJ, et al. 1982b. The Clara cell. An electron microscopy examination of the terminal bronchioles of rats and monkeys following inhalation of hexachlorocyclopentadiene. J Toxicol Environ Health 10:59-72.

Experimental design: Groups of Sprague-Dawley rats (3/dose) were exposed to HCCPD vapors for up to 14 weeks (6 hours/day, 5 days/week). Doses of 0.01, 0.05, and 0.2 ppm were used. Following exposure, animals were sacrificed and lung tissue prepared for histological examination using light and electron microscopy. No other parameters were measured.

Effects noted in study and corresponding doses: A statistically significant ($p<0.01$) dose-related increase in the number of electron-lucent inclusions in Clara cells in the lungs was reported at all exposure levels following electron microscopic examination. Light microscopy did not reveal treatment-related histopathological lesions of the lungs.

Dose and endpoint used for MRL derivation: A concentration of 0.2 ppm was used to derive the MRL, based on the presence of effects on the Clara cells of the lungs. Clara cells are nonciliated epithelial cells located in the terminal bronchiole region. The response of the Clara cells was considered to be an adaptive response to the exposure to inhaled toxicants, since Clara cells contain mixed function oxidases and are responsible for detoxifying inhaled chemicals. Thus, Clara cells are biomarkers of exposure, and not effect. This concentration was not normalized due to the chemical activity of HCCPD and its tendency to form lesions in directly exposed tissues.

[X] NOAEL [] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a minimally adverse LOAEL)
[ ] 1 [X] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: NA

APPENDIX A

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

The intermediate inhalation MRL for HCCPD is derived as follows.

$VE_A = (0.25\ m^3/d)^a \times (1000\ L/m^3) \times (1d/24\ hr) \times (1\ hr/60\ min) \times (1000\ mL/L) = 170\ mL/min$

$VE_H = (20\ m^3/d)^b \times (1000\ L/m^3) \times (1d/24\ hr) \times (1\ hr/60\ min) \times (1000\ mL/L) = 13800\ mL/min$

$RGDR_{[PU]}{}^c = (VE/SA_{PU})_A/(VE/SA_{PU})_H = (170\ mL/min/0.34\ m^3)/(13800\ mL/min/54\ m^3) = 1.95$

$NOAEL_{HEC} = NOAEL \times RGDR = 0.2\ ppm \times 1.95 = 0.39\ ppm$

$MRL = NOAEL_{HEC} \div UF$

$MRL = 0.4\ ppm \div 30$

$MRL = 0.01\ ppm$

[a]Average inhalation rate for male and female Sprague-Dawley rats for subchronic duration.
[b]Average inhalation rate for humans.
[c]Derived from equation 4-28 of EPA 1994 (EPA/600/8-90-066F).

Was a conversion used from intermittent to continuous exposure? No. A conversion factor was not used to adjust for intermittent exposure due to the corrosive nature of HCCPD. The chemical exerts a direct contact effect, and the effects are concentration- rather than time-dependent.

Other additional studies or pertinent information that lend support to this MRL: Treon JR, Cleveland FP, Cappel J, et al. 1955. The toxicity of hexachlorocyclopentadiene. Arch Ind Health 11:459-472.

Groups of mice (5), guinea pigs (2), rats (4), and rabbits (3) were exposed to vapors of HCCPD (0.13 ppm, 7 hours/day, 5 days/week, generated from 89.5% pure HCCPD) for 30 weeks. Following exposure, clinical signs and survival were monitored. Gross necropsy was performed. Pulmonary edema and bronchitis were reported in mice. Compound exposure was associated with pneumonia in rats and guinea pigs. Comparable effects were not seen in rabbits survival was not affected following compound exposure in rabbits, rats, and guinea pigs. On the other hand, mice were more sensitive to HCCPD toxicity, with death occurring in 4 of 5 mice.

Rand GM, Nees PO, Calo CJ, et al. 1982a. Effects of inhalation exposure to hexachlorocyclopentadiene on rats and monkeys. J Toxicol Environ Health 9:743-760.

Groups of Sprague-Dawley rats (40/sex/dose) were exposed to vapors of HCCPD at concentrations of 0, 0.01, 0.05, or 0.20 ppm for 90 days (up to 14 weeks) (6 hours/day, 5 days/week). Following exposure, clinical signs, food and water consumption were monitored daily, and body weights were recorded weekly during the treatment period. Standard blood chemistry, hematologic, and urinalysis parameters were evaluated. Gross necropsy was performed and organ weights (adrenal, brain, heart, kidneys, liver, lungs, ovaries, pituitary, spleen, testes, thyroid, and uterus) were determined. Histopathological examinations of major organs were performed at 4, 8, and after 13 weeks in the control and high-dose groups. There was a slight marginal increase in hemoglobin, red blood cell count, and mean corpuscular hemoglobin concentration and a decrease in mean cell volume at concentrations of 0.01 (males), 0.05 (females), and 0.2 (both sexes) ppm after 12 weeks exposure to the compound. These changes may represent a compensatory response to impaired oxygen transport and thus provide some support for impaired lung function. Adverse clinical signs (dark red eyes) were evident at concentrations of 0.05 pm or greater; however, these effects were reversible after day 20 of the 90-day exposure period. Liver weights were reduced in both sexes at all exposure levels, and kidney weights were reduced in males at comparable exposure levels. Otherwise, the compound did not cause adverse effects under conditions of this study. Food and water consumption and body weight gain were comparable in exposed and control groups. No treatment-related deaths were reported. Clinical chemistry and urinalysis did not differ significantly from controls. No gross or histopathological lesions were found.

APPENDIX A

In a separate portion of this study, 5 male and 5 female rats were exposed to 0.5 ppm HCCPD vapor for 5 days (6 hours/day) and allowed to recover for up to 21 days. Another 10 rats of each sex were exposed to this same concentration for up to 2 weeks (6 hours/day, 5 days/week) with no recovery period. All of the males and 2 females exposed for 2 weeks died. There was bronchial erosion of the epithelium, hyperplastic changes in the cuboidal and columnar cells of the epithelium, inflammatory cell infiltration, and fibroblastic proliferation in the lungs of the treated animals. After 7 days for males and 10 days for females, there were significant increases in packed cell volume, hemoglobin concentration and erythrocyte count which were hypothesized to be a compensatory response for impaired lung function.

Three males from the recovery group died with 7 days of their fifth and last exposure, but all the females and two males survived. The histopathologic changes in the lung of the recovery group survivors were resolved when the animals were examined after sacrifice at the end of the recovery period.

Rand et al. (1982a) also studied the effects of inhalation exposure to HCCPD on monkeys. Groups of cynomolgous monkeys (6/sex/dose) were exposed to vapors of HCCPD at concentrations of 0, 0.01, 0.05, or 0.2 ppm for 13 weeks. Following exposure, clinical signs, and food and water consumption were monitored daily and body weights were recorded weekly during the treatment period. Blood chemistry, hematological and urinalysis parameters were evaluated. Gross necropsy was performed and organ weights (adrenals, brain, heart, kidneys, liver, lungs, ovaries, pituitary, spleen, testes, thyroid, and uterus) were determined. Histopathological examination was performed on the following organs or tissues after 13 weeks in the control and high-dose groups: adrenals, aorta, brain, eye, heart, esophagus, stomach, intestine, kidneys, larynx, liver, lungs, nasal turbinates, ovaries, lymph nodes, spleen, urinary bladder, pancreas, pituitary, prostate, uterus, seminal vesicles, skeletal muscle, trachea, testes, thymus, thyroid, parathyroid, sciatic nerve and salivary gland. No mortalities or adverse clinical signs were reported. Body weight and food consumption were comparable in exposed and control groups. No treatment-related effects on tissue weight were reported and the compound did not cause any gross or histopathological lesions in any tissues examined. Pulmonary function tests (e.g., lung mechanics, pulmonary ventilation, and blood gas analysis) were comparable in exposed and control groups. Erythrocyte sedimentation rate, packed cell volume, hemoglobin, red blood cell count, reticulocyte count, mean corpuscular hemoglobin concentration, mean cell volume, total white blood cell count, differential count and clotting time were comparable in exposed and control groups. Blood chemistry parameters (serum urea, total protein, albumin, cholesterol, creatinine, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase and lactate dehydrogenase) were comparable in exposed and control groups. Urine parameters (volume, pH, specific gravity, protein, reducing substances, glucose, ketones, bile pigments, urobilinogen and hemoglobin) were comparable in exposed and control groups.

In a separate experiment, groups of cynomologous monkeys were exposed to HCCPD vapors for up to 14 weeks. Animals (3M, 3F) from each treatment group were evaluated to determine the effects of the compound on the lungs, especially ultrastructural changes in Clara cells of the terminal bronchioles of the lungs. Except in one monkey, the compound did not cause histopathological lesions in the terminal bronchioles under the conditions of this study. Inclusions in the Clara cells were noted in one monkey. Since the Clara cells of the terminal bronchioles contain detoxifying enzymes and function to eliminate inhaled toxicants, the appearance of inclusion bodies is considered to be an indication of exposure, and not a sign of toxicity.

Agency Contact (Chemical Manager): Carolyn Harper, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical name(s): Hexachlorocyclopentadiene
CAS number(s): 77-47-4
Date: January 15, 1999
Profile status: Final Draft
Route: [X] Inhalation [ ] Oral
Duration: [ ] Acute [ ] Intermediate [X] Chronic
Key to figure: 71
Species:rat

MRL: 0.0002 [ ] mg/kg/day [X] ppm [ ] mg/m^3

Reference: NTP. 1994. National Toxicology Program. Toxicology and carcinogenesis studies of hexachlorocyclopentadiene (CAS No. 74-47-4) in F344 rats and B6C3F1 mice. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NTP TR 437. NIH Publication No. 93-3168.

Experimental design: Groups of 50 male and 50 female rats were exposed to concentrations of 0, 0.01, 0.05, or 0.2 ppm HCCPD for 6 hours/day, 5 days/week for 2 years. At sacrifice, the tissues were examined for the occurrence of tumors and histological abnormalities.

Effects noted in study and corresponding doses: Yellow-brown pigmentation of the nose, trachea, and/or lungs was noted at sacrifice. At the lowest dose tested, 68% of the exposed females had pigmentation in the nasal epithelium; 0%, in the trachea; and 50% in the bronchioles. In males, 92% had pigmentation in the nasal epithelium; 0%, in the trachea; and 0% in the bronchioles. Although the number of affected animals and the severity of the pigmentation increased with dose, there was no clear dose-response trend. The occurrence of pigmentation apparently had little effect on survival based on a comparison of the Kaplan-Meier survival curves for the exposed and control animals. Chemical evaluation of the pigment indicated that it was a reducing substance and may have been either a ceroid or lipofuscin deposit. The 0.01 ppm dose was identified as the LOAEL in this study.

Dose endpoint used for MRL derivation: The 0.01 ppm LOAEL was selected as the basis for the MRL derivation. Exposure to this concentration of HCCPD for 6 hours/day, 5 days/week for 2 years resulted in the formation of yellow-brown pigment in the nasal, tracheal, and/or bronchial epithelium.

[ ] NOAEL [X] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [X] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [X] 3 [ ] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: NA

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

The chronic inhalation MRL for HCCPD is derived as follows.

$VE_A = (0.3\ m^3/d)^a \times (1000\ L/m^3) \times (1d/24\ hr) \times (1\ hr/60\ min) \times (1000\ mL/L) = 170\ mL/min$

$RGDR_{[PU]}{}^b = (VE/SA_{PU})_A/(VE/SA_{PU})_H = (210\ mL/min/0.34\ m^3)/(13800\ mL/min/54\ m^3) = 2.4$

$LOAEL_{HEC} = LOAEL \times RGDR = 0.01\ ppm \times 2.4 = 0.02\ ppm$

$MRL = LOAEL_{HEC} \div UF$

$MRL = 0.02\ ppm \div 90$

$MRL = 0.0002\ ppm$

[a]Average inhalation rate for male and female F344 rats for chronic duration.
[b]Derived from equation 4-28 of EPA 1994 (EPA/600/8-90-066F).

Was a conversion used from intermittent to continuous exposure? No. A conversion factor was not used to adjust for intermittent exposure due to the corrosive nature of HCCPD. The chemical exerts a direct contact effect, and the effects are concentration- rather than time-dependent.

Other additional studies or pertinent information that lend support to this MRL: NTP. 1994. National Toxicology Program. Toxicology and carcinogenesis studies of hexachlorocyclopentadiene (CAS No. 74-47-4) in F344 rats and B6C3F1 mice. U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. NTP TR 437. NIH Publication No. 93-3168.

Groups of 50 male and 50 female mice were exposed to concentrations of 0, 0.01, 0.05, or 0.2 ppm HCCPD for 6 hours/day, 5 days/week for 2 years. At sacrifice, the tissues were examined for the occurrence of tumors and histological abnormalities.

Yellow-brown pigmentation of the epithelium of the nose, trachea, and/or lungs was noted at sacrifice. At the lowest dose tested, 90% of the exposed males had pigmentation in the nasal epithelium; 58% had pigmentation in the trachea; and 4% had pigmentation in the lungs. In females, 80% had pigmentation in the nasal epithelium; 12% had pigmentation in the trachea; and 0% had pigmentation in the lings. Although the number of affected animals and the severity of the pigmentation increased with dose, there was no clear dose-response trend.

In a separate component of the NTP (1994) bioassay, groups of male mice were exposed to concentrations of 0.2 ppm HCCPD for 33 or 66 weeks, or to 0.5 ppm for 26 or 42 weeks under parallel exposure conditions (6 hours/day, 5 days/week). The animals were sacrificed at either 104 or 105 weeks and the respiratory tract tissue was examined. Pigmentation was found in the mucosa of the nose, trachea, and lungs of nearly all animals. Any pigmentation that formed in these tissues during exposure was still present 38 to 79 weeks after exposure ceased. The pigment apparently had little effect on survival because there were minimal differences among groups for the percent probability of survival or the number of animals surviving until study termination.

Agency Contact (Chemical Manager): Carolyn Harper, Ph.D.

APPENDIX A

MINIMAL RISK LEVEL WORKSHEET

Chemical name(s): Hexachlorocyclopentadiene
CAS number(s): 77-47-4
Date: January 15, 1999
Profile status: Final Draft
Route: [ ] Inhalation [X] Oral
Duration: [ ] Acute [X] Intermediate [ ] Chronic
Key to figure: 17
Species: rat

MRL: 0.1 [X] mg/kg/day [ ] ppm [ ] mg/m^3

Reference: Abdo K, Montgomery CA, Kluwe WM, et al. 1984. Toxicity of hexachlorocyclopentadiene: subchronic (13-week) administration by gavage to F344 rats and B6C3F1 mice. J Appl Toxicol 4(2):75-81.

Experimental design: Groups of F344 rats (10/sex/dose) were administered HCCPD (0, 10, 19, 38, 75, 150 mg/kg/day) in corn oil by gavage, 5 days/week for 13 weeks. Body weights were determined initially and weekly during the treatment period. Clinical signs and mortality were monitored daily. Gross necropsy was performed and organ weights (liver, right kidney, thymus, heart, brain, and lungs) were determined. Histopathological examination was performed on the following organs or tissues after 13 weeks in the control, 75, and 150 mg/kg/day dose groups: skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction (rib) thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach (also at 38, 19, and 10 mg/kg/day), duodenum, jejunum, ileum, colon, mesenteric nodes, liver, pancreas, spleen, kidney (also at 38, 19, and 10 mg/kg/day), adrenal, urinary bladder, seminal vesicle, prostate, testes, ovaries, uterus, nasal cavity, brain, pituitary, and spinal cord.

Effects noted in study and corresponding doses: Nephrosis was evident in both sexes at dose levels of 38 mg/kg/day or greater and effects were confined to the terminal portion of the proximal convoluted tubules in the inner cortex. The lower NOAEL of 10 mg/kg/day for the absence of forestomach lesions was not used as the basis of the MRL because humans do not possess a forestomach. Kidney weights were not affected. Because the batch of HCCPD used in the study also contained hexachlorobutadiene (0.5%) as and impurity, there may be some synergistic effect between the two chemicals at the highest doses. Forestomach hyperplasia was reported in females at dose levels of 19 mg/kg/day or greater. This effect was also seen in male rats, but occurred at doses of 38 mg/kg/day or greater. Focal inflammation of the forestomach was also observed in females (19 mg) and males (38 mg). Although the number of animals with inflammation increased in the exposed group compared to controls, it should be noted that the incidence of this lesion shoed a weak dose-related trend among the treatment groups. Ulcerations were detected in males in the 38 and 75 mg/kg/day dose groups, but were not reported in the high-dose group or in controls. No ulcerations were seen in female rats. Ruffled fur and inactivity occurred at dose levels of 75 mg, otherwise clinical signs were comparable in exposed and control groups. body weight was reduced a dose levels of 38 mg.

Dose endpoint used for MRL derivation: A NOAEL of 19 mg/kg/day was used to derive the MRL, based on the absence of effects on the kidneys. This dose was converted to 13.6 mg/kg/day, incorporating adjustments for intermittent exposure (5 days/week).

[X] NOAEL [ ] LOAEL

Uncertainty factors used in MRL derivation:

[ ] 1 [ ] 3 [ ] 10 (for use of a LOAEL)
[ ] 1 [ ] 3 [X] 10 (for extrapolation from animals to humans)
[ ] 1 [ ] 3 [X] 10 (for human variability)

Was a conversion factor used from ppm in food or water to a mg/body weight dose?
If so, explain: NA

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

Was a conversion used from intermittent to continuous exposure?
If so, explain: 0.19 mg/kg/day x 5/7 = 0.1357 mg/kg/day

Other additional studies or pertinent information that lend support to this MRL: Abdo K, Montgomery CA, Kluwe WM, et al. 1984. Toxicity of hexachlorocyclopentadiene: subchronic (13-week) administration by gavage to F344 rats and B6C3F1 mice. J Appl Toxicol 4(2):75-81.

Groups of B6C3F1 mice (10/sex/dose) were administered HCCPD (0, 19, 38, 75, 150 mg/kg/day) in corn oil by gavage. Body weights were determined initially and weekly during the treatment period. Clinical signs and mortality were monitored daily. Gross necropsy was performed and organ weights (liver, right kidney, thymus, heart, brain, and lungs) were determined. Histopathological examination was performed on the following organs or tissues after 13 weeks in the control, 150, and 300 mg/kg/day dose groups: skin, mandibular lymph nodes, mammary gland, salivary gland, thigh muscle, sciatic nerve, bone marrow, costochondral junction (rib) thymus, larynx, trachea, lungs and bronchi, heart, thyroid, parathyroid, esophagus, stomach (also at 38, 19, and 10 mg/kg/day), duodenum, jejunum, ileum, colon, mesenteric nodes, liver, pancreas, spleen, kidney (also at 38, 19, and 10 mg/kg/day), adrenal, urinary bladder, seminal vesicle, prostate, testes, ovaries, uterus, nasal cavity, brain, pituitary, and spinal cord.

Hyperplasia and inflammation of the forestomach were reported in both females (2/9, 22%) and males (2/10, 20%) at 38 mg/kg/day and also occurred at dose levels of 75 mg when compared to untreated controls. Although the number of animals showing forestomach lesions in he treated group was increased over untreated control levels, the incidence among all exposed groups showed a weak dose-related trend. Ulcerations were not observed in the control or exposed group (except at the high-dose in both sexes). There were also treatment-related lesions of the kidneys. Toxic nephrosis was observed in female mice at dose levels of 75 mg; kidney weights were not affected. Histopathological lesions were not seen in other organs, nor were there changes in organ weights. Clinical signs were comparable in exposed and control mice, except that ruffled fur and slight inactivity occurred at dose levels of 150 mg. Body weights were reduced at dose levels of 150 mg. Forestomach lesions appear to be the most sensitive end point under conditions of this study. A NOAEL of 19 mg/kg/day is identified for this study based on this end point.

Agency Contact (Chemical Manager): Carolyn Harper, Ph.D.

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-l 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-l and Figure 2-l 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-l

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-l) 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.

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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-l).

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 Frequencv/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 1 S), 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, dermal, and 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.

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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/m3 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.

SAMPLE

1 →

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

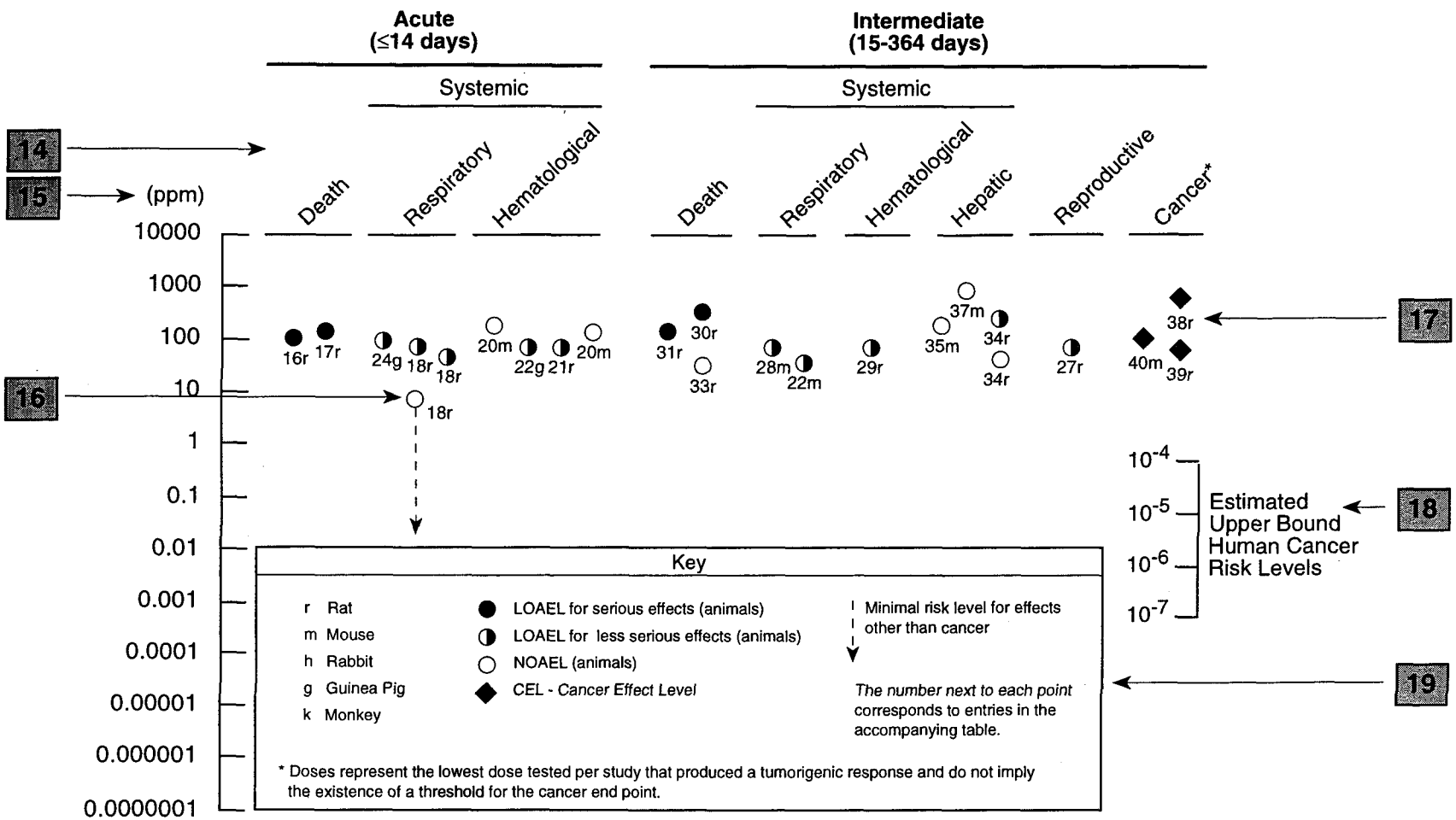
Key to figure[a]	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
2 → INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
3 → Systemic	↓	↓	↓	↓	↓		↓
4 → 18	Rat	13 wk 5d/wk 6hr/d	Resp	3[b]	10 (hyperplasia)		Nitschke et al. 1981
CHRONIC EXPOSURE							
					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] Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5 x 10 ppm^3; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

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



APPENDIX B

Chapter 2 (Section 2.5)

Relevance to Public Health

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.

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).

APPENDIX B

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
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	Best Available Technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	Cancer Effect Level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/ NA/IMCO	Department of Transportation/United Nations/ North America/International Maritime Dangerous Goods Code
DWEL	Drinking Water Exposure Level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram

EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F_1	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
ft	foot
FR	*Federal Register*
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
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
LT_{50}	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	*trans,trans*-muconic acid
MAL	Maximum Allowable Level
mCi	millicurie
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	milligram
min	minute
mL	milliliter
mm	millimeter

mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	Polycyclic Aromatic Hydrocarbon
PBPD	Physiologically Based Pharmacodynamic
PBPK	Physiologically Based Pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector
pg	picogram

pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard mortality ratio
SNARL	Suggested No Adverse Response Level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short-term exposure limit
STORET	Storage and Retrieval
TD_{50}	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram

q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result

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