

**TOXICOLOGICAL PROFILE FOR
PHENOL**

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Agency for Toxic Substances and Disease Registry

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UPDATE STATEMENT

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

QUICK REFERENCE FOR HEALTH CARE PROVIDERS

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

Primary Chapters/Sections of Interest

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

Chapter 2: Health Effects: Specific health effects of a given hazardous compound are reported by *route of exposure*, by *type of health effect* (death, systemic, immunologic, reproductive), and by *length of exposure* (acute, intermediate, and chronic). In addition, both human and animal studies are reported in this section.

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

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

- Section 1.6** **How Can (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**
-

ATSDR Information Center

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Internet: <http://atsdr1.atsdr.cdc.gov:8080>

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

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

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

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

Other Agencies and Organizations

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

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

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

Referrals

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. *Contact:* AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: aoec@dgs.dgsys.com • AOEC Clinic Director: <http://occ-env-med.mc.duke.edu/oem/aoec.htm>.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. *Contact:* ACOEM, 55 West Seegers Road, Arlington Heights, IL 60005 • Phone: 847-228-6850 • FAX: 847-228-1856.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

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

PEER REVIEW

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

1. Dr. Dietrich Hoffmann, Associate Director, Division of Environmental Carcinogenesis, American Health Foundation, Valhalla, NY.
2. Mr. Bruce Jacobs, Principal Consultant, Jacobs Environmental, Inc., Abingdon, MD.
3. Dr. Loren Koller, Dean and Professor, College of Veterinary Medicine, Oregon State University, Corvallis, OR.

These experts collectively have knowledge of phenol'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 phenol 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. Phenol has been found in at least 481 of the 1,467 current or former NPL sites. However, it's unknown how many NPL sites have been evaluated for this substance.

As more sites are evaluated, the sites with phenol may increase. This 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 phenol, 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 PHENOL?

Phenol is a colorless-to-white solid when pure; however, the commercial product, which contains some water, is a liquid. Phenol has a distinct odor that is sickeningly sweet and tarry. Most people begin to smell phenol in air at about 40 parts of phenol per billion parts of air (ppb), and begin to smell phenol in water at about 1-8 parts of phenol per million parts of water (ppm; 1 ppm is 1,000 times more than 1 ppb). These levels are lower than the levels at which adverse health effects have been observed in animals that breathed air containing phenol, or that drank

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water containing phenol. Phenol evaporates more slowly than water, and a moderate amount can form a solution with water. Phenol can catch on fire.

Phenol is both a man-made chemical and produced naturally. It is found in nature in some foods and in human and animal wastes and decomposing organic material. The largest single use of phenol is as an intermediate in the production of phenolic resins. However, it is also used in the production of caprolactam (which is used in the manufacture of nylon 6 and other synthetic fibers) and bisphenol A (which is used in the manufacture of epoxy and other resins). Phenol is also used as a slimicide (a chemical toxic to bacteria and fungi characteristic of aqueous slimes), as a disinfectant, and in medicinal preparations such as over-the-counter treatments for sore throats. Phenol ranks in the top 50 in production volumes for chemicals produced in the United States. Chapters 3 and 4 contain more information.

1.2 WHAT HAPPENS TO PHENOL WHEN IT ENTERS THE ENVIRONMENT?

Following small, single releases, phenol is rapidly removed from the air; generally, half is removed in less than 1 day. It is also relatively short-lived in the soil (generally, complete removal in 2-5 days). However, it can remain in water week or more. Phenol can remain in the air, soil, and water for much longer periods of time if a large amount of it is released at one time, or if it is constantly released to the environment. Levels of phenol above those found naturally in the environment are usually found in surface waters and surrounding air contaminated by phenol released from industrial activity and from the commercial use of products containing phenol. Phenol has been detected, however, in the materials released from landfills and hazardous waste sites, and it has been found in the groundwater near these sites. The levels of phenol found in indoor environments as a part of environmental tobacco smoke (ETS) are usually below 100 ppb, although much higher levels have been reported. One ppb or less of phenol has been found in relatively unpolluted surface water and groundwater, and low levels are also found in indoor environments and are principally derived from ETS. Only low levels of phenol are found in the organisms that live in water which also contains low levels of phenol. Chapters 4 and 5 contain more information.

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1.3 HOW MIGHT I BE EXPOSED TO PHENOL?

Since phenol is used in many manufacturing processes and in many products, as well as being naturally produced, exposure may take place where you work or at home. Phenol is present in a number of consumer products which are swallowed, rubbed on, or added to various parts of the body. These include ointments, ear and nose drops, cold sore lotions, mouthwashes, gargles, toothache drops, analgesic rubs, throat lozenges, and antiseptic lotions. Phenol has been found in drinking water, tobacco smoke, air, and certain foods, including smoked summer sausage, fried chicken, mountain cheese, and some species of fish. It is also found in urine of children and adults.

The magnitude, frequency, and likelihood of exposure, and the relative contribution of each exposure route and source to total phenol exposure cannot be estimated using information currently available. Nonetheless, for persons not exposed to phenol in the workplace, possible routes of exposure include: breathing industrially contaminated air; inhaling cigarette, cigar, or pipe smoke, or ETS polluted air; drinking water from contaminated surface water or groundwater supplies; swallowing products containing phenol; changing diapers; and coming into contact with contaminated water and products containing phenol through bathing or skin application.

Populations residing near phenol spills, waste disposal sites, or landfill sites may be at risk for higher exposure to phenol than other populations. If phenol is present at a waste site near homes that have wells as a source of water, it is possible that the well water could be contaminated. If phenol is spilled at a waste site, it is possible for a person, such as a child playing in dirt containing phenol, to have skin contact or to swallow soil or water contaminated with phenol. Skin contact with phenol or swallowing products containing phenol may lead to increased exposure. This type of exposure is expected to occur infrequently and generally occurs over a short time period.

At the workplace, exposure to phenol can occur from breathing contaminated air. However, skin contact with phenol during its manufacture and use is considered the major route of exposure in the workplace. It has been estimated that about 584,000 people in the United States are exposed

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to phenol at work. Total exposure at the workplace is potentially higher than in non-workplace settings. Chapter 5 contains more information on sources of exposure.

1.4 HOW CAN PHENOL ENTER AND LEAVE MY BODY?

Phenol can enter the body when a person drinks contaminated water or other liquids such as tea and coffee, eats contaminated food, or swallows products containing phenol. Phenol spilled on the skin easily penetrates the skin and enters the body. Phenol also enters the body through the lungs when a person breathes in air or inhales smoke from tobacco which contains phenol.

The amount of phenol that enters the body from skin contact with water containing phenol depends on the concentration of phenol in the water, the length of time of skin contact, and the amount of skin that makes contact with the contaminated water. Greater amounts of phenol will enter the body if large areas of skin come into contact with weaker solutions of phenol than if small areas of skin come into contact with the solutions of phenol. If a person is exposed to air containing phenol, phenol can enter the body through the skin and lungs. It has been determined that entry through the skin can account for as much as one-half of the phenol that enters the body when a person is exposed to phenol in air. Although it is possible for a person to be exposed to air contaminated with phenol at a waste site, such an exposure is not likely because spilled phenol will mostly remain in soil or water rather than evaporate into air. If a person swallows phenol, the intestines will change much of it to a less harmful substance. If phenol enters through the skin, it may reach organs and cause adverse effects before it is changed into a less harmful substance.

Studies in humans and animals indicate that most of the phenol that enters the body through skin contact, breathing contaminated air, eating food or drinking water, or using products containing phenol, leaves the body in the urine within 24 hours. Chapter 2 contains additional information about how phenol enters and leaves the body.

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It is also clear that phenol is produced by the body and excreted independent of external exposure to the compound. The normal range of phenol in the urine of unexposed individuals is 0.5-80 milligrams of phenol per liter of urine (mg/L).

1.5 HOW CAN PHENOL 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.

A number of effects from breathing phenol in air have been reported in humans. Short-term effects reported include respiratory irritation, headaches, and burning eyes. Chronic effects of high exposures included weakness, muscle pain, anorexia, weight loss, and fatigue; effects of chronic low-level exposures included increases in respiratory cancer, heart disease, and effects on the immune system. Virtually all of the workplace exposures associated with these effects involved exposures to other chemicals, thus it is difficult to determine whether these are solely due to phenol, or are the result of mixed, multiple, or other chemical exposures.

In animals, exposure to high concentrations of phenol in air for a few minutes irritates the lungs, and repeated exposure for several days produces muscle tremors and loss of coordination. Exposure to high concentrations of phenol for several weeks results in paralysis and severe injury to the heart, kidneys, liver, and lungs, followed by death in some cases. When exposures involve

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the skin surface, the size of the total surface area of exposed skin can influence the severity of the toxic effects.

The seriousness of the effect of a harmful substance can be expected to increase as both the level and duration of exposure increase. Repeated exposure to low levels of phenol in drinking water has been associated with diarrhea and mouth sores in humans. Ingestion of very high concentrations of phenol has resulted in death. In animals, drinking water with extremely high concentrations of phenol has caused muscle tremors and loss of coordination.

Effects reported in humans following dermal exposure to phenol include liver damage, diarrhea, dark urine, and red blood cell destruction. Skin exposure to a relatively small amount of concentrated phenol has resulted in the death of humans. Small amounts of phenol applied to the skin of animals for brief periods can produce blisters and burns on the exposed surface, and spilling dilute phenol solutions on large portions of the body (greater than 25% of the body surface) can result in death.

It is not known if phenol causes cancer in humans. However, cancer has been shown to occur in mice when phenol was applied to the skin several times each week during the whole lifetime of the animal. When it is applied in combination with certain cancer-causing chemicals, a higher rate of cancer occurs than when the carcinogens are applied alone. Phenol did not cause cancer in mice or rats when they drank water containing phenol for 2 years. The International Agency for Research on Cancer (IARC) considers phenol not classifiable as to its carcinogenicity in humans.

Phenol can have beneficial effects when used for medical reasons. It is an antiseptic (kills germs) when applied to the skin in small amounts and may have antiseptic properties when gargled as a mouthwash. It is an anesthetic (relieves pain) and is a component of certain sore-throat lozenges and throat sprays or gargles. Small amounts of phenol in water have been injected into nerve tissue to lessen pain associated with certain nerve disorders. Phenol destroys the outer layers of skin if allowed to remain in contact with skin, and small amounts of concentrated solutions of

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phenol are sometimes applied to the skin to remove warts and to treat other skin blemishes and disorders.

Chapter 2 contains a more thorough discussion of the health effects of phenol.

1.6 HOW CAN PHENOL AFFECT CHILDREN?

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

The exposure of children to phenol is likely to occur by most of the same routes experienced by adults, the major exception being that children are unlikely to be exposed due to their parents' occupations. There is clear evidence, however, that at least with certain products, children are at greater risk of accidental ingestion than adults. In the case of one product, a disinfectant containing 26% phenol, children under the age of 5 represented 60 of 80 (75%) of the poisoning cases associated with this product reported to a major poison control center between 1987-1991.

In humans, the effects of exposure to phenol on reproduction and the developing fetus are unknown. Several studies have not shown phenol to be active in developmental toxicity. However, in others, pregnant animals that drank water containing high concentrations of phenol gave birth to offspring with low birth weights and minor birth defects. The implications of these findings for humans is unclear, although it seems likely that any adverse developmental effects would require much higher doses than would normally be encountered at hazardous waste sites.

It is unknown whether infants or children are more susceptible than adults to the adverse effects of phenol; as stated above, developmental studies are inconclusive. Most of the information available on the toxic effects of phenol in infants and children comes from the use of phenol in medical treatments. Phenol was once used as an antiseptic in wound dressing products and there are several reports of deaths in children and infants following overzealous application of such

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products to burns or open wounds. All of these cases occurred decades ago, however, and there is little indication that such products, which contained relatively high levels of phenol, are still in use.

Other phenol-containing products are used as “chemical peels” to remove skin lesions, and in the treatment of chronic pain or spasticity. These uses have occasionally been associated with adverse outcomes, like cardiac arrhythmias, that have been seen in both adults and children. These effects do not appear to occur more frequently in children than adults; however, the information on such effects in children is very limited.

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

If your doctor finds that you have been exposed to significant amounts of phenol, ask if children may also be exposed. When necessary your doctor may need to ask your State Department of Public Health to investigate.

Since ETS contains phenol, reducing the amount of smoking indoors will reduce phenol exposures. Household products and over-the-counter medications containing phenol should be stored out of reach of young children to prevent accidental poisonings and skin burns. Always store household chemicals in their original labeled containers. Never store household chemicals in containers that children would find attractive to eat or drink from, such as old soda bottles. Keep your Poison Control Center’s number next to the phone.

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

Urine can be tested for the presence of phenol. This test can be used to determine if the urine has a higher than normal concentration of phenol, thus suggesting recent exposure to phenol or to substances that are converted to phenol in the body (e.g., benzene). There is no test available that will tell if a person has been exposed only to phenol since many substances are converted to phenol in the body. Because most of the phenol that enters the body is excreted in the urine

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within 24 hours, this test can only detect exposures that have occurred within 1 or 2 days prior to the test. The test results cannot be used to predict what health effects might result from exposure to phenol. Measurement of phenol in urine requires special laboratory equipment and techniques that are not routinely available in most hospitals or clinics. Chapters 2 and 6 contain more information on tests for exposure to phenol.

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 phenol include the following:

OSHA has set a limit of 5 ppm in air to protect workers during 8-hour workshifts of a 40-hour workweek. NIOSH recommends that the concentration in workroom air be limited to 5 ppm over

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a 10-hour work shift, and that the workroom air concentration should not exceed 16 ppm during a 15-minute period. Note that these workplace air limits assume no skin contact with phenol.

Phenol is listed on the Food and Drug Administration's EAFUS (Everything Added to Foods in the United States) List (FDA 1998a), and is approved as a component of food packaging materials (FDA 1998b, 1998c, 1998d).

The EPA lifetime health advisory for phenol in water is 4 mg/L. EPA has determined that the level of phenol in ambient water (lakes, streams) should be limited to 3.5 mg/L in order to protect human health from the potential toxic effects of exposure to phenol through ingestion of water and contaminated aquatic organisms.

1.10 WHERE CAN I GET MORE INFORMATION?

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

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

* Information line and technical assistance

Phone: 1-800-447-1544

Fax: (404) 639-6359

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

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*To order toxicological profiles, contact:

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

2. HEALTH EFFECTS

2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of phenol. 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.

It should be noted that phenol is the simplest form, or parent compound, of the class of chemicals commonly referred to as phenols or phenolics, many of which are natural substances widely distributed throughout the environment. There is some confusion in the literature as to the use of the term 'phenol'; in some cases it has been used to refer to a particular phenolic compound that is more highly substituted than the parent compound (Doan et al. 1979), whereas in other cases it has been used to refer to the class of phenolic compounds (Beveridge 1997). This chapter, however, addresses only those health effects which can be directly attributable to the parent compound, monohydroxybenzene, or phenol. As Deichmann and Keplinger (1981) note: "It cannot be overemphasized that the structure-activity relationships of phenol and phenol derivatives vary widely, and that to accept the properties of individual phenolic compounds as being those of phenol is a misconception and leads to error and confusion."

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

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classified into “less serious” or “serious” effects. “Serious” effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). “Less serious” effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, “less serious” LOAEL, or “serious” LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between “less serious” and “serious” effects. The distinction between “less serious” effects and “serious” effects is considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

Levels of exposure associated with carcinogenic effects (Cancer Effect Levels, CELs) of phenol are indicated in Table 2-3.

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.

2.2.1 Inhalation Exposure

2.2.1.1 Death

A cohort mortality study of workers in five formaldehyde-resin manufacturing facilities was conducted to evaluate whether excess mortality could be attributed to occupational exposure to phenol (Dosemeci et al.

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1991). Workers (exposed and non-exposed) had a mortality rate, from all causes, similar to that of the general U.S. population. Compared to either the general population or unexposed workers, exposed workers had small excesses in mortality due to Hodgkin's disease and esophageal and renal cancers. However, they also had small reductions in mortality due to: cancer of the stomach, testes, pancreas, buccal cavity/pharynx and brain; lymphosarcoma; liver cirrhosis; emphysema; diseases of the cardiovascular, circulatory, and digestive systems; motor vehicle accidents and all accidents. The ambiguity of these data, as well as the fact that dose-related trends occurred only for those diseases showing reductions in mortality, makes it difficult to assess the impact on mortality of long-term occupational exposure to phenol. However, the authors do hypothesize a protective effect for phenol based on its metabolism to chemicals that could play a role in mitigating oxidative damage.

Deichmann et al. (1944) exposed guinea pigs, rabbits, and rats to phenol vapor at levels ranging from 26 to 52 ppm for 28-88 days. After 28 days of exposure, 5 of 12 guinea pigs died, but no deaths occurred in rabbits or rats. Since only a range was given for the exposure level, the exact level of phenol in air that resulted in death of guinea pigs was not established and may be as low as 26 ppm or as high as 52 ppm. Interpretation of this study is further complicated by an apparent lack of controls. However, since the effects observed in guinea pigs and rabbits (described in subsequent sections in Chapter 2) were so severe, it is difficult to ascribe the mortality to any source other than the phenol exposure. The lower limit of the exposure range, 26 ppm, is recorded as a LOAEL in Table 2-1 and plotted in Figure 2-1. No deaths were reported in rhesus monkeys, rats, or mice exposed to 5 ppm phenol continuously for 90 days (Sandage 1961).

2.2.1.2 Systemic Effects

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. Slight increases in mortality associated with respiratory cancers were seen in two epidemiological studies of workers exposed to phenol (Dosemeci et al. 1991; Kauppinen et al. 1986). However, after adjusting for smoking-related behavior, these increases became non-significant in the Kauppinen et al. (1986) study, and neither study showed a dose-related trend; thus, the relevance of these findings to respiratory disease *per se* is somewhat uncertain. Indeed in the latter study, there were slight, yet nonsignificant reductions in mortality associated with emphysema among exposed workers, leading the

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

Key to figure ^a	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
ACUTE EXPOSURE							
Systemic							
1	Mouse (Swiss OF1)	5 min	Resp			166 M (50% decrease in respiration rate)	De Ceaurriz et al. 1981
Immunological/Lymphoreticular							
2	Mouse (CD-1)	5 d 3 hr/d		5 F			Aranyi et al. 1986
Neurological							
3	Rat Harlan-Wistar	1 hr		234 F			Flickinger 1976
4	Rat Harlan-Wistar	8 hr			234 F		Flickinger 1976
INTERMEDIATE EXPOSURE							
Death							
5	Gn Pig (NS)	4 wk 5 d/wk 7 hr/d				26 (5/12 deaths)	Deichmann et al. 1944

TABLE 2-1. Levels of Significant Exposure to Phenol - Inhalation (continued)

Key to figure ^a	Species (strain)	Exposure/ duration/ frequency	System	NOAEL (ppm)	LOAEL		Reference
					Less serious (ppm)	Serious (ppm)	
Systemic							
6	Monkey (Rhesus)	90 d continuous	Resp	5 M			Sandage 1961
			Hemato	5 M			
			Hepatic	5 M			
			Renal	5 M			
			Bd Wt	5 M			
7	Rat (White)	15 d continuous	Hemato	26			Dalin and Kristoffersson 1974
			Hepatic		26	(serum activities of ALT, AST, LDH, and GLDH increased 2-6-fold; increased serum magnesium)	
			Bd Wt	26			
8	Rat (Sprague- Dawley)	90 d continuous	Resp	5 M			Sandage 1961
			Hemato	5 M			
			Hepatic	5 M			
			Renal	5 M			
			Bd Wt	5 M			
9	Mouse (NS)	90 d continuous	Resp	5 M			Sandage 1961
			Hemato	5 M			
			Hepatic	5 M			
			Renal	5 M			
			Bd Wt	5 M			

TABLE 2-1. Levels of Significant Exposure to Phenol - Inhalation (continued)

Key to figure ^a	Species (strain)	Exposure/duration/frequency	System	NOAEL (ppm)	LOAEL		Reference	
					Less serious (ppm)	Serious (ppm)		
10	Gn Pig (NS)	6 wk 5 d/wk 7 hr/d	Resp				26 (acute lobular pneumonia with occasional abscesses and vascular damage)	Deichmann et al. 1944
			Cardio				26 (necrosis of the myocardium, extensive reactive inflammation)	
			Hepatic				26 (fatty changes, centrolobular degeneration and necrosis)	
			Renal				26 (edema of the convoluted tubules, slightly advanced focal cortical lesions, glomerular degeneration)	
11	Rabbit (NS)	12 wk 5 d/wk 7 hr/d	Resp				26 (confluent lobular pneumonia, chronic purulent bronchitis, hyperplastic peribronchial tissue, degenerative changes in pulmonary vessels)	Deichmann et al. 1944
			Cardio				26 (myocardial degeneration, necrosis of muscle bundles, interstitial fibrosis, lymphocytic infiltration)	
			Hepatic				26 (centrolobular degeneration and necrosis)	
			Renal				26 (edema of the convoluted tubules, focal cortical lesions, glomerular degeneration)	
Neurological								
12	Monkey (Rhesus)	90 d continuous		5 M				Sandage 1961

TABLE 2-1. Levels of Significant Exposure to Phenol - Inhalation (continued)

Key to figure ^a	Species (strain)	Exposure/duration/frequency	System	LOAEL		Reference
				NOAEL (ppm)	Less serious (ppm)	
13	Rat (White)	15 d continuous			26 (mild motor disorders during the first 4 days of exposure, 4.4° decrease in sliding angle)	Dalin and Kristoffersson 1974
14	Rat (Sprague-Dawley)	90 d continuous		5 M		Sandage 1961
15	Mouse (NS)	90 d continuous		5 M		Sandage 1961
16	Gn Pig (NS)	6 wk 5 d/wk 7 hr/d			26 (hindlimb paralysis)	Deichmann et al. 1944

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^aThe number corresponds to entries in Figure 2-1.

ALT = alanine aminotransferase; AST = aspartate aminotransferase; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); F = female; GLDH = glutamate dehydrogenase; Gn Pig = guinea pig; Hemato = hematological; hr = hour(s); LDH = lactate dehydrogenase; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s)

Figure 2-1. Levels of Significant Exposure to Phenol - Inhalation
Acute (≤ 14 days)

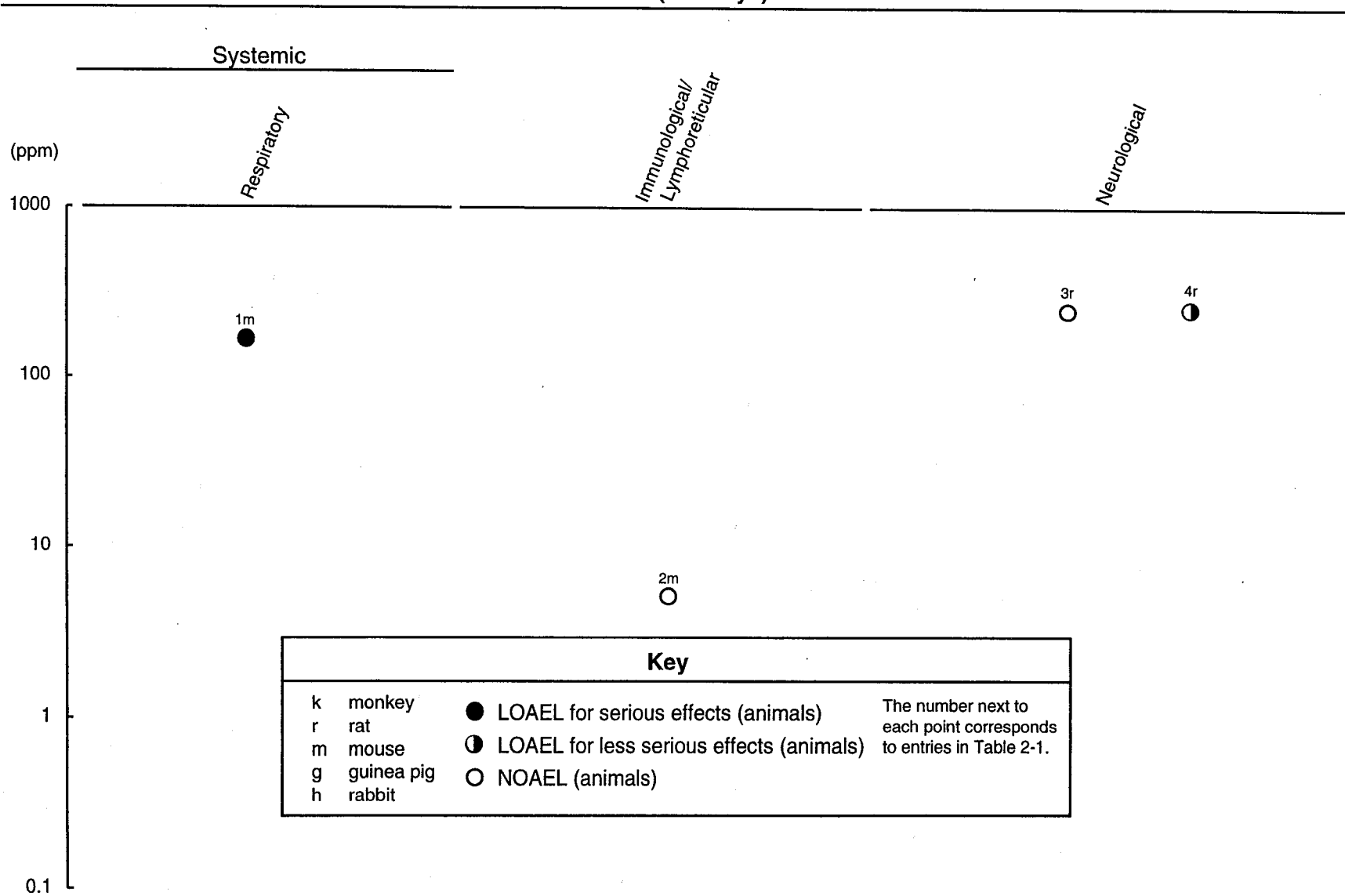
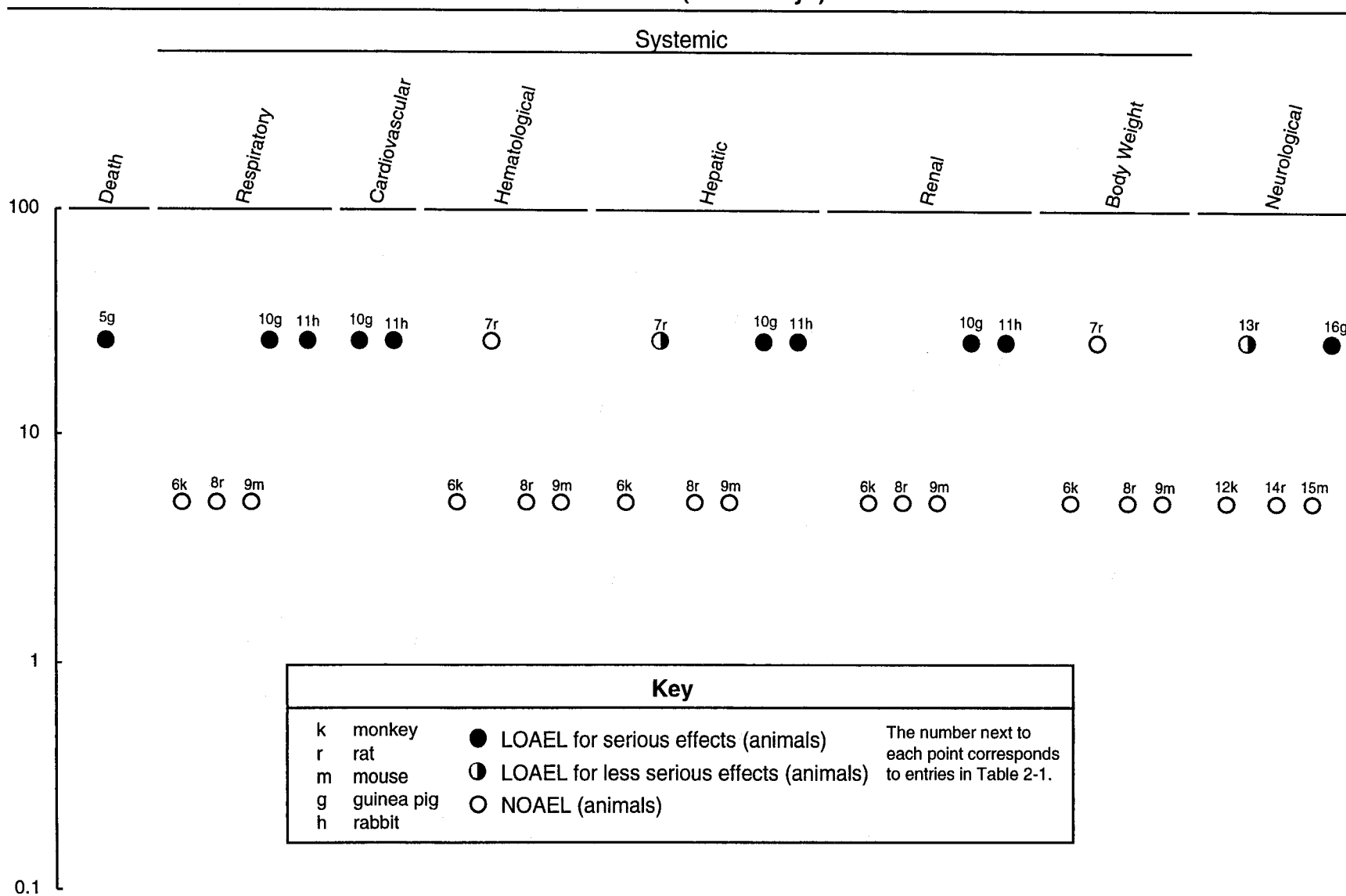


Figure 2-1. Levels of Significant Exposure to Phenol - Inhalation (continued)
 Intermediate (15-364 days)



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authors to suggest that exposure to phenol could have a protective effect for diseases involving free radical damage. (For more detail see above and Section 2.2.1.8.)

A case-control study of office workers was conducted by Baj et al. (1994) to evaluate the risks of chronic exposures to “inhaled formaldehyde, phenol, and isomers of organic chlorohydrocarbons from Ksylamit™ . . .” which is a widely used liquid wood preservative. It should be noted that in the report, Ksylamit™ is indicated to consist of “. . . a mixture of chlorinated benzenes, pentachlorophenol, alphachloronaphthalene, chloroparaffin and kerosene . . .”, and that the authors provide no discussion of how phenol and formaldehyde are produced through the use of such a mixture. Twenty-two workers (18 women and 4 men) exposed for at least 6 months were the cases, and 29 non-exposed, non-smoking volunteers matched for age, sex, and place of residence were the controls. The authors indicate that all exposed workers developed chronic complaints, among them cough and sore throat, but that no remarkable increase in morbidity was found during the 6 months of exposure to Ksylamit™ nor during the 3-year follow-up study (details of which were not provided). The authors attribute these symptoms to the irritant effect of the inhaled Ksylamit™ probably (based on the references provided) due to the formaldehyde vapor they assert emanates from the wood-preserving liquid.

In laboratory animals, phenol is a respiratory irritant. De Ceaurriz et al. (1981) reported a dose-response function for reflex apnea, an index of respiratory irritation, in mice exposed to phenol vapor. From the log dose-response function for decreased breathing rate, the RD₅₀ (RD designates respiratory depression), or level of phenol in air that resulted in a 50% decrease in breathing rate during a 5-minute head-only exposure, was established as 166 ppm. Based on the RD₅₀ the study authors estimated that a concentration of 17 ppm (0.1xRD₅₀) would be a LOAEL for respiratory irritation in humans, and a concentration of 2 ppm (0.01xRD₅₀) would be a NOAEL.

In a study in which female Harlan Wistar rats were exposed for 1 hour to a phenol aerosol at a concentration of 234 ppm, then held for 2 weeks post-exposure, Flickinger (1976) observed signs of nasal irritation during exposure. However, all animals were normal by the post-exposure day 1, and no abnormal lesions were observed upon gross autopsy. No histopathology was performed; thus, this study is not presented as a LOAEL for rats.

Inflammation, cellular infiltration, pneumonia, bronchitis, endothelial hyperplasia, and capillary thrombosis occurred in guinea pigs exposed by inhalation to 26-52 ppm phenol for 41 days (Deichmann et al. 1944).

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Rabbits exhibited qualitatively similar but less severe effects after 88 days of similar exposure. Since only a range was given for the exposure level (26-52 ppm), the exact level of phenol in air that resulted in respiratory effects was not established and may be as low as 26 ppm or as high as 52 ppm. Interpretation of this study is further complicated by an apparent lack of controls. However, the lung pathology was so severe, particularly in the guinea pigs, that it is difficult to ascribe the effects to any source other than the phenol exposure. The lower limit of the exposure range, 26 ppm, can be considered a LOAEL for respiratory effects in guinea pigs and rabbits. Rats were also exposed to 26-52 ppm in a manner similar to rabbits and guinea pigs (Deichmann et al. 1944). The study authors indicate that there was no gross or microscopic evidence of injury, but the organs examined from the rats were not stated. Therefore, this study is not presented as a NOAEL for rats.

No significant histological abnormalities of the lungs were detected in rhesus monkeys, rats, or mice exposed to 5 ppm phenol continuously for 90 days (Sandage 1961).

Cardiovascular Effects. In a cohort mortality study of workers in a large rubber and tire manufacturing plant, Wilcosky and Tyroler (1983) found a significant increase in mortality from ischemic heart disease in phenol exposed workers. Of the 25 solvents used in the plant, phenol exposure showed the strongest association with mortality from heart disease, greater even than that observed for exposure to carbon disulfide, the only known occupational cause of atherosclerosis.

In a cohort-mortality study of workers from five phenol-formaldehyde resin plants, Dosemeci et al. (1991) found a slight reduction in mortality due to heart disease. These authors hypothesized a protective effect of phenol exposures; however, these results clearly conflict with those of Wilcosky and Tyroler (1983). As a consequence, without more definitive studies, it is difficult to assess the cardiovascular risk to humans, if any, posed by occupational exposure to phenol.

Myocardial injury was reported in guinea pigs exposed to 26-52 ppm for 41 days, and rabbits exhibited qualitatively similar but less severe effects after 88 days of similar exposure (Deichmann et al. 1944). The injury was characterized by myocardial inflammation, degeneration, and necrosis, interstitial fibrosis, and lymphocyte infiltration. Since only a range was given for the exposure level (26-52 ppm), the exact level of phenol in air that resulted in myocardial injury was not established and may be as low as 26 ppm or as high as 52 ppm. Interpretation of this study is further complicated by an apparent lack of controls. However, the heart pathology was so severe that it is difficult to ascribe the effects to any source other than the phenol

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exposure. The lower limit of the exposure range, 26 ppm, can be considered a LOAEL for myocardial injury in guinea pigs and rabbits.

Gastrointestinal Effects. Historical information in a case report (Merliss 1972) indicates that ‘carbolic marasmus’ was a common occupational disorder of physicians and their assistants during the mid-19th Century when carbolic acid sprays (1:40 phenol in water) were commonly used for antiseptics in operating rooms. Among the characteristics of this disorder were anorexia leading to progressive weight loss and excess production of saliva. Similar gastrointestinal effects were observed in one of the author’s patients who was involved in the daily distillation of phenol over a 13.5 year period. Exposed both via inhalation of the vapors and dermally from frequent spills, the patient’s symptoms included both loss of appetite and weight loss.

A cohort mortality study of workers in five phenol-formaldehyde resin manufacturing plants found that exposed workers showed a slight reduction in death rate due to cancers of the digestive system as compared to both non-exposed workers and the general population (Dosemeci et al. 1991). In a study of rats exposed continuously for 15 days to 26 ppm phenol vapor, Dalin and Kristoffersson (1974) noted the absence of impacts on the digestive system and attributed this to the relatively low exposure levels (as compared to studies using oral dosing).

Hematological Effects. A case-control study of office workers was conducted by Baj et al. (1994) to evaluate the risks of chronic exposures to “inhaled formaldehyde, phenol and isomers of organic chlorohydrocarbons from Ksylamitr™” which is a widely used liquid wood preservative. It should be noted that in the report, Ksylamitr™ is indicated to consist of “a mixture of chlorinated benzenes, pentachlorophenol, alpha-chloronaphthalene, chloroparaffin and kerosene,” and that the authors provide no discussion of how phenol and formaldehyde are produced through the use of such a mixture. Twenty-two workers (18 women and 4 men) exposed for at least 6 months were the cases, and 29 non-exposed, non-smoking volunteers matched for age, sex, and place of residence were the controls. Using blood and urine samples drawn after 6 months of exposure, cases and controls were compared on a variety of biochemical, hematological, and immunological parameters. The exposed group showed no differences in any of the blood chemistry parameters examined, serum bilirubin, alanine, and aspartate aminotransferase activity, but had about a 30% increase in eosinophils, a 25% increase in monocytes, and a 70% decrease in erythrocytes. Measurement of the office air at the end of the 6-month period revealed a level of phenol of 0.34 ppm. Although the authors contend that their observations support the concern that chronic exposure to phenol could adversely

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affect the hematopoietic system, it is important to consider not only that other volatile chemicals, chlorinated organics, were present in the wood-preserving liquid, but also that the chemical composition provided for Ksylamit™ opens up the possibility that the effects being evaluated result from exposure to pentachlorophenol rather than to phenol. This is particularly true since it was not possible to determine from the information presented if the analytical methods used would differentiate between phenol and pentachlorophenol.

Hematocrit and hemoglobin concentrations were not affected in rats exposed to 26 ppm phenol in air continuously for 15 days (Dalín and Kristoffersson 1974). Detailed hematological evaluations including red and white blood cell, reticulocyte, and platelet counts; white cell differential; hemoglobin and sulfhemoglobin, red cell fragility tests, as well as corpuscular volume, corpuscular hemoglobin, and corpuscular hemoglobin concentrations, did not reveal any effects in rhesus monkeys, rats, or mice exposed continuously to 5 ppm phenol in air for 90 days (Sandage 1961).

Musculoskeletal Effects. A case of muscle pain and weakness was described in an individual after intermittent chronic inhalation and dermal exposure to vapors and solutions of phenol, cresol, and xylene (Merliss 1972). The symptoms lessened when the subject was removed from exposure. Although the exposure concentrations were not reported, the study author stated that the patient often detected heavy odors, and that phenol was often spilled on his clothes resulting in skin irritation. Since phenol is absorbed readily from the skin, dermal absorption of phenol may have contributed to the systemic effects that were observed. The above symptoms may represent neurological effects rather than injury to the muscle tissue.

In a study in which female Harlan Wistar rats were exposed for 8 hours to a phenol aerosol at a concentration of 234 ppm, Flickinger (1976) observed a slight loss of coordination with spasm of the muscle groups at 4 hours. By 8 hours, frank tremors were observed leading to a severe loss of coordination; however, all animals were normal by post-exposure day 1, and no abnormal lesions were observed upon gross autopsy.

Hepatic Effects. Enlarged liver and elevated serum levels of hepatic enzymes indicative of liver injury (lactate dehydrogenase, 2 times above normal; aspartate aminotransferase, 21 times above normal; alanine aminotransferase, 100 times above normal) were observed in an individual following chronic daily exposure to vapors and spills of phenol (Merliss 1972). The symptoms lessened when the individual was removed from the site of exposure. Although the exposure concentrations were not reported, the study author stated that the patient often detected heavy odors and that phenol was often spilled on his clothes resulting in skin

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irritation. Since phenol is absorbed readily from the skin, dermal absorption may have contributed to the systemic effects that were observed.

No effects on activities of liver enzymes (alanine aminotransferase, aspartate aminotransferase, γ glutamyltranspeptidase, alkaline phosphatase) in the serum or changes in serum bilirubin or ceruloplasmin were noted in 22 workers exposed for 6 months to vapors from a wood-treatment liquid containing phenol, formaldehyde, and organic chlorohydrocarbons (Baj et al. 1994). Although the study authors considered a significant increase in serum iron to reflect an adverse effect on the liver that they attributed to phenol exposure, it is important to consider not only that other volatile chemicals, chlorinated organics, were present in the wood-preserving liquid, but also that the chemical composition provided for KsylamitTM opens up the possibility that the effects being evaluated result from exposure to pentachlorophenol rather than phenol. Dosemeci et al. (1991) saw a dose-related decrease in mortality from liver cirrhosis in a cohort of workers occupationally exposed to phenol during their employment at five phenol-formaldehyde resin plants. These findings are complicated by the fact that workers were also exposed to other chemicals; however, the authors hypothesize that exposure to phenol could have a protective effect for diseases involving free radical damage. For more detail, see above and Section 2.2.1.8.

Centrilobular degeneration and necrosis of the liver were reported in guinea pigs exposed by inhalation to 26-52 ppm phenol for 41 days, and rabbits exhibited qualitatively similar but less severe effects after 88 days of similar exposure (Deichmann et al. 1944). Since only a range was given for the exposure level (26-52 ppm), the exact level of phenol in air that resulted in hepatic injury was not established and may be as low as 26 ppm or as high as 52 ppm. Interpretation of this study is further complicated by an apparent lack of controls. However, the liver pathology was so severe, particularly in the guinea pigs, that it is difficult to ascribe the effects to any source other than the phenol exposure.

Elevated activities of liver enzymes (lactate dehydrogenase, aspartate aminotransferase, alanine aminotransferase, glutamate dehydrogenase) were found in the serum of rats exposed continuously to 26 ppm phenol vapor for 15 days (Dalin and Kristoffersson 1974). Increased concentration of these enzymes in serum is often associated with liver injury but is not conclusive evidence for the type or severity of injury. Therefore, 26 ppm can be considered a less serious LOAEL in rats. Serum levels of magnesium were also increased in these rats, an effect the study authors suggested may also be a sign of liver injury. No significant histological abnormalities were detected in the livers of rhesus monkeys, rats, or mice exposed continuously to 5 ppm phenol in air for 90 days (Sandage 1961).

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Renal Effects. In a case of chronic phenol poisoning, dark urine and glucose in the urine were noted in a man following intermittent exposure to vapors and solutions of phenol (Merliss 1972). The urine tested negative for protein and urobilinogen. The urine cleared 2-3 months after removal from exposure. Although the exposure concentrations were not reported, the study author stated that heavy odors were often detectable, and that phenol was often spilled on the patient's clothes resulting in skin irritation. Since phenol is absorbed readily from the skin, dermal absorption may have contributed to the systemic effects that were observed.

Renal proximal tubule and glomerular injury was reported in guinea pigs exposed by inhalation to 26-52 ppm phenol for 41 days, and rabbits exhibited qualitatively similar but less severe effects after 88 days of similar exposure (Deichmann et al. 1944). Since only a range was given for the exposure level (26-52 ppm), the exact level of phenol in air that resulted in renal injury was not established and may be as low as 26 ppm or as high as 52 ppm. Interpretation of this study is further complicated by an apparent lack of controls. However, the kidney pathology was so severe, particularly in the guinea pigs, that it is difficult to ascribe the effects to any source other than the phenol exposure. The lower limit of the exposure range, 26 ppm, can be considered a LOAEL for renal injury in guinea pigs and rabbits. Rats were also exposed to 26-52 ppm in a manner similar to rabbits and guinea pigs (Deichmann et al. 1944). The study authors indicated that there was no gross or microscopic evidence of injury, but the organs examined from the rats were not stated. Therefore, this study is not presented as a NOAEL for rats. No significant histological abnormalities were detected in the kidneys of rhesus monkeys, rats, or mice exposed continuously to 5 ppm phenol in air for 90 days (Sandage 1961).

Dermal Effects. Historical information in a case report Merliss (1972) indicates that 'carbolic marasmus' was a common occupational disorder of physicians and their assistants during the mid-19th Century. Among the characteristics of this disorder was an odd form of pigmentation which commonly occurred in the urine but also occasionally colored the sclera of the eyes, the skin over the nose, and the cheek bones. NIOSH (1984) conducted a survey in an Oregon hospital in response to concerns about respiratory problems and contact dermatitis in housekeeping staff members who were exposed frequently to germicidal solutions containing phenol and other solvents (formaldehyde, cellosolve, ethanolamine). According to the survey, the housekeeping staff reported significantly more symptoms of cough, itching, sinus problems, and dermatitis than other employees. Air concentrations of phenol in the work areas were below the limit of detection (<0.01 ppm). Urinary phenol levels in housekeeping staff were not significantly different from those of other employees. Thus, while it is likely that the employees came into contact with irritants, the cause of the reported symptoms could not be assigned to phenol or any other specific substance in the work environment.

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No studies were located regarding dermal effects in animals following inhalation exposure to phenol.

Ocular Effects. A case-control study of office workers was conducted by Baj et al. (1994) to evaluate the risks of chronic exposures to “inhaled formaldehyde, phenol and isomers of organic chlorohydrocarbons from Ksylamit™ which is a widely used liquid wood preservative reported to consist of “a mixture of chlorinated benzenes, pentachlorophenol, alpha-chloronaphthalene, chloroparaffin, and kerosene.” Twenty-two workers (18 women and 4 men) exposed for at least 6 months were the cases, and 29 non-exposed, non-smoking volunteers matched for age, sex, and place of residence were the controls. The authors indicate that all of the exposed workers developed chronic complaints, among them burning eyes, but that no remarkable increase in morbidity was found during the 6 months of exposure to Ksylamit™, nor during the 3-year follow-up study (details of which were not provided). The authors attribute these symptoms to the irritant effect of the inhaled Ksylarnit™ probably (based on the references provided) due to the formaldehyde vapor they assert emanates from the wood-preserving liquid.

In a study in which female Harlan Wistar rats were exposed for 1 hour to a phenol aerosol at a concentration of 234 ppm, then held for 2 weeks post-exposure, Flickinger (1976) observed signs of ocular irritation during exposure. However, all animals were normal by post-exposure day 1, and no abnormal lesions were observed upon gross autopsy.

Body Weight Effects. Historical information in a case report (Merliss 1972) indicates that ‘carbolic marasmus’ was a common occupational disorder of physicians and their assistants during the mid-19th Century. Among the characteristics of this disorder were anorexia accompanied by progressive weight loss. The author reported that his patient, a 44-year-old man involved in the daily distillation of phenol, showed many of the symptoms of this condition, including lack of appetite and severe weight loss, probably due to his daily workplace exposures to phenol vapors. Although the exposure concentrations were not reported, the report indicated that the patient often detected heavy odors, and that phenol was often spilled on his clothes resulting in skin irritation. Since phenol is absorbed readily from the skin, dermal absorption may have contributed to the systemic effects that were observed.

Body weight effects were not observed in adult female Harlan Wistar rats exposed to an aerosol containing 234 ppm phenol for 8 hours (Flickinger 1976), nor in rats exposed continuously to 26 ppm phenol in air for 15 days (Dalin and Kristoffersson 1974), nor in rhesus monkeys, rats, or mice exposed continuously to 5 ppm phenol in air for 90 days (Sandage 1961).

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Other Systemic Effects. Dalin and Kristoffersson (1974) reported elevated serum concentrations of potassium and magnesium in rats exposed to 26 ppm phenol vapor continuously for 15 days. While not necessarily adverse, this effect may be related to the muscle tremors and neurological effects observed following inhalation exposure to phenol (see Section 2.2.1.4).

2.2.1.3 Immunological and Lymphoreticular Effects

A case-control study of office workers was conducted by Baj et al. (1994) to evaluate the risks of chronic exposures to “inhaled formaldehyde, phenol and isomers of organic chlorohydrocarbons from Ksylamit™,” which is a widely used liquid wood preservative. Twenty-two workers (18 women and 4 men) exposed for at least 6 months were the cases, and 29 non-exposed, non-smoking volunteers matched for age, sex, and place of residence were the controls. Using blood samples drawn after 6 months of exposure, cases and controls were compared on a variety of immunological parameters. The exposed group showed significantly decreased ($P < 0.05$) levels of the CD3+, CD4+, and CD8+ subsets of T-lymphocytes, a significant decrease ($p < 0.001$) in lymphocyte responsiveness to the mitogen PHA, a significant decrease ($p < 0.05$) in NK cell cytotoxicity, and a significant decrease ($p < 0.0001$) in the mixed lymphocyte response assay. Measurement of the office air at the end of the 6 month period revealed a level of phenol of 0.34 ppm. Although the authors contend that their observations support the concern that chronic exposure to phenol could adversely affect the immune system, it is important to consider not only that other volatile chemicals, chlorinated organics, were present in the wood-preserving liquid, but also that the chemical composition provided for Ksylamit™ opens up the possibility that the effects being evaluated resulted from exposure to pentachlorophenol rather than phenol. This is particularly true since it was not possible to determine from the information presented if the analytical methods used would differentiate between phenol and pentachlorophenol.

An increased susceptibility to *Streptococcus zooepidemicus* aerosol was not observed in mice exposed to 5 ppm phenol for 3 hours, or for 5 daily 3-hour periods (Aranyi et al. 1986). Neither did the phenol exposures affect pulmonary bactericidal activity towards *Klebsiella pneumoniae*. Although tests for vulnerability to infectious agents do not represent a comprehensive evaluation of immunological competence, the 5-ppm level can be considered a NOAEL for this specific immunological effect, and is recorded in Table 2-1 and plotted in Figure 2-1.

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2.2.1.4 Neurological Effects

Historical information in a case report (Merliss 1972) indicates that ‘carbolic marasmus’ was a common occupational disorder of physicians and their assistants during the mid- 19th Century. Among the characteristics of this disorder were anorexia, headache, and vertigo. The author reported that his patient, the subject of the case report, showed many of the symptoms of this condition, although his chief complaints were weakness and muscle pain in his arms and legs, progressive weight loss, and excess production of saliva. The symptoms lessened when the subject was removed from the site of exposure. Although it is possible that these symptoms resulted from injury to the muscle, it is more likely that they represent a neurological effect. No information on exposure concentrations was presented; however, the report indicated that the patient often detected heavy odors and that phenol was often spilled on his clothes resulting in skin irritation. Since phenol is absorbed readily from the skin, dermal absorption may have contributed to the systemic effects that were observed.

A case-control study of office workers was conducted by Baj et al. (1994) to evaluate the risks of chronic exposures to “inhaled formaldehyde, phenol and isomers of organic chlorohydrocarbons from Ksylamit™”, which is a widely used liquid wood preservative. Twenty-two workers (18 women and 4 men) exposed for at least 6 months were the cases, and 29 non-exposed, non-smoking volunteers matched for age, sex, and place of residence were the controls. The workers complained of a variety of chronic symptoms, among them headache and fatigue. Measurement of the office air at the end of the 6 month period revealed a level of phenol of 0.34 ppm. Although these symptoms could be a sign that chronic inhalation exposure to phenol could adversely affect the neurological system, it is important to consider not only that other volatile chemicals, chlorinated organics, were present in the wood-preserving liquid, but also that the chemical composition provided for Ksylamit™ opens up the possibility that the effects being evaluated resulted from exposure to pentachlorophenol rather than phenol. This is particularly true since it was not possible to determine from the information presented if the analytical methods used would differentiate between phenol and pentachlorophenol.

Female Harlan Wistar rats exposed for 1 hour or 8 hours to 234 ppm phenol delivered in an aerosol demonstrated no neurological effects at 1 hour, a slight loss of coordination with spasm of the muscle groups at 4 hours, and frank tremors leading to a severe loss of coordination by 8 hours (Flickinger 1976). All animals were normal by post-exposure day 1, and no abnormal lesions were observed upon gross autopsy

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performed at the end of a 14-day observation period. These exposure levels are recorded in Table 2-1 and are plotted in Figure 2-1 as a NOAEL, a less serious LOAEL, and a serious LOAEL.

Rats exposed continuously to 26 ppm showed numerous symptoms and signs of neurological impairment, including muscle tremors, twitching, and disturbances in walking rhythm and posture during the first 3-5 days of exposure, and impaired performance (4.4° decrease in sliding angle) on a tilting plane test after 15 days of exposure (Dalin and Kristoffersson 1974). These effects are indicative of neurological impairment. Because the tremors did not last during the whole exposure period, the effects were not considered severe.

Hindlimb paralysis was reported in guinea pigs exposed to 26-52 ppm phenol for 41 days (Deichmann et al. 1944). Rabbits and rats exhibited no overt neurological effects after 88 and 74 days of similar exposure, respectively. Since only a range was given for the exposure level (26-52 ppm), the exact level of phenol in air that resulted in hindlimb paralysis was not established and may be as low as 26 ppm or as high as 52 ppm. Interpretation of this study is further complicated by an apparent lack of controls. However, the neurological effect was so severe in the guinea pigs that it is difficult to ascribe the effects to any source other than the phenol exposure. The lower limit of the exposure range, 26 ppm, is recorded in Table 2-1 and plotted in Figure 2-1 as a LOAEL for serious neurological effects in guinea pigs. Since the presence or absence of overt neurological effects such as paralysis is not a sensitive endpoint for detecting neurological effects, 26-52 ppm is not considered a reliable NOAEL for neurological effects in rats and rabbits.

There are several differences in the experimental designs of the Dalin and Kristoffersson (1974) and Deichmann et al. (1944) studies that may account for the different results regarding neurological effects in rats. Dalin and Kristoffersson (1974) reported subtle effects that may have been overlooked in the Deichmann et al. (1944) study. Furthermore, Dalin and Kristoffersson (1974) subjected the rats to a specific test for neurological impairment, the tilting plane test. Although exposure concentrations were the same in both studies, Dalin and Kristoffersson (1974) exposed rats continuously, while Deichmann et al. (1944) exposed rats intermittently. Because phenol is metabolized quite rapidly (see Section 2.6.3), rats exposed intermittently may not develop neurological effects.

Histopathological changes in the brain were not observed in rhesus monkeys, rats, or mice exposed continuously to 5 ppm phenol in air for 90 days (Sandage 1961)

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The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species for acute and intermediate-duration exposure are recorded in Table 2-1 and plotted in Figure 2-1.

No studies were located regarding the following health effects in humans or animals after inhalation exposure to phenol:

2.2.1.5 Reproductive Effects

2.2.1.6 Developmental Effects

2.2.1.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.5.

2.2.1.8 Cancer

In a nested case-control study of cancers associated with chemical exposures in the wood industry, Kauppinen et al. (1986) found a significantly increased risk of respiratory system cancer associated with exposure to phenol and phenol in wood dust. As is often the case in occupational settings, these exposures were confounded by smoking and exposures to other materials like pesticides. The increased risk observed for exposure to phenol was almost 5-fold (odds ratio of 4.94), but showed no dose-related increase. This risk dropped to 4-fold with adjustments for smoking history, and to less than 3-fold (and non-significant) when workers exposed to both phenols and pesticides were excluded from the analysis”

Similar to the findings of Kauppinen et al. (1986), a large (14,861) cohort mortality study of workers in the phenol-formaldehyde resin manufacturing industry found nondose-related increases in the risk of several respiratory system cancers in workers exposed to phenol (Dosemeci et al. 1991). The authors develop a semiquantitative exposure assessment by assigning exposure levels (none, low, medium, and high) to each job category. The increased risks were small; for instance, for cancer of the larynx or lung, standard mortality ratios (SMRs) of 1.1 were less than those found for non-exposed workers. For a number of other cancers, including those of the esophagus, rectum, bladder, kidney, and Hodgkin’s disease, the SMRs found for phenol-exposed workers were greater than those for the non-exposed workers, but none were considered indicative of “important excesses” of these diseases by the authors.

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No studies were located regarding cancer in animals following inhalation exposure to phenol.

2.2.2 Oral Exposure

2.2.2.1 Death

There have been numerous reports of suicide or suicide attempts involving ingestion of large amounts of phenol. However, the lack of accurate documentation of dose levels in these cases makes it difficult to identify a minimal dose at which lethality occurs. Deichmann and Klepinger (1981), in summarizing the literature, indicated that an oral dose as low as 1 g could be fatal in humans, but that occasionally patients had survived doses as high as 65 g. Assuming that these patients were male with an average weight of 70 kg, the lower limit on the dose for death would be 14 mg/kg and the upper limit would be approximately 930 mg/kg. In a review of the toxicology of phenol, Bruce et al. (1987) summarized human oral lethality data from numerous case reports and estimated 140 mg/kg to be the minimal dose at which death occurs. Stajduhar-Caric (1968) reported a case in which a woman ingested \approx 10-20 g of phenol and died within hours. The lower limit of the ingested dose was converted to 172 mg/kg, assuming a 58 kg body weight, to derive a dose for death which is recorded in Table 2-2 and plotted in Figure 2-2.

The oral LD₅₀ has been determined in rats treated by gavage with phenol in water; the LD₅₀ was found to decrease with increasing concentration of phenol in the gavage fluid. The reported LD₅₀ values were 340 mg/kg in rats gavaged with a solution of 200,000 ppm phenol and 530 mg/kg in rats gavaged with a solution of 20,000 ppm phenol (Deichmann and Witherup 1944). After rats were treated by gavage with 600 mg/kg in a 5% solution, 9 of 30 five-week-old rats, 18 of 20 ten-day-old rats, and 12 of 20 adult rats died indicating that the 10-day-old rat is more sensitive to phenol than rats in the other age groups tested (Deichmann and Witherup 1944). In pregnant rats treated on gestation days 6-15, seven of 10 rats died at a dose of 125 mg/kg/day when treated with a volume of 1 mL/kg, while 1 of 6 rats died at a dose of 160 mg/kg/day when treated with a volume of 5 mL/kg (Jones-Price et al. 1983a). In a 1-day dosing regimen study, female rats were given 0, 12, 40, 120, or 224 mg/kg in order to determine a single-dose oral LD₅₀ of 400 mg/kg (Berman et al. 1995). Mortality was observed only at the highest dose where 2 of 8 rats treated died. All female rats treated for 14 days with a dose of 120 mg/kg/day died (Berman et al. 1995; Moser et al. 1995). In a 14-day dosing regimen with the same doses (except the 224 mg/kg), all animals died at the dose of 120 mg/kg.

TABLE 2-2. Levels of Significant Exposure to Phenol - 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	Human	once				172 F (death)	Stajduhar-Caric 1968
2	Rat (Fischer- 344)	once (GW)				400 F (LD ₅₀)	Berman et al. 1995
3	Rat (Fischer- 344)	14 d 1x/d (GW)				120 F (8/8 died)	Berman et al. 1995
4	Rat (Wistar)	once (GW)				340 (LD ₅₀)	Deichmann and Witherup 1944
5	Rat (CD)	10 d Gd 6-15 1 x/d (GW)				125 F (7/10 maternal deaths, treated with a volume of 1 mL/kg)	Jones-Price et al. 1983a
6	Rat (CD)	10 d Gd 6-15 1 x/d (GW)				160 F (1/6 maternal deaths, treated with a volume of 5 mL/kg)	Jones-Price et al. 1983a
7	Mouse (CD-1)	10 d Gd 6-15 1 x/d (GW)				280 F (4/35 maternal deaths)	Jones-Price et al. 1983b
8	Mouse (NS)	once (GO)				300 M (5/10 deaths)	Von Oettingen and Sharpless 1946
9	Rabbit (White)	once (GW)				420 (5/10 deaths)	Deichmann and Witherup 1944

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TABLE 2-2. Levels of Significant Exposure to Phenol - 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)	
Systemic							
10	Rat (Fischer- 344)	once (GW)	Hepatic	224 F			Berman et al. 1995
			Renal	120 F	224 F (renal tubular necrosis, protein casts, papillary hemorrhage)		
			Endocr	120 F	224 F (unspecified changes in the adrenal gland)		
			Bd Wt	224 F			
11	Rat (Fischer- 344)	14 d 1x/d (GW)	Hepatic	40 F			Berman et al. 1995
			Renal	40 F			
			Endocr	40 F			
			Bd Wt	40 F			
12	Rat (CD)	10 d Gd 6-15 1 x/d (GW)	Hepatic	120 F			Jones-Price et al. 1983a
			Bd Wt	120 F			
13	Rat (Fischer- 344)	14 d Gd 6-19 (GW)	Resp			40 F (dyspnea, rales)	Narotsky and Kavlock 1995
			Bd Wt			40 F (20% decrease in maternal body weight gain)	
14	Mouse (Swiss CD-1)	once - Gd 13 (GW)	Hemato		265 F (30-60% reduction in the ratio of poly/normo chromatic erythrocytes in the bone marrow of pregnant dams)		Ciranni et al. 1988
15	Mouse (CD-1)	10 d Gd 6-15 1 x/d (GW)	Hepatic	280 F			Jones-Price et al. 1983b
			Bd Wt	140 F		280 F (67% decrease in absolute maternal body weight gain)	

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

Key to figure ^a	Species (Strain)	Exposure/Duration/Frequency (Specific Route)	System	LOAEL		Reference
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	
Immunological/Lymphoreticular						
16	Rat (Fischer- 344)	once (GW)		120 F	224 F (necrosis or atrophy of the spleen or thymus)	Berman et al. 1995
17	Rat (Fischer- 344)	14 d 1x/d (GW)		40 F		Berman et al. 1995
Neurological						
18	Rat (Sprague-Dawley)	once (G)				207 M (muscle twitching, convulsions, coma) Liao and Oehme 1981
19	Rat (Fischer- 344)	once (GW)		40 F		120 F (mild-to-severe whole-body tremors, decreased motor activity) Moser et al. 1995
20	Rat (Fischer- 344)	14 d 1x/d (GW)		12 F	40 F (increased rearing)	Moser et al. 1995
21	Mouse (CD-1)	10 d Gd 6-15 1 x/d (GW)		70 F	140 F (mild tremors on the first 3 days of dosing)	280 F (tremors, ataxia in pregnant dams) Jones-Price et al. 1983b
Reproductive						
22	Rat (CD)	10 d Gd 6-15 1 x/d (GW)		120 F		Jones-Price et al. 1983a
23	Mouse (CD-1)	10 d Gd 6-15 1 x/d (GW)		280		Jones-Price et al. 1983b

TABLE 2-2. Levels of Significant Exposure to Phenol - 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)	
Developmental							
24	Rat (CD)	10 d Gd 6-15 1 x/d (GW)		60	120	(7% decrease in average fetal body weight)	Jones-Price et al. 1983a
25	Rat (Fischer- 344)	14 d Gd 6-19 (GW)		40		53.3 (significant decrease in the number of live-born pups, associated with severe respiratory effects in the dams)	Narotsky and Kavlock 1995
26	Mouse (CD-1)	10 d Gd 6-15 1 x/d (GW)		140		280 (18% decreased fetal body weight, cleft palate 8/214)	Jones-Price et al. 1983b
INTERMEDIATE EXPOSURE							
Systemic							
27	Human	< 6 mo (W)	Gastro Renal Dermal	0.003 0.003 0.003	0.14 0.14 0.14	(nausea, diarrhea) (dark urine) (mouth sores, skin rash)	Baker et al. 1978

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TABLE 2-2. Levels of Significant Exposure to Phenol - 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)	
28	Rat (Fischer- 344)	13 wk ad libitum (W)	Resp	1694 F			NCI 1980
			Cardio	1694 F			
			Gastro	1694 F			
			Musc/skel	1694 F			
			Hepatic	1694 F			
			Renal	1694 F			
			Endocr	1694 F			
			Dermal	1694 F			
Bd Wt	467 M	1556M (16% decrease in body weight gain associated with decreased water intake)	1694 F (26% decrease in body weight gain associated with decreased water intake)				
		508 F					
29	Mouse (CD-1)	28 d ad libitum (W)	Resp	33.6 M			Hsieh et al. 1992
			Cardio Hemato	33.6 M	1.8 M (32% decrease in red blood cell count)		
			Hepatic	33.6 M			
			Renal	33.6 M			
			Bd Wt	33.6 M			
30	Mouse (B6C3F1)	13 wk ad libitum (W)	Resp	2642 F			NCI 1980
			Cardio	2642 F			
			Gastro	2642 F			
			Musc/skel	2642 F			
			Hepatic	2642 F			
			Renal	2642 F			
			Endocr	2642 F			
			Dermal	2642 F			
			Bd Wt	741 M	2468 M (80% decrease in body weight gain associated with decreased water intake)		

TABLE 2-2. Levels of Significant Exposure to Phenol - 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)	
Immunological/Lymphoreticular							
31	Mouse (CD-1)	28 d ad libitum (W)		1.8 M	6.2 M (decreased antibody production response to sheep red blood cells)		Hsieh et al. 1992
Neurological							
32	Mouse (CD-1)	28 d ad libitum (W)			1.8 M (decreased levels of dopamine in the corpus striatum)		Hsieh et al. 1992
Reproductive							
33	Rat (Fischer- 344)	13 wk ad libitum (W)		1694 F 1556 M			NCI 1980
34	Mouse (B6C3F1)	13 wk ad libitum (W)		2642 F 2468 M			NCI 1980
CHRONIC EXPOSURE							
Systemic							
35	Rat (Fischer- 344)	103 wk ad libitum (W)	Resp Cardio Gastro Musc/skel Hepatic Renal Endocr Dermal Bd Wt	721 F 721 F 721 F 721 F 721 F 721 F 721 F 721 F 360 F	322 M (about 12% decrease associated with a 20% decrease in water intake) 721 F (about 17% decrease associated with a 10% decrease in water intake)		NCI 1980

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

Key to figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL		Reference
				NOAEL (mg/kg/day)	Serious (mg/kg/day)	
36	Mouse (B6C3F1)	103 wk ad libitum (W)	Resp	1204 F		NCI 1980
			Cardio	1204 F		
			Gastro	1204 F		
			Musc/skel	1204 F		
			Hepatic	1204 F		
			Renal	1204 F		
			Endocr	1204 F		
			Dermal	1204 F		
Bd Wt	1204 F					

^aThe number corresponds to entries in Figure 2-2. Differences in levels of health effects and cancer effects between males and females are not indicated in Figure 2-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = female; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day(s); (GO) = gavage, oil; (GW) = gavage, water; Hemato = hematological; LD₅₀ = lethal dose (50% kill); LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); mo = month(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; (W) = drinking water; wk = week(s); x = time(s)

Figure 2-2. Levels of Significant Exposure to Phenol - Oral
Acute (≤14 days)

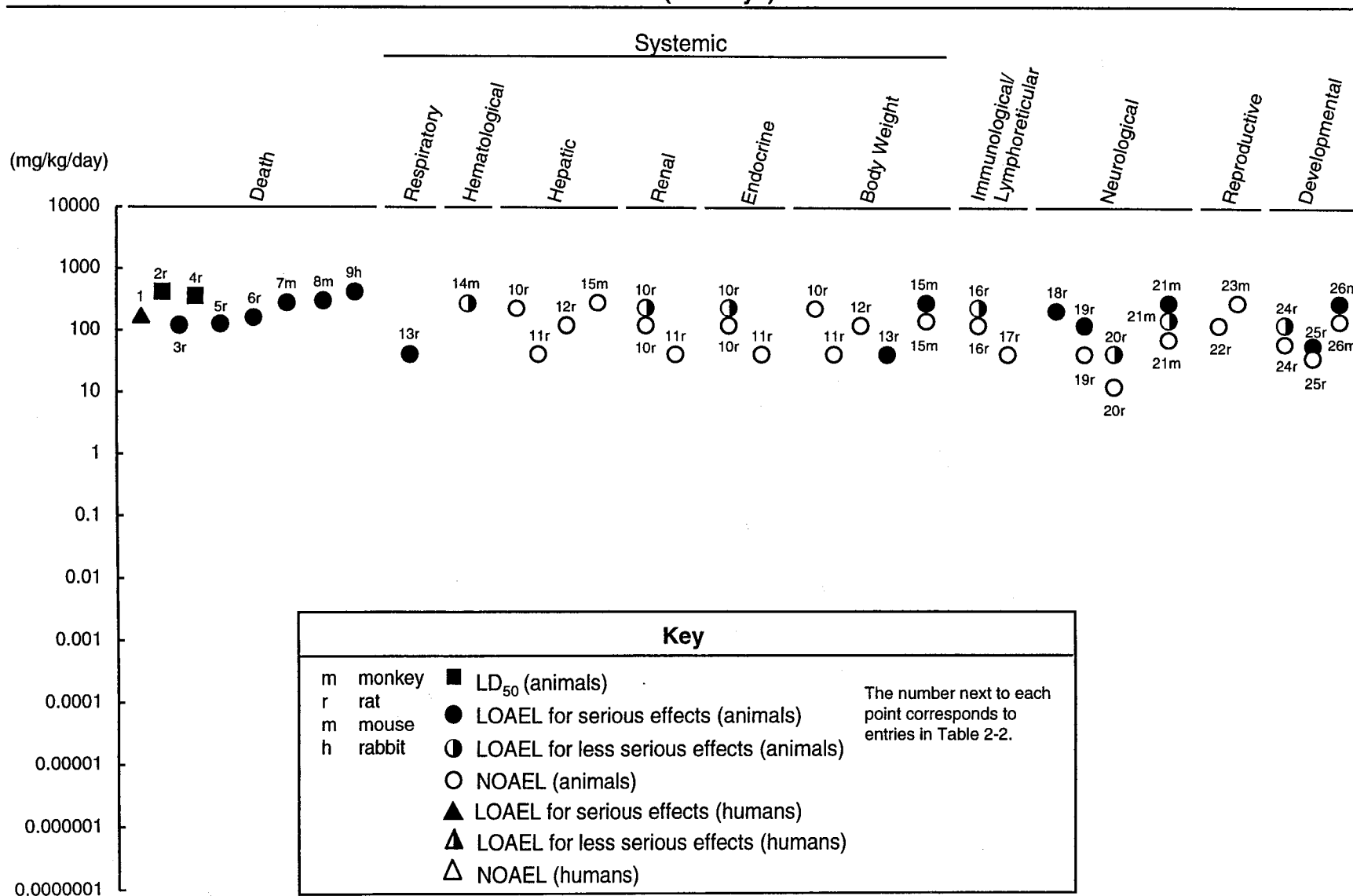
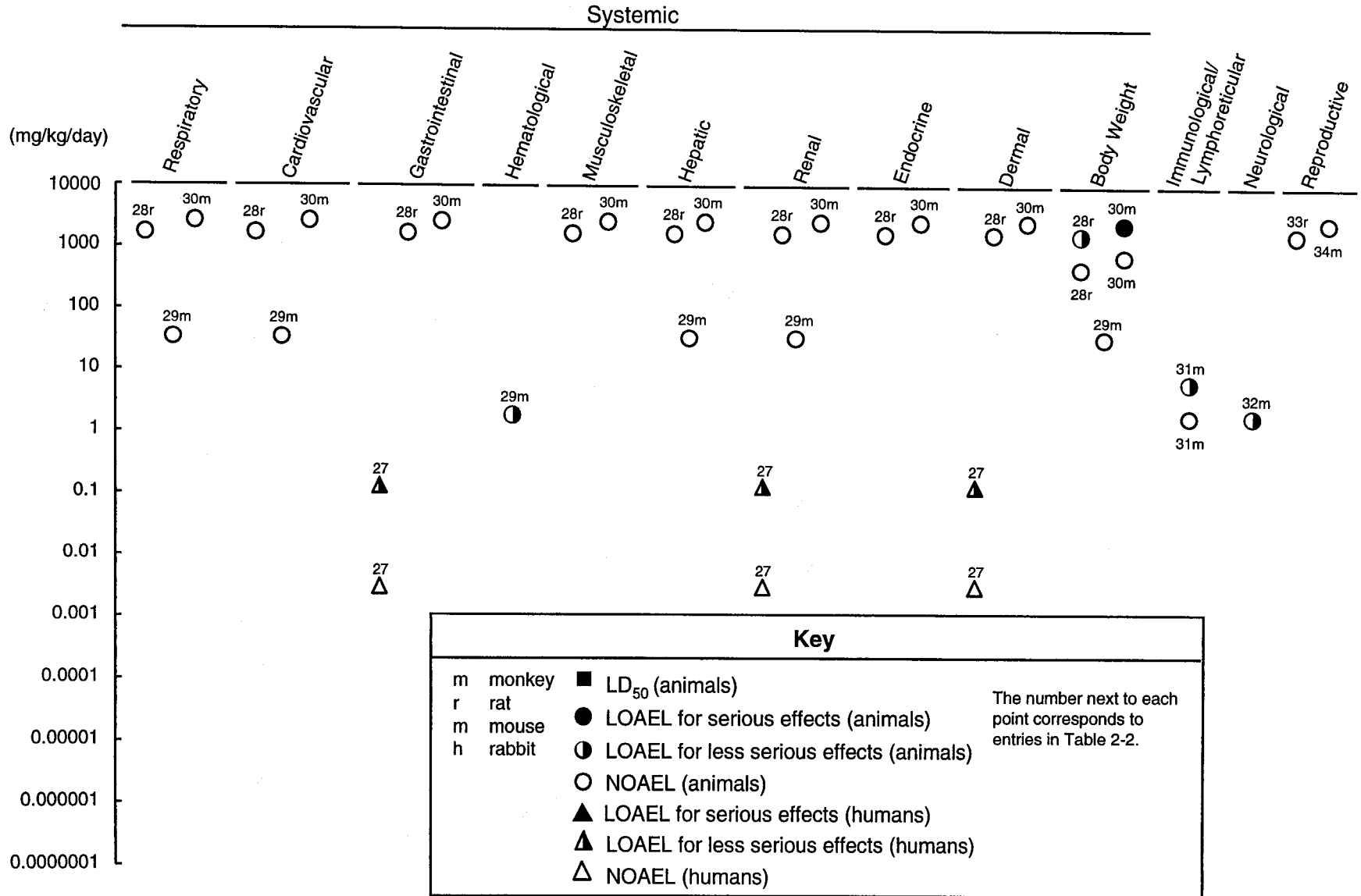
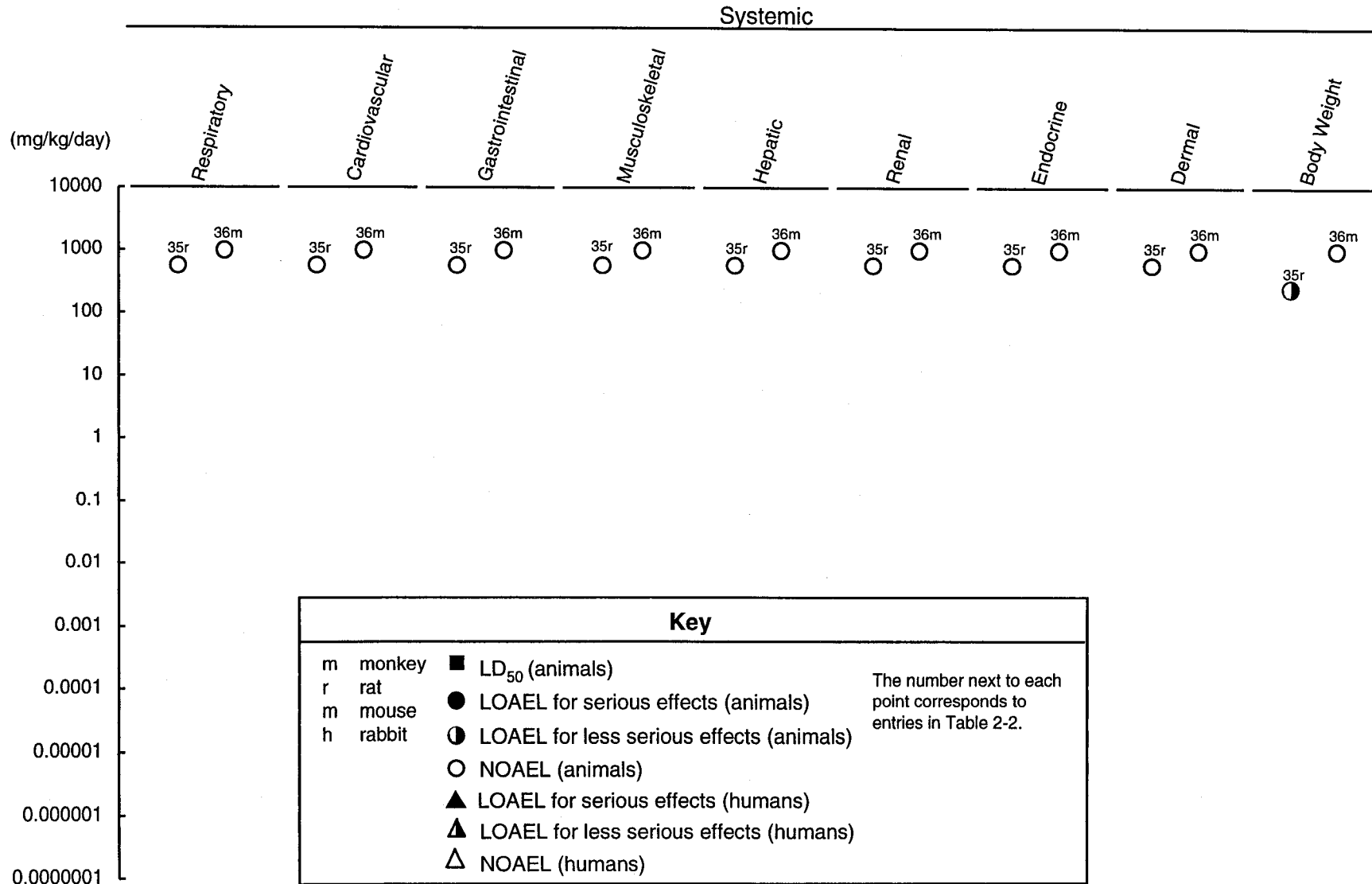


Figure 2-2. Levels of Significant Exposure to Phenol - Oral (continued)
 Intermediate (15-364 days)



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Figure 2-2. Levels of Significant Exposure to Phenol - Oral (continued)
Chronic (≥365 days)



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The oral LD₅₀ of phenol has been estimated as 300 mg/kg in mice (von Oettingen and Sharpless 1946). Five of 10 rabbits treated with an oral dose of 420 mg/kg died (Deichmann and Witherup 1944). In pregnant mice treated on gestation days 6-15, four of 35 mice died at a dose of 280 mg/kg/day (Jones-Price et al. 1983b).

Flickinger (1976) gave male albino rats single doses of 0, 200, 398, 795, and 1,580 mg/kg phenol by gavage and held the animals for 14 days post-dosing in order to determine an oral LD₅₀. No animals died following the 0, 200, or 398 mg/kg doses; 4 of 5 animals died the first day following the 795 mg/kg dose, and 5 of 5 animals died within 2 hours following 1,580 mg/kg dose. From these data, the authors estimated an oral LD₅₀ of 650 mg/kg.

No effect on survival was observed in mice treated with phenol in the drinking water at doses up to 33.6 mg/kg/day for 28 days (Hsieh et al. 1992). Survival was not affected in rats and mice treated with phenol in drinking water for 13 or 103 weeks (NCI 1980). Both species were treated with drinking water concentrations up to 10,000 mg/L in the 13-week study (maximum doses in mg/kg/day: 1,694 for female rats, 1,556 for male rats; 2,643 for female mice, 2,468 for male mice), and up to 5,000 mg/L in the 103-week study (maximum doses in mg/kg/day: 721 for female rats, 645 for male rats; 1,204 for female mice, 1,180 for male mice).

The LD₅₀ values and doses resulting in death from each reliable study in each species in the acute-duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.2 Systemic Effects

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

Respiratory Effects. Stajduhar-Caric (1968) reported on a case in which a woman who ingested ~10-20 g of phenol, became comatose and died within a matter of hours. During the course of the poisoning and treatment, initially an increase in respiration was observed, then irregularities in breathing, and finally cessation of respiration. Upon autopsy, marked hyperemia of the tracheal and bronchial mucous membranes were observed as well as pulmonary edema. According to Deichmann and Keplinger (1981), the progression of impacts on the respiratory system summarized above are typical of oral poisonings in humans, although

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often the intermediate stages are characterized by a decrease in respiration rate and magnitude. According to these authors, in acute intoxication, death usually results from respiratory failure.

Dyspnea and rales were observed in pregnant rats treated by gavage with phenol in water on gestation days 6-19 (Narotsky and Kavlock 1995). The respiratory effects were observed at both 40 and 53.3 mg/kg/day. Furthermore, developmental toxicity occurred on the litters of 1 of 5 low-dose and 3 of 16 high-dose dams that exhibited these effects, although not all dams with severe respiratory effects had abnormal outcomes.

Gross pathological examinations did not reveal any adverse changes in the lungs of mice treated with phenol in drinking water at doses of 1.8, 6.2, or 33.6 mg/kg/day for 28 days (Hsieh et al. 1992).

In a study reported by the National Cancer Institute (NCI 1980), rats exposed to 16-1,694 mg/kg/day (100-10,000 mg/L) and mice exposed to 25-2,642 mg/kg/day (100-10,000 mg/L) phenol in drinking water exhibited no indication of histopathological effects on the respiratory system after 13 weeks of exposure. No histological abnormalities of the respiratory tract were observed in rats or mice exposed to 2,500 or 5,000 ppm phenol in drinking water for 103 weeks (mg/kg/day doses: 322 or 645 for male rats; 360 or 721 for female rats; 590 or 1,180 for male mice; 602 or 1,204 for female mice) (NCI 1980).

Cardiovascular Effects. In a recent report on the clinical treatment of phenol poisoning, Langford et al. (1998) provide a summary of a case report in which a woman accidentally consumed an ounce of 89% phenol which had been mistakenly been given to her in preparation for an in-office procedure. Her immediate reaction upon consuming the phenol was to clutch her throat and collapse, and within 30 minutes she was comatose and had gone into respiratory arrest. Treatment was initiated with an endotracheal intubation. Ventilation with a bag and mask led to the detection of a lamp oil odor. Within an hour she developed ventricular tachycardia which responded to cardioversion; however, she subsequently developed (in the first 24 hours) supraventricular and ventricular dysrhythmias, metabolic acidosis, and experienced a grand mal seizure. After a 15-day hospital stay, she was completely recovered with no evidence of impaired motility or compromised gastrointestinal or cardiovascular systems.

Gross pathological examinations did not reveal any adverse changes in the hearts of mice treated with phenol in drinking water at doses of 1.8, 6.2, or 33.6 mg/kg/day for 28 days (Hsieh et al. 1992). In a study reported by the National Cancer Institute (NCI 1980), rats exposed to 16-1,694 mg/kg/day (100-10,000 ppm) and

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mice exposed to 25-2,642 mg/kg/day (100-10,000 ppm) phenol in drinking water exhibited no indication of histopathological effects on the heart after 13 weeks of exposure. Histological abnormalities of the heart were not evident in rats after 103 weeks of exposure to 322 or 645 mg/kg/day for males or 360 or 721 mg/kg/day for females (2,500 or 5,000 ppm) or in mice after exposure to 590 or 1,180 mg/kg/day for males or 602 or 1,204 mg/kg/day for females (2,500 or 5,000 ppm). Cardiovascular function was not evaluated in these studies.

Gastrointestinal Effects. In a recent study on the clinical treatment of phenol poisoning, Langford et al. (1998) provide a summary of a case report in which a woman accidentally consumed an ounce of 89% phenol which had been mistakenly been given to her in preparation for an in-office procedure. Her immediate reaction upon consuming the phenol was to clutch her throat and collapse, and within 30 minutes she was comatose and had gone into respiratory arrest. Treatment was initiated with an endotracheal intubation, which revealed her mouth and hypopharynx to be white. Esophagitis and upper gastrointestinal bleeding occurred in the first week, and an examination of the esophagus on day 8 revealed hyperkeratosis, erythema, and a friable mucosa. After a 15-day hospital stay, she was completely recovered with no evidence of impaired motility or compromised gastrointestinal system.

In a retrospective study of 158 persons exposed to phenol in drinking water for several weeks following an accidental spill of phenol, significantly ($p < 0.01$) increased gastrointestinal symptoms (mouth sores, nausea, diarrhea) were reported by 17 of the 39 most highly-exposed individuals (Baker et al. 1978). Exposure concentrations for the most highly-exposed group were > 0.1 mg/L, and the study authors estimated phenol intake during this period as 10-240 mg/person/day (0.14-3.4 mg/kg/day assuming a 70-kg body weight). Symptom rates were not increased among 61 persons exposed to concentrations of 0.1 mg/L (0.003 mg/kg/day assuming 2 L water per day and a 70-kg body weight) and less. Dermal exposure was not considered in these estimates of dose.

A case control study of 6,913 individuals living near a Korean river contaminated with 30 tons of 100% phenol found nausea, vomiting, diarrhea, and abdominal pain among 1,824 exposed subjects compared to 1,064 unexposed subjects (Kim et al. 1994). The level of phenol measured in the two reservoirs that served the community was 0.05 mg/L after the spill, while that in the chlorinated tap water was 0.0084 mg/L. It is uncertain whether the chlorination process may have converted a majority of the phenol to chlorophenol, thus possibly implicating this chemical as the cause of the effects.

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In a study reported by the National Cancer Institute (NCI 1980) rats exposed to 16-1,694 mg/kg/day and mice exposed to 25-2,642 mg/kg/day phenol in drinking water exhibited no indication of histopathological effects on the gastrointestinal system after 13 weeks of exposure. No histological abnormalities of the gastrointestinal tract were observed in rats or mice exposed to 2,500 or 5,000 mg/L phenol in drinking water for 103 weeks (mg/kg/day doses: 322 or 645 for male rats; 360 or 721 for female rats; 590 or 1,180 for male mice; 602 or 1,204 for female mice) (NCI 1980).

Hematological Effects. No studies were located regarding hematological effects in humans following oral exposure to phenol.

A 30-60% decrease in the ratio of polychromatic to normochromatic erythrocytes was observed in the bone marrow of pregnant mice treated by gavage with a single dose of 265 mg/kg phenol in water on gestation day 13 (Ciranni et al. 1988). Dose-related and significant decreases in red blood cell counts were observed in mice treated with phenol in the drinking water at doses of 1.8, 6.2, or 33.6 mg/kg/day for 28 days (Hsieh et al. 1992). Red blood cell counts in cells $\times 10^6/\text{mm}^3$ were 7.17 in controls, 4.9 at the low dose, 4.64 at the middle dose, and 3.23 at the high dose. A significant decrease in hematocrit was only observed at the high dose (48% control, 44.1% high dose), and no changes were observed in total spleen cellularity, leucocyte numbers, or leucocyte differentials.

Musculoskeletal Effects. No studies were located regarding musculoskeletal effects in humans following oral exposure to phenol.

Rats exposed to 16-1,694 mg/kg/day (100-10,000 mg/L) and mice exposed to 25-2,642 mg/kg/day (100-10,000 mg/L) phenol in drinking water exhibited no histological abnormalities of the bone after 13 weeks of exposure (NCI 1980). No histological abnormalities of the bone were observed in rats or mice exposed to 2,500 or 5,000 mg/L phenol in drinking water for 103 weeks (mg/kg/day doses: 322 or 645 for male rats; 360 or 721 for female rats; 590 or 1,180 for male mice; 602 or 1,204 for female mice) (NCI 1980).

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Hepatic Effects. Serum markers of liver effects, bilirubin, glucose, cholesterol, and aspartate aminotransferase were not affected in 39 persons exposed to phenol in the drinking water at an estimated dose of 0.14-3.4 mg/kg/day for several weeks (Baker et al. 1978). Because these examinations were completed 7 months after the spill, this study does not provide conclusive evidence that there was no reversible liver damage.

Serum markers of liver effects (lactic dehydrogenase, alkaline phosphatase, alanine aminotransferase, bilirubin) and histopathological changes in the liver were observed in rats given single gavage doses of 224 mg/kg or 14 daily gavage doses of 40 mg/kg phenol in water (Berman et al. 1995). Changes in liver weight were not observed in pregnant rats treated by gavage with 120 mg/kg/day phenol in water on gestation days 6-15 (Jones-Price et al. 1983a), or in pregnant mice treated by gavage with 280 mg/kg/day phenol in water on gestation days 6-15 (Jones-Price et al. 1983b).

Gross pathological examinations did not reveal any lesions in mice treated with phenol in the drinking water at a dose of 33.6 mg/kg/day for 28 days (Hsieh et al. 1992).

In a study sponsored by the National Cancer Institute (NCI 1980), rats exposed to 16-1,694 mg/kg/day (100-10,000 ppm) and mice exposed to 25-2,642 mg/kg/day (100-10,000 ppm) phenol in drinking water exhibited no histological abnormalities of the liver after 13 weeks of exposure. No histological abnormalities of the liver were observed in rats or mice exposed to 2,500 or 5,000 ppm phenol in drinking water for 103 weeks (NCI 1980). Estimated mg/kg/day doses were 322 or 645 for male rats, 360 or 721 for female rats, 590 or 1,180 for male mice, and 602 or 1,204 for female mice.

Renal Effects. Although not adverse, dark urine (as a result of oxidation products of phenol or a result of hemoglobin or its breakdown products in the urine) is a common symptom observed in humans exposed to phenol. In persons exposed to about 0.14-3.4 mg/kg/day phenol in drinking water for several weeks after an accidental spill, dark urine was reported by 17.9% of the most highly-exposed individuals, while only 3.4% of the controls reported the effect (Baker et al. 1978). This difference was not statistically significant. A 3.3-fold increase in the prevalence of dark urine was reported by persons exposed to unspecified doses of phenol after an accidental spill in Korea (Kim et al. 1994). It is not known if the chlorination process, which may have converted a majority of the phenol to chlorophenol, contributed to this effect.

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Renal tubular necrosis, protein casts, and papillary hemorrhage were not observed in rats treated with a single gavage dose of 120 mg/kg phenol in water, but were seen in 60% of animals examined at the next highest dose of 224 mg/kg (Berman et al. 1995). No histopathological changes in the kidney were observed after 14 daily doses of 12 mg/kg/day, but were observed in 3 of 8 animals given 14 daily doses of 40 mg/kg/day (Berman et al. 1995).

Gross pathological examinations did not reveal any adverse changes in the kidneys of mice treated with phenol in drinking water at doses of 1.8, 6.2, or 33.6 mg/kg/day for 28 days (Hsieh et al. 1992).

Rats exposed to 16-1,694 mg/kg/day (0.1-10 mg/L) and mice exposed to 25-2,642 mg/kg/day (100-10 mg/L) phenol in drinking water exhibited no indication of histopathological effects on the kidney after 13 weeks of exposure (NCI 1980). Compound-related histological changes in the kidneys were not observed in rats or mice exposed to 2,500 or 5,000 ppm phenol in drinking water for 103 weeks (NCI 1980). Estimated mg/kg/day doses were 322 or 645 for male rats, 360 or 721 for female rats, 590 or 1,180 for male mice, and 602 or 1,204 for female mice. A higher incidence of inflammation of the kidney was reported in male rats exposed to 624 mg/kg/day (96%) than in controls (74%); however, because of the high incidence of inflammation in the controls, it is impossible to ascertain whether this was related to the exposure to phenol (NCI 1980). A high age-related incidence of inflammation is expected in male rats of the Fischer-344 strain used in this study. Kidney function, including glomerular filtration rate and glomerular sieving, however, was not evaluated in this study. Furthermore, histological examination was limited to standard light microscopic examinations which would not have detected functionally significant glomerular abnormalities like disruption of the glomerular basement membrane or immune complex deposition.

Endocrine Effects. No studies were located regarding endocrine effects in humans following oral exposure to phenol.

Unspecified microscopic changes were observed in the adrenal glands of rats given a single gavage dose of 224 mg/kg phenol in water (Berman et al. 1995). No adrenal gland effects were observed in rats given a single gavage dose of 12,40, or 120 mg/kg or 14 daily gavage doses of 4, 12, or 40 mg/kg (Berman et al. 1995).

Rats exposed to 16-1,694 mg/kg/day (100-10,000 mg/L) and mice exposed to 25-2,642 mg/kg/day (100-10,000 mg/L) phenol in drinking water exhibited no histopathological changes in the pancreas,

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pituitary, adrenal glands, thyroid, or parathyroid after 13 weeks of exposure (NCI 1980). Exposure-related histopathological changes in the pancreas, pituitary, adrenal glands, thyroid, or parathyroid were also not observed in rats and mice exposed to 2,500 or 5,000 ppm phenol in drinking water for 103 weeks (NCI 1980). Estimated mg/kg/day doses were 322 or 645 for male rats, 360 or 721 for female rats, 590 or 1,180 for male mice, and 602 or 1,204 for female mice.

Dermal Effects. Skin rash and mouth sores were reported in persons living near a site with contaminated well water resulting from an overturned tanker car carrying 37,900 L of 100% phenol (Baker et al. 1978). The level of phenol in the drinking water of this cohort was >0.1 mg/L, and while substantial oral exposure probably occurred, dermal exposure cannot be ruled out. Increases in the prevalence of skin rashes and sore throats were reported by persons drinking water from a river contaminated by an accidental spill of phenol (Rim et al. 1994). Because the water was chlorinated before use, the effect may also have been a result of exposure to chlorophenol.

Rats exposed to 16-1,694 mg/kg/day (100-10,000 mg/L) and mice exposed to 25-2,642 mg/kg/day (100-10,000 mg/L) phenol in drinking water exhibited no histopathological changes in the skin after 13 weeks of exposure (NCI 1980). Exposure-related histopathological changes in the skin were also not observed in rats and mice exposed to 2,500 or 5,000 mg/L phenol in drinking water for 103 weeks (NCI 1980). Estimated mg/kg/day doses were 322 or 645 for male rats, 360 or 721 for female rats, 590 or 1,180 for male mice, and 602 or 1,204 for female mice.

Ocular Effects. No studies were located regarding ocular effects in humans or animals following oral exposure to phenol.

Body Weight Effects. No effects on body weight were observed in rats treated with a single gavage dose of 224 mg/kg phenol in water or 14 daily gavage doses of 40 mg/kg (Berman et al. 1995; Moser et al. 1995). Maternal body weight gain was approximately 20% lower in rats treated by gavage with 40 or 53.3 mg/kg/day phenol in water on gestation days 6-19 (Narotsky and Kavlock 1995). Maternal body weight gain was 67% lower than controls in mice treated by gavage with 280 mg/kg/day phenol in water on gestation days 6-15, with no effects on body weight gain observed at 140 mg/kg/day (Jones-Price et al. 1983b). Body weight gain was not affected in pregnant rats treated by gavage with 120 mg/kg/day phenol in water on gestation days 6-15 (Jones-Price et al. 1983a).

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Body weight was not affected in mice treated with phenoP in drinking water at a dose of 33.6 mg/kg/day for 28 days (Hsieh et al. 1992). During 13-week studies in rats and mice treated with phenol in drinking water, decreased body weight gain was associated with decreased water intake (NCI 1980). In rats provided with the highest concentration (10,000 ppm), body weight gain was decreased by 26% in females at 1,694 mg/kg/day, and by 16% in males at 1,556 mg/kg/day. An effect on body weight gain was not observed in rats at 3,000 ppm (467 mg/kg/day for males, 508 mg/kg/day for females). In mice provided with the highest concentration (10,000 ppm), body weight gain was decreased by 33% in females at 2,642 mg/kg/day, and by 80% in males at 2,468 mg/kg/day. An effect on body weight gain was not observed in mice at 3,000 ppm (741 mg/kg/day for males, 793 mg/kg/day for females).

Decreased mean body weight associated with decreased water intake was also observed in rats in a 103-week study (NCI 1980). At the high concentration (5,000 ppm), body weight was 19% lower than controls in males (645 mg/kg/day) and 17% lower than controls in females (721 mg/kg/day). At the low concentration (2,500 ppm), body weight was 12% lower than controls in males (322 mg/kg/day) and within 10% of controls in females (360 mg/kg/day). Body weight was not affected in mice treated with phenol in drinking water for 103 weeks at doses up to 1,180 for males and up to 1,204 mg/kg/day for females (NCI 1980).

2.2.2.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans following oral exposure to phenol.

Necrosis or atrophy of the spleen or thymus was observed in 4 of 6 rats given a single gavage dose of 224 mg/kg of phenol in water, and 1 of 7 given 120 mg/kg/day (Berman et al. 1995). Based on this effect, which was not further described, the study authors considered 224 mg/kg to be a LOAEL for immunological effects. One of 8 animals given 12 mg/kg/day, and 2 of 8 given 40 mg/kg/day for 14 days showed these same effects.

Hsieh et al. (1992) conducted a 28 day study of the immunotoxicologic impact of phenol in which CD-1 mice were provided drinking water at nominal concentrations of 0, 5, 20, or 100 mg/L (measured concentrations of 4.7, 19.5, and 95.2 mg/L; equivalent doses of 0, 1.8, 6.2, or 33.6 mg/kg/day). When challenged with sheep red blood cells, a significant decrease was observed in the splenic concentration of anti-erythrocyte antibody-forming cells and in the anti-erythrocyte antibody titer at the two highest doses, while a significant decrease in

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the absolute number of anti-erythrocyte antibody-forming cells present in the spleen was observed only at the top dose.

Rats exposed to 16-1,694 mg/kg/day (100-10,000 ppm) and mice exposed to 25-2,642 mg/kg/day (100-10,000 ppm) phenol in drinking water exhibited no histopathological changes in the bone marrow, spleen, or lymph nodes after 13 weeks of exposure (NCI 1980). Exposure-related histopathological changes in the bone marrow, spleen, or lymph nodes were also not observed in rats or mice exposed to 2,500 or 5,000 ppm phenol in drinking water for 103 weeks (NCI 1980). Estimated mg/kg/day doses were 322 or 645 for male rats, 360 or 721 for female rats, 590 or 1,180 for male mice, and 602 or 1,204 for female mice.

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

2.2.2.4 Neurological Effects

Headaches were reported six times more frequently by persons using drinking water contaminated with phenol than by controls (Rim et al. 1994). The water was used after chlorination; therefore, chlorophenol may have contributed to the observed effects.

Acute oral phenol poisoning in rabbits and rats was characterized by muscular tremors in the head region, which eventually spread to other regions of the body, with the lower extremities being the last affected. Loss of coordination and convulsions preceded death at doses of 300-940 mg/kg (Deichmann and Witherup 1944). Liao and Oehme (1981) described tremors of the muscles around the eyes, followed by convulsions and coma, in rats after a sublethal oral dose of 207 mg/kg phenol. Mild-to-severe whole-body tremors and decreased motor activity were reported in rats given a single gavage dose of 120 mg/kg phenol in water (Moser et al. 1995). A dose of 40 mg/kg resulted in no neurological effects following a single dose, while increased rearing was reported following 14 daily doses (Moser et al. 1995). Pregnant mice treated by gavage with phenol in water on gestation days 6-15 exhibited tremors and ataxia at 280 mg/kg/day, mild tremors on the first 3 days of dosing at 140 mg/kg/day, and no adverse neurological effects at 70 mg/kg/day (Jones-Price et al. 1983b).

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Mice exposed for 28 days to phenol in drinking water exhibited a significant reduction in dopamine level in the corpus striatum at the 1.8 mg/kg/day dose, and significantly decreased levels of norepinephrine, serotonin, and Shydroxyindoleacetic acid in the hypothalamus at the 6.2 mg/kg/day dose (Hsieh et al. 1992). Levels of neurotransmitters in other brain regions were also significantly altered at higher doses of phenol.

Rats exposed to 16-1,694 mg/kg/day and mice exposed to 25-2,642 mg/kg/day phenol in drinking water exhibited no abnormal histology of the brain after 13 weeks of exposure (NCI 1980). Histopathological changes in the brain were not evident after 103 weeks of exposure to 322 or 645 mg/kg/day in male rats, 360 or 721 mg/kg/day in female rats, 590 or 1,180 mg/kg/day in male mice, and 602 or 1,204 mg/kg/day in female mice (NCI 1980). However, this study did not include tests for neurological impairment or histopathological examinations of tissues in the nervous system other than the brain.

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

2.2.2.5 Reproductive Effects

No studies were located regarding reproductive effects in humans following oral exposure to phenol.

No effects on the number of offspring produced were observed in rats treated by gavage with 120 mg/kg/day phenol (Jones-Price et al. 1983a) or in mice treated by gavage with 280 mg/kg/day phenol (Jones-Price et al. 1983b) on gestation days 6-15. No evidence of impaired reproduction was found in rats exposed to phenol in drinking water at <5,000 ppm (estimated 571 mg/kg/day) for 3 generations or at <1,000 ppm (estimated 114 mg/kg/day) for 5 generations (Heller and Purse11 1938). Data regarding breeding habits, controls, and the methods used to evaluate the rats for reproductive impairment were not reported in sufficient detail to establish reliable NOAELs or LOAELs for presentation in Table 2-2 and Figure 2-2.

Rats exposed to 16-1,694 mg/kg/day (100-10,000 ppm) and mice exposed to 25-2,642 mg/kg/day (100-10,000 ppm) of phenol in drinking water exhibited no histopathological changes in the prostate, testes, uterus, or ovaries after 13 weeks of exposure (NCI 1980). Exposure-related histopathological changes in the prostate, testes, uterus, or ovaries were also not observed in rats or mice exposed to 2,500 or 5,000 ppm phenol in drinking water for 103 weeks (NCI 1980). Estimated mg/kg/day doses were 322 or 645 for male rats, 360 or 721 for female rats, 590 or 1,180 for male mice, and 602 or 1,204 for female mice.

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The highest NOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Table 2-2 and plotted in Figure 2-2.

2.2.2.6 Developmental Effects

No studies were located regarding developmental effects in humans following oral exposure to phenol.

In a multi-generational study of the effect of various levels of phenol administered orally in water, Heller and Pursell (1938) saw no effect on growth, reproduction, and normal rearing of young over 5 generations of rats given concentrations of ~1,000 mg/L phenol in drinking water (estimated dose of 114 mg/kg/day) nor over 3 generations of rats given concentrations of ~5,000 ppm (estimated dose 571 mg/kg/day). CD rat dams given doses as high as 120 mg/kg showed no maternal toxicity at any dose. There was, however, a dose related decrease in the average live fetal body weight per litter increase in the proportion of gravid uteri with resorption sites at the low- (30 mg/kg/day) and mid-dose (60 mg/kg/day), but not at the high-dose group.

Phenol in water was administered to pregnant rats by gavage (5 mL/kg) at dose levels of 0,30,60, or 120 mg/kg/day on days 6-15 of gestation (Jones-Price et al. 1983a). A dose-related decrease in fetal body weight with increasing dose was observed, with 60 mg/kg/day established as the NOAEL and 120 mg/kg/day as the LOAEL. Teratogenic effects were not observed and no signs of maternal toxicity were observed at any dose level. In a preliminary range-finding study conducted by Jones-Price et al. (1983a), a decrease in maternal weight gain and an increased incidence of maternal mortality were observed at >160 mg/kg. Tremors, a typical symptom of phenol toxicity, were also observed.

In a study of the developmental toxicity of substituted phenols, Kavlock (1990) examined the effects of 0, 100, 333, 667 and 1,000 mg/kg phenol given by gavage on day 11 of gestation. Twenty-seven chemicals were tested in this study. In order for the data to be comparable, a single vehicle was used consisting of a 4:4:1:1 mixture of water, Tween 20, propylene glycol, and ethanol. Because of the massive quantities of data such a study generates, the author focused his analytic efforts on five key variables, four of which were sampled at two time points. The 5 variables were maternal weight change (at 24 and 72 hours post-dosing), litter size (postnatal day [PD] 1 and 6), perinatal loss, pup weight (in g on PD 1 and 6), and litter biomass (in g on PD 1 and 6).

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Within these five parameters, a significant impact of phenol dosing was seen only on maternal weight change, and only at the two highest doses. However, at these same doses, a syndrome of malformations involving the limbs and tail was seen. At a dose of 667 mg/kg, pups in 21.4% of the litters were affected. (At a dose of 1,000 mg/kg, pups in 27.3% of the litters were affected.) The effect on tails was one of shortening or crimping (i.e., 'kinky' tails). The hindlimb effect consisted of paralysis and/or palsy. In animals with palsy, the limb function would alternate between normal strides and a several second-long period of tetany. Because limb function matures postnatally, this effect was not evident in the newborn but required 7-10 days to become obvious. In the case of phenol, the syndrome did not interfere with postnatal growth and viability; thus, by the statistical criteria used in the report to categorize developmental potency, phenol was not considered an active developmental toxicant.

In a subsequent study, Narotsky and Kavlock (1995) found that a significant decrease in the number of liveborn pups associated with severe respiratory effects in the dams was observed in pregnant rats treated by gavage with 53.3 mg/kg/day phenol in water on gestation days 6-19. In addition, in one high dose litter, two of four surviving pups had kinked tails; this finding was not analyzed for significance but was consistent with earlier observations (Kavlock 1990) and may reflect a teratogenic effect of phenol. Developmental effects were not significant at 40 mg/kg/day.

Phenol in water was administered to pregnant mice by gavage (10 mL/kg) at dose levels of 0, 70, 140, or 280 mg/kg/day on days 6-15 of gestation (Jones-Price et al. 1983b). Decreased maternal weight gain, tremors, and increased maternal mortality were observed at 280 mg/kg/day. In the fetuses, growth retardation, decreased prenatal viability, abnormal structural development, and an increased incidence of cleft palate were observed at 280 mg/kg/day. Developmental effects were not observed at 140 mg/kg/day. In pregnant mice that received 265 mg/kg phenol by gavage on day 13 of gestation, Ciranni et al. (1988) found no evidence of fetal cellular toxicity, as measured by a reduction in the polychromatic erythrocyte/normochromatic erythrocyte

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

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2.2.2.7 Genotoxic Effects

No studies were located regarding genotoxic effects in humans following oral exposure to phenol.

In pregnant female mice given 265 mg/kg phenol by gavage on day 13 of gestation, Ciranni et al. (1988) found no evidence of genotoxicity, as measured by an increase in micronuclei in maternal bone marrow or fetal liver.

An increase in DNA synthesis was observed in the kidneys of suckling mice treated by gavage with a dose of phenol 15-50% of the LD₅₀ (Amlacher and Rudolph 1981). DNA synthesis in the liver of mice treated by gavage with a single dose of 300 or 600 mg/kg phenol was not affected (Miyagawa et al. 1995).

Spermatocytes were examined for chromosomal aberrations in mice from a multigeneration study (Bulsiewicz 1977). The mice were treated by gavage with phenol in water at concentrations of 0, 0.08, 0.8, or 8 mg/L (approximately 0.006, 0.06, or 0.6 mg/kg/day). Both male and female mice were treated for 30 days before mating. Female mice continued to receive phenol during gestation and lactation; this procedure was repeated for five generations. Three F₃ and F₅ mice treated with 0.8 mg/kg/day became moribund and refused to eat and were killed before the end of the study. No spermatocytes from these mice were available for examination. The lack of spermatogenesis in these mice is probably secondary to their poor health rather than a direct effect of phenol. Chromosomal aberrations were detected in 27% of the spermatogonia and 5% of the primary spermatocytes in the 0.006 mg/kg/day group, in 52% of the spermatogonia and 22% of the primary spermatocytes in the 0.06 mg/kg/day group, and in 81% of the spermatogonia and 24% of the primary spermatocytes in the 0.6 mg/kg/day group. No data on the control group were provided. The study focused on chromosomal aberrations; no information on the reproductive success, teratogenicity, or any other health effects in exposed mice was reported.

Other genotoxicity studies are discussed in Section 2.5.

2.2.2.8 Cancer

No studies were located regarding carcinogenicity in humans following oral exposure to phenol.

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The carcinogenicity of orally administered phenol was examined in rats and mice in a study reported by the National Cancer Institute (NCI 1980). Rats and mice received 0,2,500, or 5,000 ppm in drinking water for 103 weeks. Calculated intakes for rats were 322 and 645 mg/kg/day for males and 360 and 721 mg/kg/day for females. Calculated intakes for mice were 590 and 1,180 mg/kg/day for males and 602 and 1,204 mg/kg/day for females. Statistically significant increased incidences of pheochromocytomas of the adrenal gland and leukemia or lymphomas were observed in male rats exposed to 322 mg/kg/day (2,500 ppm), but not in male rats exposed to 645 mg/kg/day (5,000 ppm). No significant effects were seen in female rats or mice of either sex exposed to either exposure level. Since cancer occurred only in males of one of the two species tested and a positive dose-response relationship could not be established, these results are inconclusive regarding the carcinogenic potential of orally administered phenol.

2.2.3 Dermal Exposure

2.2.3.1 Death

Application of phenol to the skin can be lethal. Death occurred within 10 minutes after $\approx 25\%$ of an individual's body surface was exposed to liquid phenol (Griffiths 1973). The cause of death was reported to be cardiac and respiratory depression. In another report, an individual died after being painted with a brush that had been soaked in a solution of phenol and thoroughly washed before use (Lewin and Cleary 1982). In neither case was the dose known with sufficient accuracy to establish a lethal dose.

A 10-year-old boy was hospitalized with serious burns; during the next 2.5 days his burns were treated by applying 7.5 L of an antiseptic solution containing 2% phenol; his urine became dark, respiration became labored, he fell into a coma, and died. *Post mortem* analysis of urine showed 200 mg/L of conjugated phenol (Cronin and Brauer 1949).

Lethality associated with dermal exposure to phenol is greatly influenced by the surface area exposed as well as the concentration of the applied solution. Mortality can vary depending on concentration; a dose of 100% phenol may be less toxic than the same dose of phenol given as a diluted solution. When a dose of 53.5 mg/kg was applied to the shorn backs of rats, 100% phenol resulted in the death of 1 of 5 rats, 33% resulted in the death of 3 of 5 rats, 50% resulted in the death of 4 of 5 rats, and 66% phenol resulted in the death of all 5 rats (Conning and Hayes 1970). In rats treated with 3,000 mg/kg phenol in a 6% solution over 1/6 of the total body surface, all 22 treated animals died (Deichmann and Witherup 1944). Increased lethality

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with decreased concentration has also been observed in rabbits treated dermally with 2,000 mg/kg; 95% phenol resulted in the death of 53% of treated rabbits, while 10% phenol in water resulted in the death of 100% of treated rabbits (Deichmann and Witherup 1944). The cause of death was not stated in these studies.

In rats given a single treatment of 5% phenol in water to achieve a dose of 3,000 mg/kg, 10-day-old rats were more sensitive than 5-week-old rats or adult rats (Deichmann and Witherup 1944). Within 2-14 hours after dosing, 13 of twenty 10 day-old rats died; 5 of twenty 5-week-old rats died 2-3 hours after dosing, and 9 of 20 adult rats died 30-180 minutes after dosing.

The dermal LD₅₀ of undiluted phenol in rats was reported to be 669.4 mg/kg (Conning and Hayes 1970). The LD₅₀ of an unspecified concentration of phenol in rabbits was reported to be 1,400 mg/kg (Vernot et al. 1977). Flickinger (1976) determined a dermal LD₅₀ by exposing male albino rabbits to 0, 252, 500, 1,000, or 2,000 mg/kg phenol which was placed “in contact” with “abraded and intact skin for a maximum period of 24 hours.” No animals died in the 0, 252, or 500 mg/kg groups whereas 3 of 4 in the 1,000 mg/kg group and all in the 2,000 mg/kg group died the first day following dosing. From these data the authors estimated a “single dose skin penetration LD₅₀ of 850 mg/kg.

Among pigs treated with a single dose of 500 mg/kg of undiluted phenol on 35-40% of the total body surface (about 1,136 cm²; 0.44 mg/cm²/kg), 2 of 3 died (Pullin et al. 1978). The study authors reported that a general state of lethargy, cyanosis, convulsions, and coma were observed 5-7 minutes before death.

No effects on survival were observed in mice treated dermally with an unspecified volume of 5% phenol (3 times/week) or 10% phenol (2 times/week) in acetone for 12 months (Wynder and Hoffmann 1961).

Pretreatment with a single dose of 7,12-dimethylbenz[a]anthracene (DMBA) followed by phenol resulted in increased skin tumors and decreased survival.

All LOAEL and LD₅₀ values from each reliable study are recorded in Table 2-3.

TABLE 2-3. Levels of Significant Exposure to Phenol - Dermal^a

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	LOAEL			Reference
			NOAEL (mg/cm2/kg)	Less Serious (mg/cm2/kg)	Serious (mg/cm2/kg)	
ACUTE EXPOSURE						
Death						
Rat (Alderly Park)	24 hr				669.4 F (LD ₅₀) mg/kg	Conning and Hayes 1970
Rat (Wistar)	once				3000 mg/kg (13/20 deaths 10-day-old, 5/20 deaths 5-week-old, 9/20 deaths adult)	Deichmann and Witherup 1944
Rabbit (New Zealand)	NS				1400 F (LD ₅₀) mg/kg	Vernot et al. 1977
Pig (Mixed breed)	24 hr				0.44 F (2/3 died)	Pullin et al. 1978
Systemic						
Human	1 hr	Cardio			75 M (cardiac arrhythmia) mg/kg	Warner and Harper 1985

TABLE 2-3. Levels of Significant Exposure to Phenol - Dermal (continued)^a

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/cm ² /kg)	LOAEL		Reference
				Less Serious (mg/cm ² /kg)	Serious (mg/cm ² /kg)	
Rat (Alderly Park)	24 hr	Renal			107.1 F (severe hemoglobinuria, hematin casts in the tubules)	Conning and Hayes 1970
		Dermal			107.1 F (severe edema, coagulative necrosis, erythema)	
Mouse (ICR)	once	Dermal	12 F	15 F (skin irritation indicated by thickening of treated ear)		Patrick et al. 1985
Rabbit (NS)	once	Cardio			23.8 M (cardiac arrhythmias, ventricular tachycardia)	Wexler et al. 1984
Pig (Mixed breed)	24 hr	Resp			0.44 F (dyspnea)	Pullin et al. 1978
		Dermal			0.44 F (necrosis of the skin)	
Neurological						
Rat (Alderly Park)	24 hr				107.1 F (severe muscle tremors, marked twitching, generalized convulsions, loss of consciousness and prostration)	Conning and Hayes 1970

TABLE 2-3. Levels of Significant Exposure to Phenol - Dermal (continued)^a

Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/cm ² /kg)	LOAEL		Reference
				Less Serious (mg/cm ² /kg)	Serious (mg/cm ² /kg)	
Pig (Mixed breed)	24 hr				0.44 F (twitching, tremors)	Pullin et al. 1978
INTERMEDIATE EXPOSURE						
Cancer						
Mouse (S albino)	24-32 wk 1 x/wk				20% (CEL: skin tumor promotor)	Salaman and Glendenning 1957
CHRONIC EXPOSURE						
Death						
Mouse (Swiss)	15 mo 2-3 x/wk					Wynder and Hoffmann 1961
Cancer						
Mouse (Swiss)	15 mo 2-3 x/wk				5% (CEL: skin tumor promotor)	Wynder and Hoffmann 1961

^aStudies in which dose units could not be expressed as mg/cm²/kg have their dose units listed following the dose levels.

Cardio = cardiovascular; CEL = cancer effect level; F = female; hr = hour(s); LD₅₀ = lethal dose (50% kill); LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory; wk = week(s); x = time(s)

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2.2.3.2 Systemic Effects

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 2-3.

Respiratory Effects. No studies were located regarding respiratory effects in humans following dermal exposure to phenol.

Dyspnea was reported in pigs treated with a single dose of 500 mg/kg of undiluted phenol over 35-40% of the total body surface area (0.44 mg/cm²/kg) (Pullin et al. 1978). This treatment resulted in the death of two of the three treated pigs.

Cardiovascular Effects. There have been several reports of cardiac arrhythmias associated with application of phenol solutions to the skin in connection with the surgical procedure of skin peeling (Gross 1984; Truppmann and Ellenby 1979; Warner and Harper 1985). In this procedure, a mixture of phenol (\approx 50% w/v), hexachlorophene, and croton oil is applied to the skin while the patient is under anesthesia. In a series of 54 patients in which the whole face was peeled in 1 day, cardiac arrhythmias were reported in 39%, while in a series of patients in which half the face was treated on 1 day, and the second half was treated 24 hours later, cardiac arrhythmias were reported in 22% (Gross 1984). The study author also indicated that the arrhythmias were less severe in the patients treated over a longer period of time.

Cardiac arrhythmia and bradycardia were reported in a man that splashed an unspecified concentration of a phenol-water solution over his face, chest wall, hand, and both arms (Horch et al. 1994). The cardiac effects were noted during the first 6 hours after exposure. The serum levels of phenol in μ g/L were 11,400 after 1 hour, 17,400 after 4 hours, and 6,000 after 8 hours.

Cardiac arrhythmia has also been noted in rabbits treated with 2 mL of a 50% phenol solution on a 15-cm² area (23.8 mg/cm²/kg) (Wexler et al. 1984). Reducing plasma concentrations of phenol by forced diuresis or a longer application time reduced the cardiac effects.

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Gastrointestinal Effects. During the first few days after a man splashed a phenol-water solution (concentration not stated) on his face, chest wall, hand, and both arms, he complained of nausea and vomited twice (Horch et al. 1994). A worker who was partially immersed for only a few seconds in a shallow vat containing a mixture of 40% phenol in dichloromethane, collapsed after showering and was taken to a hospital where he was found to have burns over 50% of his body. Initial observations were stable; however, after drinking fluids, he developed nausea and vomiting (Foxall et al. 1989).

No studies were located regarding gastrointestinal effects in animals following dermal exposure to phenol.

Hematological Effects. No studies were located regarding hematological effects in humans following dermal exposure to phenol.

Hemoglobinuria and hematin casts were reported in the renal tubules of rats treated dermally with 107.7 mg/kg phenol (Conning and Hayes 1970). These observations are indicative of red blood cell hemolysis; however, this was not confirmed with hematological examinations.

Musculoskeletal Effects. Muscle pain in the arms and legs was reported in a case of chronic phenol poisoning (Merliss 1972). The man worked in a laboratory for 13.5 years where he distilled phenol several times a day. During the process, heavy odors were detectable, phenol was often spilled on his clothes, and he noted skin irritation. The man recovered after 2-3 months away from the exposure.

No studies were located regarding musculoskeletal effects in animals following dermal exposure to phenol.

Hepatic Effects. Two days after a man was splashed with a phenol-water solution over his face, chest wall, hand, and both arms, serum bilirubin increased 2-fold (Horch et al. 1994). After 5 days, serum bilirubin returned to normal. An enlarged and tender liver and increased liver enzymes in the serum were reported in a case of chronic phenol poisoning (Merliss 1972). Lactate dehydrogenase was about 2-fold greater than normal, aspartate aminotransferase was about 21-fold greater than normal, and alanine aminotransferase was about 100-fold greater than normal. The man worked in a laboratory for 13.5 years where he distilled phenol several times a day. During the process, heavy odors were detectable, phenol was often spilled on his clothes, and he noted skin irritation.

No studies were located regarding hepatic effects in animals following dermal exposure to phenol.

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Renal Effects. A case of acute renal failure was reported by Foxall et al. (1989) in a worker who accidentally fell into a shallow vat containing a mixture of phenol (40%) in dichloromethane. The worker was partially immersed for only a few seconds and avoided ingesting any of the solution. He showered immediately, subsequently collapsed and was admitted to the hospital with surface burns over 50% of his body (involving the face, chest, genitals, and both legs). Following admission he became anuric and plasma creatinine levels rose. He was transferred to the regional renal unit where he was diagnosed with phenol-induced burns, acute tubular necrosis, and fluid overload. For the first 2 weeks, the patient demonstrated amino aciduria, glycosuria, and lactic aciduria consistent with renal cortical necrosis. This was followed by a period of polyuria revealing a biochemical pattern consistent with renal papillary damage. Treatment consisted of administration of a diuretic intravenously and hemodialysis daily for a week followed by an additional 18 days of hemodialysis at gradually increasing intervals. The patient was discharged 42 days after admission once renal clinical chemistry values had returned to normal, although NMR spectroscopic analysis still revealed abnormalities consistent with renal papillary damage. One year after the incident the patient was still polyuric.

Dark urine was reported in a case of chronic phenol poisoning (Merliss 1972). The man worked in a laboratory for 13.5 years where he distilled phenol several times a day. During the process, heavy odors were detectable, phenol was often spilled on his clothes, and he noted skin irritation. The study authors indicated that the urine was so dark that it suggested hemoglobinuria. Glucose was present in the urine, although the urine was negative for homogentistic acid (a substance whose presence can cause urine to darken upon standing) and urobilinogen. The urine cleared 2-3 months after the subject was removed from phenol exposure.

Hemoglobinuria and hematin casts in the distal convoluted tubules and tubular lumens located in the medulla and papilla were reported in rats after a single dermal exposure to 107.1 mg/kg liquid phenol (Conning and Hayes 1970). These phenomena are probably related to red blood cell lysis and increased glomerular filtration of hemoglobin. Hemoglobinuria is characteristic of lethal or near-lethal exposures by the dermal route.

Dermal Effects. Application of phenol to the skin of humans results in dermal inflammation and necrosis (Horch et al. 1994; Merliss 1972; Truppman and Ellenby 1979). Data concerning minimal effective exposure levels in humans were not found. NIOSH (1984) conducted a survey in an Oregon hospital in response to concerns about respiratory problems and contact dermatitis in housekeeping staff members who

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were exposed frequently to germicidal solutions containing phenol and other solvents (formaldehyde, cellosolve, ethanolamine). The housekeeping staff reported significantly more symptoms of cough, itching, sinus problems, and dermatitis than did other employees. Air concentrations of phenol in the work areas were below the limit of detection (<0.01 ppm). Urinary phenol levels in the housekeeping staff members were not significantly different from those of the other employees. Thus, while it is likely that the employees came into contact with irritants, the cause of the reported symptoms could not be attributed to phenol or any other specific substance in the work environment. Therefore, this study is not recorded in Table 2-3.

Application of 0.1 mL of molten phenol/kg (\approx 100 mg/kg) (Brown et al. 1975) or 107.1 mg/kg (Conning and Hayes 1970) to the skin of rats for 24 hours (surface area not reported) produced severe edema, erythema, and necrosis. In pigs, application of 500 mg/kg molten phenol to 35-40% of the body surface ($0.44 \text{ mg/cm}^2/\text{kg}$) resulted in skin discoloration after 20-30 minutes of exposure and severe necrosis after 8 hours of exposure. Two of 3 pigs died within 95 minutes after exposure (Pullin et al. 1978). Necrosis, hyperemia of superficial dermal vessels, and dense perivascular infiltration of lymphocytes and neutrophils were noted in the skin of pigs treated dermally with an unspecified amount of 89% phenol (Hunter et al. 1992). The dose-effect relationship and time course for skin irritation and inflammation have been studied in mice (Patrick et al. 1985). The endpoint examined was swelling (increased thickness) of the ear after dermal application to the ear pinna. Application of $12 \text{ mg/cm}^2/\text{kg}$ of phenol to the ear resulted in swelling in 4 of 9 mice within 1 hour after application. Severity of skin irritation increased as the concentration of the applied phenol solution increased. Swelling persisted for 6 weeks after application of $18 \text{ mg/cm}^2/\text{kg}$. Swelling was observed in only 1 of 8 mice treated with $12 \text{ mg/cm}^2/\text{kg}$ phenol. Application of an unspecified amount of a 1:6 or 1:9 phenol: water solution to the skin of guinea pigs for 1 minute resulted in erythema and increased skin vascular permeability indicated by dye permeability (Steele and Wilhelm 1966).

Skin crusts were reported on mice exposed repeatedly to 5 mg phenol as a 5% (w/v) solution for 32 weeks, whereas skin ulceration was observed in mice exposed to 5 mg phenol as a 20% (w/v) solution (Salaman and Glendenning 1957). The skin ulceration healed in 4 weeks after the end of the exposure. In a 52-week study, mice were exposed 2 times each week to 41.7 or 83.3 mg/kg of phenol in a 5 or 10% solution in benzene (Boutwell and Bosch 1959). Severe skin damage was reported after 36 weeks in the mice exposed to 83.3 mg/kg. Skin papillomas were reported in mice exposed at 4 1.7 mg/kg. Because phenol was applied in benzene which is also a skin irritant, this study is not presented in Table 2-3.

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Ocular Effects. No studies were located regarding ocular effects in humans following dermal exposure to phenol.

A modified Draize test was used to assess ocular damage resulting from application of 5% phenol to the center of the cornea in New Zealand rabbits (Murphy et al. 1982). The eyes of 1 group of rabbits were irrigated with water 30 seconds after exposure, while the eyes of another group were unirrigated. Conjunctivitis developed in all treated groups and lasted through the 7 days of observation. Corneal opacities became apparent in 4 of 9 rabbits 24 hours after phenol application in unirrigated eyes, but only 1 hour after application in 4 of 9 rabbits receiving irrigation. The opacities lasted through the 7-day observation period in the unirrigated eyes, but were cleared by day 7 in the irrigated eyes. Based on these observations, phenol was designated as a severe eye irritant in unirrigated eyes, and as a moderate eye irritant in irrigated eyes (Murphy et al. 1982).

Body Weight Effects. A man chronically exposed to phenol at a laboratory where he distilled it several times a day was 71.5 inches tall, weighed 135 pounds, and was described as emaciated (Merliss 1972). Loss of appetite and a slow weight loss were symptoms that the subject reported during the 13.5 years he worked at the laboratory. During the distillation process, heavy odors were detectable, phenol was often spilled on his clothes, and he noted skin irritation.

No studies were located regarding body weight effects in animals following dermal exposure to phenol.

Other Systemic Effects. No studies were located regarding other systemic effects in humans following dermal exposure to phenol.

Direct application of phenol to the inner ear of rats has resulted in external otitis, inner ear damage, and decreased brain-stem auditory response (Schmidt et al. 1990), and inflammation of the tympanic membrane (Schmidt and Hellstrom 1993). These studies were conducted because phenol has been used as a topical anesthetic in infected ears.

2.2.3.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological or lymphoreticular effects in humans or animals following dermal exposure to phenol.

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2.2.3.4 Neurological Effects

Fatal dermal exposure to an 80% phenol solution in a 24-year-old man being treated for skin rash was characterized by severe convulsions prior to death (Lewin and Cleary 1982).

Muscle tremors and convulsions are characteristic effects of acute dermal phenol toxicity in laboratory animals. Tremors that developed into convulsions and prostration were reported in rats exposed to 107.1 mg/kg liquid phenol; application surface areas were not reported (Conning and Hayes 1970). In pigs, application of 500 mg/kg over 35-40% of the body surface (0.44 mg/cm²/kg) resulted in muscular tremors in the head region within 3-5 minutes of exposure (Pullin et al. 1978). This was followed by dilation of the pupils, loss of coordination, and excess salivation and nasal discharge within 5 minutes of exposure. It was followed by convulsions, coma, and death 5-7 minutes after exposure in two of three pigs. Direct application of a dose of 37.5 mg/kg phenol to the inner ear resulted in a reduced threshold for auditory brainstem response (Schmidt et al. 1990).

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

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 cancer in humans following dermal exposure to phenol.

In a study of the promoting effects of phenol, mice were exposed to 9,10-dimethyl-1,2-benzanthracene (DMBA) (300 µg) followed by weekly dermal exposure to 5 mg phenol in either a 5 or 20% phenol solution in acetone for 32 weeks (Salaman and Glendenning 1957). Exposure to DMBA followed by phenol (5 or

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20%) resulted in a significantly greater incidence of tumors, including carcinomas, than exposure to 20% phenol alone; tumors, but no carcinomas, resulted from exposure to 20% phenol, and no tumors resulted from exposure to 5% phenol. Application of 5% phenol alone resulted in skin “crusting” at the site of application, whereas 20% phenol resulted in skin ulceration. The study authors concluded that phenol was an effective tumor promoter after a single application of DMBA. Although this study did not include a group of animals which had been exposed to DMBA alone, the authors indicated that previous work done in their laboratory provided the data from such animals and that it was thus the comparison between such historical information and the information from this study which led to their conclusion about the promotional effects of phenol.

A similar promoting activity was observed when an unspecified volume of 10% phenol in acetone was placed on the backs of mice 2 times/week for 12 months and when 5% phenol in acetone was placed on the backs of mice 3 times/week for 12 months (Wynder and Hoffmann 1961). CELs from these studies are presented in Table 2-3.

Additional studies indicate that phenol applied to the skin is a cancer promoter and possibly a complete carcinogen (i.e., promoter and initiator) in mice. Boutwell and Bosch (1959) examined the carcinogenic effects of phenol in several strains of mice. Mice were exposed to a single dermal application of DMBA (75 mg) followed by repeated dermal applications of a 5 or 10% phenol solution in benzene (41.7 or 83.3 mg/kg/treatment), twice each week for 52 weeks. Two other experimental groups of mice were exposed to DMBA alone or phenol alone. Severe skin damage, decreased body weight, and increased mortality were observed in phenol-treated animals. Sutter strain mice (inbred for 3 generations for susceptibility to the initiator DMBA) treated with DMBA followed by 10% phenol developed papillomas (95% in 13 weeks) and carcinomas (43% in 42 weeks) at a much higher incidence than mice treated with DMBA alone (14% with papillomas at 42 weeks; no carcinomas), or phenol alone (36% with papillomas at 52 weeks; no carcinomas). One fibrosarcoma was observed after 52 weeks of exposure to phenol alone. An elevated incidence of papilloma was also observed in CAF1, C3H, and Holtzmann mice exposed to DMBA followed by phenol, and in Holtzmann mice exposed to 10% phenol alone. The promoting effect of phenol was dose related; application of 5% phenol (41.7 mg/kg) following DMBA treatment resulted in fewer tumors than a similar protocol using DMBA followed by 10% phenol (83.3 mg/kg). Phenol elicits skin tumors in mice even without treatment with DMBA. Ten out of 30 albino mice treated twice weekly for 12 weeks with a 20% phenol solution in dioxane developed papilloma of the skin; also, 8 out of 30 mice treated with 10% phenol solution in benzene for 15 weeks developed papilloma, and 3 developed carcinoma of the skin (Boutwell and

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Bosch 1959). Because the phenol was administered in benzene or dioxane, both of which are skin irritants and/or de-fatting agents, this study is not presented in Table 2-3.

The effect of phenol on benzo[a]pyrene (B [a]P) carcinogenicity has been examined (Van Duuren and Goldschmidt 1976; Van Duuren et al. 1971) 1973). Dermal application of 3 mg phenol in acetone simultaneously with 5 µg B [a]P resulted in significantly fewer tumors than application of B [a]P alone. Application surface areas were not reported and could not be estimated from the description of the application procedure. Mice treated dermally with B [a]P followed by dermal application of brewed tea on alternate days over a period of 55 days developed epithelial cell carcinoma or exhibited various stages of squamous cell tumors (Kaiser 1967). The brewed tea contained an unspecified level of phenol, the presumed cancer promoter in this experiment, as well as cresols and dimethylphenols.

2.3 TOXICOKINETICS

Phenol is readily absorbed and widely distributed following inhalation, oral, and dermal exposure. The distribution of phenol is thought to be dependent on blood flow. Conjugates with glucuronic acid and sulfate are the major metabolites of phenol, although small amounts of the hydroxylation products catechol and hydroquinone are also produced. Sulfotransferase and glucuronyltransferases are present in most tissues, although the major sites of phenol conjugation are the gastrointestinal tract, liver, lung, and kidney. Because of the large capacity of the intestines and liver to conjugate phenol, the fact that the first-pass effect occurs following oral exposure but not following dermal exposure may contribute to the greater potential for phenol to result in adverse effects following dermal exposure. Phenol and its conjugates are predominantly excreted in the urine.

2.3.1 Absorption

2.3.1.1 Inhalation Exposure

Phenol is absorbed readily after inhalation exposure. Eight subjects were exposed to phenol vapors (1.6-5.2 ppm) for 8 hours (Piotrowski 1971). Subjects were exposed through a face mask in order to eliminate the possibility of percutaneous absorption. The concentration of phenol in inhaled and exhaled air was determined, and urine was analyzed for total phenol (phenol and phenol conjugates). Steady-state

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appeared to be achieved within 3 hours after initiating exposure; steady-state retention was 60-88%. Urinary recovery of phenol that had been retained in the lungs was $99\pm 8\%$ within 24 hours after initiating exposure.

Total urinary phenol was determined at about 7 hours into an 8-hour shift in Bakelite workers exposed to airborne phenol at 0.16-32 ppm (Ohtsuji and Ikeda 1972). Daily urinary excretion of total phenol was 99% of the estimated amount inhaled indicating that phenol is readily absorbed. However, lung retention was not measured, and the contribution of percutaneous absorption to urinary phenol could not be evaluated in this study.

Rats exposed by intratracheal instillation to [^{14}C]-labeled phenol also demonstrated rapid absorption kinetics, with most of the radioactivity being excreted within 72 hours (Hughes and Hall 1995).

2.3.1.2 Oral Exposure

Based on the rapid excretion of phenol and its metabolites in urine, it has been concluded that phenol is readily absorbed by the oral route in humans (Capel et al. 1972) and a variety of mammalian species including monkeys (Capel et al. 1972), rodents (Capel et al. 1972; Edwards et al. 1986; Hughes and Hall 1995; Kao et al. 1979; Kenyon et al. 1995), dogs (Capel et al. 1972), rabbits (Capel et al. 1972), cats (Capel et al. 1972; French et al. 1974), and pigs (Capel et al. 1972; Kao et al. 1979). In 3 men given a single oral dose of 0.01 mg/kg [^{14}C]-labeled phenol in food or drink, about 90% (range 85-98%) of the dose was excreted in the urine in 14 hours (Capel et al. 1972). In this same study, urinary recovery of orally administered [^{14}C]-labeled phenol was determined in 18 other mammalian species; mean 24-hour recoveries of ^{14}C ranged from 95% in the rat to 31% in the squirrel monkey. Rats exposed orally to radiolabeled phenol demonstrated rapid absorption and excretion, with most of the radioactivity being excreted within 72 hours (Hughes and Hall 1995). The gastrointestinal absorption of phenol has also been studied in rats with *in situ* preparations. The absorption kinetics of [^{14}C]-labeled phenol administered directly into the small intestines of rats were described as first-order, with a rate constant for intestinal absorption of $0.127\pm 0.003 \text{ minute}^{-1}$ and a half-life in the intestines of 5.5 ± 0.5 minutes (Humphrey et al. 1980). Two hours after [^{14}C]-labeled phenol was injected into the small intestines of anesthetized rats, recoveries in the urine were $77.9\pm 2\%$ after a 12.5-mg/kg dose, and $76.9\pm 5.8\%$ after a 25-mg/kg dose (Kao et al. 1979).

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2.3.1.3 Dermal Exposure

Phenol is absorbed quite readily through the skin, and the skin is considered the primary route of entry during occupational exposure (ACGIH 1991). Whole-body skin exposures in human subjects were completed with subjects lightly clothed and unclothed (Piotrowski 1971). The subjects were exposed to phenol vapor (35% humidity, 26°C) at concentrations of 1.3, 2.6, or 6.5 ppm for 6 hours. Fresh air was supplied to the subjects through a face mask in order to prevent absorption of phenol through the lungs. The total amount of phenol excreted in urine during and after exposure (minus baseline excretion) was used as a measure of absorption. Absorption increased proportionately with exposure level. Percutaneous clearance (mg phenol absorbed through the skin per hour/mg phenol per m³ of air) was estimated to be 0.35 m³/hour. Thus, an amount of phenol equivalent to that contained in 0.35 m³ of air was absorbed through the skin each hour.

The data reported by Piotrowski (1971) provide a basis for comparing the relative contributions of lung and percutaneous absorption during exposures to phenol vapor. Assuming a ventilation rate for the human of 0.8 m³/hour (EPA 1986a) and a steady-state lung retention of inhaled phenol of 0.7 (Piotrowski 1971), clearance of airborne phenol through the lung is ≈ 0.6 m³/hour. Thus, an amount of phenol equivalent to that contained in 0.6 m³ of air was absorbed through the lungs each hour. It can be concluded that at any given exposure level within the range of 5-25 mg/m³ (1.3-6.4 ppm), percutaneous absorption (0.35 m³/hour) will be $\approx 1/2$ that of absorption through the lungs (0.6 m³/hour).

Percutaneous absorption of phenol applied in solution directly to the forearm (15.6 cm²) of volunteers has been measured (Baranowska-Dutkiewicz 1981). Absorption rate from a 2-mL reservoir of an aqueous phenol solution (2.5, 5.0, or 10.0 g/L) was constant for 60 minutes (0.08 mg/cm²/hour) and increased proportionately with applied concentration. Approximately 13% of the applied dose was absorbed in 30 minutes, of which 80% (range 58-98%) was recovered in the urine within 24 hours.

When human skin was treated *in vitro* with 0.0013-0.0027 mg/cm² [¹⁴C]-labeled phenol and left unoccluded, 20% of the radioactivity was absorbed when analyzed 72 hours later, while 7% remained on the skin surface (Hotchkiss et al. 1992). Covering the skin with a teflon cap resulted in the absorption of 47%, with 3% recovered in the skin. When rat skin was subjected to the same exposure regime in this study, 72 hours later 24% of the radioactivity was absorbed with 22% recovered in the skin when the skin was unoccluded, and 36% was absorbed with 3-4% recovered in the skin when the skin was occluded.

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In rats in which a 0.03-mg/kg dose of [¹⁴C]-labeled phenol was placed on the skin, only 1-5% of the dose remained in the body 72 hours later (Hughes and Hall 1995). The dermal absorption of phenol was studied in three pigs in which undiluted phenol was placed on the skin for 1 minute, and the peak plasma level was determined (Pullin et al. 1978). Plasma levels were not measurable in 1 pig treated with a dose of 90 mg/kg over a surface area of 91.6 cm². In pigs treated with a dose of 500 mg/kg, peak plasma levels of 0.9 and 30.5 ppm were reported in pigs treated over surface areas of 91.6 and 1,135.5 cm², respectively.

Permeability coefficients for phenol in isolated skin patches from nude mice have been determined (Behl et al. 1983). The permeability coefficient increased as the concentration of the applied aqueous phenol solution increased; doubling the concentration from 20 to 40 g/L resulted in a 12-fold increase in mean permeability coefficient (0.007-0.085 cm/hour). The value obtained for the permeability coefficient when 60 g/L was applied to the skin patch (0.169 cm/hour) was similar to that obtained for skin patches in which the stratum corneum had been removed. It was concluded that phenol concentrations exceeding 20 g/L may destroy a diffusion barrier normally provided by the intact stratum corneum, permitting increased percutaneous absorption.

Dermal absorption of phenol in the presence of various types of soil was measured *in vitro* using skin patches from pigs (Skowronski et al. 1994). Maximum phenol penetration occurred between 2 and 4 hours after treatment in all cases. Compared to samples with no soil present, the presence of sandy soil reduced the peak penetration by one-half, and the presence of clay soil reduced peak penetration by two-thirds.

2.3.2 Distribution

2.3.2.1 Inhalation Exposure

No studies were found regarding tissue distribution of phenol in humans after inhalation exposure.

Rats exposed by intratracheal instillation to radiolabeled phenol were sacrificed 72 hours later and analyzed for tissue distribution of the radioactivity (Hughes and Hall 1995). Of the radioactivity remaining in the body (1-5%), a majority was distributed in the lungs (0.13%), skin (0.13%), blood (0.07%), muscle (0.03%), fat (0.02%), and liver (0.02%).

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No information was found on the placental transfer and distribution of phenol; however, Ghantous and Danielsson (1986) examined this question for benzene, the principal metabolite of which is phenol. Mice at gestation day 11, 14, and 17, were exposed by inhalation to ^{14}C benzene and the distribution of benzene and its volatile and non-volatile metabolites examined using whole body autoradiography and assessment of tissue concentrations of ^{14}C (day 17 only). The authors indicated that the exposure regimen (50 μCi of ^{14}C benzene in maize oil, volatilized by gentle heating) would theoretically produce 2,000 ppm in the inhalation chamber. Measurements of the difference between the amount added to the chamber and the amount inhaled by the animals indicated an uptake of 90% (i.e., 45 μCi). These authors did not specifically characterize the metabolites, but were able to show that the ^{14}C labeled volatile and non-volatile activity crossed the placental barrier. There was no evidence of preferential accumulation. Indeed, the concentration of volatile and nonvolatile radioactivity in fetal tissues was much lower than that observed in the corresponding maternal tissues. As a metric of the relative accumulation, the authors noted that compared to maternal brain tissue, fetal uptake of benzene was only 8%.

2.3.2.2 Oral Exposure

No studies were found regarding tissue distribution of phenol in humans after oral exposure.

Data are available for rabbits (Deichmann 1944) and rats (Hughes and Hall 1995; Liao and Oehme 1981). In these species, distribution is rapid, with peak tissue concentrations achieved in most tissues within 1 hour after dosing. The highest peak concentrations and fraction of administered dose are found in the liver; >90% of the administered dose is eliminated from tissues within 24 hours.

The levels of phenol in various tissues of 5 rabbits given a lethal (LD_{50}) oral dose of phenol (500 mg/kg) were determined (Deichmann 1944). The rabbits were killed within 1-3 minutes after dosing when twitching, the first sign of systemic toxicity, appeared. The highest concentrations of total phenol (free plus conjugates) were found in the liver (20.9-30.4 mg/100 g tissue), lungs (5.1-17.1 mg/100 g), blood (6.1-12.6 mg/100 g), brain and spinal cord (3.1-10.4 mg/100 g), and kidneys (2.3-7.1 mg/100 g).

The kinetics of tissue distribution of [^{14}C]-labeled phenol in rats given 207 mg/kg of [^{14}C]-labeled phenol, a sublethal ($\approx 0.5 \times \text{LD}_{50}$) oral dose, were studied (Liao and Oehme 1981). Although all rats survived for 16 hours, signs of systemic toxicity were observed including twitching of muscles around the eyes and ears, convulsions, and coma persisting for 15-30 minutes. Thirty minutes after dosing, 28.4% of administered ^{14}C

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was recovered in tissues (liver, kidney, adrenal, thyroid, spleen, blood, lung, thymus, brain, testes, heart, muscle, and fat). Sixteen hours after dosing, 0.3% of the administered dose was recovered in tissues. Concentrations of ^{14}C were highest in all tissues 30 minutes after dosing, with the exception of the thyroid gland, in which peak concentrations were achieved after 2 hours. The highest concentration and fraction of administered dose were found in the liver; 42% (range 29-56%) of the administered dose was recovered in the liver 30 minutes after dosing. Approximately 67-85% of the ^{14}C in blood was present in the plasma fraction, of which 41-50% was bound to plasma proteins or other macromolecules. The elimination half-time for ^{14}C was <4 hours. Based on their results, the study authors suggested that blood flow determines the tissue uptake of the radiolabel from phenol.

Rats exposed orally to radiolabeled phenol were sacrificed 72 hours later and analyzed for tissue distribution of the radioactivity (Hughes and Hall 1995). Of the radioactivity remaining in the body, a majority was distributed in the muscle (0.08%), skin (0.07%), fat (0.02%), liver (0.02%), and blood (0.02%).

No evidence of exposure-related DNA adduct formation in femur bone marrow, Zymbal gland, liver, or spleen was seen in rats treated orally with 75 mg/kg/day phenol for 4 days (Reddy et al. 1990). In this study, concurrent *in vitro* exposures of these tissues did produce adducts, suggesting that efficient detoxification and excretion mechanisms may be operating *in vivo*.

2.3.2.3 Dermal Exposure

No studies were found regarding tissue distribution of phenol in humans after dermal exposure.

Rats exposed dermally to radiolabeled phenol were sacrificed 72 hours later and analyzed for tissue distribution of the radioactivity (Hughes and Hall 1995). Of the radioactivity remaining in the body (1-5%), a majority was distributed in the skin (0.021%), muscle (0.02%), fat (0.03%), liver (0.01%), and blood (0.02%).

2.3.2.4 Other Routes of Exposure

No studies were located regarding distribution of phenol in humans after exposure by other routes.

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Microdialysis sampling has been used in rats infused with phenol (0.181 nmol/minute for 90 minutes) to study excretion into the bile (Scott and Lunte 1993). For all phenol metabolites, bile concentrations were higher than liver concentrations indicating that the metabolites are actively excreted in the bile.

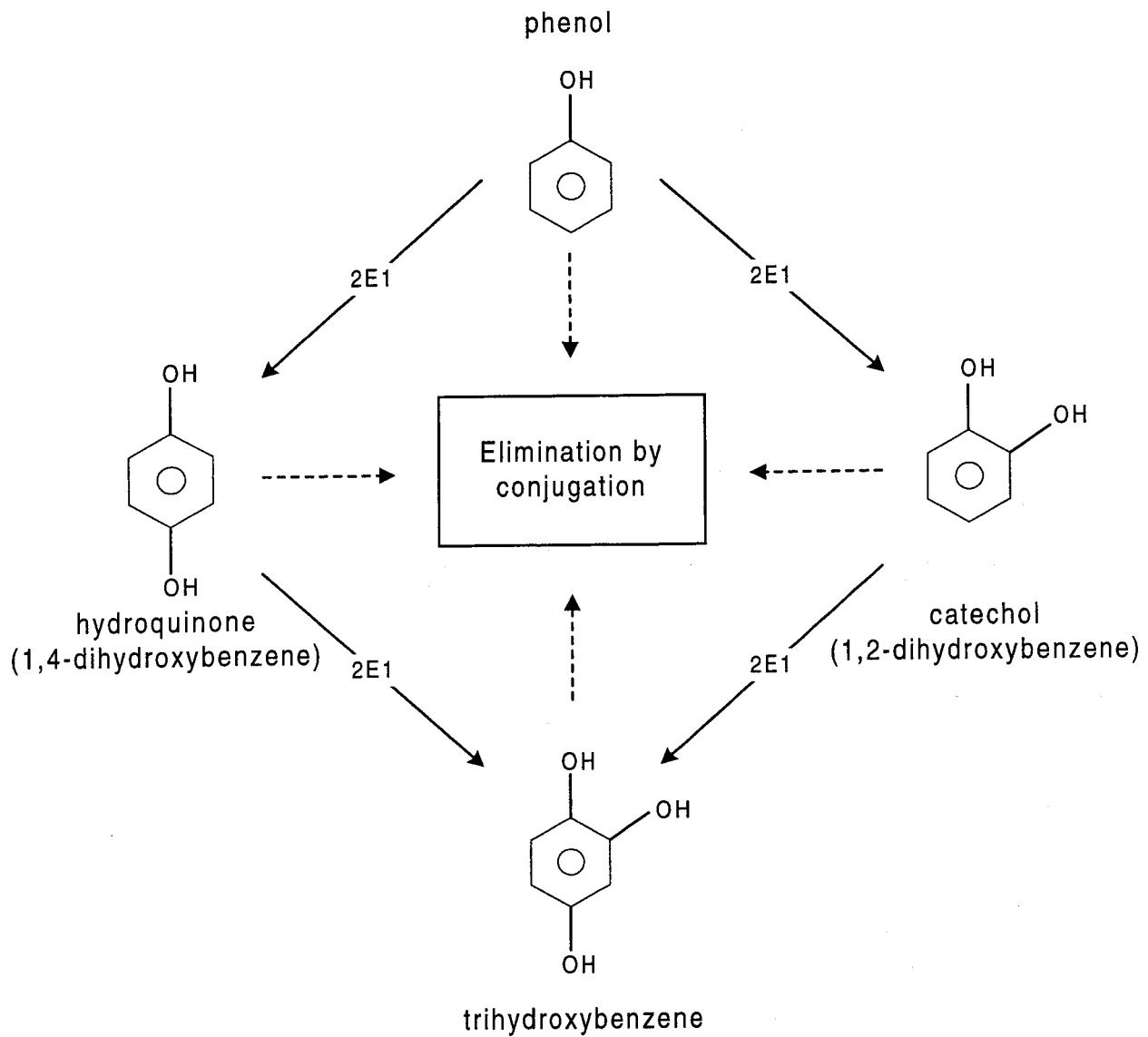
The distribution of phenol in the liver has been studied in mice treated intravenously with 31.4 mg/kg phenol (Davies and Lunte 1996). Microdialysis probes used to monitor the distribution of phenol metabolites in three regions of the liver (anterior, median, posterior) indicated that phenol-glucuronide was the most prevalent metabolite in all three regions, but the level was significantly lower in the anterior region compared to the other regions. When phenol was delivered to the liver through microdialysis probes, no regional differences in the delivery of phenol or metabolite formation were observed, indicating that clearance of phenol from the liver is dominated by blood flow rather than metabolism.

2.3.3 Metabolism

Figure 2-3 shows the metabolic pathways that transform phenol prior to its excretion in the urine. Three different enzymes systems catalyze the reactions that transform phenol. Cytosolic phenol sulfotransferases catalyze the transfer of inorganic sulfur from the activated 3'-phosphoadenosine-5'-phosphosulfate donor molecule to the hydroxyl group on phenol. Microsomal membrane-located uridine diphosphate glucuronosyltransferases (UDP-glucuronosyltransferases) catalyze the transfer of an activated glucuronic acid molecule to the hydroxyl moiety of phenol to form an O-glucuronide conjugate. Cytochrome P4502E1, also microsomally located, catalyzes the hydroxylation of phenol to form hydroquinone (and to a much lesser extent catechol), which is then acted upon by the phase II enzymes (Benet et al. 1995; Campbell et al. 1987; Gut et al. 1996; McFadden et al. 1996). All three enzyme systems are found in multiple tissues and there is competition among them not only for phenol but for subsequent oxidative products, like hydroquinone. As a consequence, the relative amount of the products formed can vary based on species, dose and route of administration. *In vivo*, the gastrointestinal tract, liver, lung, and kidney appear to be the major sites of phenol sulfate and glucuronide conjugation of simple phenols (Cassidy and Houston 1984; Powell et al. 1974; Quebbemann and Anders 1973; Tremaine et al. 1984).

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Figure 2-3. Scheme for Metabolism of Phenol*



—2E1→ Oxidative reaction catalyzed by cytochrome P450 2E1

-----> Conjugation reactions (may be catalyzed by phenol sulfotransferase, UDP-glucuronosyl transferase, or glutathione-S-transferase)

*Adapted from Schlosser et al. 1998

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Four principal metabolites have been identified in mammals: two phenol and two hydroquinone conjugates (of sulfate and glucuronide) (Capel et al. 1972; Kenyon et al. 1995; Wheldrake et al. 1978). In humans, rats, and mice, given low doses of phenol orally, sulfate conjugates of phenol were found to predominate. However, in guinea pigs, pigs, and fruit bats, the glucuronide conjugates were dominant (Capel et al. 1972). In humans given an oral dose of 0.01 mg/kg, 77% of the urinary ^{14}C was identified as phenyl sulfate, 16% as phenyl glucuronide, with trace amounts (<1%) as the sulfate and glucuronide conjugates of hydroquinone (Capel et al. 1972).

In mice, phenyl sulfate was the predominant urinary metabolite for low doses (1-21 mg/kg) of phenol administered either by gavage and intravenously; however, as the dose increased, a decrease in phenol sulfation and a concomitant increase in glucuronidation of both phenol and hydroquinone was seen suggesting saturation of the sulfation pathway (Kenyon et al. 1995). The degree of saturation appeared to be slightly greater following gavage administration, and intravenous administration resulted in higher proportions of the products of oxidative metabolism, with male mice being more sensitive than female mice. These latter observations suggest that the oxidative pathway become more prominent when phenol is introduced directly into the circulation, bypassing an initial intestinal sulfate conjugation process, and also suggests, that the sulfate conjugation process saturates at a lower concentration in males than in females.

Similarly, in the rat, the ratio of phenyl sulfate/glucuronide conjugates in urine decreases from 2.6 to 0.7 when the intravenous dose level is increased from 1.2 to 25 mg/kg (Weitering et al. 1979). This phenomenon appears to be, at least in part, the result of a lower K_m for the sulfotransferase enzyme for phenol rather than for the glucuronyltransferase enzyme (Koster et al. 1981; Mulder and Scholtens 1977; Ramli and Wheldrake 1981). Treatment of rats with an intraperitoneal dose of phenol (23-188 mg/kg) has also been shown to result in dose-dependent decreases in hepatic 3'-phosphoadenosine 5'-phosphosulfate (PAPS), the cosubstrate for the sulfate conjugation of phenol, as well as sulfate (Kim et al. 1995). The depletion of PAPS may also contribute to the saturation of sulfation at high doses of phenol.

All three enzyme systems have other substrates, which can competitively inhibit the metabolism of phenol thereby changing the balance among metabolites. Inhibition of phenol sulfotransferase with chlorinated phenols (e.g., pentachlorophenol) results in increased glucuronide conjugation of simple phenols (Mulder and Scholtens 1977). Similarly, benzene is metabolized by CYP2E1, thus high exposures to benzene may competitively inhibit phenol metabolism resulting in decreasing hydroquinone production (and its corresponding sulfate and glucuronide conjugates) (Medinsky et al. 1995; Schlosser et al. 1993).

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Age- and sex-related changes in phenol sulfoconjugation were studied in hepatic cytosolic preparations from fetal, newborn, and adult rats (Iwasaki et al. 1993). Phenol sulfoconjugation activity was higher in adult males (1.94 ± 0.1 nmol/mg/min) than females (1.07 ± 0.03 nmol/mg/min), although there were no sex-related differences in the younger rats. Activity in fetal rats was very low (0.04 ± 0.01 nmol/mg/min). Activity at 2 days after birth was $\frac{1}{2}$ that in adult females and $\frac{1}{4}$ that in adult males, and remained constant until 25 days after birth. At 2 years of age, activity was intermediate between young adult male and female activities, and there were no sex-related differences.

Several other minor metabolites of phenol have been identified *in vitro*. The formation of 1,4-dihydroxybenzene and 1,2-dihydroxybenzene in a 20: 1 molar ratio was observed in isolated rat liver microsomes incubated with phenol (Sawahata and Neal 1983). Further catalysis to-p-benzoquinone, 4,4'-biphenol, and biphenquinone has been demonstrated in microsomes and in *in vitro* peroxidase preparations. The benzoquinone products react nonenzymatically with nucleophiles, including cysteine and reduced glutathione, to yield S-conjugates of 1,4-dihydroxybenzene and 4,4-biphenol (Eastmond et al. 1986; Lunte and Kissinger 1983; Subrahmanyam and O'Brien 1985).

2.3.4 Elimination and Excretion

Phenol, in its free and conjugated forms, is a normal constituent of human urine. Piotrowski (1971) reported 8.7 ± 2.0 mg/day as the daily excretion rate of total phenol (free plus conjugates) in human subjects with no known exposure to phenol. Others have reported a range of values. In a study of workers employed in the distillation of high-temperature phenolic fractions of tar, the rate mean values of phenol in the urine of 13.8 mg/L in 26 male non-exposed workers and 67.8 mg/L in 89 exposed workers were reported (Bieniek 1994). The highest concentration was found 2 hours after the end of the work shift. Quint et al. (1998) evaluated the urinary phenol concentration before and after using phenol to chemically cauterize the lesion created by excision of chondroblastoma in 11 patients. Preoperatively, the average urinary concentration of phenol was 5.1 mg/L. Ling and Hanninen (1991) studied the effect of phenol on serum and urinary concentrations in patients who switched from a conventional diet to an uncooked "vegan" diet. Patients were tested at week 0, were on the vegan diet for 4 weeks, and then on the regular diet for the second month. Urinary and serum levels of phenol were measured at weeks 0, 2, 4, and 9. A significant decrease in both urinary and serum concentrations of phenol was seen within 2 weeks of adopting the vegan diet. At 2 weeks, the serum concentration had dropped from about .75 mg/L to 0.5 mg/L (about 30%), and levels in urine had dropped from about 7 mg/L to about 3 mg/L (about 60%). These data indicate that phenol is a natural

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product of metabolism that may vary significantly depending at least on diet, but probably also due to other factors.

Horch et al. (1994) make the statement “urine phenol concentrations should be monitored in exposed persons to determine if they are within normal range (0.5-81 mg/L),” but they provide no citation for the range given. It should be noted that as late as 1980, gas chromatographic analyses of urine used to determine phenol levels showed fairly large interlaboratory variation (Van Roosmaleu et al. 1981). Thus the range of values given above, if derived from multiple references including the older literature, may be artificially broad.

2.3.4.1 Inhalation Exposure

Phenol absorbed through the lungs is excreted rapidly in urine in its free and conjugated forms. Within 24 hours after human subjects inhaled phenol at concentrations of 6-20 mg/m³ (1.5-5.1 ppm), 99±8% of the phenol retained in the lungs was excreted (Piotrowski 1971). The urinary excretion of phenol was studied in 106 men occupationally exposed to phenol, cresols, xyenols, and other phenolic derivatives, and 26 unexposed controls (Bieniek 1994). Urine samples were taken after 4 hours at work, and in 16 workers every 2 hours for 24 hours after an 8-hour shift. The mean level of phenol in urine of the exposed workers was 87.3 mg/L, compared to 11.7 mg/L in controls. The highest phenol concentrations were recorded between 8 and 10 hours after the beginning of the exposure. Exposure concentrations were not reported in this study.

Urinary excretion of total phenol (free and conjugates) is considered a biomarker of exposure for phenol. The biological exposure index (BEI) for phenol, for exposure to 5 ppm in air, is 250 mg/g creatinine when measured at the end of the shift (ACGIH 1991).

In rats exposed by intratracheal instillation to radiolabeled phenol, elimination was 95% complete after 72 hours, with the primary elimination route being through the urine (Hughes and Hall 1995). Fecal elimination was slower and accounted for less overall.

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2.3.4.2 Oral Exposure

Phenol absorbed from the gastrointestinal tract is excreted rapidly in urine as free phenol or conjugates (Capel et al. 1972; Deichmann 1944; Edwards et al. 1986; French et al. 1974; Kao et al. 1979; Kenyon et al. 1995; Lao and Oehme 1981). In 3 human subjects who received a single oral dose of 0.01 mg/kg [¹⁴C]-labeled phenol, the mean 24-hour urinary recovery of ¹⁴C was 90% (range 85-90%) of the administered dose (Capel et al. 1972). In this same study, urinary recovery of orally administered [¹⁴C]-labeled phenol was determined in 18 other mammalian species; the mean 24-hour recoveries of ¹⁴C ranged from 95% in the rat to 31% in the squirrel monkey.

Both urinary and fecal excretion of ¹⁴C was determined in rats administered an oral dose of 1.2 mg/kg of [¹⁴C]-labeled phenol (Edwards et al. 1986). Rats excreted 80.3±11.2% in the urine and 1.8±1.6% in the feces in 24 hours. In rats exposed orally to radiolabeled phenol, elimination was 95% complete after 72 hours, with the primary elimination route being through the urine (Hughes and Hall 1995). Fecal elimination was slower and less overall.

2.3.4.3 Dermal Exposure

Phenol absorbed through the skin is rapidly excreted in urine as free phenol or conjugates. Following an industrial accident in which a phenol-water solution was splashed over a man's face, chest wall, hand, and both arms, phenol in the urine decreased from 566 mg/L after 4 hours to 0.75 mg/L 46 hours after the exposure (Horch et al. 1994). Subjects exposed to dermally applied reservoirs containing phenol solutions (2.5-10 mg/L) excreted 80% (range 58-98%) of the absorbed phenol in the urine within 24 hours (Baranowska-Dutkiewicz 1981). Another study in which human subjects were dermally exposed for 7 hours to phenol vapors, both clothed and unclothed, while breathing clean air to avoid inhalation exposure, found that almost 100% of the absorbed phenol was excreted in the urine within 1 day, with clothing providing no apparent protection (Piotrowski 1971).

In rats exposed dermally to radiolabeled phenol, elimination was 95% complete after 72 hours, with the primary elimination route being through the urine (Hughes and Hall 1995). Fecal elimination was slower and less overall.

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2.3.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

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

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

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993).

PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

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

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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 2-4 shows a conceptualized representation of a PBPK model.

If PBPK models for phenol 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.

PBPK models for phenol are discussed below.

2.3.5.1 Summary of PBPK Models

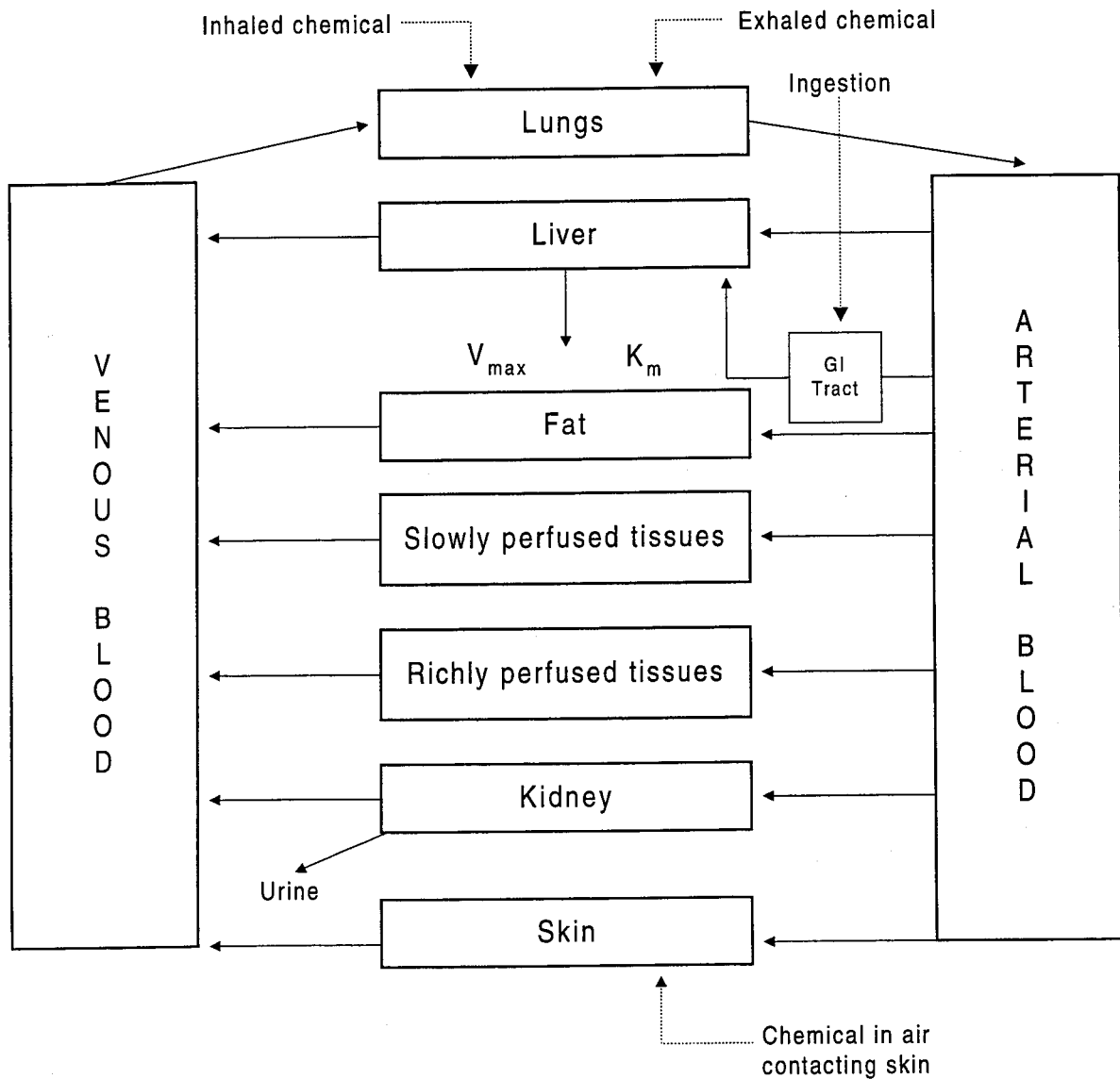
Physiologically based pharmacokinetic models regarding phenol have typically been developed as part of the attempt to understand the toxicity of benzene, of which phenol is the primary metabolite. Human exposure to benzene is widespread, and much of the toxicity of benzene is due to the action of its metabolites. Thus, while no studies were located involving PBPK models specific to phenol exposure, several models relating to benzene exposure exist and are appropriate to this discussion.

2.3.5.2 Phenol PBPK Model Comparison

The complexities of benzene and phenol metabolism are not yet fully understood, and so appropriate PBPK models are still being developed. Several factors involving the metabolism and toxic effects of these chemicals should be considered. First is the apparent differential toxicity of the two chemicals, benzene being generally more toxic and carcinogenic, while phenol has no apparent carcinogenicity following inhalation and oral exposure. Second is the fact that phenol is a metabolite of benzene and also competes with benzene for the same oxidation enzymes, so that either chemical may inhibit the metabolism of the other chemical by saturating all available active enzyme sites. Finally, each chemical has several metabolic pathways that may be followed, some of which may produce metabolites more toxic than the parent compounds.

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Figure 2-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



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

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Thus, modeling the kinetics of benzene and phenol metabolism involves considering an array of compounds which may themselves be responsible for any observed toxic effects.

The two models discussed below are derived from *in vitro* and *in vivo* rodent studies. It is important to keep in mind that these models were developed specifically to describe benzene metabolism, and as such, they may not fully consider the metabolism of phenol. PBPK models specific to phenol have yet to be developed.

2.3.5.3 Discussion of Models

The Bois et al. (1991) Model

A PBPK model was developed by Bois et al. (1991) to explore the question of why benzene, but not phenol, is carcinogenic in rats and humans.

Risk assessment. The levels of phenol in blood and bone marrow and total hydroquinone (an oxidation metabolite of phenol) predicted by the model were substantially higher after phenol administration than after benzene administration” This result seems to refute the argument that phenol or hydroquinone plays a direct role in the carcinogenicity of benzene, and suggests that other metabolites must therefore be involved. The study authors suggest that catechol, a potentially genotoxic oxidation metabolite produced in much larger amounts following benzene as opposed to phenol administration, may contribute to benzene’s carcinogenicity.

Description of the model. Beginning with a compartmentalized model of phenol distribution, which includes fat, well-perfused tissue, poorly-perfused tissue, bone marrow, liver, lung, and gut (which incorporated first-pass effects), the model addresses the notion that first-pass gut metabolism and the phenol-to-hydroquinone pathway are responsible for the carcinogenic effects. Monte Carlo simulation of 64 parameters was performed. Because of the large number of parameters utilized in this model, standard fitting techniques could not be easily incorporated. Thus, the study authors used parameter ranges rather than individual values, which had the effect of reducing the statistical power of the results, allowing only general statements rather than precise predictions to be made about the expected tissue distributions of phenol. Metabolic transformations in both the liver and bone marrow were also included. Experimental conditions, similar to those used in a National Cancer Institute oral study of phenol (NCI 1980), were incorporated into the model.

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Calibration was done using data from a study involving intravenous, intra-arterial, intraduodenal, and hepatic portal exposure to benzene (Cassidy and Houston 1984).

Different compartments pertaining to separate metabolic systems were assessed by selective injection as follows: jugular vein to assess first-pass metabolism across lung, hepatic portal vein to assess hepatic firstpass metabolism, duodenum to assess intestinal mucosa metabolism, and carotid artery to assess immediate tissue distribution.

Validation of the model. Validation of this model using empirical data was not done, and this may cast doubt on some of its predictions. Of particular interest is the prediction that hydroquinone production is greater following phenol administration as compared to benzene administration. This is in opposition to the prediction of the Medinsky et al. (1995) model, described below.

Target tissues. The target tissues were blood and bone marrow. The expected levels of phenol in blood and bone marrow, and total hydroquinone were substantially higher after phenol administration than after benzene administration.

Species extrapolation. Extrapolation of this model from the rodent studies on which it is based to human exposure has not yet been done.

Interroute extrapolation. This model concerned itself primarily with the injection route of exposure, although the use of several injection sites was intended to simulate various distribution routes for orally ingested phenol. Extrapolation to other routes was not done.

The Medinsky et al. (1995) Model

The model by Medinsky et al. (1995) considered the dosimetry of benzene and its metabolites in bone marrow in order to help explain their hematotoxic and myelotoxic effects. It is well known that none of the metabolites alone produces the effects seen with benzene exposure. Although it is not yet a fully developed PBPK model, this study lays the groundwork for further model development.

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Risk assessment. Urinary metabolite profiles resulting from oral exposure indicated that excretion of hydroquinone glucuronide was greater after benzene exposure compared with phenol exposure, suggesting that hydroquinone, a genotoxic compound, is produced in greater amounts after benzene exposure, and thus may play a role in benzene's carcinogenicity. This contrasts with the prediction of the Bois et al. (1991) model described above. The study authors further suggest that this increased hydroquinone production after benzene administration may be due to the zonal distribution of metabolizing enzymes in the liver and the effects of first-pass intestinal conjugation of phenol

Description of the model. Benzene and its metabolites (phenol, catechol, and hydroquinone) were assumed to compete for the same reaction site on the enzyme cytochrome P-450 2E1. In addition, phenol can undergo both oxidation and conjugation, although the enzymes for each of these reactions are localized in different compartments of the liver, and competition between them is thereby regulated. This model incorporates observations made in an earlier kinetic study that investigated benzene and phenol metabolism *in vitro* in mouse and rat liver microsomes (Schlosser et al. 1993). In that study, the following reaction sequences were postulated: benzene → phenol → catechol → trihydroxybenzene and phenol → hydroquinone → trihydroxybenzene.

The Medinsky et al. (1995) model also incorporates results from an *in vivo* study that quantified urinary metabolites in mice treated orally with phenol (Kenyon et al. 1995). Differences in the metabolism of phenol and benzene were incorporated as possible explanations for the differences between these two chemicals in terms of their carcinogenic potency.

Validation of the model. Validation of the model was performed using data from rat and mouse liver microsome preparations (Schlosser et al. 1993). The assumption that benzene and its metabolites compete for the same enzyme reaction site was supported in part by the observation of a lag time in the benzene-to-hydroquinone reaction as compared to the phenol-to-hydroquinone reaction. This lag could be explained by the fact that benzene is first hydrolyzed to phenol, which is then hydrolyzed to hydroquinone, and if all compounds are substrates for P-450 2E1, the kinetics of this pathway would be slowed compared to those of the direct phenol-to-hydroquinone pathway. The model also adequately predicted phenol depletion and concomitant hydroquinone formation resulting from phenol incubations.

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Target tissues. The target tissue considered by this model was primarily the bone marrow.

Species extrapolation. Extrapolation of this model from the rodent studies on which it is based to human exposure has not yet been done.

Interroute extrapolation. This model concerned itself primarily with the oral route of exposure. Extrapolation to other routes was not done.

2.4 MECHANISMS OF ACTION

2.4.1 Pharmacokinetic Mechanisms

Absorption of phenol occurs fairly rapidly via the inhalation (Hughes and Hall 1995; Ohtsuji and Ikeda 1972; Piotrowski 1971), oral (Capel et al. 1972; Edwards et al. 1986; French et al. 1974; Hughes and Hall 1995; Kao et al. 1979; Kenyon et al. 1995), and dermal (Baranowska-Dutkiewicz 1981; Hughes and Hall 1995; Piotrowski 1971) routes. Because it is an irritant, tissue damage, inflammation, or other irritation effects may occur at the sites of absorption. Because of its high pK_a ionization will not occur within the acid environment of the gut. The action of gut microflora on phenol breakdown is not expected to be significant.

When it is absorbed through the lungs, gut, or skin, phenol enters the bloodstream where it can then be distributed throughout the body. The dilution of phenol in water enhances the dermal absorption of phenol, as indicated by the greater toxicity of a water-phenol solution compared to neat phenol (Conning and Hayes 1970).

Conjugation with glucuronic acid and conjugation with sulfate are the main routes of detoxification of phenol. Following oral exposure, much of the metabolism is expected to occur during a first-pass through the intestines and the hepatic system, where phenol may be further oxidized or conjugated to form glucuronides and sulfides. A lack of first-pass metabolism following skin absorption may contribute to the toxicity of phenol following dermal exposure (Skowronski et al. 1994). Phenol that is absorbed is rapidly excreted in the urine as free phenol or conjugates (Baranowska-Dutkiewicz 1981; Capel et al. 1972; Deichmann 1944; Edwards et al. 1986; French et al. 1974; Hughes and Hall 1995; Kao et al. 1979; Kenyon et al. 1995; Liao and Oehme 1981; Piotrowski 1971).

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2.4.2 Mechanisms of Toxicity

Phenol is a hydrolyzed metabolite of benzene and is itself further hydrolyzed or conjugated to produce other compounds. Therefore, the toxic effects of phenol exposure may be due to a combination of the parent compound and its metabolites. The major tissues in which metabolism appears to occur are the liver, gut, lung, and kidney (Cassidy and Houston 1984; Powell et al 1974; Quebbemann and Anders 1973; Tremaine et al. 1984). Since phenol, benzene, and their major metabolites all seem to compete for the same P450 and conjugating enzymes, metabolic reactions are presumed to be saturable.

It has been suggested that phenol exposure results in cardiac effects because it blocks the cardiac sodium channel subtype, with little effect on sodium channels in skeletal muscle (Zamponi et al. 1994). Phenol does not appear to be carcinogenic following oral exposure (NCI 1980), although the chemical combinations that result from benzene and phenol metabolism may contain compounds that do initiate or promote cancer. Metabolites such as hydroquinone and catechol have been demonstrated to be genotoxic and clastogenic.

2.4.3 Animal-to-Human Extrapolations

Although mammals all metabolize phenol to the same metabolites, the amounts of each metabolite vary between species. For example, in the old world monkeys and prosimians, sulfation is the major phenol conjugation pathway, while in the new world monkeys, glucuronidation predominates (Mehta et al. 1978). Cats and pigs have low activities of phenol glucuronyltransferase, and metabolize phenol to phenyl sulfate nearly exclusively (Capel et al. 1972; French et al. 1974; Miller et al. 1976). Because humans have a greater capacity to glucuronidate phenol, cats and pigs would not be good models for the metabolism of phenol by humans.

2.5 RELEVANCE TO PUBLIC HEALTH

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

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Overview

There is a long history of human exposure to phenol. Phenol was once used by surgeons in the operating room as an antiseptic. Effects in humans attributed to chronic phenol exposure include anorexia, progressive weight loss, diarrhea, headache, vertigo, salivation, and a dark coloration of the urine (Merliss 1972).

Methemoglobinemia and hemolytic anemia, as well as liver damage, have also been reported following human exposure to phenol (ACGIH 1991). Direct skin contact with phenol results in irritation and necrosis. Unfortunately, the doses resulting in these effects are not well defined, and the reports describing these effects are anecdotal. The irritation effect on the skin has been used for medical purposes, as in the use of phenol for the surgical procedure of skin peeling. During this procedure, exposure to phenol has resulted in cardiac arrhythmias (Gross 1984; Truppmann and Ellenby 1979; Warner and Harper 1985).

Human exposure to low levels of phenol is widespread because it is contained in many consumer products including mouthwashes, gargles, tooth drops, throat lozenges, and ointments (Douglas 1972; EPA 1980). Phenol is a normal product of protein metabolism, and it is also a metabolite of benzene. In persons not exposed to phenol or benzene, the total phenol concentration in the urine generally does not exceed 20 mg/L and is usually <10 mg/L (ACGIH 1991).

Phenol is absorbed from the lungs, gastrointestinal tract, and skin. A study that examined the absorption of phenol vapor through the skin indicates that it is readily absorbed (Piotrowski 1971), and dermal absorption is considered the primary route of entry for vapor, liquid, and solid phenol (ACGIH 1991). Conjugation of phenol with glucuronic acid and conjugation with sulfate are the main detoxification pathways. Conjugation occurs predominantly in the lungs, gastrointestinal tract, liver, and kidneys. The skin has relatively low potential to detoxify phenol. Therefore, absorption through the skin represents the greatest hazard from phenol because it readily passes through the skin, and because there is no first-pass metabolic effect as is observed following oral exposure.

Exposure of animals to high doses of phenol results in neurological effects including muscle tremor and loss of coordination (Conning and Hayes 1970; Dalin and Kristoffersson 1974; Jones-Price et al. 1983b; Liao and Oehme 1981; Moser et al. 1995; Pullin et al. 1978). Examples of additional effects reported in animals exposed to phenol include decreased red blood cell counts (Hseih et al. 1992), decreased body weight gain (NCI 1980), and skin necrosis and inflammation following direct application (Brown et al. 1975; Conning and Hayes 1970; Patrick et al. 1985). Exposure of pregnant animals to phenol (at doses that resulted in

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maternal toxicity, including dyspnea and rales, and decreased maternal body weight gain) has resulted in a decrease in the number of live births and reduced fetal body weights (Jones-Price et al. 1983a; Nartosky and Kavlock 1995). It is not known if phenol causes reproductive or developmental effects in humans.

Decreased body weight gain associated with decreased water intake was the only adverse effect noted in rodents in a study of chronic exposure to phenol (NCI 1980). Phenol did not cause cancer in either rats or mice in this study. Phenol (20% in acetone) has been shown to act as a cancer promoter following skin application (Salaman and Glendenning 1957). *In vitro* studies have shown that phenol can cause chromosomal aberrations in mammalian cells (Bulsiewicz 1977; Ciranni et al. 1988), although other studies have shown negative results (Barale et al. 1990; Chen and Eastmond 1995a; Pashin et al. 1987). *In vitro* studies have shown both positive results (Crebelli et al. 1987; Demerec et al. 1951; Gocke et al. 1981; Morimoto and Wolff 1980; Paschin and Bahitova 1982) and negative results (Florin et al. 1980; Haworth et al. 1983; Nagel et al. 1982; Pool and Lin 1982) for genotoxic effects. It is not known if phenol can cause cancer in humans.

Minimal Risk Levels for Phenol

Inhalation MRLS

No MRLs were derived for inhalation exposure to phenol. Human inhalation studies of phenol alone were not identified. Inhaled phenol is a respiratory irritant in animals and decreased respiration rate in mice by 50% during a 5 minute exposure at 166 ppm (De Ceaurriz et al. 1981). Based on their studies in mice, De Ceaurriz et al. (1981) estimated that a level of 2 ppm would be a NOAEL for respiratory effects in humans. A study in rhesus monkeys, rats, and mice did not find significant effects following a 90-day continuous exposure at 5 ppm (Sandage 1961). Intermittent exposure of guinea pigs and rabbits to 26-52 ppm phenol resulted in severe respiratory, cardiovascular, hepatic, and renal toxicity (Deichmann et al. 1944). Similar effects were not observed in rats exposed in a similar manner.

Oral MRLs

An acute-duration oral MRL was not derived for phenol. The lowest LOAEL was a serious effect reported in a developmental study (Narotsky and Kavlock 1995). Dyspnea, rales, and a 20% decrease in maternal body weight gain were reported in pregnant rats treated by gavage with phenol in water at a dose of 40 mg/kg/day

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on gestation days 6-19. A significant decrease in the number of liveborn pups was observed at 53.3 mg/kg/day and was associated with severe respiratory effects. This study is limited in that the number of dams with respiratory effects was not stated.

An intermediate oral MRL was not derived for phenol. The lowest LOAEL reported for an intermediate exposure was for a less serious effect reported in an immunological study (Hsieh et al. 1992). A significant decrease in red blood cells was seen in CD-1 mice given phenol in drinking water for 4 weeks at a concentration of 4.7 mg/L (1.8 mg/kg/day). However, this was a single report; similar effects have not been reported in humans except for mixed exposures where the presence of phenol was reported but may have been chlorophenol (Baj et al. 1994).

Furthermore, phenol is a United States Pharmacopeia (USP) approved ingredient used in a number of over-the-counter treatments for sore throats, including gargles, sprays, and lozenges. Cepastat® cherry and extra strength throat lozenges, for example, contain 14.5 and 29 mg phenol/lozenge, respectively. If a patient were to take the maximum dose per day of 300 mg (the 'not to exceed' dosage recommended for a maximum of 7 days for adults and children 6 or older) (PDR 1998), this could result in doses as high as 8 mg/kg/day.

Death. Reported deaths associated with phenol are rare and largely confined to intentional oral exposure (suicides) and accidents involving exposure of a large fraction of the skin surface (>25%) to concentrated phenol solutions (Griffiths 1973; Lewin and Cleary 1982; Stajduhar-Caric 1968). The death of a woman was reported following subarachnoid injection of 3 mL of a 6% phenol solution in glycerin to achieve a cervical subarachnoid block (Holland and Yousef 1978). At autopsy, the effects noted included demyelination, degeneration of cervical nerve roots, fibrous thickening of leptomeninges, and cerebellar cortical infarct.

The minimal lethal oral dose in humans was estimated to be \approx 140 mg/kg (Bruce et al. 1987), which is similar to the lethal oral dose for a variety of animal species (see Table 2-2). Regardless of the route of administration, the sequence of events leading to death appears to be similar in a variety of animal species: muscle weakness and tremors, loss of coordination, paralysis, convulsions, coma, and respiratory arrest. These symptoms implicate central or peripheral nervous system toxicity as a primary cause of death. Injury to other organ systems may also contribute to death. In one inhalation study, extensive injury to the lung, heart, liver, and kidney was reported in guinea pigs exposed to lethal concentrations of phenol in air (Deichmann et al. 1944). However, these findings have not been corroborated. In a dermal lethality study, hematuria and related kidney damage were noted in rats at necropsy, suggesting that hemolysis may have

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contributed to the cause of death (Conning and Hayes 1970). Phenol diluted with water was more toxic than neat phenol, suggesting that water enhances the absorption of phenol.

An injection study indicates that phenol was more toxic to rabbits following intravenous injection compared to subcutaneous or intraperitoneal injection (Deichmann and Wither-up 1944). Following injection of a 5% aqueous phenol solution, the LD₅₀ values were 180 mg/kg following intravenous injection and 620 mg/kg following subcutaneous or intraperitoneal injection. Death is unlikely to occur at concentrations of phenol that occur in the environment or at hazardous waste sites.

Systemic Effects

Respiratory Effects. Following inhalation exposure, phenol is a respiratory irritant at high concentrations (ACGIH 1991; De Ceaurriz et al. 1981). In a review by Babich and Davis (1981), it was observed that inhalation of phenol causes damage to lungs including hyperemia, infarcts, bronchopneumonia, purulent bronchitis, and hypoplasia of the peribronchial tissues. Acute lobular pneumonia, with occasional abscesses and vascular damage, was seen in guinea pigs exposed to high concentrations of phenol by inhalation (Deichmann et al. 1944). Widespread confluent lobular pneumonia, lesions of chronic purulent bronchitis, hyperplastic peribronchial tissue, and degenerative changes in pulmonary vessels were seen in rabbits similarly exposed in the same study. At lower concentrations, respiratory effects have not been reported following inhalation exposure of monkeys, rats, or mice (Sandage 1961). Dyspnea and rales have been reported in pregnant rats following gavage dosing with phenol (Narotsky and Kavlock 1995). An *in vitro* study using tracheal mucosa of the rabbit has shown that exposure to a concentration of 0.1% phenol in water resulted in ciliostasis after about 55 minutes, while a concentration of 5% resulted in ciliostasis after 2.5 minutes (Dalhamn and Lagerstadt 1966). This study suggests that inhalation exposure to phenol may decrease mucociliary clearance. Studies in which phenol was administered in drinking water did not report respiratory effects (Hsieh et al. 1992; NCI 1980). Following dermal exposure, dyspnea was reported in pigs after undiluted phenol was applied to 35-40% of the total body surface area (Pullin et al. 1978). Respiratory effects are unlikely to occur at concentrations of phenol that occur in the environment or near hazardous waste sites.

Cardiovascular Effects. Cardiac arrhythmias have been reported in individuals undergoing chemical face peels involving application of concentrated solutions of phenol (50%) in combination with hexachlorophene and croton oil to extensive areas of the face (Gross 1984; Truppmann and Ellenby 1979; Warner and Harper

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1985). Cardiac arrhythmia and bradycardia have also been reported following accidental skin exposure to phenol (Horch et al. 1994), and in children with cerebral palsy treated with intramuscular injection with 5% phenol (Morrison et al. 1991). A relationship between cardiac arrhythmias and blood levels of phenol has not been observed (Gross 1984; Morrison et al. 1991). Exposures resulting in cardiac effects are likely to occur only during clinical procedures or when concentrated solutions of phenol are accidentally spilled on the skin. The mechanism for cardiac effects has not been elucidated. Cardiac arrhythmias have been demonstrated in rabbits exposed to 300 mg/kg or ≈ 67 mg/cm² of skin (Wexler et al. 1984). Following intermediate-duration inhalation exposure to relatively high concentrations of phenol, necrosis of the myocardium and inflammation have been observed in guinea pigs and rabbits (Deichmann et al. 1944). Following oral exposure of rodents, gross (Hsieh et al. 1992) or histopathologic changes (NCI 1980) in the heart have not been observed. Cardiovascular effects are unlikely to occur at concentrations of phenol that occur in the environment or near hazardous waste sites.

Gastrointestinal Effects. Signs of gastrointestinal irritation, including mouth sores, nausea, and diarrhea, have been reported in humans exposed to drinking water containing 5-126 mg/L (0.14-3.4 mg/kg/day) of phenol (Baker et al. 1978). No effects were observed in persons exposed to concentrations of 0.1 mg/L or less (oral dose of 0.003 mg/kg/day). The source of the phenol was a rail accident in which $\approx 38,000$ L of 100% phenol were spilled on the soil and contaminated several local wells. Phenol intake in several families that drew drinking water from nearby wells was estimated to have been 10-240 mg/person/day for several weeks. Increased prevalence of nausea, vomiting, diarrhea, and abdominal pain was also reported following a spill of phenol into a drinking water source in Korea (Kim et al. 1994). Because the water was used after chlorination, chlorophenol may have contributed to the adverse effects. Nausea and vomiting have also been reported following accidental dermal exposure to phenol (Horch et al. 1994). Because gastrointestinal effects can occur following dermal exposure, it is likely that the effect may be a secondary neurological effect rather than just a result of direct irritation of the gastrointestinal tract.

Histopathological changes in the gastrointestinal tract have not been observed in rats or mice exposed to phenol in the drinking water for intermediate or chronic durations (NCI 1980). An *in vitro* study using antral mucosa isolated from the stomach of rabbits indicated that 5 millimolar (mM) phenol resulted in a gradual decrease in luminal acid loss, a gradual increase in tissue electrical resistance, and a gradual decrease in short circuit current (Fuhro and Fromm 1978). This study indicates that phenol can have a direct effect on the gastrointestinal tract. Gastrointestinal effects are likely to occur at higher environmental exposures, which could occur during an accidental exposure or from drinking water contaminated by a large spill. At the lower

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doses resulting from more typical environmental exposures such as those near hazardous waste sites, gastrointestinal effects are not likely to occur.

Hematological Effects. A decrease in red blood cell counts was observed in persons exposed to a wood treatment liquid containing phenol, formaldehyde, and organic chlorohydrocarbons (Baj et al. 1994). Although only limited data were identified, hemolytic anemia and methemoglobinemia are considered to be well-documented complications of phenol poisoning in humans (ACGIH 1991).

Treatment-related decreases in red blood cell counts were observed in mice treated with phenol in the drinking water for 28 days (Hsieh et al. 1992). The EOAEL dose for this response was 4.7 mg/L which the authors estimated to be a daily dose of 1.8 mg/kg. A reduction in the ratio of polychromatic to normochromatic red blood cells in the bone marrow was observed in pregnant mice treated by gavage with a single dose of phenol on gestation day 13 (Ciranni et al. 1988). The observation of hemoglobinuria and hematin casts in the distal convoluted tubules and tubular lumens in rats treated with a single dermal application of phenol (Conning and Hayes 1970) indicates red blood cell lysis and increased glomerular filtration of hemoglobin.

Hematological effects were not reported in monkeys, rats, or mice exposed to 5 ppm phenol in air for 90 days (Sandage 1961), or in rats exposed to 26 ppm continuously for 15 days (Dalin and Kristoffersson 1974). Studies in which the ratio of polychromatic to normochromatic red blood cells in the bone marrow of mice treated with one (Barale et al. 1990) or three (Chen and Eastmond 1995a) intraperitoneal injections of phenol did not show an adverse effect.

Hematological effects are likely to occur following exposure to high doses of phenol, which could occur during an accidental exposure. At the lower doses resulting from environmental exposure and exposure near hazardous waste sites, hematological effects are not likely to occur.

Musculoskeletal Effects. Muscle pains in the arms and legs were reported by a man who worked in a laboratory for 13.5 years where he distilled phenol several times a day (Merliss 1972). Because heavy odors were detected and phenol was spilled on his clothes resulting in skin irritation, dermal and inhalation exposures were involved. Histopathological changes in the bone were not observed in rats or mice provided with phenol in the drinking water for 13 or 103 weeks (NCI 1980). Musculoskeletal effects are unlikely to occur at the exposure levels found in the environment or near hazardous waste sites.

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Hepatic Effects. An increase in serum iron, which may reflect an adverse liver effect, was observed in workers exposed for 6 months to phenol in a wood treatment liquid (Baj et al. 1994). Elevated concentrations of hepatic enzymes in serum, and an enlarged and tender liver suggestive of liver injury, were reported in an individual who had been exposed repeatedly to phenol vapor for 13.5 years (Merliss 1972). Since phenol was also spilled on his clothes resulting in skin irritation, dermal and inhalation exposures were involved. A 2-fold increase in serum bilirubin was observed in a man who was accidentally splashed with a phenol solution over his face, chest wall, hand, and both arms (Horch et al. 1994). Changes in liver enzymes were not observed in persons exposed to phenol in drinking water for several weeks after an accidental spill (Baker et al. 1978). This study is not conclusive because the measurements were completed 7 months after the exposure.

Hepatotoxicity, characterized histologically by centrilobular necrosis, and elevated hepatic enzymes in serum were reported in separate studies in which laboratory animals were exposed to phenol in air at concentrations ≥ 26 ppm (Dalin and Kristoffersson 1974; Deichmann et al. 1944). Hepatic effects were not observed in monkeys, rats, or mice exposed to 5 ppm phenol in air continuously for 90 days (Sandage 1961). Hepatic effects have also not been observed in rodents following oral exposure to phenol (Berman et al. 1995; Hsieh et al. 1992; Jones-Price et al. 1983a, 1983b; NCI 1980).

Phenol is catabolized by liver microsomal monooxygenases to hydroxylated products (e.g., 1,4-dihydroxybenzene) that can undergo further conversion to a variety of electrophilic substances (e.g., benzoquinones). Such reactions may be involved in generating reactive toxic intermediates in the liver (Eastmond et al. 1986; Lunte and Kissinger 1983; Subrahmanyam and O'Brien 1985). Based on the available data, hepatic effects are unlikely to occur at the exposure levels found in the environment or near hazardous waste sites.

Renal Effects. Dark urine has been reported in persons occupationally exposed to phenol (inhalation and dermal) (ACGIH 1991; Merliss 1972) and following oral exposure (Baker et al. 1978; Kim et al. 1994). It has been stated that the dark urine is a result of oxidation products of phenol (Baker et al. 1978). The dark urine may also be a result of increased hemoglobin in the urine as suggested by the Merliss (1972) case report. In this case it took 2-3 months for the urine to clear after exposure was ended, which is not consistent with pharmacokinetic data that indicate that absorbed phenol is excreted in the urine in 1 day (Piotrowski 1971). A study in rats treated dermally with phenol, which found severe hemoglobinuria and hematin casts in

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the tubules (Conning and Hayes 1970), suggests that hemoglobin or hemoglobin breakdown products could contribute to the dark urine observed in humans.

Edema in the convoluted tubules, cortical lesions, and glomerular degeneration were reported in guinea pigs and rabbits exposed to 26 ppm phenol in air (Deichmann et al. 1944). Histopathological changes in the kidneys were not observed in monkeys, rats, or mice exposed continuously to 5 ppm phenol in air for 90 days (Sandage 1961). Renal tubular necrosis, protein casts, and papillary hemorrhage were observed in the kidneys of rats treated once by gavage at a dose of 224 mg/kg (Berman et al. 1995). Changes in the kidneys were not observed after a single dose of 120 mg/kg or 14 daily doses of 40 mg/kg (Berman et al. 1995). Histopathological changes in the kidneys were not observed in rats or mice following intermediate- or chronic-duration oral exposure to phenol (Hsieh et al. 1992; NCI 1980). Direct infusion of 0.1, 1, or 5% phenol in saline into the renal circulation did not affect glomerular filtration rate or renal plasma blood flow (Coan et al. 1982). Concentration-dependent histological effects that were noted included basophilic and eosinophilic material in the lumen of proximal and distal tubules, vacuolization and dilation of proximal tubules, and necrotic glomeruli. Thus, phenol can be considered a direct-acting nephrotoxin when administered directly into the vasculature. Since this exposure route is not relevant to humans at or near hazardous waste sites, renal effects are not expected to occur.

Endocrine Effects. No studies regarding endocrine effects in humans were identified. Unspecified histological changes in the adrenal glands were observed in rats treated once by gavage at a dose of 224 mg/kg (Berman et al. 1995). Changes in the adrenal glands were not observed after a single dose of 120 mg/kg or 14 daily doses of 40 mg/kg (Berman et al. 1995). Histopathological changes in the pancreas, pituitary, adrenal glands, thyroid, or parathyroid were not observed in rats or mice following intermediate- or chronic-duration oral exposure to phenol (NCI 1980). Because endocrine gland function has not been examined in humans or animals following phenol exposure, the data are not sufficient to conclude whether phenol will result in endocrine effects at exposure levels in the environment or near hazardous waste sites.

Dermal Effects. In humans, application of concentrated solutions of phenol to the skin (>5%) results in inflammation and necrosis at the site of application, and this characteristic has resulted in the use of phenol for face peeling (Gross 1984; Truppmann and Ellenby 1979; Warner and Harper 1985). Increases in skin rash, mouth sores, and throat sores have been reported in humans following drinking water exposures, which would include oral and dermal routes of exposures (Baker et al. 1978; Kim et al. 1994). Following accidental skin exposure, pain, redness, and edema occurred immediately (Horch et al. 1994; Merliss 1972). In an in

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vitro assay using human skin cultures, 10% phenol in water was considered corrosive (Perkins et al. 1996). In a review by Babich and Davis (1981), it is observed that dermal applications of phenol induce eczema, inflammation, discolorations, necrosis, sloughing, and gangrene.

The results of a study in pigs suggest that exposure to as little as 0.44 mg/kg/cm² can produce skin necrosis (Pullin et al. 1978). Skin irritation as indicated by thickening of the treated ear was observed in mice in which phenol was directly applied to the ear (Patrick et al. 1985). Erythema and increased skin permeability in guinea pigs (Steele and Wilhelm 1966), and necrosis of the skin in pigs (Hunter et al. 1992) have been reported following dermal exposure to phenol. Histopathological changes in the skin have not been reported in rats or mice following intermediate- or chronic-duration oral exposure to phenol (NCI 1980). Dermal effects are likely to occur at higher environmental exposures, which could occur during an accidental exposure or from drinking water contaminated by a large spill. At the lower doses resulting from more typical environmental exposures such as those near hazardous waste sites, dermal effects are not likely to occur.

Ocular Effects. Direct application of 5% phenol to the eyes of rabbits resulted in severe irritation, conjunctivitis, and corneal opacity (Murphy et al. 1982). No other reports of ocular effects in humans or animals were identified. Based on the limited data, ocular effects are unlikely to occur at the concentrations that occur in the environment or near hazardous waste sites.

Body Weight Effects. A man occupationally exposed (inhalation, dermal) to phenol for 13.5 years was described as emaciated, and the symptoms reported included loss of appetite and slow weight loss (Merliss 1972). No effects on body weight have been reported in animals exposed to phenol by inhalation (Dalin and Kristoffersson 1974; Sandage 1961). Following oral exposure, decreased maternal body weight gain has been reported in rats (Narotsky and Kavlock 1995) and mice (Jones-Price et al. 1983b) exposed during gestation. Decreased body weight gain associated with decreased water intake was observed in rats and mice exposed to phenol in drinking water for 13 weeks, and in rats but not mice exposed for 103 weeks (NCI 1980). Additional oral studies of phenol in rats (Berman et al. 1995; Jones-Price et al. 1983a; Moser et al. 1995) and mice (Hsieh et al. 1992) have not reported body weight effects. No studies regarding the effects of phenol on body weight following dermal exposure were identified. Based on the available data, effects on body weight are not likely to occur at exposure levels in the environment or near hazardous waste sites.

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Other Systemic Effects. Direct application of phenol to the tympanic membrane in the ear of rats resulted in inflammation (Schmidt and Hellstrom 1993). When phenol was placed in the ear of rats after tympanic membrane puncture, inflammation and a reduction in auditory brainstem response were observed (Schmidt et al. 1990). These studies indicate that direct application of phenol to the ear for treatment of ear infection should be used with caution.

Immunological and Lymphoreticular Effects. Occupational exposures to “inhaled formaldehyde, phenol and isomers of organic chlorohydrocarbons from Ksylamit™ which is a widely used liquid wood preservative, were associated with immunological effects such as decreased levels of CD4, suppressed mitogen-induced lymphocyte proliferation, and significantly decreased natural killer cell cytotoxicity. However, it should be noted that in the report Ksylamit™ is indicated to consist of “a mixture of chlorinated benzenes, pentachlorophenol, alpha-chloronaphthalene, chloroparaffin and kerosene” and that the authors provide no discussion of how phenol and formaldehyde are produced through the use of such a mixture (Baj et al. 1994).

Increased susceptibility to *Streptococcus zooepidemicus* and bactericidal activity toward *Klebsiella pneumoniae* were not observed in mice exposed by inhalation to 5 ppm phenol for 3 hours or for 3 hours/day for 5 days (Aranyi et al. 1986). Necrosis or atrophy of the spleen or thymus, which was not described further, was observed in rats given a single gavage dose of 240 mg/kg phenol (Berman et al. 1995). Effects on the spleen or thymus were not observed in rats given a single dose of 120 mg/kg or 14 daily doses of 40 mg/kg (Berman et al. 1995). Decreased antibody production was observed in mice treated with phenol in the drinking water at a dose of 6.2 mg/kg/day, with no immunological effects observed at 1.8 mg/kg/day (Hsieh et al. 1992). Histopathologic changes in the spleen or thymus were not observed in rats or mice exposed to phenol in the drinking water for 13 or 103 weeks (NCI 1980).

Using a series of *in vitro* assays, Wilmer et al. (1994) determined that exposure of epidermal keratinocytes to phenol had a profound effect on the cell's expression, production, and release of a number of proinflammatory cytokines and their precursor mRNAs. The pattern of cytokine effect for phenol was complex and different from those observed with other contact irritants. In order to determine if the pattern was related to histological differences *in vivo*, 10 µL phenol in acetone at concentrations ranging from 30 to 50% (doses ranged from 233 mg/kg to 1,398 mg/kg) was applied once to the surface of mouse ears and the skin examined for swelling and histopathologic changes at 3 and 24 hours. The results were moderate but significant ($p < 0.05$) dose-related increases in ear thickness at both time points, although the swelling was

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greatest at 3 hours and somewhat diminished (by about 10%) at 24 hours. Histopathologic examination revealed that the treatment induced an extensive, albeit discontinuous, epidermal necrosis which in some areas extended into the subepidermis and resembled local ischemia. Macrophage infiltration of the epidermis was mild to moderate, whereas edema was moderate. Although these data clearly indicate the immunotoxicity of phenol in relatively high doses, they are not sufficient to conclude whether or not phenol will result in immunological/lymphoreticular effects at exposure levels found in the environment or near hazardous waste sites.

Neurological Effects. An increase in the number of headaches was reported by persons exposed to phenol in drinking water following an accident (Kim et al. 1994). Muscle tremors, loss of coordination, paralysis, and convulsions are indicative of phenol poisoning in laboratory animals following all routes of exposure (Conning and Hayes 1970; Deichmann et al. 1944; Itoh 1995; Jones-Price et al. 1983b; Liao and Qehme 1981; Moser et al. 1995; Pullin et al. 1978). Inhalation exposure of guinea pigs at 26-52 ppm (Deichmann et al. 1944), oral exposure of rats at 120 mg/kg (Moser et al. 1995), and dermal exposure of rats at 107.1 mg/kg produced these effects (Conning and Hayes 1970).

The mechanism for the neurological effects of phenol has not been elucidated, although effects on the neuromuscular junction (Blaber and Gallagher 1971) and central nervous system have been implicated (Suzuki and Kisara 1985). Intra-arterial injection of phenol (0.25 mg) directly into the hindlimb of a cat facilitated synaptic transmission and contraction of electrically-stimulated skeletal muscle, but did not elicit contractions in the unstimulated muscle (Blaber and Gallagher 1971). In this same preparation, phenol antagonized neuromuscular blockade by tubocurarine, suggesting the possibility of a presynaptic mechanism of action at the neuromuscular junction. Tremors induced by subcutaneous injection of a 1% (w/v) solution of phenol in mice were enhanced by central but not peripheral nerve monoamine depleters, suggesting an involvement of the central monoamine pool in phenol-induced tremor (Suzuki and Kisara 1985). Changes in serum electrolytes may also contribute to the neurological symptoms observed in animals. In one study, serum magnesium and potassium levels were found to be elevated in rats after 15 days of continuous exposure to 26-52 ppm in air; during this period, the rats showed signs of impaired coordination (Dalin and Kristofferson 1974). Elevated serum potassium and magnesium could cause or contribute to centrally or peripherally mediated muscle tremors; however, a cause and effect relationship has not been established. Changes in neurotransmitter levels in the brains of mice treated with phenol have also been reported (Hsieh et al. 1992) and may contribute to the neurological effects of phenol.

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Based on the available data, obvious neurological effects are not likely to occur at exposure levels found in the environment or near hazardous waste sites. The data are not sufficient to conclude whether more subtle function changes in the nervous system may occur.

Reproductive Effects. Studies regarding reproductive effects in humans following exposure to phenol were not identified. In a multi-generation study in rats treated with phenol in the drinking water, many young died at a dose of 914 mg/kg/day, while stunted growth of the offspring was observed at 800 mg/kg/day (Heller and Purse 1938). Few details of this study were provided. No effects on reproduction were noted in rats (Jones-Price et al. 1983a) or mice (Jones-Price et al. 1983b) treated by gavage with phenol on gestation days 6-15. Histopathological changes in reproductive organs were not observed in rats or mice treated with phenol in the drinking water for 13 or 103 weeks (NCI 1980). Based on the limited available data, reproductive effects are unlikely to occur in humans following exposure to phenol at concentrations found in the environment or near hazardous waste sites.

Developmental Effects. Studies regarding developmental effects in humans following exposure to phenol were not identified. Gavage treatment of rats (Jones-Price et al. 1983a; Narotsky and Kavlock 1995) and mice (Jones-Price et al. 1983b) with phenol during gestation has resulted in decreased fetal body weight, a decrease in the number of liveborn pups, and an increase in cleft palate of mice. With the exception of a study in rats, which noted a decrease in fetal body weight (Jones-Price et al. 1983a), the developmental effects were associated with maternal toxicity which included severe respiratory effects (Narotsky and Kavlock 1995) and decreased maternal weight gain (Jones-Price et al. 1983b; Narotsky and Kavlock 1995). The lowest dose associated with maternal and developmental effects was 53.3 mg/kg/day given to rats (Narotsky and Kavlock 1995). The results of a modified frog embryo teratogenesis assay-Xenopus (FETAX) showed malformations only at concentrations of phenol resulting in lethality, suggesting that phenol does not have a high potential for teratogenic effects (Bernardini et al. 1996). Based on the limited available data, developmental effects are unlikely to occur in humans following exposure to phenol at concentrations found in the environment or near hazardous waste sites.

Genotoxic Effects. Phenol has been evaluated for genotoxicity in both *in vivo* (Table 2-4) and *in vitro* (Table 2-5) test systems. Increases in chromosomal aberrations have been reported in spermatocytes (Bulsiewicz 1977), bone marrow, and fetal liver (Ciranni et al. 1988) from mice treated with phenol. Other studies have not reported chromosomal aberrations in bone marrow from mice treated with phenol (Barale et al. 1990; Chen and Eastmond 1995a; Pashin et al. 1987) or in *Drosophila* (Gocke et al. 1981; Sturtevant

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1952). Negative results were reported in a micronucleus assay in bone marrow isolated from mice treated with phenol (Gocke et al. 1981). Phenol has tested positive for increased DNA synthesis in tubular renal and liver epithelial cells from mice treated with phenol (Amlacher and Rudolph 1981), with negative results for DNA synthesis reported in rat testes (Skare and Schrotel 1984) and rat liver (Miyagawa et al. 1995).

Both negative (Florin et al. 1980; Haworth et al. 1983; Nagel et al. 1982; Pool and Lin 1982) and positive (Demerec et al. 1951; Gocke et al. 1981) results for gene mutations in bacteria have been reported following phenol exposure. A single study of gene mutation in Chinese hamster ovary cells was positive (Pas&in and Bahitova 1982). *In vitro* studies regarding chromosomal aberrations in eukaryotic cells have been positive in *Aspergillus* (Crebelli et al. 1987) and in human lymphocytes (Erexson et al. 1985; Morimoto and Wolff 1980; Morimoto et al. 1983), and negative in human lymphocytes (Jansson et al. 1986), mouse lymphoma cells (Pellack-Walker and Blumer 1986), and Chinese hamster ovary cells (Sze et al. 1996). *In vitro* assays for DNA synthesis have been negative in rat liver mitochondria (Schwartz et al. 1985), and positive in human fibroblasts (Poirier et al. 1975) and HeLa cells (Painter and Howard 1982). The mixed results in both the *in vivo* and *in vitro* assays indicate that under certain conditions, especially at higher doses, phenol has the potential to be genotoxic. However, at the exposure levels likely to occur near hazardous waste sites, phenol is not anticipated to be genotoxic.

Cancer. A small non-significant excess of respiratory cancers among phenol-exposed wood industry workers was not clearly related to phenol exposure (Kauppinen et al. 1986). Although small non-significant excesses of Hodgkin's disease and of lung, esophageal, and kidney cancers were noted, mortality from cancer was not clearly related to phenol exposure in phenol production workers (Dosemeci et al. 1991).

Phenol has been tested in animals for carcinogenicity by the oral and dermal routes, but results are equivocal. In a chronic NCI cancer bioassay (NCI 1980), a significant incidence of tumors (pheochromocytomas of the adrenal gland, leukemia, or lymphomas) occurred only in male rats exposed to the lowest dose level (2,500 ppm, 277 mg/kg/day) of phenol but not in male or female mice or male rats exposed to a higher dose level (5,000 ppm, 624 mg/kg/day). Since tumors occurred only in males in one of the two species tested, and since a positive dose-response relationship was not established, this study does not provide sufficient evidence to conclude that phenol is carcinogenic when administered by the oral route. Dermal application of phenol has been shown to result in tumors in mice; phenol is a tumor promoter when it is applied after the application of the tumor initiator DMBA (Boutwell and Bosch 1959; Salaman and Glendenning 1957; Wynder and Hoffmann 1961). However, this effect occurs at dose levels of phenol that produce severe skin

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

Species (test system)	End point	Results	Reference
Mammalian cells:			
Mouse bone marrow	Chromosomal aberration	-	Barale et al. 1990; Chen and Eastmond 1995a; Pashin et al. 1987
Mouse spermatocytes	Chromosomal aberration	+	Bulsiewicz 1977
Bone marrow from pregnant mice	Chromosomal aberration	+	Ciranni et al. 1988
Mouse fetal liver cells	Chromosomal aberration	+	Ciranni et al. 1988
Mouse bone marrow	Micronucleus	-	Gocke et al. 1981
Mouse tubular renal and liver epithelial	DNA synthesis	+	Amlacher and Rudolph 1981
Rat testes	DNA synthesis	-	Skare and Schrotel 1984
Rat liver	DNA synthesis	-	Miyagawa et al. 1995
Insects:			
<i>Drosophila</i>	Chromosomal aberration	-	Gocke et al. 1981; Sturtevant 1952

DNA = deoxyribonucleic acid; - = negative results; + = positive results

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

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
<i>Salmonella</i>	Gene mutation	-	-	Florin et al. 1980; Haworth et al. 1983; Pool and Lin 1982;
<i>Salmonella</i>	Gene mutation	+	-	Gocke et al. 1981
<i>Escherichia coli</i>	Gene mutation	-	-	Nagel et al. 1982
<i>E. coli</i>	Gene mutation	No data	+	Demerec et al. 1951
Eukaryotic organisms:				
<i>Aspergillus</i>	Chromosomal aberration	No data	+	Crebelli et al. 1987
V79 Chinese hamster cells	Gene mutation	+	-	Paschin and Bahitova 1982
Chinese hamster ovary cells	Micronuclei	+	+	Miller et al. 1995
Chinese hamster ovary cells (DNA strand breaks)	Chromosomal aberration	No data	-	Sze et al. 1996
Mouse lymphoma (DNA strand breaks)	Chromosomal aberration	No data	-	Pellack-Walker and Blumer 1986
Rat liver mitochondria	DNA synthesis	No data	-	Schwartz et al. 1985
Human lymphocytes	Chromosomal aberration	+	+	Morimoto and Wolff 1980; Morimoto et al. 1983
Human lymphocytes	Chromosomal aberration	No data	-	Jansson et al. 1986
Human lymphocytes	Chromosomal aberration	No data	+	Erexson et al. 1985

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

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Human diploid fibroblasts	DNA synthesis	No data	+	Poirier et al. 1975
HeLa cells	DNA synthesis	+	No data	Painter and Howard 1982

DNA = deoxyribonucleic acid; - = negative results; + = positive results

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lesions, and in one study (Boutwell and Bosch 1959), phenol was administered in benzene, which is also a dermal irritant. Dermal application of phenol partially inhibits B[a]P-induced tumor formation when it is applied simultaneously with B[a]P (Van Duuren et al. 1971,1973).

Based on the inadequate evidence for the carcinogenicity of phenol in humans and animals, IARC considers phenol not classifiable as to its carcinogenicity in humans (IARC 1989). Based on a complete lack of human carcinogenicity data, and inadequate animal data, EPA placed phenol in group D, not classifiable as to human carcinogenicity. Therefore, an increase in cancer cases would not be expected to be observed in populations exposed to phenol at concentrations found in the environment or near hazardous waste sites.

2.6 CHILDREN'S SUSCEPTIBILITY

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

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in section 5.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both pre-natal and post-natal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their

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bodies as extracellular water, and their brains and livers are proportionately larger (Widdowson and Dickerson 1964; Foman et al. 1982; Owen and Brozek 1966; Altman and Dittmer 1974; Foman 1966). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns and at various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes, unique enzymes may exist at particular developmental stages (Leeder and Kearns 1997; Komori et al. 1990; Vieira et al. 1996; NRC 1993). 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; West et al. 1948; NRC 1993). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility while others may decrease susceptibility to the same chemical. For example, the fact that infants breathe more air per kilogram of body weight than adults may be somewhat counterbalanced by their alveoli being less developed, so there is a disproportionately smaller surface area for absorption (NRC 1993).

Based on a very limited data set, it is likely that most of the effects of phenol exposure, including cardiac arrhythmias and central nervous system depression, observed in adults will be observed in children if exposures are comparable. The data are insufficient to determine whether children will be especially sensitive to such effects, however.

IARC (1989), citing Hinkel and Kintzel(1968), indicated that a newborn infant whose umbilicus had been bound with a bandage containing 2% phenol, died after 11 hours. Another newborn whose skin ulcer was treated with a solution of 30% phenol:60% camphor developed circulatory failure, cerebral intoxication, and methemoglobinemia, but recovered after a blood transfusion. Rogers et al. (1978) evaluated the percutaneous absorption of phenol in 16 infants, aged 2-5 months, who were treated for seborrheic eczema with Magenta Paint B.P.C., a medicine containing 4% phenol. The treatment consisted of twice daily painting of the napkin and skin folds (representing about 11-15% of the body surface) with the Magenta paint over 48 hours, with an average of 32 mL of paint (approximately 1,300 mg of phenol) applied to each child. Phenol was detected

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in the urine of four of the infants; however, no information on concentration was presented. Liver function tests run on 8 of the 16 treated infants showed no abnormalities. The study was initiated because of the observation of signs of central nervous system depression in a 6-month-old who had been treated over a much larger area (all of the body except the face), and because of other observations that children with fair complexions or those who received treatment shortly after bathing became 'mildly shocked and drowsy.

In a 5-year (1987-1991) retrospective review of acute exposures to a phenol-containing disinfectant (Creolin Disinfectant™ [26% phenol]) reported to a regional poison control center, Spiller et al. (1993) identified 96 patients, 16 of which were lost to follow-up. There were 60 oral-only exposures, 7 dermal-only, 12 oral/dermal exposures, and 1 inhalation exposure. Sixty (75%) of the patients were under 5 years of age. It was not possible to determine from the information presented the degree of concordance between the 60 patients with oral-only exposures and the 60 under the age of 5, but it is clear that oral exposure of young children is the predominant characteristic of this population of exposed individuals. In this regard, children have clearly been demonstrated to be at greater risk of exposure to phenol via the accidental ingestion of phenol-containing disinfectants.

There are also several reports in the literature indicating that children are susceptible to the effects of phenol, but the findings are mixed with regard to any special sensitivity. In 1 report, a 10 year-old male developed cardiac arrhythmias following a chemical peeling procedure initiated to remove a 12x17 cm hairy nevus of the left scapula and nape. The procedure was performed under general anesthesia (initial conditions: nitrous oxide 60%/halothane 3%; maintenance: 90%/1%), with continuous electrocardiogram monitoring. An hour into the procedure, which involved the application of a solution of phenol (60% phenol, 0.8% croton oil in hexachlorophene soap and water) to the entire surface of the nevus, multifocal and coupled premature ventricular complexes developed. Two intravenous doses of 50 mg lidocaine were ineffective at regulating the arrhythmias; however, 250 mg of bretylium sulfate given by infusion was successful (Warner and Harper, 1985). Although this was a severe reaction, it is difficult to determine, based on a sample size of one, whether it reflects a special sensitivity based on age. In an additional case report, another 10 year-old boy was hospitalized with serious burns; during the next 2.5 days his burns were treated by applying 7.5 L of antiseptic solution containing 2% phenol; his urine became dark, respiration became labored, he fell into a coma, and died. Post mortem analysis of urine revealed 200 mg/L of conjugated phenol (Cronin and Brauer 1949).

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Wood (1978), in a review of the use of phenol as a neurolytic agent, summarized the results of a number of studies including one in which children with cerebral palsy were given nerve blocks with 3% phenol in water as a treatment for spasticity. Out of 150 blocks on 46 children, 9 were associated with complications, 8 with muscle weakness, and 1 with painful paresthesia. This degree of complication was twice that reported by another group who reported on 98 blocks, presumably in adults, with a complication rate of 3% with all complications being transient paresthesia. The first group concluded that in children the risk was too great for the benefit of the procedure. These two studies in combination suggest that children may be especially sensitive to phenol given by injection. Interestingly, a later study (Morrison et al. 1991) involving 24 pediatric patients similarly treated for spasticity with injections of 5% phenol in water at the motor point of insertion during halothane anesthesia concluded that there was no increase in the incidence of complications. In this study the complications of concern were cardiac arrhythmias and the incidence was 19%, yet the authors concluded that the procedure appeared “appropriate to perform in the day-surgery context.” The difference in these studies is likely due to the fact that the earlier study evaluated the incidence of delayed complications, whereas the Morrison et al (1991) work evaluated the incidence of an immediate complication, e.g., cardiac arrhythmias. There was no indication in the Morrison et al. (1991) study that delayed complications such as subsequent muscle weakness or paresthesia were evaluated.

A second series of reports in the literature purport to discuss the toxicity of phenol to newborns. These, however, deal with an excessive level of hyperbilirubinemia, or jaundice, in newborns in hospital nurseries where a phenolic disinfectant detergent was used to clean the nursery and its equipment (bassinets and mattresses) (Doan et al. 1979, Wysowski et al. 1978). Review of these reports indicated that the detergent did not contain phenol *per se*, rather it contained more complex phenolics such as o-benzyl-p-chlorophenol and p-tertiary amylphenol.

In animals, several studies suggest a variable toxicity of phenol depending on age. Deichmann and Wither-up (1944) compared the response to oral and subcutaneous administration of phenol in 3 age groups of rats: 10 days old, 5 weeks old, and adults. At a dose of 600 mg/kg orally, death occurred in 90% of 10 day-old rats, in 30% of 5-week-old rats, and in 60% of adult rats. Similarly, 3,000 mg/kg administered subcutaneously caused death in 65% of 10 day-old, 25% of 5-week-old, and 45% of adult animals.

There is some evidence of developmental toxicity, although in some instances the effects noted have shown a typical dose-response relationship, while in others an inverse dose-response relationship has been observed. In a study of the developmental toxicity of substituted phenols, Kavlock (1990) examined the effect of 0,

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100, 333, 667, and 1,000 mg/kg phenol given by gavage on day 11 of gestation. Twenty-seven chemicals were tested in this study. In order for the data to be comparable, a single vehicle was used which consisted of a 4:4:1:1 mixture of water, Tween 20, propylene glycol, and ethanol. Because of the massive quantities of data such a study generates, the author focused his analytic efforts on five principal parameters, four of which were sampled at two time points. The 5 parameters were maternal weight change (at 24 and 72 hours postdosing), litter size (postnatal day [PD] 1 and 6), perinatal loss, pup weight (in g on PD 1 and 6), and litter biomass (in g on PD 1 and 6).

Within these five parameters, a significant impact of phenol dosing was seen only on maternal weight change, and only at the two highest doses. However, at these same doses, a syndrome of malformations involving the limbs and tail was seen. At a dose of 667 mg/kg, pups in 21.4% of the litters were affected. (At a dose of 1,000 mg/kg, pups in 27.3% of the litters were affected.) The effect on tails was one of shortening or crimping (i.e., 'kinky' tails). The hindlimb effect consisted of paralysis and/or palsy. In animals with palsy, the limb function would alternate between normal strides and a several second-long periods of tetany. Because limb function matures postnatally, this effect was not evident in the newborn but required 7-10 days to become obvious. In the case of phenol, the syndrome did not interfere with postnatal growth and viability; thus, by the statistical criteria used in the report to categorize developmental potency, phenol was not considered an active developmental toxicant. In a subsequent study with Fischer 344 rats given phenol by gavage, Narotsky and Kavlock (1995) found a significant impact of phenol on litter size with full resorption occurring in 1 of 14 low-dose and 2 of 15 high-dose litters. In addition, another high-dose litter showed excessive perinatal mortality and kinked tails in two of the surviving four pups; this finding was not analyzed for significance but was consistent with earlier observations (Kavlock 1990) and may reflect a teratogenic effect of phenol. These findings may be related to maternal toxicity since all of the dams of these litters showed severe respiratory distress; however, other dams with similar respiratory effects delivered apparently normal litters.

In a multi-generational study of the effect of various levels of phenol administered orally in water, Heller and Pursell (1938) saw no effect on growth, reproduction, or rearing of young over 5 generations of rats given concentrations of ~1,000 mg/L (estimated dose of 114 mg/kg/day), or over 3 generations of rats given concentrations of ~5,000 ppm (estimated dose 571 mg/kg/day). In a study by Jones-Price et al. (1983a), CD rat dams given doses as high as 120 mg/kg phenol showed no maternal toxicity at any dose. There was, however, a dose-related decrease in the average live fetal body weight per litter as compared to controls, but the percent of resorptions per litter decreased with increasing dose. In a parallel study in CD-1 mice, dams

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given 0, 70, 140, or 280 mg/kg/day showed significant toxicity at the high dose. There were no significant changes in incidence of resorptions or a dead, or malformed fetuses. There was a significant dose-related decrease in the average live fetal body weight per litter, however.

In rats, the ability of the liver to sulfonate phenol develops with age. Analysis of 105,000 g hepatic supernatants indicated that fetal rats show very low activity (about 3% of the average of 7-week old male and female values which show a male to female ratio of almost 2). By post-natal day 2, the activity increases more than 10 fold in both sexes, a level that is maintained through day 24 (Iwasaki et al. 1993).

Although no reports were found that specifically evaluated age-related changes in the phase I and phase II metabolic transformations of phenol, in general it is known that there is a reduced capacity to metabolize xenobiotics in the first 15 days of life, and that the different enzyme systems have different time courses of development thereafter (Morselli et al. 1980). Thus for example, glucuronide conjugation reactions are considerably reduced in the young and reach adult values only after the age of 3 in humans, whereas sulfate conjugations and oxidative reactions catalyzed by the cytochrome P450 enzymes apparently develop more rapidly (Benet et al. 1995; Morselli et al. 1980). Thus, there could be age-related differences in the balance among metabolites, particularly at high doses where the glucuronide metabolites begin to dominate.

No information was found on the placental transfer and distribution of phenol, however, Ghantous and Danielsson (1986) examined this question for benzene, the principal metabolite of which is phenol. Mice at gestation day 11, 14, and 17, were exposed by inhalation to ^{14}C benzene and the distribution of benzene and its volatile and non-volatile metabolites examined using whole body autoradiography and assessment of tissue concentrations of ^{14}C (day 17 only). The authors indicated that the exposure regimen (50 μCi of ^{14}C benzene in maize oil, volatilized by gentle heating) would theoretically produce 2,000 ppm in the inhalation chamber. Measurements of the difference between the amount added to the chamber and the amount inhaled by the animals indicated an uptake of 90% (i.e., 45 μCi). These authors did not specifically characterize the metabolites, but were able to show that the ^{14}C labeled volatile and non-volatile activity crossed the placental barrier. There was no evidence of preferential accumulation. Indeed, the concentration of volatile and nonvolatile radioactivity in fetal tissues was much lower than that observed in the corresponding maternal tissues. As a metric of the relative accumulation, the authors noted that compared to maternal brain tissue, fetal uptake of benzene was only 8%.

No information was found on the accumulation of phenol in breast milk.

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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 an incomplete understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s), or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to phenol 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 phenol are discussed in Section 2.7.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the

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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 Phenol

Biological monitoring for exposure to phenol is possible by measuring blood or urine levels of the parent compound. However, it should be noted that phenol and metabolites of phenol may also come from other sources. For example, phenol is a metabolite of benzene and of protein metabolism. Urine samples taken from male workers employed in the distillation of high-temperature phenolic fractions of tar revealed a phenol excretion rate of 4.20 mg/hour compared to a control rate of 0.53 mg/hour for non-exposed workers (Bieniek 1994). Samples were taken 4 hours into the workers' workday, but the worker exposure levels were not reported.

The biological exposure index (BEI) for occupational exposure to 5 ppm phenol is 250 mg total phenol in urine/g creatinine (ACGIH 1998). The urine should be collected at the end of the 8-hour work shift. The sample can be stored in the refrigerator for 4 days or frozen for at least 3 months before analysis. ACGIH (1998) warns that the test is nonspecific and should not be used when workers are exposed to benzene or to household products or medications that contain phenol. Dermal exposure may result in overestimation of inhalation exposure.

Phenol can also be measured in the urine after oral exposure, although a dose-response relationship between oral exposure to phenol and phenol in the urine has not been established. In persons not exposed to phenol or benzene, the total phenol concentration in the urine does not exceed 20 mg/L and is usually <10 mg/L (ACGIH 1998).

2.7.2 Biomarkers Used to Characterize Effects Caused by Phenol

Specific biomarkers used to characterize effects caused by phenol have not been identified. Dark urine has been reported in persons exposed to phenol (orally, dermally, or by inhalation) (ACGIH 1991; Baker et al. 1978; Cronin and Bainer 1949; Kim et al. 1994; Merliss 1972) and following oral exposure. The dark urine may be a result of an oxidation product of phenol or hemoglobin or hemoglobin breakdown products. Further research is required to identify the cause of the dark urine. If it is the result of an oxidation product of phenol, it should be considered a biomarker of exposure.

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Phenol can result in hemolytic anemia. Therefore, red blood cell counts may serve as a useful biomarker of effect following exposure to phenol. Measurement of liver enzymes in the serum following phenol exposure would also be useful to determine if liver effects have occurred.

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

2.8 INTERACTIONS WITH OTHER CHEMICALS

Phenol is a tumor promoter in laboratory animals. In mice, dermal exposure to phenol in benzene (Boutwell and Bosch 1959) or in acetone (Salaman and Glendenning 1957; Wynder and Hoffmann 1961) increased the incidence of tumors resulting from dermal exposure to the tumor initiator, DMBA. When injected with mixtures of phenol and hydroquinone, a hydrolyzed metabolite of phenol, mice exhibited significantly depressed bone marrow erythropoiesis compared to injection with phenol alone (Chen and Eastmond 1995a). The involvement of peripheral acetylcholine in phenol-induced tremors was implicated by studies in which mice were injected with phenol and pentobarbital, an inhibitor of acetylcholine release (Itoh 1995).

2.9 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to phenol than will most persons exposed to the same level of phenol 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 phenol, or compromised function of target organs affected by phenol. Populations who are at greater risk due to their unusually high exposure to phenol are discussed in Section 5.7, Populations With Potentially High Exposure.

Potentially, individuals with low activities of the enzymes phenol sulfotransferase and glucuronyltransferase may be more susceptible to phenol toxicity. Persons with ulcerative colitis may have an impaired capacity to sulfate phenol (Ramakrishna et al. 1991), which may increase the amount of unchanged phenol that is absorbed following oral exposure. Neonates may also be more susceptible to toxicity from dermally-applied phenol because of increased skin permeability and proportionately greater surface area. A study in which 10-day old rats were more sensitive to lethality following oral exposure to phenol than 5-week-old or adult rats

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(Deichmann and Witherup 1944) further suggests that the young may be more sensitive to phenol. (For a more detailed discussion please see Section 2.6.) Because phenol is a vesicant, individuals with sensitive skin or pulmonary incapacity may be more sensitive to phenol. Individuals with kidney or liver diseases that impair metabolism or excretion of phenol and phenol metabolites may be more susceptible to phenol.

2.10 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to phenol. 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 phenol. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to phenol: Bronstein AC, Currance PL. 1988. Emergency care for hazardous materials exposure. Washington, DC: CV Mosby Company; Ellenhorn MJ, Barceloux DG. 1988. Medical toxicology-diagnosis and treatment of human poisoning. New York, NY: Elsevier; Stutz DR, Ulin S. 1992. Hazardous materials injuries-a handbook for pre-hospital care. 3rd ed. Beltsville, MD: Bradford Communications Corp.

2.10.1 Reducing Peak Absorption Following Exposure

Human exposure to phenol may occur by inhalation, ingestion, or dermal contact. Mitigation methods for reducing exposure to phenol include the general recommendation of separating contaminated food, water, air, and clothing from the exposed individual. Externally, phenol can produce mild irritation; acute exposure may produce dermatitis and abnormal pigmentation (HSDB 1998). Dermal exposure to relatively low concentrations of phenol (5-6%) over a sufficient surface area can result in death. Therefore, speed in removing phenol from the skin is important (HSDB 1998). Because a study has shown that dilution in water increases the dermal absorption of phenol (Conning and Hayes 1970), it has been recommended that polyethylene be used to remove dermal contamination with phenol (Ellenhorn and Barceloux 1988). Because water is readily available, others believe that its use is more appropriate for the decontamination of skin following phenol exposure (Pullin et al. 1978).

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2.10.2 Reducing Body Burden

Phenol is excreted in the breath, urine, and feces. Mitigation strategies to increase urinary output and dilute the chemical once it is in the bloodstream may be useful. One method for this may be increased hydration of the individual in order to stimulate diuresis. Information on the distribution of phenol is limited and provides little insight on how distribution might be altered to facilitate any attempts at mitigation of effects.

2.10.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism of action of phenol in the body is not well understood. Reports of cardiac arrhythmias resulting from phenol exposure are not uncommon (Gross 1984; Horch et al. 1994; Truppman and Ellenby 1979; Warner and Harper 1985). Methods to interfere with the mechanism of action for phenol were not identified.

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 phenol 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 phenol.

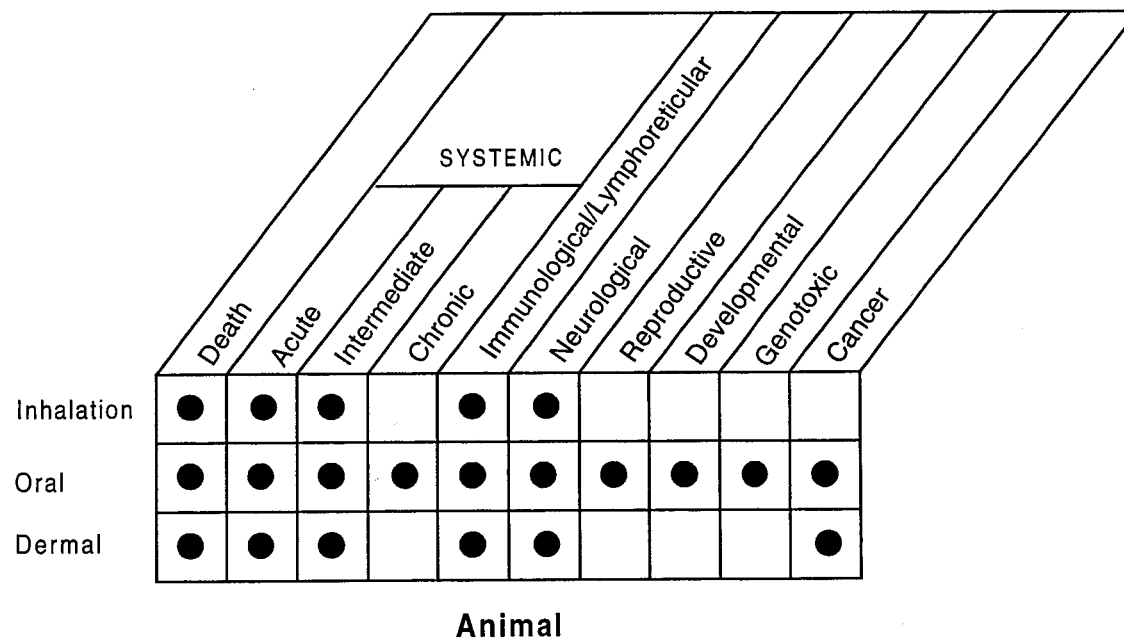
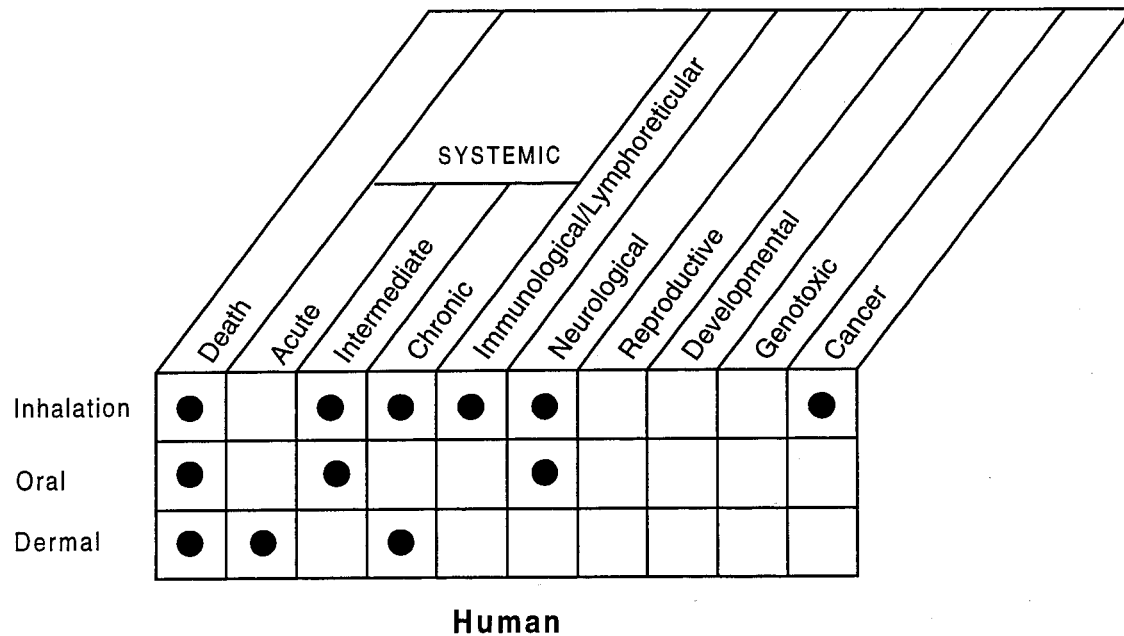
The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean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

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to phenol are summarized in Figure 2-5. The purpose of this figure is to illustrate the existing information concerning

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FIGURE 2-5. Existing Information on Health Effects of Phenol



● Existing Studies

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

Information regarding human health effects of exposure to phenol is almost exclusively limited to acute effects of dermal and oral exposure derived from the case report literature (Baj et al. 1994; Griffiths 1973; Gross 1984; Horch et al. 1994; Lewin and Cleary 1982; Merliss 1972; Stajduhar-Caric 1968; Truppman and Ellenby 1979; Warner and Harper 1985). In all of these cases, death or very serious effects were observed (e.g., cardiac arrhythmias), and most cases involved massive exposure levels. Two intermediate-duration exposure studies were found concerning health effects in small populations exposed to phenol in contaminated drinking water (Baker et al. 1978; Kim et al. 1994). One study regarding cancer following occupational exposure to phenol did not indicate an exposure-related effect (Dosemeci et al. 1991).

Data on toxicity of phenol in laboratory animals have been reported for acute and intermediate exposure by the inhalation, oral, and dermal routes. One immunotoxicity study was reported for the inhalation route; rats were exposed to phenol and challenged with infectious bacteria (Aranyi et al. 1986). Several studies provide data on neurologic effects of phenol administered by the inhalation, oral, and dermal routes. Data are extensive regarding genotoxicity of phenol in bacterial systems and mammalian systems (see Table 2-5). Data regarding the oral carcinogenicity of phenol in rats and mice have been reported (NCI 1980), as well as data on the dermal carcinogenicity, and the tumor-promoting and tumor-inhibiting activities of phenol (Boutwell and Bosch 1959; Salaman and Glendenning 1957; Van Duuren and Goldschmidt 1976; Wynder and Hoffmann 1961).

2.11.2 Identification of Data Needs

Acute-Duration Exposure. Phenol is a direct irritant that acts at the site of contact following acute exposure (Conning and Hayes 1970; De Ceaurriz et al. 1981; Hunter et al. 1992; Murphy et al. 1982; Patrick et al. 1985; Pullin et al. 1978; Steele and Wilhelm 1966). Cardiac arrhythmias are the most prominent effect observed in humans during accidental exposure and medical treatments with phenol (Gross 1984; Horch et al.

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1994; Truppman and Ellenby 1979; Warner and Harper 1985). Other effects observed in animals following acute exposure to phenol include difficulty breathing (Narotsky and Kavlock 1995; Pullin et al. 1978), hematological effects (Ciranni et al. 1988), kidney effects (Berman et al. 1995; Conning and Hayes 1970), unspecified histopathological changes in the adrenal glands (Berman et al. 1995), decreased maternal weight gain in rats exposed during gestation (Jones-Price et al. 1983b; Narotsky and Kavlock 1995), necrosis or atrophy of the spleen or thymus (Berman et al. 1995), and nervous system effects including muscle twitching, convulsions, and coma (Jones-Price et al. 1983b; Liao and Oehme 1981; Moser et al. 1995). Fetotoxic effects include decreased fetal body weight (Jones-Price et al. 1983a, 1983b) and a decrease in the number of liveborn pups associated with maternal toxicity (Narotsky and Kavlock 1995). The lowest dose resulting in adverse effects following oral exposure was 40 mg/kg/day, a dose associated with difficulty in breathing and a decrease in maternal body weight gain (Narotsky and Kavlock 1995).

The available data were not sufficient for the development of acute-duration inhalation or oral MRLs. Additional data are necessary to further define the dose response of phenol following inhalation, oral, and dermal exposure. Because the oral toxicity of phenol varies with the concentration of the dose, studies using varying concentrations would be useful.

Intermediate-Duration Exposure. Adverse effects have been reported following intermediate-duration occupational exposure to phenol (Baj et al. 1994) and intermediate-duration exposure of humans to phenol in the drinking water (Baker et al. 1978; Kim et al. 1994). The effects reported include decreased red blood cell counts (Baj et al. 1994), gastrointestinal effects, dark urine, and direct skin effects (Baker et al. 1978; Kim et al. 1994).

Intermediate-duration inhalation studies were all single concentration studies at concentrations that resulted in serious effects (26-52 ppm) (Deichmann et al. 1944), or no effects (5 ppm) (Sandage 1961). Therefore, an intermediate-duration inhalation MIX was not derived for phenol. The serious effects noted included pneumonia, necrosis of the myocardium, fatty degeneration of the liver, glomerular degeneration, and hindlimb paralysis (Deichmann et al. 1944). Additional inhalation studies that examine the concentration-related response to phenol following intermediate-duration exposure would be useful.

Following intermediate-duration oral exposure to phenol, a decrease in red blood cell counts occurred in mice treated with phenol in drinking water at a dose of 1.8 mg/kg/day for 28 days (Hsieh et al. 1992). Other effects reported in animals following intermediate-duration oral exposure to phenol included decreased body

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weight gain associated with decreased water intake (NCI 1980), decreased production of antibodies, and decreases in neurotransmitter levels in the brain (Hsieh et al. 1992). The decreased red blood cell counts in the Elsieh et al. (1992) study are considered a less serious effect from which a LOAEL of 1.8 mg/kg/day for intermediate exposure can be derived.

Skin ulcerations were reported in mice treated dermally with 20% phenol in acetone once each week for 24-32 weeks (Salaman and Glendenning 1957). Because humans are more likely to be dermally exposed to phenol in water, additional intermediate-duration studies examining the effects of dermal exposure to different concentrations of phenol in water are necessary. Additional intermediate-duration studies should include hematological effects as an endpoint.

Chronic-Duration Exposure and Cancer. Mortality was not increased in workers occupationally exposed to phenol (Dosemeci et al. 1991). Effects reported in a case of chronic phenol poisoning, in which exposure was by both the inhalation and dermal routes, included muscle pains in the arms and legs, enlarged and tender liver with increased levels of liver enzymes in the serum, dark urine, and emaciation (Merliss 1972).

No chronic-duration inhalation studies in animals were identified. The only systemic effect in a chronic-duration oral study of phenol was decreased body weight gain in rats associated with decreased water intake (NCI 1980). This study did not include tests for neurologic impairment or hematologic studies, both critical effects of phenol exposure. Skin damage has been reported in mice treated dermally with phenol in benzene for chronic durations (Boutwell and Bosch 1959). Because of the limited chronic data available, chronic-duration MRLs for phenol were not derived. A chronic-duration inhalation study of phenol in animals would be useful to help predict effects in humans exposed to phenol by inhalation. Additional chronic studies of phenol including neurological function tests and hematologic studies are necessary. Because drinking water is a likely route of exposure for humans, drinking water studies would be more relevant than gavage studies for predicting human health effects. A chronic-duration dermal study of phenol in water is also necessary to predict human health effects following dermal exposure to phenol.

In the occupational studies of phenol, chronic exposure was not clearly related to a carcinogenic effect (Dosemeci et al. 1991; Kauppinen et al. 1986). Phenol was also not clearly carcinogenic in an oral carcinogenicity study in rats and mice (NCI 1980). Additional carcinogenicity studies of inhalation exposure are needed

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Skin studies have indicated that phenol can act as a promotor following treatment with a polyaromatic hydrocarbon (Boutwell and Bosch 1959; Salaman and Glendenning 1957). These studies are limited because phenol was administered in benzene (Boutwell and Bosch 1959) or acetone (Salaman and Glendenning 1957). An additional dermal carcinogenicity study in which phenol is administered in water is necessary to predict the carcinogenicity of phenol following dermal exposure.

Genotoxicity. Phenol has been tested extensively for genotoxicity in a variety of *in vivo* (Amlacher and Rudolph 1981; Barale et al. 1990; Bulsiewicz 1977; Chen and Eastmond 1995a; Ciranni et al. 1988; Gocke et al. 1981; Miyagawa et al. 1995; Pashin et al. 1987; Skare and Schrotel 1984; Sturtevant 1952) and *in vitro* (Crebelli et al. 1987; Demerec et al. 1951; Erexson et al. 1985; Florin et al. 1980; Gocke et al. 1981; Haworth et al. 1983; Jansson et al. 1986; Morimoto and Wolff 1980; Morimoto et al. 1983; Nagel et al. 1982; Painter and Howard 1982; Paschin and Bahitova 1982; Pellack-Walker and Blumer 1986; Poirier et al. 1975; Pool and Lin 1982; Schwartz et al. 1985; Sze et al. 1996) tests. The results of these assays have been equivocal. Phenol appears to be potentially genotoxic, although this may be more a result of the action of its metabolites than the parent compound. Additional genotoxicity studies of phenol do not seem to be necessary.

Reproductive Toxicity. No studies regarding reproductive effects in humans following exposure to phenol were identified. Only one multigeneration reproductive study in rats has been reported (Heller and Pursell 1938). This study lacked controls, and the methods used to evaluate reproductive performance were not sensitive enough to detect possible reproductive effects (e.g., controlled evaluations of breeding performance). Effects on reproduction were not observed in rats or mice treated by gavage with phenol on gestation days 6-15 (Jones-Price et al. 1983a, 1983b). Histopathological changes in reproductive organs were not observed in rats or mice treated with phenol in the drinking water for 13 or 103 weeks (NCI 1980). Additional studies concerning reproductive effects following any route of exposure were not identified. Controlled multi-generation studies of phenol in rodents by inhalation and oral exposure are necessary to determine if phenol has the potential for causing reproductive effects in humans.

Developmental Toxicity. No studies regarding developmental effects in humans following exposure to phenol were identified. Phenol has been evaluated for developmental effects in rats and mice, but only by the oral route and then only by gavage (Jones-Price et al. 1983a, 1983b; Kavlock 1990; Narotsky and Kavlock 1995). Additional studies examining developmental effects in animals exposed to phenol are necessary.

2. HEALTH EFFECTS

Ideally, a multi-generation study by an oral route such as food or drinking water and by inhalation are needed to determine if environmental exposures to phenol place the fetus, infants, or children at additional risk.

Immunotoxicity. Immunological effects were reported in workers exposed to a mixture of phenol, formaldehyde, and organic chlorohydrocarbons for 6 months, although there is some question whether the exposure was due to phenol or a substituted phenol (Baj et al. 1994). Increased susceptibility to bacteria was not observed in mice exposed by inhalation to phenol (Aranyi et al. 1986). Necrosis or atrophy of the spleen or thymus, which was not described further, was observed in rats given a single gavage dose of phenol (Berman et al. 1995). Effects on the spleen or thymus were not observed in rats given 14 daily doses of phenol (Berman et al. 1995). Decreased antibody production was observed in mice treated with phenol in the drinking water (Hsieh et al. 1992). Histopathologic changes in the spleen or thymus were not observed in rats or mice exposed to phenol in the drinking water for 13 or 103 weeks (NCI 1980). Effects on the immune system have not been studied following dermal exposure to phenol, and no studies regarding the ability of phenol to induce sensitivity were identified. Because immunologic effects have been noted in some studies, additional studies regarding immunological effects following inhalation or oral exposure to phenol are needed to further define the dose-response curve.

Neurotoxicity. An increase in the number of headaches was reported by persons exposed to phenol in drinking water following an accident (Kim et al. 1994). Neurological effects (muscle tremor, loss of coordination) have been reported in laboratory animals following exposure by all routes (Conning and Hayes 1970; Deichmann et al. 1944; Itoh 1995; Jones-Price et al. 1983b; Liao and Oehme 1981; Moser et al. 1995; Pullin et al. 1978). However, these studies used only a single dose level, and sensitive methods for evaluating neurotoxicity were not included in the studies. The dose-effect relationship for the neurological effect has not been established, and additional studies by all routes of exposure are needed.

Epidemiological and Human Dosimetry Studies. Retrospective epidemiological studies on small groups of individuals revealed an increased incidence of gastrointestinal symptoms, dark urine, and skin effects associated with drinking water contaminated with phenol (Baker et al. 1978; Kim et al. 1994). The exposure routes in these studies probably included dermal and inhalation, in addition to oral.

A study of workers from phenol production facilities did not find an association between phenol and mortality from various causes, including cancer (Dosemeci et al. 1991). Urinary levels of total phenol have been shown

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to correlate with atmospheric phenol concentration when there is limited dermal exposure, and no exposure to benzene (ACGIH 1991; Ohtsuji and Jkeda 1972).

Levels of total urinary phenol (phenol plus phenol conjugates) measured at the end of the workshift correlated with atmospheric phenol concentrations, suggesting that this measurement may be useful in predicting recent exposure to phenol vapor.

Additional epidemiological studies might focus on the effects of low levels of phenol in the air, water, or soil near hazardous waste sites. These studies should carefully consider possible confounding factors including exposure to multiple chemicals, smoking and drinking habits, age, and gender. The endpoints that need to be carefully considered are hematological, kidney and liver, cardiovasculars, developmental, neurological, and genotoxic effects. A dosimetric model which predicts total exposure to phenol from contaminated water is needed. This model should consider inhalation, oral, and dermal exposure. This model is needed to predict the concentration of phenol in water that is safe for human exposure.

Biomarkers of Exposure and Effect

Exposure. Measurement of total phenol in the urine is the most useful biomarker following inhalation exposure to phenol (ACGIH 1991). The test is nonspecific and should not be used when workers are exposed to benzene, to household products, or to medications containing phenol. Dermal exposure may also result in overestimation of inhalation exposure. In persons not exposed to phenol or benzene, the total phenol concentration in the urine does not exceed 20 mg/L and is usually <10 mg/L (ACGIH 1991). Phenol can also be measured in the urine after oral exposure, although a dose-response relationship between oral exposure to phenol and phenol in the urine has not been established. Benzene metabolism yields not only phenol, 1,4-dihydroxybenzene, and their sulfates and glucuronides, but also the benzene-specific *t,t*-muconic acid. For both *t,t*-muconic acid and *S*-phenylmercapturic acid, significant correlations were shown with benzene concentrations in air and in blood (Popp et al. 1994; Stommel et al. 1989). Thus, determination of urinary concentrations of these metabolites allows delineation of the portion of metabolites stemming from phenols and the portion derived from benzene exposure. Further research on the relationship between exposure doses and urinary levels of phenol is needed.

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Effect. Specific biomarkers used to characterize effects caused by phenol have not been identified. Dark urine has been reported in persons occupationally exposed to phenol (inhalation, dermal) (ACGIH 1991; Merliss 1972), and following oral exposure (Baker et al. 1978; Kim et al. 1994). The dark urine may be a result of an oxidation product of phenol or hemoglobin. Further research is required to identify the cause of the dark urine.

Absorption, Distribution, Metabolism, and Excretion. The toxicokinetics of phenol have been studied extensively in laboratory animals and humans. Phenol is readily absorbed from the lungs, gastrointestinal tract, and skin. A study that examined the absorption of phenol vapor through the skin indicates that it is readily absorbed and clothing does not serve as a barrier (Piotrowski 1971). Dermal absorption is considered the primary route of entry for vapor, liquid, and solid phenol (ACGIH 1991). Conjugation of phenol with glucuronic acid and conjugation with sulfate are the main detoxification pathways. Conjugation occurs predominantly in the lungs, gastrointestinal tract, liver, and kidneys. The skin has relatively low potential to detoxify phenol. Therefore, absorption through the skin may represent the greatest hazard from phenol because it readily passes through the skin and because there is no first-pass metabolic effect as is observed following oral exposure. Further studies regarding the metabolism of phenol following dermal exposure are needed. *In vitro* studies of phenol metabolism have demonstrated that reactive intermediates are produced during the metabolism of phenol (Eastmond et al. 1986; Eunte and Kissinger 1983; Subrahmanyam and O'Brien 1985). These reactive compounds may be involved in mediating phenol toxicity. Further investigation of these compounds in tissues suspected of being targets for phenol toxicity (i.e., the lungs, skin, liver, kidney, and heart) are needed to provide information for extrapolating from animals to humans.

There is no PBPK model specifically designed for phenol, although phenol, as a major metabolite of benzene has been considered in the two PBPK models of benzene discussed in this profile (Bois et al. 1991; Medinsky et al. 1995). Neither of these models adequately explains the differences in carcinogenicity observed between benzene and phenol, and both models need additional refinements in order to incorporate all the observations and be validated by one another. Additional work on one or both of these models is needed.

Comparative Toxicokinetics. The metabolism and excretion of orally administered phenol in 18 animal species have been compared to metabolism and excretion in humans (Capel et al. 1972). The rat was the most similar to the human with respect to the fraction of administered dose excreted in urine in 24 hours (95%) and the number and relative abundance of the 4 principal metabolites excreted in urine (sulfate and

2. HEALTH EFFECTS

glucuronide conjugates of phenol and 1,4-dihydroxybenzene). The rat excreted a larger fraction of the orally administered dose than the guinea pig or the rabbit (Capel et al. 1972) and appears to be the least susceptible of the three species to respiratory, cardiovascular, hepatic, renal, and neurological effects of inhaled phenol (Deichmann et al. 1944). More rapid metabolism and excretion of absorbed phenol may account for the lower sensitivity of the rat to systemic effects of phenol. More information on the relative rates of metabolism of phenol in various species is needed to identify the most appropriate animal model for studying potential health effects in humans.

Methods for Reducing Toxic Effects. Removing a person from phenol exposure is the most important method for reducing toxic effects of phenol. This is especially important following dermal exposure, after which speed in removing phenol from the skin is important (HSDB 1998). Because a study has shown that dilution in water increases the dermal absorption of phenol (Conning and Hayes 1970), it has been recommended that polyethylene be used to remove dermal contamination with phenol (Ellenhorn and Barceloux 1988). Because water is readily available, others believe that its use is more appropriate for the decontamination of skin following phenol exposure (Pullin et al. 1978). Further research on the best way to remove phenol from the skin without increasing absorption is needed. The general recommendations for reducing the absorption of phenol following acute oral exposure are well established and have a proven efficiency (HSDB 1998). No additional investigations are considered necessary at this time.

No clinical treatments, other than supportive measures, are currently available to enhance elimination of phenol following exposure. Studies designed to assess the potential risks or benefits of increasing ventilation to enhance pulmonary elimination or of stimulating excretion of phenol and its metabolic products are needed.

Children's Susceptibility. Data needs relating to prenatal developmental exposures are discussed above in the Developmental Toxicity subsection.

Deichman and Witherup (1944) found that 10-day-old rats were more sensitive to lethality following oral exposure to phenol than 5-week-old or adult rats; however, this work has never been repeated and there was little other information evaluating the toxicity of phenol at various ages. Such studies need to be conducted in order to follow up this earlier observation and determine if children of certain ages may be more at risk than others.

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There was no information found that specifically evaluated age-related changes in the phase I and phase II metabolic transformations of phenol. However, in general it is known that there is a reduced capacity to metabolize xenobiotics in the first 15 days of life, and that the different enzyme systems have different time courses of development thereafter (Morselli et al. 1980). For example, glucuronide conjugation reactions are considerably reduced in the young, and reach adult values only after the age of 3 in humans, whereas sulfate conjugations and oxidative reactions catalyzed by the cytochrome P450 enzymes apparently develop more rapidly (Benet et al. 1995; Morselli et al. 1980). Thus, there could be age-related differences in the balance among metabolites, particularly at high doses where the glucuronide metabolites begin to dominate. Studies are needed to examine whether age affects the metabolism of phenol, and particularly whether it changes the balance between phase I and phase II metabolism at either high or low doses.

There was no information found on the placental transfer of phenol or on the concentrations of phenol present in breast milk. There is evidence that benzene and its (not specifically identified) metabolites do cross the placenta, although there is no evidence of selective accumulation (Ghantous and Danielsson 1986). Additional studies of this issue are needed to determine if phenol and its metabolites are among the metabolites of benzene that cross the placenta, and if so whether phenol behaves like benzene in the lack of accumulation. Information is also needed on the content of phenol in breast milk under various conditions, e.g. smoking versus non-smoking mothers, in order to determine if breast milk could ever be a source of phenol exposure for children.

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

2.11.3 Ongoing Studies

Ongoing studies regarding the toxicity and pharmacokinetics of phenol were not identified.

3. CHEMICAL AND PHYSICAL INFORMATION

3.1 CHEMICAL IDENTITY

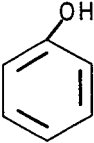
Information regarding the chemical identity of phenol is located in Table 3-1.

3.2 PHYSICAL AND CHEMICAL PROPERTIES

Information regarding the physical and chemical properties of phenol is located in Table 3-2.

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-1. Chemical Identity of Phenol

Characteristic	Information	Reference
Chemical name	Phenol	Lide 1993
Synonym(s)	Benzenol, hydroxybenzene, monophenol, oxybenzene, phenyl alcohol, phenyl hydrate, phenyl hydroxide, phenylic acid, phenylic alcohol	Lewis 1996
Registered trade name(s)	Carbolic acid, phenic acid, phenic alcohol	Gardner et al. 1978
Chemical formula	C ₆ H ₆ O	Lide 1993
Chemical structure		Budavari et al. 1989
Identification numbers:		
CAS registry	108-95-2	OHM/TADS 1998
NIOSH RTECS	SJ3325000	RTECS 1998
EPA hazardous waste	U188	EPA 1998b
OHM/TADS	7216849	OHM/TADS 1998
DOT/UN/NA/IMO shipping	IMO 6.1	HSDB 1997
	UN 1671 (solid)	
	UN 2312 (molten)	
	UN 2821 (solution)	
HSDB	113	HSDB 1998
NCI	C50124	Lewis 1996

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

3. CHEMICAL AND PHYSICAL INFORMATION

TABLE 3-2. Physical and Chemical Identity of Phenol

Property	Information	Reference
Molecular weight	94.11	Lide 1993
Color	Colorless to light pink	HSDB 1998
Physical state	Crystalline solid liquid (w/8% H ₂ O)	
Melting point	43°C	Lide 1993
Boiling point	181.8°C	Lide 1993
Density:		
At 20°C	1.0545@45°C/4°C	Lide 1993
Vapor density	3.24	Lewis 1996
Odor	Distinct aromatic, somewhat sickening, sweet and acrid odor	HSDB 1998
Odor threshold:		
Water	7.9 ppm (w/v)	Amoore and Hautala 1983
	1 ppm (w/v)	Baker et al. 1978
Air	0.040 ppm (v/v)	Amoore and Hautala 1983
Solubility:		
Water at 25°C	87 g/L	Lide 1993
Organic solvent(s)	Very soluble in alcohol, chloroform, ether, benzene, acetone, water	Lide 1993
Partition coefficients:		
Log K _{ow}	1.46	HSDB 1998
Log K _{oc}	1.21–1.96	Artiola-Fortuny and Fuller 1982; Boyd 1982; Briggs 1981; Sacan and Balcioglu 1996; Scott et al. 1983
Vapor pressure:		
at 25°C	0.3513	HSDB 1998
Henry's law constant:	4.0×10 ⁻⁷ m ³ /mol	Lide 1993
Autoignition temperature	715°C	Lewis 1996
Flashpoint, open cup	85°C	HSDB 1998
Flashpoint, closed cup	79°C	NIOSH 1997
Flammability limits (in air, by % v)	1.7%–8.6%	NIOSH 1997
Conversion factors:		
ppm (v/v) to mg/m ³ in air (20°C)	ppm (v/v) × 3.92 = mg/m ³	
mg/m ³ to ppm (v/v) in air (20°C)	mg/m ³ × 0.255 = ppm (v/v)	

atm = atmosphere; v = volume; w = weight

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

4.1 PRODUCTION

Table 4-1 lists the number of facilities in each state that manufacture or process phenol, the intended use, and the range of maximum amounts of phenol that are stored onsite. The data listed in Table 4-1 are derived from the Toxics Release Inventory (TRI) (TRI96 1998). Only certain types of facilities were required to report. Therefore, this is not an exhaustive list.

Phenol has been obtained by distillation from petroleum and synthesis by oxidation of cumene or toluene, and by vapor-phase hydrolysis of chlorobenzene (USITC 1987). In 1995, 95% of U.S. phenol production was based on oxidation of cumene except at one company that used toluene oxidation and a few companies that distilled phenol from petroleum (CMR 1996). In 1995 the total annual capacity of phenol production approached 4.5 billion pounds (CMR 1996).

4.2 IMPORT/EXPORT

According to the National Trade Data Bank (1996), imports of phenol were 28.7 million kg (63.1 million pounds) and exports of phenol were 138.2 million kg (304 million pounds) in 1995.

4.3 USE

The two major uses of phenol in 1995 were the production of bisphenol-A (35%) and the production of phenolic resins (34%) (CMR 1996). The largest use for bisphenol-A is as an intermediate in the production of epoxy resins (Thurman 1982). Phenol-formaldehyde resins comprise over 95% of this market (Thurman 1982). The plywood adhesive industry required 26% of the total production of phenolic resins in 1977. These low-cost, versatile, thermoset resins have other major uses in the construction, automotive, and appliance industries (Thurman 1982).

Other major uses of phenol include the production of caprolactam (15%), aniline (5%), alkylphenols (5%), xlenols (5%), and miscellaneous uses (1%) (CMR 1996). Phenol is used as a slimicide (a chemical toxic to bacteria and fungi characteristic of aqueous slimes) and as a general disinfectant in solution or mixed with

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

Table 4-1. Facilities that Manufacture or Process Phenol

State ^a	Number of Facilities	Range of Maximum Amounts on Site in Pounds ^b	Activities and Uses ^c
AL	31	0-49,999,999	1, 5, 6, 7, 8, 9, 12, 13
AR	14	0-9,999,999	1, 2, 5, 6, 7, 8, 9, 11, 13
AZ	4	100-99,999	8, 12, 13
CA	24	100-9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 11, 12, 13
CO	1	1,000-9,999	12
CT	8	100-99,999	7, 8, 9, 12, 13
DE	1	10,000-99,999	7
FL	10	100-999,999	1, 6, 7, 9, 13
GA	27	0-999,999	1, 2, 3, 5, 6, 7, 8, 9, 11, 13
IA	8	0-99,999	7, 9, 11, 12
ID	1	100-999	1, 6
IL	36	0-9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
IN	33	100-49,999,999	1, 2, 3, 4, 5, 7, 8, 9, 11, 12, 13
KS	8	0-9,999,999	1, 4, 5, 6, 7, 8, 9, 12
KY	11	100-9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12
LA	28	100-99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 11, 12, 13
MA	8	1,000-99,999	7, 8, 9, 12
MD	2	100-99,999	1, 6, 7, 8, 9
ME	7	100-99,999	1, 2, 5, 6, 7, 8, 13
MI	32	0-9,999,999	1, 5, 6, 7, 8, 9, 11, 12, 13
MN	10	1,000-9,999,999	1, 5, 6, 7, 8, 9, 12
MO	10	0-999,999	7, 8, 10, 11, 12, 13
MS	19	0-999,999	1, 5, 6, 7, 9, 12, 13
MT	2	1,000-999,999	1, 6, 7
NC	26	100-9,999,999	1, 5, 6, 7, 8, 9, 11, 12, 13
NE	3	1,000-99,999	7, 9, 12
NH	3	100-99,999	1, 6, 12
NJ	9	0-9,999,999	1, 3, 5, 6, 7, 8, 13
NY	21	100-9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 12, 13
OH	57	0-49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
OK	8	100-99,999	1, 5, 6, 8, 9, 11, 12, 13
OR	18	100-9,999,999	1, 6, 7, 8, 9, 12
PA	33	0-99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
PR	1	1,000-9,999	9
RI	2	1,000-99,999	7, 8
SC	25	0-9,999,999	1, 5, 6, 7, 8, 10, 11, 13
TN	17	100-99,999	1, 5, 6, 7, 8, 9, 11, 12, 13
TX	66	100-99,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
UT	3	1,000-999,999	1, 3, 5, 6, 7, 11, 13
VA	18	0-49,999,999	1, 2, 3, 5, 6, 7, 8, 9, 11, 12, 13
VI	1	1,000-9,999	1, 2, 3, 4, 5, 7
VT	1	1,000-9,999	2, 3, 9, 11

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

**Table 4-1. Facilities that Manufacture or Process Phenol
(continued)**

State ^a	Number of Facilities	Range of Maximum Amounts on Site in Pounds ^b	Activities and Uses ^c
WA	12	0-9,999,999	1, 3, 4, 5, 6, 7, 8
WI	30	100-9,999,999	1, 5, 6, 7, 8, 9, 11, 12, 13
WV	7	1,000-9,999,999	1, 3, 5, 6, 7, 8, 9
WY	2	100-99,999	1, 4, 5, 6

Source: TRI96 1998

a Post office state abbreviations used

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

c Activities/Uses:

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

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

slaked lime for toilets, stables, cesspools, floors, drains, and other areas (Budavari et al. 1989; Hawley 1981). Phenol is used in medicinal preparations including ointments, ear and nose drops, cold sore lotions, mouthwashes, gargles, toothache drops, analgesic rubs (Douglas 1972), throat lozenges (EPA 1980), and antiseptic lotions (Musto et al. 1977).

4.4 DISPOSAL

Phenol is listed as a toxic substance under Section 313 of the Emergency Planning and Community Right to Know Act (EPCRA) under Title III of the Superfund Amendments and Reauthorization Act (SARA) (EPA 1998c). Disposal of wastes containing phenol is controlled by a number of federal regulations (see Chapter 7).

Phenol may be disposed of by controlled burning or by feeding dilute amounts to sewage organisms. Because shock loadings will be fatal to organisms, sludge acclimation is generally required for efficient digestion by bacteria. Potassium permanganate (100–500 ppm) can be used to disrupt the structure of phenol, forming aliphatic acids (OHM/TADS 1988). Phenol can be recovered economically from solutions of greater than 1% phenol by steam stripping, distillation, or adsorption onto carbon (OHM/TADS 1988).

According to the TRI, about 8.5 million pounds (3.8 million kg) of phenol were transferred to landfills and/or other treatment facilities, and about 3.3 million pounds (1.5 million kg) were sent to publicly-owned treatment works (POTWs) in 1996 (see Table 5-1) (TRI96 1998).

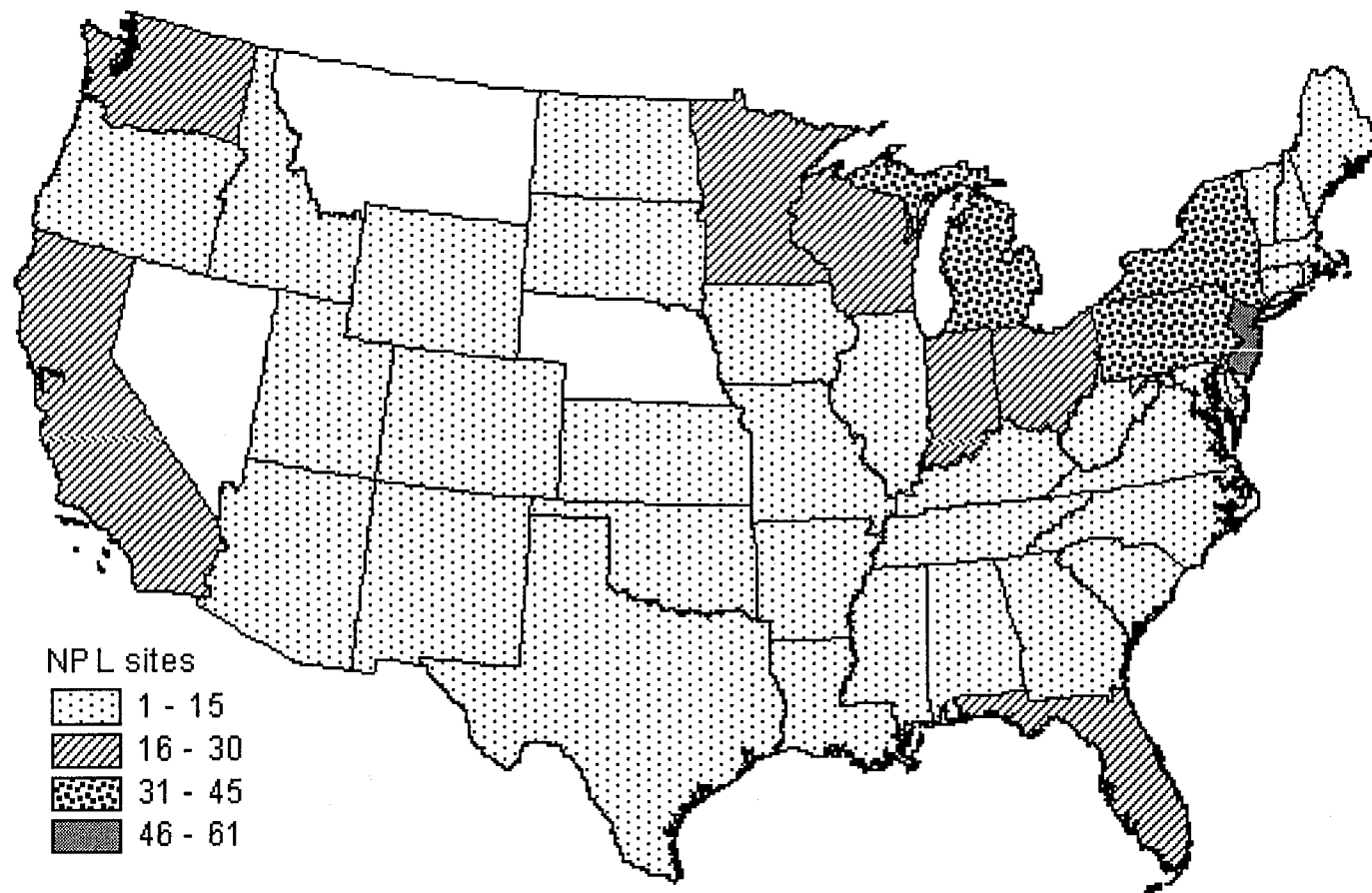
5. POTENTIAL FOR HUMAN EXPOSURE

5.1 OVERVIEW

Phenol has been identified in at least 481 of the 1,467 current or former EPA National Priorities List (NPL) hazardous wastes sites (HazDat 1998). However, the number of sites evaluated for phenol is not known. The frequency of these sites within the United States can be seen in Figure 5-1. Of these sites, 477 are located in the United States and 4 are located in the Commonwealth of Puerto Rico.

Phenol is released primarily to the air and water as a result of its manufacture and use and as a result of wood burning and auto exhaust. Phenol mainly enters the water from industrial effluent discharges. Phenol disappears rapidly in air by gas-phase hydroxyl radical reaction (estimated half-life 14.6 hours), but may persist in water for a somewhat longer period. Half-lives for biodegradation range from less than 1 day in samples of lake water to 9 days in estuarine water; a typical half-life for photooxidation by photochemically produced peroxy radicals is approximately 19 hours. In soil, phenol will generally biodegrade rapidly; however, biodegradation of phenol in water or soil may be hindered or precluded by the presence of high, toxic concentrations of phenol or other chemicals, or by other factors such as a lack of nutrients or microorganisms capable of degrading phenol. If biodegradation is sufficiently slow, phenol in sunlit water will undergo photooxidation with photochemically produced peroxy radicals, and phenol in soil will leach to groundwater. Since plants can metabolize phenol readily, exposure through eating food derived from plants grown in phenol-containing soil is probably minimal. Phenol may remain in air, water, and soil for much longer periods if it is continually or consistently released to these media from point sources.

Phenol has been measured in effluents (up to 53 ppm), ambient water (from 1.5 to >100 ppb), drinking water (not quantified), groundwater (from 1.9 to >10 ppb), rain (0.075–1.2 ppb), sediment (>10 ppb), and ambient air (0.03–44 ppb). Occupational exposures occur through inhalation and dermal exposure; air concentrations monitored in various workplaces range from 0.1 to 12.5 mg/m³ (0.03–32 ppm). Occupational as well as consumer exposure may also occur through dermal contact with phenol or phenol-containing products.

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

NPL sites

- 1 - 15
- 16 - 30
- 31 - 45
- 46 - 61

* Derived from HazDat 1998

5. POTENTIAL FOR HUMAN EXPOSURE

5.2 RELEASES TO THE ENVIRONMENT

According to the TRI, in 1996, a total of about 23.5 million pounds (10.6 million kg) of phenol was released to the environment from 689 large processing facilities (TRI96 1998). Table 5-1 lists amounts released from these facilities. In addition, an estimated 3.3 million pounds (1.5 million kg) were released by manufacturing and processing facilities to publicly owned treatment works (POTWs) and an estimated 8.5 million pounds (3.8 million kg) were transferred offsite (TRI96 1998). The TRI data should be used with caution because only certain types of facilities are required to report. This is not an exhaustive list.

Phenol has been identified in a variety of environmental media (air surface water, groundwater, soil, and sediment) collected at 481 of the 1,467 NPL hazardous waste sites (HazDat 1998).

5.2.1 Air

According to the TRI, in 1996, the estimated releases of phenol of 9.5 million pounds (4.3 million kg) to air from 635 large processing facilities accounted for about 5% of total environmental releases (TRI96 1998). Table 5-1 lists amounts released from these facilities. The TRI data should be used with caution, however, since only certain types of facilities are required to report. This is not an exhaustive list.

During manufacturing, phenol is released primarily to the atmosphere from storage tank vents and during transport loading (Delaney and Hughes 1979). Other major sources of release to the atmosphere are residential wood burning and automobile exhaust (Scow et al. 1981). Volatilization from environmental waters and soils has been shown to be a slow process (see Section 5.3.1) and is not expected to be a significant source of atmospheric phenol. Phenol has been detected at a concentration of 0.36 ppb in the emissions of a waste incinerator plant in Germany (Jay and Stieglitz 1995). Phenol is also found in cigarette smoke and in plastics (Graedel 1978), but no data are available to determine the extent of exposure to phenol from these sources.

5.2.2 Water

According to the TRI, in 1996, the estimated releases of phenol of 72,55 pounds (32,650 kg) to water from 220 large processing facilities accounted for about 0.3% of total environmental releases (TR196 1998).

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

State ^b	Number of Facilities	Total of reported amounts released in pounds per year ^a							Total Environment ^c
		Air ^c	Water	Land	Underground Injection	POTW ^d Transfer	Off-site Waste Transfer		
AL	30	396,256	5,344	13,899	0	4,055	39,513	459,067	
AR	14	59,333	1,071	327	1,392	0	6,133	68,256	
AZ	4	3,668	0	0	0	0	13,756	17,424	
CA	25	100,792	2,714	0	0	426,725	144,299	674,530	
CO	1	0	0	0	0	0	3,345	3,345	
CT	8	16,581	0	0	0	5,987	47,591	70,159	
DE	1	63	0	0	0	5	0	68	
FL	9	130,619	404	10	0	3,900	136,647	271,580	
GA	26	283,854	1,166	3,325	0	6,799	110,232	405,376	
IA	8	59,447	552	2,262	0	0	748,476	810,737	
ID	1	755	5	5	0	0	0	765	
IL	36	672,577	1,878	3,215	0	1,430,152	602,140	2,709,962	
IN	33	1,194,276	9,329	3,372	110,000	1,579	380,631	1,699,187	
KS	8	194,981	1,720	232	548	4,114	24,601	226,196	
KY	11	235,558	855	7,502	0	152,690	629,679	1,026,284	
LA	28	263,918	3,431	850	130,311	0	466,678	865,188	
MA	7	59,264	0	0	0	338	14,141	73,743	
MD	2	45,805	0	0	0	4,400	16,300	66,505	
ME	7	37,555	302	118	0	2	737	38,714	
MI	33	193,425	7,652	9,642	0	65,089	211,701	487,509	
MN	10	135,671	1,293	3	0	250	12,319	149,536	
MO	10	84,683	1	0	0	605	95,795	181,084	
MS	18	144,137	2,738	543	0	224	818	148,460	
MT	2	1,380	250	0	0	0	5	1,635	
NC	26	335,372	1,095	765	0	737	114,352	452,321	
NE	3	56,207	0	0	0	0	2,044	58,251	
NH	3	2,114	0	1	0	0	16,573	18,688	
NJ	9	51,810	6,287	230	0	317,750	81,035	457,112	
NY	21	151,883	555	0	0	37,294	1,030,762	1,220,494	

**Table 5-1. Releases to the Environment from Facilities that Manufacture or Process Phenol
(continued)**

State ^b	Number of Facilities	Total of reported amounts released in pounds per year ^a						
		Air ^c	Water	Land	Underground Injection	POTW ^d Transfer	Off-site Waste Transfer	Total Environment ^e
OH	55	1,237,909	2,288	18,125	460,000	43,438	1,681,659	3,443,419
OK	7	37,511	471	19	0	0	12,455	50,456
OR	18	73,458	625	1	0	2,984	21,868	98,936
PA	32	364,657	2,625	1,021	0	213,875	192,753	774,931
PR	1	640	0	0	0	0	255	895
RI	1	197	0	0	0	2,316	1,642	4,155
SC	24	1,415,260	6,381	8,622	0	807	119,508	1,550,578
TN	17	326,085	345	1,028	0	60,316	57,481	445,255
TX	66	532,158	5,889	2,940	1,343,119	436,982	718,088	3,039,176
UT	3	6,407	32	12,000	0	0	198	18,637
VA	18	250,313	295	68,894	0	26,471	11,531	357,504
VI	1	54,876	1,504	44	0	0	0	56,424
VT	1	9,722	0	0	0	0	0	9,722
WA	12	172,668	1,833	29	0	750	5,454	180,734
WI	30	65,344	990	0	0	29,655	423,747	519,736
WV	7	87,398	635	25	0	0	283,914	371,972
WY	2	5,915	0	10	0	0	0	5,925

Source: TRI96 1998

^aData in TRI are maximum amounts released by each facility

^bPost office state abbreviations used

^cThe sum of fugitive and stack releases are included in releases to air by a given facility

^dPOTW= publicly owned treatment works

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

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Table 5-1 lists amounts released from these facilities. The TRI data should be used with caution, however, since only certain types of facilities are required to report. This is not an exhaustive list.

The most common anthropogenic sources of phenol in natural water include coal tar (Thurman 1982) and waste water from manufacturing industries such as resins, plastics, fibers, adhesives, iron, steel, aluminum, leather, rubber (EPA 1981), and effluents from synthetic fuel manufacturing (Parkhurst et al. 1979). Phenol is also released from paper pulp mills (Keith 1976) and wood treatment facilities (Goerlitz et al. 1985). Other releases of phenol result from commercial use of phenol and phenol-containing products, including slimicides, general disinfectants (Hawley 1981; Budavari et al. 1989), and medicinal preparations such as ointments, ear and nose drops, cold sore lotions, mouthwashes, gargles, toothache drops, analgesic rubs (Douglas 1972), throat lozenges (EPA 1980), and antiseptic lotions (Musto et al. 1977). It has been estimated that 3.8 kg/day of phenol are released to Newark Bay, in New Jersey, from municipal treatment facilities (Crawford et al. 1995). Two natural sources of phenol in aquatic media are animal wastes and decomposition of organic wastes (EPA 1980). No data are available to determine the extent of exposure from these sources.

5.2.3 Soil

According to the TRI, in 1996, the estimated releases of phenol of 159,059 pounds (71,577 kg) to soil from 102 large processing facilities accounted for about 0.7% of total environmental releases (TR196 1998). Table 5-1 lists amounts released from these facilities. The TRI data should be used with caution, however, since only certain types of facilities are required to report. This is not an exhaustive list.

Phenol may be released to the soil during its manufacturing process, loading and transport when spills occur, and when it leaches from hazardous waste sites and landfills (Xing et al. 1994). Generally, data on concentrations of phenol found in soil at sites other than hazardous waste sites are lacking. This may be due in part to a rapid rate of biodegradation and leaching (see Sections 5.3.1 and 5.3.2.3). Phenol can be expected to be found in soils that receive continuous or consistent releases from a point source. Phenol that leaches through soil to groundwater spends at least some time in that soil as it travels to the groundwater. Phenol has been found in groundwater, mainly at or near hazardous waste sites.

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5.3 ENVIRONMENTAL FATE

5.3.1 Transport and Partitioning

Phenol is released into the air and discharged into water from both manufacturing and use. Based on its high water solubility (see Table 3-2) and the fact that it has been detected in rainwater, some phenol may wash out of the atmosphere; however, it is probable that only limited amounts wash out because of the short atmospheric half-life of phenol. During the day, when photochemically produced hydroxyl radical concentrations are highest in the atmosphere, very little atmospheric transport of phenol is likely to occur.

In water, neither volatilization nor sorption to sediments and suspended particulates is expected to be an important transport mechanism. Using the Henry's Law constant, a half-life of 88 days was calculated for evaporation from a model river 1 m deep with a current of 1 m/second, and with a wind velocity of 3 m/second (Lyman et al. 1982). The biological treatment of waste water containing phenol has shown that less than 1% of phenol is removed by stripping (Kincannon et al. 1983; Petrasek et al. 1983).

Phenol has been reported in sediments at up to 608 ppm dry weight; however, it is not known whether the location of the site where this concentration was reported is at or near a point source of release, such as a hazardous waste dump. The average concentration (6.1 ppb dry weight) of the sediment concentration contained in the STORET database (EPA 1988b) and the concentration found in the Pacific Ocean near Los Angeles (10 ppb dry weight) is probably more representative of ambient sediment phenol concentrations. The concentrations of the overlying waters were not reported. The moderately low soil sorption partition coefficient (1.21-1.96) suggests that sorption to sediment is not an important transport process. There is very little sorption of phenol onto aquifer materials (Ehrlich et al. 1982), suggesting that phenol sorption to sediments may also be minimal. Based on the soil adsorption coefficient, phenol released to soil is expected to leach to groundwater; however, the rate of phenol biodegradation in the soil may be so rapid, except in cases of large releases such as spills or continuous releases such as leaching from landfill sites, that the probability of groundwater contamination may be low (Ehrlich et al. 1982). Phenol has been detected in groundwater as a result of leaching through soil from a spill of phenol (Delfino and Dube 1976), from landfill sites (Clark and Piskin 1977), and from hazardous waste sites (Plumb 1987). The sorption coefficient for phenol by soils increases with increasing soil organic matter which may indicate that soil organic matter may be the primary phenol sorbent in soil (Xing et al. 1994).

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Phenol is not expected to bioconcentrate significantly in aquatic organisms. Reported log bioconcentration factors (BCF) in fish for phenol include 0.28 for goldfish, (Kobayashi et al. 1979) and 1.3 for golden orfe (Freitag et al. 1984). The highest mean level of phenol detected in bottom fish from Commencement Bay in Tacoma, WA, was 0.14 ppm (Nicola et al. 1987). The levels of phenol in the water or sediments were not stated.

Since the pK_a of phenol is 9.686 at 20°C it will exist in a partially dissociated state in water and moist soil. Therefore, its transport in these media in the environment would be affected by the pH of the medium.

Although it has been shown that plants readily uptake phenol (Cataldo et al. 1987), bioaccumulation does not take place due to a high rate of respiratory decomposition of phenol to CO₂.

5.3.2 Transformation and Degradation

5.3.2.1 Air

Because phenol absorbs light in the region of 290-330 nm (Sadtler 1960), it might photodegrade directly in the atmosphere. The gas-phase reaction of phenol with photochemically produced hydroxyl radicals is probably a major removal mechanism in the atmosphere. An estimated half-life for phenol for this reaction is 0.61 days (Hendry and Kenley 1979). The reaction of phenol with nitrate radicals during the night may constitute a significant removal process. This is based on a rate constant of 3.8×10^{12} cm³/molecule second for this reaction, corresponding to a half-life of 15 minutes at an atmospheric concentration of 2×10^8 nitrate radicals per cm³ (Atkinson et al. 1987). The reaction of phenol with nitrate radicals present in the atmosphere during smog episodes may decrease the half-life of phenol in polluted atmospheres. The above data indicate that phenol has a short half-life in the atmosphere, probably less than 1 day.

5.3.2.2 Water

Because phenol absorbs light in the region of 290-330 nm (Sadtler 1960), it might photodegrade directly in surface waters. As a class, phenols react relatively rapidly in sunlit natural water via reaction with photochemically produced hydroxyl radicals and peroxy radicals; typical half-lives for hydroxyl and peroxy radical reactions are on the order of 100 and 19.2 hours of sunlight, respectively (Mill and Mabey 1985). The estimated half-life for the reaction of phenol with photochemically produced singlet oxygen in sunlit

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surface waters contaminated by humic substances is 83 days (assuming Switzerland summer sunlight and a singlet oxygen concentration of 4×10^{-14} molar [M]) (Scully and Hoigne 1987). The rate constant for the reaction of phenol with ozone in water has been reported to range from 1.5×10^{-5} to 6×10^{-5} milliseconds⁻¹ (Beltran and Alvarez 1996).

Phenol is readily biodegradable in natural water, provided the concentration is not high enough to cause significant inhibition. Complete degradation in less than 1 day has been reported in water from three lakes; the rates of degradation increase with increasing concentration of phenol and increasing trophic levels of water, and are affected by the concentration of organic and inorganic nutrients in the water (Rubin and Alexander 1983). Complete removal of phenol in river water has been reported after 2 days at 20 °C and after 4 days at 4 °C (Ludzack and Ettinger 1960). The degradation of phenol is somewhat slower in salt water, and a half-life of 9 days has been reported in an estuarine river (Lee and Ryan 1979). Rapid degradation of phenol also has been reported in various sewage and water treatment processes. Removal in aerobic activated sludge reactors is frequently >90% with a retention time of 8 hours (Stover and Kincannon 1983). In aerobic reactors using municipal seed (conventional activated sludge organisms) and in reactors using an industrial seed (mixture of organisms), it was noted that concentrations as low as 50 mg/L inhibited organism respiration rates, but complete inhibition was not observed at concentrations as high as 200 mg/L (Davis et al. 1981). Utilization is also very high in anaerobic reactors, although acclimation periods are longer and degradation usually takes about 2 weeks (Boyd et al. 1983; Healy and Young 1978). One method of phenol breakdown is accomplished by the bacterium *Pseudomonas* sp. CF600, which uses a set of enzymes encoded by the plasmid *dmp* operon (Powlowski and Shingler 1994). The use of sequence batch reactors (SBR) in treating sludge contaminated with phenolic compounds has proven effective in breaking down the compounds biologically with no evidence of phenol volatility (Al-Harazin et al. 1991). Levels as high as a 1-time treatment of 1,600 mg/L can be broken down by 75% with a 1-day retention time. Lower concentrations as high as 800 mg/L can be broken down to less than 0.5 mg/L with a 1-day retention time. The alga *Ochromonas dunica* has also been shown to degrade phenol (Semple and Cain 1996). When grown in the dark with 0.1-1 mM phenol as the sole carbon source, phenol was removed within 3 days. Because of biodegradation, groundwater is generally free of phenol even though it is highly mobile in soil (HSDB 1997). However, monitoring data in Section 5.4.2 contain groundwater concentrations in areas of large phenol releases.

While the evidence presented in the literature cited above suggests that phenol can be rapidly and virtually completely degraded under both natural water and sewage treatment plant conditions, monitoring data

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presented in Section 5.4 below indicate that phenol, despite this apparent biodegradability, is still present in the environment. This suggests that the exact conditions under which phenol is rapidly degraded are not present in all instances. In some situations, the concentration of phenol may be too high or the populations of microorganisms may not be present in sufficient concentration for significant biodegradation to occur.

5.3.2.3 Sediment and Soil

Available data indicate that phenol biodegrades in soil under both aerobic and anaerobic soil conditions. The half-life of phenol in soil is generally less than 5 days (Baker and Mayfield 1980; HSDB 1998), but acidic soils and some surface soils may have half-lives of between 20 and 25 days (HSDB 1998). Mineralization in an alkaline, para-brown soil under aerobic conditions was 45.5, 48, and 65% after 3, 7, and 70 days, respectively (Haider et al. 1974). Half-lives for degradation of low concentrations of phenol in two silt loam soils were 2.70 and 3.51 hours (Scott et al. 1983). Plants have been shown to be capable of metabolizing phenol readily (Cataldo et al. 1987).

While degradation is slower under anaerobic conditions, evidence presented in the literature suggests that phenol can be rapidly and virtually completely degraded in soil under both aerobic and anaerobic conditions (HSDB 1998).

Phenol is not expected to adsorb to sediment in the water column (HSDB 1998).

5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to phenol depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. In reviewing data on phenol levels monitored or estimated 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.

5.4.1 Air

There are very few monitoring data concerning the presence of phenol in ambient air. Phenol was found at a median concentration of 30 parts per trillion (ppt) in seven samples from 1 U.S. urban/suburban site in 1974 and at an overall median concentration of 5,000 ppt in 83 samples from 7 source-dominated sites between

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1974 and 1978 (Brodzinsky and Singh 1982). The individual medians of the 7 source sites ranged from 520 to 44,000 ppt (Brodzinsky and Singh 1982). During a smog episode in West Covina, CA, in July of 1973, phenol concentrations ranged from 16 to 91 ppt, with a mean concentration of 60 ppt (Cronn et al. 1977). Phenol was detected, but not quantified, in air above the Niagara River in September of 1982 (Hoff and Chan 1987). Phenol concentrations in 2 urban areas ranged from 13 to 91 ppt and from <5 to 75 ppb with 50% of all measurements less than 8 ppb (Scow et al. 1981). Phenol was found at approximately 1 ppb in the ambient air near a fishmeal factory in Japan (Hoshika et al. 1981).

Phenol and other volatile organic compounds were measured in the air of 50 homes or apartments in Finland (Kostiainen 1995). The average concentration was 0.23 ppb, with a range of 0-0.77 ppb. Phenol levels were not significantly higher in houses in which people complained of symptoms that resembled those of a sick building syndrome.

5.4.2 Water

Phenol has been detected in surface waters, rainwater, sediments, drinking water, groundwater, industrial effluents, urban runoff, and at hazardous waste sites. Background levels of phenol from relatively pristine sites can be as high as 1 ppb for unpolluted groundwater and have been reported to range from 0.01 to 1 ppb in unpolluted rivers (Thurman 1985). Phenol has been detected in Lake Huron water at 3-24 ppb (Konasewich et al. 1978) and industrial rivers in the United States at 0-5 ppb (Sheldon and Hites 1978, 1979). The annual mean concentration of phenol in water from the lower Mississippi River was 1.5 ppb (EPA 1980). River water in an unspecified location in the United States was reported to contain 10-100 ppb of phenol (Junglaus et al. 1978). Phenol was detected, but not quantified, in a Niagara River watershed (Elder et al. 1981) and in 2 of 110 raw water samples analyzed during the National Organic Monitoring Survey (EPA 1980). In the STORET database, 7% of 2,181 data points for U.S. surface waters were positive for the presence of phenol; the mean and range of the reported concentrations were 533 ppb and 0.002-46,700 ppb, respectively (EPA 1988c).

In general, higher levels of phenol appear to be found in lakes and rivers that serve as water sources and discharge receivers for industrial and population centers, probably as a result of industrial activity and commercial use of phenol-containing products. For example, the presence of higher levels of phenol in the Delaware River near Philadelphia is the result of industrial effluents discharged into the sewer system (Sheldon and Hites 1979).

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The presence of phenol in drinking water probably results from using contaminated surface water or groundwater as a source. Its presence in groundwater is probably the result of release to soil, often industrial releases or leachate from waste dumps, and the subsequent leaching of phenol through the soil to the groundwater. Phenol has been detected, but not quantified, in drinking water in the United States from 5 of 14 drinking water treatment plants (Fielding et al. 1981). It was detected in drinking water in Great Britain between March and December of 1976 in 2 of 4 sites (groundwater source) and in 30% of an unspecified number of sites (surface water source) (Fielding et al. 1981). Phenol levels in tap water, spring water, and mineral water in Italy were 0.58, 0.051, and 0.161 $\mu\text{g/L}$, respectively (Achilli et al. 1995). Phenol was detected at a maximum concentration of 1,130 ppm in 9 wells in Wisconsin after a spill, and was detected for at least 1.5 years after the spill (Delfino and Dube 1976). It was found at concentrations up to 10.4 ppm in groundwater from a sand aquifer adjacent to waste ponds at a wood-preserving facility in Florida (Goerlitz et al. 1985), and was detected at 6.5-10,000 ppb in 2 aquifers 15 months after the completion of a coal gasification project (Stuermer et al. 1982). Phenol was detected at a maximum concentration of 1.9 ppm in leachates from landfill sites in Illinois (Clark and Piskin 1977). Near a landfill in central Florida, phenol was found in groundwater and surface water at about 17 and 15 ppb, respectively (Chen and Zoltek 1995). In the STORET database, 18.3% of 3,443 data points for U.S. groundwaters are positive for the presence of phenol; the mean and range of the reported concentrations are 1.499 ppm (mean) and from not detected to 420 ppm (range) (EPA 1988c). Phenol was detected, but not quantified, in the groundwater at 13.6% of 178 CERCLA hazardous waste sites (Plumb 1987).

Phenol was detected during seven rain events in Portland, OR between February and April of 1984. Concentrations in rain ranged from more than 75 to 1,200 ppt, and averaged above 280 ppt. Gas-phase concentrations ranged from 220 (56.1 ppt) to 410 ng/m^3 (105 ppt) and averaged 320 ng/m^3 (82 ppt) (Leuenberger et al. 1985).

Phenol has been detected in the effluent discharges of a variety of industries. It was found in petroleum refinery waste water at concentrations of 33.5 ppm (Pfeffer 1979) and 100 ppb (Paterson et al. 1996), in the treated and untreated effluent from a coal conversion plant at 4 and 4,780 ppm, respectively (Parkhurst et al. 1979), and in shale oil waste water at a maximum of 4.5 ppm (Hawthorne and Sievers 1984). It has also been detected in the effluent from a chemical specialties manufacturing plant at 0.01-0.30 ppm (Junglaus et al. 1978), in effluent from paper mills at 5-8 ppb (Keith 1976; Paterson et al. 1996), and at 0.3 ppm in a 24-hour composite sample from a plant on the Delaware River, 2 and 4 miles downriver from a sewage treatment plant (Sheldon and Hites 1979).

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Phenol has also been found in the primary and secondary effluent from the Los Angeles City Treatment Plant at concentrations of 32 and <10 ppb, respectively (Young et al. 1983). It was found in 3 of 86 samples of runoff from 2 of 15 cities at 3-10 ppb by the U.S. Nationwide Urban Runoff Program as of July of 1982 (Cole et al. 1984). In the STORET database, 50% of 525 data points for U.S. industrial effluents were positive for the presence of phenol. The mean and range of the reported concentrations were 215 and 1.0-29,000 ppb, respectively (EPA 1988c).

5.4.3 Sediment and Soil

Very few data concerning the presence of phenol in soils were found. Phenol generally does not adsorb very strongly to soils and tends to leach rapidly through soil, which may account for the lack of monitoring data, since any phenol released to soils is likely to leach to groundwater.

Sediment collected 6 km northwest of the Los Angeles County waste-water treatment plant discharge zone at Palos Verdes, CA, contained 10 ppb (dry weight) phenol (Gossett et al. 1983). In the STORET database, 9.7% of 1,158 data points for U.S. sediment were positive for the presence of phenol. The mean and range of the reported concentrations (dry weight) were 6.1 ppm (mean) and from not detected to 608 ppm (range) (EPA 1988c).

5.4.4 Other Environmental Media

Phenol has been reported at concentrations of 7 and 28.6 ppm in smoked summer sausage and smoked pork belly, respectively (EPA 1980), and was identified but not quantified in mountain cheese (Dumont and Adda 1978), fried bacon (Ho et al. 1983), fried chicken (Tang et al. 1983), and black fermented tea (Kaiser 1967). Phenol has also been found in honey at concentrations ranging from 0 (detection limit 0.1 ppm) to 19 ppm (Spoms 1981). It was present each time the honey was collected with phenol-treated boards.

Phenol has been found in bottomfish from 5 sites in Commencement Bay in Tacoma, WA, at a highest maximum average and overall maximum concentration of 0.14 and 0.22 ppm, respectively (Nicola et al. 1987). Phenol has been reported to be a natural component of animal matter; it has been found at 0-1.6 ppm in rabbit muscle tissue (EPA 1980).

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Phenol is also found in medicinal preparations including ointments, ear and nose drops, cold sore lotions, mouthwashes, gargles, toothache drops, and analgesic rubs (Douglas 1972). A commercial antiseptic lotion was reported to contain 1.4% phenol (Musto et al. 1977). Package labeling information indicates that commercial throat lozenges contain up to 29 mg of phenol per lozenge (PDR 1998). Other consumer products such as disinfectants and cleaners may contain concentrations of phenol ranging from 0.45-26% (CA EPA 1998; Forum for Scientific Excellence, Inc. 1990). It has been found that the smoke of 1 nonfilter cigarette contains 60-140 μg of phenol, 19-35 μg for a filter-tipped cigarette, and 24-107 μg in cigars (IARC 1986; NCI 1998).

5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Data concerning concentrations of phenol in ambient air are insufficient to estimate the potential for exposure by inhalation. However, it is known that the smoke of 1 nonfilter cigarette contains 60-140 μg phenol, while levels of phenol range from 19-35 μg in the smoke of filter-tipped cigarettes, and from 24-107 μg in the smoke of cigars (IARC 1986; NCI 1998). Indoor environments polluted with tobacco smoke contain measurable amounts of phenol (Guerin et al. 1982).

Phenol concentrations in surface and drinking waters are expected to vary with location and proximity to varying industrial and municipal discharges. Considering the lack of quantitative, current monitoring data and the probable seasonal, spatial, and temporal variations in the concentrations of phenol at these sources, it is not possible to estimate accurately a potential daily dose of phenol from drinking contaminated water or from dermal exposure to contaminated water. Nonetheless, it is probable that only those systems that receive their water from contaminated surface water and groundwater contain phenol. Ingestion of phenol via consumption of food cannot be estimated from the available data.

Few data concerning occupational exposures to phenol were located. The average airborne concentrations of phenol to which workers were exposed at three locations within two wood creosote impregnation plants ranged from 0.03 to 0.5 ppm (Heikkila et al. 1987). A phenol concentration of approximately 0.5 ppm was measured in the workroom air at a casting factory in Osaka City, Japan (Kuwata et al. 1980), and concentrations as high as 3.2 ppm were measured in Japanese Bakelite factories (Ohtsuji and Ikeda 1972). Considering the lack of quantitative monitoring data for phenol in occupational atmospheres, it is not possible to estimate the potential for occupational exposure to phenol. The data, however, do show that exposure to phenol through breathing and dermal contact with contaminated workroom atmospheres is

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possible. The National Occupational Exposure Survey (NOES) conducted by NIOSH estimated that 584,385 workers were exposed to phenol in the United States (NOES 1990). The NOES database does not contain information on the frequency, concentration, or duration of exposures. The survey provides only estimates of workers potentially exposed to chemicals in the workplace.

Exposure to phenol also occurs through the use and subsequent ingestion of phenol-containing products, including mouthwashes, gargles, toothache drops, (Douglas 1972), and throat lozenges (EPA 1980). Cepastat[®] lozenges, an over-the-counter remedy for sore throats, contain up to 29 mg phenol/lozenge (PDR 1998). If a patient (adults and children over 6) takes the maximum recommended dose of 300 mg phenol/day, this would result in an approximate dose of 4-8 mg/kg/day.

Dermal exposure also occurs through the use of phenol-containing ointments, ear and nose drops, analgesic rubs (Douglas 1972), and antiseptic lotions (Musto et al. 1977). It is not possible to estimate dose levels for these sources given the available data.

The estimated relative contributions of the various exposure routes and sources of total phenol exposure cannot be estimated using the available data. Nonetheless, for persons not exposed to phenol in the workplace, exposure will most likely result from: inhalation of contaminated ambient air, primarily in the vicinity of industries and municipalities that release significant amounts of phenol into the atmosphere; ingestion of drinking water from contaminated surface waters or groundwaters; ingestion of phenol-containing products; and dermal exposure to contaminated water and to phenol-containing products. Dermal contact with phenol or ingestion of phenol-containing products probably constitutes the largest consumer exposure, although this exposure may occur on an acute basis. Inhalation and dermal exposures appear to be most significant in occupational settings. Total phenol exposure for workers exposed to phenol in the workplace is probably substantially higher than for those not exposed in the workplace.

5.6 EXPOSURES OF CHILDREN

This section focuses on exposures from conception to maturity at 18 years in humans and briefly considers potential pre-conception exposure to germ cells. Differences from adults in susceptibility to hazardous substances are discussed in 2.6 Children's Susceptibility.

5. POTENTIAL FOR HUMAN EXPOSURE

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).

Oral, dermal, and combined oral-dermal exposures are the most likely routes by which children will be exposed to phenol. Oral exposure to low levels of phenol among children is likely because many consumer products contain phenol, particularly in medicines such as gargles, tooth drops, throat lozenges, ointments, and others (Douglas 1972; EPA 1980). Products other than medicines that contain phenols include general disinfectants, cleaners, and epoxies.

Accidental phenol poisoning from the ingestion of these products and these mentioned previously could result, depending on the product ingested, since the range of concentrations in consumer products range from 0.45-26% (CA EPA 1998; Douglas 1972; EPA 1980; Forum for Scientific Excellence, Inc. 1990; Musto 1977; Spiller et al. 1993). In the case of accidental ingestion, health effects may be the result of phenol and/or other chemical constituents depending on their concentrations in the product. In a study by Spiller et al. (1993), the mean age of accidental acute exposure cases to a disinfectant containing 26% phenol reported to regional poison control centers was 10 years, and 75% of the cases involved children less than 5 years old.

Some foods containing phenol have been identified (see Section 5.4.4) and could result in low levels of phenol exposure in children. In addition, phenol is produced endogenously as a breakdown product of protein metabolism; normal concentrations in urine generally do not exceed 20 mg/L (ACGIH 1991).

Since phenol can be readily absorbed through the skin (ACGIH 1991), children may be more susceptible to low levels of phenol exposure since they have a higher skin-surface-area to weight ratio. Since young children are more likely to come in contact with the floor and other low-lying areas, they may be exposed to phenol found in consumer products such as general disinfectants used to clean toilets, floors, drains, and other areas (Budavari 1989; CA EPA 1998; Hawley 1981).

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Exposure to phenol through inhalation is a less probable route than oral and dermal. It is known that both cigarettes and cigars contain small amounts (19-140 µg) of phenol (IARC 1986; NCI 1998), and smoking these products indoors produces a measurable amount of phenol (Guerin et al. 1982). If children are present in indoor environments polluted with tobacco smoke, they may be exposed to low levels of phenol.

5.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

Populations with potentially high exposure to phenol generally include those who are exposed to relatively highly contaminated environments over long periods of time. These include populations exposed to both identified and unidentified phenol-containing waste disposal sites and landfills. Populations residing in the vicinity of industries that manufacture or use phenol and large population centers may be exposed to potentially high levels of phenol. Persons who work at establishments that manufacture or use phenol have a risk for high exposure to phenol. Populations that regularly ingest food contaminated with phenol or that regularly ingest or come in contact with phenol-containing products are at risk for high exposure to phenol. Populations that live near a phenol spill site, especially those whose water supply sources are near the spill sites, have a risk for high exposure to phenol. Relatively high exposure may also result from exposure to emissions from municipal waste incinerators and cigarette smoke, although no quantitative data concerning phenol emission from these sources were located.

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 phenol 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 phenol.

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

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5.8.1 Identification of Data Needs

Physical and Chemical Properties. Knowledge of physical and chemical properties is essential for estimating the partitioning of a chemical in the environment. Information about the physical and chemical properties of phenol is available (Hawley 1981; HSDB 1998; IARC 1989), and the database is adequate for the input requirements of environmental models that predict the behavior of a chemical under specific conditions.

Production, Import/Export, Use, Release, and Disposal. According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxics Release Inventory (TRI), which contains this information for 1996, became available in May of 1998. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

Additional production data are available from the Chemical Marketing Reporter (CMR 1996), and import/export data for phenol are available on the National Trade Data Bank (NTDB 1996). Additional data are not needed at this time.

Environmental Fate. Based on the physical properties of phenol, volatilization and sorption of phenol to sediments are not expected to be important transport mechanisms (Lyman et al. 1982). The adsorption of phenol to soils has been shown to increase with increasing organic matter (Xing et al. 1994). Photochemical degradation of phenol is thought to be an important process both in air (Hendry and Kenley 1979) and water (Scully and Hoigne 1987). Phenol is also readily biodegradable (Ludzack and Ettinger 1960; Rubin and Alexander 1983; Scott et al. 1983; Stover and Kincannon 1983). Additional studies that examine the volatilization and sorption of phenol to soil and sediments are needed to help predict the environmental fate of phenol.

Bioavailability from Environmental Media. Data from monitoring studies indicate that phenol is present in the environment (Brodzinsky and Singh 1982; Gossett et al. 1983; Hoff and Ghan 1987; Konasewich et al. 1978; Scow et al. 1981; Sheldon and Hites 1978,1979; Thurman 1985) as well as in environmental organisms (Nicola et al. 1987). Exposure to phenol is most likely to be highest in areas at or near industrial centers and population centers where drinking and bathing water, ambient air, and certain foods, such as fish, are obtained from sources contaminated with phenol. Reliable data on the bioavailability

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of phenol from inhaled air and from skin exposed to phenol vapor have been reported for humans (Piotrowski 1971). Studies of bioavailability of phenol from ingested soil and foods and dermal contact with contaminated water are needed for evaluating the hazards posed by ingesting materials that have been contaminated with phenol.

Food Chain Bioaccumulation. No studies were located regarding the food chain bioaccumulation of phenol from environmental media. Data from monitoring studies indicate that phenol is present in the environment as well as in environmental organisms (Nicola et al. 1987). The available bioaccumulation studies are concerned only with exposure of fish to aqueous concentrations of phenol. Although the results of these studies indicate a low potential for bioaccumulation (see Section 5.3.1), the detection of phenol in fish (see Section 5.4.4) indicates that phenol can be found in aquatic organisms; it is possible that food chain bioaccumulation may occur. A clearer understanding of the potential for bioaccumulation would aid in determining how levels in the environment affect the food chain and potentially impact human exposure levels. A study examining phenol levels in organisms from several trophic levels is needed.

Exposure Levels in Environmental Media. Phenol has been measured in air (Brodzinsky and Singh 1982; Cronn et al. 1977; Scow et al. 1981), water (EPA 1980; Sheldon and Hites 1978, 1979; Thurman 1985), and sediments (Gosset et al. 1983). Additional more recent monitoring data are needed to help estimate human exposure to phenol.

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

Exposure Levels in Humans. Data concerning exposure levels in humans are incomplete and not current (Heikkila et al. 1987; Kuwata et al. 1980; Qhtsuji and Ikeda 1972). A detailed recent database of exposure would be helpful in determining the current exposure levels, thereby allowing the estimation of the average daily dose associated with various scenarios such as living near a hazardous waste site or landfill, or with drinking water containing phenol. An environmental media monitoring program would provide the necessary information for estimating environmental exposures, while a detailed examination of the uses of phenol and the kinds of potential exposure in addition to workplace monitoring would probably provide adequate workplace information. The environmental media that would provide the most useful information

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are air, groundwater, and surface and drinking water in urban and industrial locations, and air, groundwater, and surface water at hazardous waste sites. Performing the monitoring over a 1-year period would allow estimation of seasonal variations.

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

Exposures of Children. Children are likely to be exposed to low levels of phenol from the use of many consumer products including medicines and cleaning agents (Budavari et al. 1989; Douglas 1972; EPA 1980; Hawley 1981). There are no known data that quantify the level of exposure to phenol in children. It is likely that young children may be exposed to low levels of phenol because they come into contact with the floor and other areas where disinfectants containing phenol might be used. More studies are needed to assess whether children differ in their weight-adjusted intake of phenol, as little or no information is known. Studies are needed to measure the baseline phenol level in children's urine in order to use phenol levels in urine as a biomarker of exposure.

Exposure Registries. No exposure registries for phenol 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

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

No additional on-going studies regarding environmental fate or exposure data for phenol were located.

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 phenol, its metabolites, and other biomarkers of exposure and effect to phenol. 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

Analytical methods for the detection of phenol in biological materials are summarized in Table 6- 1. Phenol is expected to be present in blood and urine in its free acid and conjugated forms (glucuronide and sulfate). The average urinary phenol concentration in unexposed individuals is 9.5 ± 3.6 mg/L when corrected to a standard specific gravity of 1.024 (Piotrowski 1971). In exposed individuals, the urinary phenol level may vary from 10 to 200 mg/L (Tesarova and Packova 1983). The two common methods for quantifying conjugated phenol are chemical and enzymatic hydrolysis of the conjugate to the free phenol form. The chemical method uses acidic hydrolysis (Baldwin et al. 1981; Needham et al. 1984). Both the nature of the acid (sulfuric versus perchloric) and the temperature should be controlled carefully to obtain a quantitative yield and to avoid thermal decomposition of other phenolic or related compounds that may interfere with phenol quantification (Baldwin et al. 1981; Rick et al. 1982). The best available method appears to be specific enzyme hydrolysis or hydrolysis at ambient temperature with sulfuric acid. Enzymatic hydrolysis with an extract of *Helix pomatia* has also been used to liberate phenol from its conjugates (Ahmed and Hale 1994).

TABLE 6-1. Analytical Methods for Determining Phenol in Biological Samples

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Whole blood	Sample extracted with ethyl acetate, extract concentrated and analyzed (for free phenol), packed blood cells previously extracted for free phenol incubated with β -glucuronidase containing sulfatase at 37°C, extracted with ethyl acetate after addition of normal saline solution and extract concentrated and analyzed (for conjugated phenol)	GC-FID	<1 mg/mL	97% (free phenol); 103% (conjugated phenol)	O'Grodnick et al. 1983
	Sample with spiked internal standard extracted with ethyl acetate and extract concentrated and analyzed	GC-FID	0.1 mg/L	>90% at concentrations above 0.5 mg/L	Handson and Hanrahan 1983
Urine	Sample mixed with phosphoric acid, passed through a pre-column at 165°C for hydrolysis of conjugates (for free and conjugated phenol) and analyzed	GC-FID	NG	89% (for conjugates)	Baldwin et al. 1981
	Sample refluxed with HClO ₄ , solvent extracted, concentrated, and separated by TLC; spot developed by <i>p</i> -nitro-benzenediazonium fluoroborate, removed quantitatively and solvent extracted (for free and conjugated phenol) and analyzed	Spectrophotometry	NG	NG	Bienick and Wilczok 1986
	Acidified sample steam distilled, reacted with ammonia, <i>N</i> -chloro-succinimide, and sodium nitroprusside at basic pH (method probably for free phenol) and analyzed	Spectrophotometry	0.3 mg/L	>95%	Amlathe et al. 1987

TABLE 6-1. Analytical Methods for Determining Phenol in Biological Samples (*continued*)

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urine (continued)	Sample heated with HCl to 95°C; diethyl ether added; mixture cooled to 0°C and allowed to separate into two phases; clear ether layer used for analysis	GC-FID	0.5 µg/mL	94–95%	NIOSH 1994
	Sample incubated with glucuronidase and sulfatase at pH 5 and 37°C, H ₂ SO ₄ added and steam distilled (total phenol) and analyzed	HPLC-electrochemical detector	2 ng/injection	95–107%	Schaltenbrand and Coburn 1985
	Sample hydrolyzed at room temperature and extracted with methyl <i>tert</i> -butyl ether (total phenol) and analyzed	GC-FID	NG	NG	Rick et al. 1982
	Sample spiked with internal standard, hydrolyzed with H ₂ SO ₄ , and extracted with ethyl acetate (free and conjugated) and analyzed	GC-FID	NG	93–97% at 20–70 mg/L	Needham et al. 1984
	Sample spiked with internal standard, distilled with H ₂ SO ₄ in a special apparatus, distillate directly injected into GC (free and conjugated)	GC-FID	0.1 mg/L	99% at 5.9 mg/L	Van Roosmalen et al. 1981

FID = flame ionization detector; GC = gas chromatography; H₂SO₄ = sulfuric acid; HCl = hydrochloric acid; HClO₄ = perchloric acid; HPLC = high performance liquid chromatography; NG = not given; TLC = thin layer chromatography

6. ANALYTICAL METHODS

High-performance liquid chromatographic separation with electrochemical detection may provide the best sensitivity for phenol quantification in biological samples. The use of gas chromatography with a flame ionization detector may be a more versatile method, if other non-ionic pollutants must be quantified. The advantages and disadvantages of different methods available for the quantification of phenol and metabolites in biological and environmental samples have been discussed by Tesarova and Packova (1983).

The level of phenol detected in blood or urine may not accurately reflect actual phenol exposure because phenol may also appear as a metabolite of benzene or other drugs. It has been shown that under certain acidic conditions used for the hydrolysis of conjugated phenols, acetyl salicylic acid (aspirin) may produce phenol (Baldwin et al. 1981) and yield spuriously higher values for phenol in blood and urine.

For occupational exposure, it is recommended that urine samples be collected at the end of an 8-hour work shift (ACGIH 1991). Small amounts of thymol can be used as a preservative, and the urine can be stored for 4 days if refrigerated, or at least 3 months if frozen

6.2 ENVIRONMENTAL SAMPLES

Analytical methods for detecting phenol in environmental samples are summarized in Table 6-2. The accuracy and sensitivity of phenol determination in environmental samples depends on sample preconcentration and pretreatment and the analytical method employed. The recovery of phenol from air and water by the various preconcentration methods is usually low for samples containing low levels of phenol. The two preconcentration methods commonly used for phenols in water are adsorption on XAD resin and adsorption on carbon. Both can give low recoveries, as shown by Van Rossum and Webb (1978). Solvent extraction at acidic pH with subsequent solvent concentration also gives unsatisfactory recovery for phenol. Even during carefully controlled conditions, phenol losses of up to 60% may occur during solvent evaporation (Handson and Hanrahan 1983). The in situ acetylation with subsequent solvent extraction as developed by Sithole et al. (1986) is probably one of the most promising methods.

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Urban air	Sample collected in bubbler containing NaOH, derivatized as nitrobenzeneazo compound	HPLC-UV	0.05 ppb for 150-L sample; 58–60% at 0.33–0.5 µg phenol	72.3% at 10–50 µg phenol	Kuwata et al. 1980
Occupational air	Sorption on activated carbon, desorption by solvent and derivatized to trimethylsilyl product	GC-FID	0.5 mg/m ³ (0.13 ppm)	96–102% at 2.5–100 mg/m ³	Yrjanheikki 1987
	Sorption on XAD-2, desorption by acetonitrile and concentrated if necessary	HPLC-electrochemical detector and HPLC-UV	8 µg/m ³ (2.04 ppb) with 12 L air (electrochemical); 0.16 mg/m ³ (0.04 ppm) with 12 L air (UV)	NG	Nieminen and Heikkilä 1986
	Sample collected with a thermal desorption tube using a sorbent capable of capturing a C ₆ organic compound	GC-MS	100 ng/tube or less	NA	NIOSH 1994
Total particulate matter in cigarette smoke	Extract particulate matter with NaOH, buffer to a pH 4.6	HPLC-fluorescence spectrophotometer	0.3 mg/L	91% at 20–30 µg	Tomkins et al. 1984
Industrial emission, auto exhaust, and tobacco smoke	Sample collected in NaOH bubbler and derivatized to <i>p</i> -nitrobenzene-diazonium tetrafluoroborate	HPLC-UV	0.05 ppb for 150 L sample	NG	Kuwata et al. 1980

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Drinking water, waste water, natural water	Direct distillation or distillation of solvent-cleaned sample (if necessary) at acidic pH, react with 4-amino-antipyrine and potassium ferricyanide at pH 8, extract in chloroform	Spectrophotometric	1 µg/L for 500-mL sample	NG	APHA/AWWA/WPCF 1985
Waste water and natural water	None	GC-FID	<1 mg/L	NG	APHA/AWWA/WPCF 1985
Water	Direct distillation or distillation of solvent-cleaned sample at acidic pH, react with 4-amino antipyrine and potassium ferricyanide at pH 10 or extract colored complex in chloroform	Spectrophotometric (ASTM Method D-1783)	<5 µg/L (chloroform extract); <0.1 mg/L (direct)	NG	ASTM 1978
Water, waste water	Acidified sample extracted with solvent, concentrated or derivatized to pentafluorobenzylbromide product	GC-FID; GC-ECD (for derivatized EPA Method 604)	0.14 µg/L (FID); 2.2 µg/L (ECD)	41% (FID); NG (ECD)	EPA 1982
	Sample extracted in acidic pH, extract concentrated	GC-MS (EPA Method 625); HRGC-MS (EPA Method 625.1)	1.5 µg/L (GC-MS); 1–10 µg/L (HRGC-MS)	36% (GC-MS) at 10–1,500 µg/L; 25% (GC-MS) at 8.3 µg/L; 42% (HRGC-MS) at 20 µg/L	Eichelberger et al. 1983; EPA 1982
Water	Sample passed through graphitized carbon black, eluted with methylene chloride	Ion-suppression; reversed phase LC with UV detection	50–100 ng/L	91–97%	Di Corcia et al. 1996

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Water	Sample passed through a mixed XAD-4/8 column, solvent eluted and concentrated	GC-MS	NG	46–70% (distilled water); 9% (tap water)	Van Rossum and Webb 1978
Waste water	Distillation of acidified solution, reacted with ammonia, <i>N</i> -chloro-succinimide, and sodium nitro-prusside at basic pH	Spectrophotometric	<0.3 mg/L	96.7% at 3 mg/L	Amlathe et al. 1987
Potable water and raw source water	Sample acetylated <i>in situ</i> by addition of acetic anhydride, solvent extracted and concentrated; alternatively, extracted acidic sample derivatized by pentafluorobenzyl bromide and cleaned up by column chromatography	HRGC-ECD (for pentafluorobenzyl derivative); HRGC-MS (for acetyl derivative)	<50 ng/L (pentafluorobenzyl); <50 ng/L (acetyl derivative)	10–64% (pentafluorobenzyl derivative); 70–132% (acetyl derivative)	Sithole et al. 1986
Sediment	Homogenized sample solvent extracted at acidic pH, fractionated by GPC and fractions concentrated	HRGC-MS	NG	112–128% at 400 ng/g	Lopez-Avila et al. 1983
Groundwater	Solvent extraction in acidic pH, extract concentrated	GC-MS (EPA-CLP Method)	10 µg/L	NG	EPA 1987
Soil, sediment	Sample mixed with anhydrous powdered Na ₂ SO ₄ , solvent extracted ultrasonically, extract subjected to GPC if necessary, extract concentrated	GC-MS (EPA-CLP Method)	330 µg/kg	NG	EPA 1987
Water and waste water	Phenols separated on a Nova-Pak Phenyl column eluted with ammonium acetate:acetonitrile	LC-ED	0.5 mg/L	91–100%	Paterson et al. 1996

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference
Groundwater	Solvent extraction, column chromatographic cleanup, concentration of extract	GC-MS (EPA Method 8250A)	1.5 mg/L	$(0.43c+1.26)/c \times 100$ where c is the actual concentration	EPA 1994a
Soil, sludge, or solid waste	Extracted by soxhlet or sonication, extract subjected to column chromatographic cleanup and concentrated	GC-MS (EPA Method 8250A)	1.5 mg/kg	$(0.43c+1.26)/c \times 100$ where c is the actual concentration	EPA 1994a
Groundwater	Solvent extraction, column chromatographic cleanup, concentration of extract	HRGC-MS (EPA Method 8270B)	10 μ g/L	$(0.43c+1.26)/c \times 100$ where c is the actual concentration	EPA 1994b
Soil, sludge, and solid waste	Extracted soxhlet or sonication, extract subjected to column chromatographic cleanup, concentrated	HRGC-MS (EPA Method 8270C)	660 μ g/kg	$(0.43c+1.26)/c \times 100$ where c is the actual concentration	EPA 1996b
Honey	Sample dissolved in water, steam distilled; distillate cleaned up by column chromatography	HPLC-UV	0.1 ppm (for 10 g sample)	98% at 111 μ g added phenol	Sporns 1981

C_6 = 6 carbon; ECD = electron capture detector; ED = electrochemical detection; FID - flame ionization detector; GC = gas chromatography; GPC = gel permeation chromatography; HPLC = high performance liquid chromatography; HRGC = high resolution gas chromatography; LC = liquid chromatography; MS = mass spectrometry; Na_2SO_4 = sodium sulfate; NaOH = sodium hydroxide; NG = not given; UV = ultraviolet detection

6. ANALYTICAL METHODS

Capillary columns may provide the best method for the separation of phenols prior to their quantification (Eichelberger et al. 1983; Shafer et al. 1981; Sithole et al. 1986). Of the various methods available for detection, the two commonly used methods that are most sensitive are mass spectrometry and flame ionization detection. Although electron capture detectors provide good sensitivities for higher chlorine-substituted phenols, they are poor for phenol itself (Sithole et al. 1986). The best method for the quantification of phenol may be mass spectrometric detection in the selected ion mode, but the loss of qualitative information may be significant (Eichelberger et al. 1983).

6.3 ADEQUACY OF THE DATABASE

Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of phenol 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 phenol.

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

6.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect. Measurement of total phenol in urine serves as a biomarker of exposure for persons occupationally exposed to phenol (ACGIH 1991). Specific biomarkers used to characterize effects caused by phenol have not been identified. Dark urine has been reported in persons occupationally exposed to phenol (inhalation, dermal) (ACGIH 1991; Merliss 1972) and following oral exposure (Baker et al. 1978; Kim et al. 1994). The dark urine may be a result of an oxidation product of phenol, or hemoglobin and hemoglobin breakdown products. Further research is required to identify the cause of the dark urine and relate it to exposure concentration.

6. ANALYTICAL METHODS

Methods for Determining Parent Compounds and Metabolites in Biological Materials. The analytical methods available (Amlathe et al. 1987; Baldwin et al. 1981; Bieniek and Wilczok 1986; Handson and Han&an 1983; Needham et al. 1984; O'Grodnick et al. 1983; Rick et al. 1982; Schaltenbrand and Coburn 1985; Van Roosmalen et al. 1981) are adequate for the quantification of phenol and its conjugates in biological samples. The study of the levels of parent compound in human blood, urine, or other biological matrices can be useful in deriving a correlation between the levels of this compound found in the environment and those found in human tissue or body fluid.

The changes in metabolite concentrations in human blood, urine, or other appropriate biological media over time may be useful in estimating phenol's rate of metabolism in humans. In some instances, the quantification of metabolites may be useful in correlating the exposure doses to the human body burden. Studies that correlate phenol exposure with levels of metabolites in human biological matrices are not available for this compound, although analytical methods for the quantification of the metabolites are available.

Methods for Determining Parent Compounds and Degradation Products in Environmental Media. The analytical methods available (Eichelberger et al. 1983; EPA 1982,1986b, 1987; Kuwata et al. 1980; Nieminen and Heikkila 1986; NIOSH 1994; Sithole et al. 1986; Tomkins et al. 1984; Van Rossum and Webb 1978; Yrjanheikki 1978) are adequate for the quantification of phenol in environmental materials. Knowledge of the levels of this compound in environmental media, such as air, water, and food, can be used to indicate exposure of humans to this compound through the inhalation of air and ingestion of drinking water and foods containing phenol.

Although the products of environmental biotic and abiotic degradation of phenol have been identified adequately, no systematic study measuring the concentrations of the degradation products in the environment was found. Analytical methods are available for determining the levels of the degradation products such as hydroxylated phenol. Knowledge of the levels of degradation products would allow the development of a monitoring program designed to assess the ambient concentrations of phenol degradation products in the environment. Such a program could provide information concerning both human and environmental exposure to phenol since it might allow an estimation of the concentration of phenol in the environment prior to degradation.

6. ANALYTICAL METHODS

6.3.2 Ongoing Studies

The Environmental Health Laboratory Sciences Division of the National Center for Environmental Health, Centers for Disease Control and Prevention, is developing methods for the analysis of phenol and other volatile organic compounds in blood. These methods use purge and trap methodology, high resolution gas chromatography, and magnetic sector mass spectrometry, which gives detection limits in the low parts per trillion (ppt) range.

A search of federal research programs has indicated that no additional research is in progress for improving the method of phenol quantification in biological or environmental samples.

7. REGULATIONS AND ADVISORIES

International, national, and state regulations and guidelines pertinent to human exposure to phenol are summarized in Table 7-1. The IARC classification for phenol is Group 3, not classifiable with regard to its carcinogenicity to humans (IARC 1989).

The permissible exposure limit time-weighted average (PEL-TWA) is 5 ppm (OSHA 1997). ACGIH (1998) and NIOSH (1992) also recommend a TWA exposure limit of 5 ppm for occupational exposure.

Phenol is regulated by the Clean Water Effluent Guidelines for the following industrial point sources: electroplating, organic chemicals, steam electric, asbestos, timber products processing, metal finishing, paving and roofing, paint formulating, ink formulating, gum and wood, carbon black, metal molding and casting, aluminum forming, and electrical and electronic components (EPA 1988a). EPA has established a Reportable Quantity (RQ) of 1,000 pounds (EPA 1998b). The lifetime health advisory for phenol in water is 4 mg/L (EPA 1996a). The EPA cancer classification for phenol is D, not classifiable as to human carcinogenicity (IRIS 1998).

The EPA reference dose (RfD) of 0.6 mg/kg/day (IRIS 1998) is based on a NOAEL of 60 mg/kg/day for developmental effects (decreased fetal body weights) observed in rats at a dose of 120 mg/kg/day (Jones-Price et al. 1983a).

7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Phenol

Agency	Description	Information	References
<u>INTERNATIONAL</u>			
IARC	Carcinogenic classification	Group 3 ^a	IARC 1989
<u>NATIONAL</u>			
Regulations:			
a. Air:			
OSHA	PEL-TWA	5 ppm (19 mg/m ³)	OSHA 1997 (29 CFR 1910.1000)
b. Other:			
EPA	Reportable quantity	454 kg (1,000 lbs)	EPA 1998b (40 CFR 302.4)
	Required reporting under Title III SARA	Yes	EPA 1998c (40 CFR 372)
	Designated as a hazardous substance	Yes	EPA 1998a (40 CFR 116.4)
FDA	Indirect food additive	Yes	FDA 1998b (21 CFR 175 subsections 300, 380, & 390) FDA 1998c (21 CFR 176.170) FDA 1998d (21 CFR 177 subsections 1210, 1580, 2410, & 2600)
Guidelines:			
a. Air:			
ACGIH	TLV-TWA	5 ppm (19 mg/m ³)	ACGIH 1998
EPA	RfC (inhalation)	None listed	IRIS 1998
NIOSH	REL (TWA)	5 ppm (19 mg/m ³)	NIOSH 1997
	REL (ceiling)	15.6 ppm (60 mg/m ³)	NIOSH 1997
b. Water:			
EPA	MCLG	None listed	EPA 1996c
	MCL	None listed	EPA 1996c
	Health advisories:		EPA 1996c
	1-day (child)	6 mg/L	
	1-day (adult)	None listed	
	10-day (child)	6 mg/L	
	10-day (adult)	None listed	
	Longer term (child)	6 mg/L	
	Longer term (adult)	20 mg/L	
	Lifetime	4 mg/L	
	DWEL	20 mg/L	EPA 1996c
	Ambient water quality criteria for protection of human health		IRIS 1996
	Water and fish	3.5 mg/L	
	Fish only	None	

7. REGULATIONS AND ADVISORIES

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

Agency	Description	Information	References
<u>NATIONAL (Continued)</u>			
	Ambient water quality criteria for aquatic organisms		IRIS 1996
	Freshwater (acute)	10 .2 mg/L	
	Freshwater (chronic)	2.56 mg/L	
	Marine (acute)	5.8 mg/L	
	Marine (chronic)	None listed	
b. Other:			
ACGIH	Biological exposure index	250 mg/ g creatinine	ACGIH 1998
EPA	RfD (oral)	0.6 mg/kg/day	IRIS 1998
EPA	CEGL	None listed	IRIS 1996
	Carcinogenic classification	Group D ^c	IRIS 1998
<u>STATE</u>			
Regulations:			
a. Air:	Acceptable ambient air concentrations		
Connecticut	(30 min)	1900 µg/m ³	CT Bureau Air Manage 1998
	(8 hour)	380 µg/m ³	CT Bureau Air Manage 1998
Louisiana	(8 hour)	452 µg/m ³	LA Air Qual. Div. 1998
Massachusetts	(24 hour)	52.33 µg/m ³	MA Div. Air Qual. Con. 1998
New Hampshire		63 µg/m ³	NH Air Res. Div. 1998
New York	(Short term)	4500 µg/m ³	NY Div. Air Res 1998
	(1 year)	9.6 µg/m ³	NY Div. Air Res 1998
North Dakota	(8 hour)	190 µg/m ³	ND Env. Health Sec. 1998a
South Carolina		190 µg/m ³	SC Bureau Air Qual. 1998
Vermont	(8 hour)	1900 µg/m ³	VT Air Pol. Control Div. 1998
Washington	(24 hour)	63 µg/m ³	WA Air Qual. Program 1998
b. Water:			
Kentucky	Domestic Water Supply	3.5 mg/L	KY Div. Water 1998
Louisiana	Drinking Water Supply	5 µg/L	LA Water Res. Div. 1998
Mississippi	Human Health (Water and Organisms)	300 µg/L	MS Sur. Water Div. 1998
Missouri	Drinking Water Supply	100 µg/L	MO Water Pol. Con. Pro. 1998
Nevada	Municipal or Domestic Supply	3.5 mg/L	NV Water Res. Div. 1998
New Hampshire	Human Health (Water and Organisms)	21 mg/L	NH Water Sup. Pol. Con. 1998
North Dakota	Human Health (Water and Organisms)	21 mg/L	ND Env. Health Sec. 1998b

7. REGULATIONS AND ADVISORIES

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

Agency	Description	Information	References
<u>STATE</u> (Continued)			
Oklahoma	Human Health (Water and Organisms)	20.9 mg/L	OK Water Qual. Div. 1998
Pennsylvania	Human Health (Water and Organisms)	300 µg/L	PA Bureau Water Sup. Com. Health 1998
Rhode Island	Human Health (Water and Organisms)	21 mg/L	RI Div. Water Res. 1998
South Dakota	Human Health (Water and Organisms)	21 mg/L	SD Office Drink. Water 1998
South Carolina	Human Health	3.5 mg/L	SC Div. Water Res. 1998
Tennessee	Human Health (Water and Organisms)	21 mg/L	TN Water Pol. Con. 1998
Utah	Domestic Purposes	21 mg/L	UT Div. Drink. Water 1998
Vermont	Human Health (Water and Organisms)	21 mg/L	VT Water Qual. Div. 1998
Virginia	Human Health (Water and Organisms)	21 mg/L	VA Dept. Env. Qual. 1998
Wyoming	Human Health	21 mg/L	WY Water Qual. Div. 1998

^aGroup 3: Not classifiable as to its carcinogenicity to humans

^bGroup A4: Not classifiable as a human carcinogen

^cGroup D: Not classifiable as to human carcinogenicity

ACGIH = American Conference of Governmental Industrial Hygienists; CEGL = continuous exposure guidance level; CFR = Code of Federal Regulations; DWEL = Drinking Water Equivalent Level; EPA = Environmental Protection Agency; IARC = International Agency for Research on Cancer; MCL = Maximum Concentration Level; MCLG = Maximum Concentration Level Goal; NIOSH = National Institute for Occupational Safety and Health; OSHA = Occupational Safety and Health Administration; PEL = Permissible Exposure Limit; REL = Recommended Exposure Limit; RfC = Reference Concentration; SARA = Superfund Amendments and Reauthorization Act; TLV = Threshold Limit Value; TWA = Time-Weighted Average

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9. GLOSSARY

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

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

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

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

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

Carcinogen-A chemical capable of inducing cancer.

Ceiling Value-A concentration of a substance that should not be exceeded, even instantaneously.

Chronic Exposure-Exposure to a chemical for 365 days or more, as specified in the Toxicological Profiles.

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

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

EPA Health Advisory-An estimate of acceptable drinking water levels for a chemical substance based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

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

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

9. GLOSSARY

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_{L10} (LC_{L0})-The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

Lethal Concentration₍₅₀₎ (LC₅₀)-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₍₁₀₎ (LD₁₀)-The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

Lethal Dose₍₅₀₎ (LD₅₀)-The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time₍₅₀₎ (LT₅₀)-A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

lowest-Observed-Adverse-Effect Level (LOAEL)-The lowest dose of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

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

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

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

Monte Carlo - A statistical technique commonly used to quantitatively characterize the uncertainty and variability in estimates of exposure or risk. The analysis uses statistical sampling techniques to obtain a probabilistic approximation to the solution of a mathematical equation or model.

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

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

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

9. GLOSSARY

Permissible Exposure Limit (PEL)-An allowable exposure level in workplace air averaged over an 8-hour Shift

q₁*-The upper-bound estimate of the low-dose slope of the dose-response curve as determined by the multistage procedure. The q₁* can be used to calculate an estimate of carcinogenic potency, the incremental excess cancer risk per unit of exposure (usually µg/L for water, mg/kg/day for food, and µg/m³ for air).

Reference Dose (RfD)-An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure of the human population to a potential hazard that is likely to be without risk of deleterious effects during a lifetime. The RfD is operationally derived from the NOAEL (from animal and human studies) by a consistent application of uncertainty factors that reflect various types of data used to estimate RfDs and an additional modifying factor, which is based on a professional judgment of the entire database on the chemical. The RfDs are not applicable to nonthreshold effects such as cancer.

Reportable Quantity (RQ)-The quantity of a hazardous substance that is considered reportable under CERCLA. Reportable quantities are (1) 1 pound or greater or (2) for selected substances, an amount established by regulation either under CERCLA or under Sect. 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity-The occurrence of adverse effects on the reproductive system that may result from exposure to a chemical. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

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

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

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

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

Time-Weighted Average (TWA)-An allowable exposure concentration averaged over a normal 8-hour workday or 40-hour workweek.

Toxic Dose (TD₅₀)-A calculated dose of a chemical, introduced by a route other than inhalation, which is expected to cause a specific toxic effect in 50% of a defined experimental animal population.

Uncertainty Factor (UF)-A factor used in operationally deriving the RfD from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using LOAEL data rather than NOAEL data. Usually each of these factors is set equal to 10.

APPENDIX A

ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99-499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

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

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

APPENDIX B

USER'S GUIDE

Chapter 1

Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

Chapter 2

Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1) 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 2-1 and Figure 2-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

LEGEND

See LSE Table 2-1

- (1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data

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exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures.

- (2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15-364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.
- (3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).
- (4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 2-1).
- (5) Species The test species, whether animal or human, are identified in this column. "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 2.3, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.
- (6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to 1,1,2,2-tetrachloroethane via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.
- (7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.
- (8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for

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the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote “b”).

- (9) LOAEL A lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into “Less Serious” and “Serious” effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs .
- (10) Reference The complete reference citation is given in chapter 8 of the profile.
- (11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.
- (12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote “b” indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND

See Figure 2-1

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

- (13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.
- (14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.
- (15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale “y” axis. Inhalation exposure is reported in mg/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

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NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote “b” in the LSE table).

- (17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.
- (18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA’s Human Health Assessment Group’s upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1^*).
- (19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health end points by addressing the following questions.

- 1 . What effects are known to occur in humans?
- 2 . What effects observed in animals are Likely to be of concern to humans?
- 3 . What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers end points in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

SAMPLE

1

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

2

3

4

Key to figure ^a	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)		
INTERMEDIATE EXPOSURE							
	5	6	7	8	9		10
Systemic	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5d/wk 6hr/d	Resp	3 ^b	10 (hyperplasia)		Nitschke et al. 1981
<hr style="border-top: 1px dashed black;"/>							
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

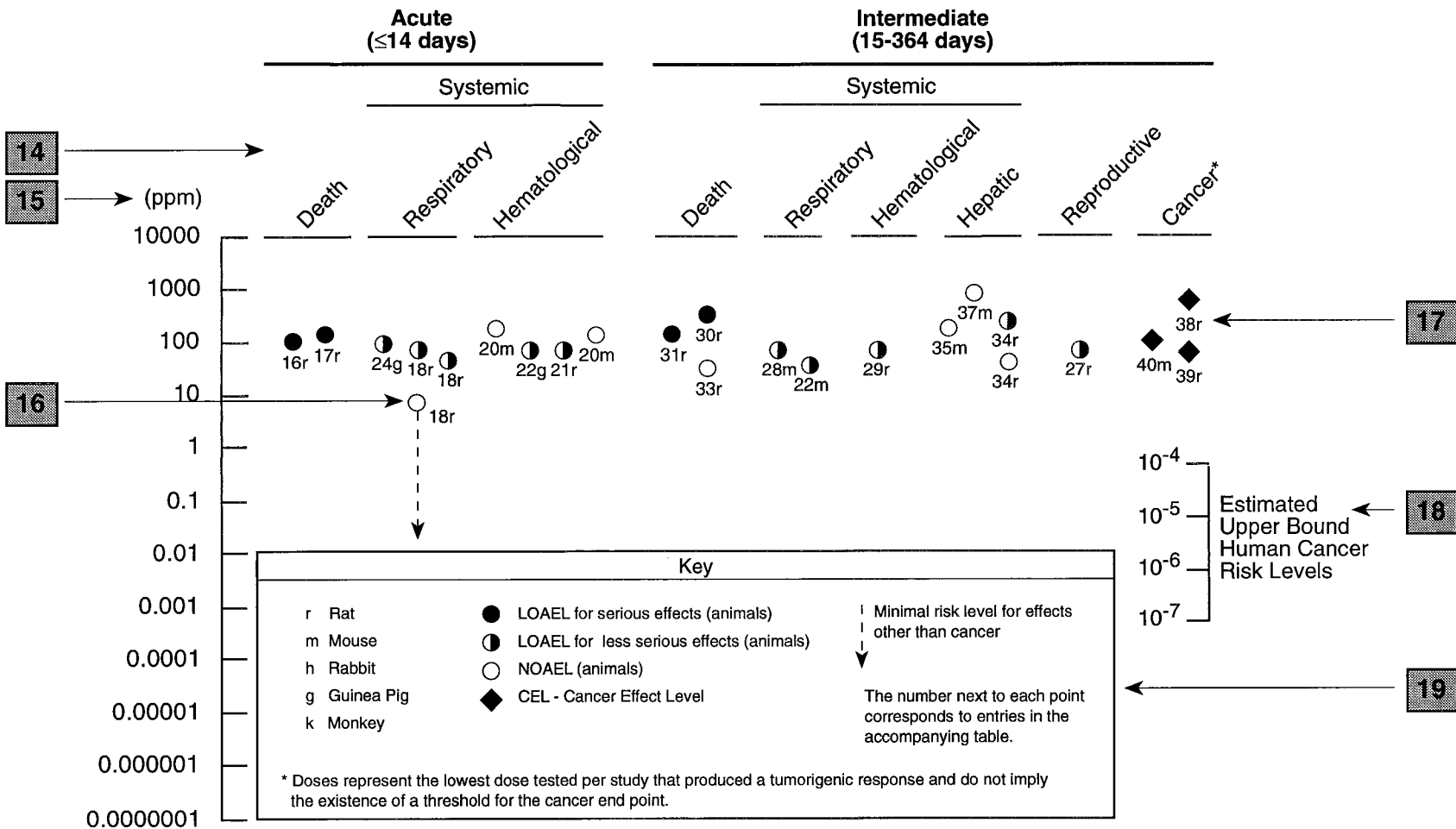
12

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

^b 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

APPENDIX B

Chapter 2 (Section 2.5)

Relevance to Public Health

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2.5, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.8, "Interactions with Other Substances," and 2.9, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UP) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

APPENDIX C**ACRONYMS, ABBREVIATIONS, AND SYMBOLS**

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
AML	acute myeloid leukemia
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
d	day
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
F	Fahrenheit
F ₁	first filial generation
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
fpm	feet per minute
ft	foot
FR	<i>Federal Register</i>
g	gram
GC	gas chromatography
gen	generation
HPLC	high-performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health

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IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
K _d	adsorption ratio
kg	kilogram
kkg	metric ton
K _{oc}	organic carbon partition coefficient
K _{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC _{Lo}	lethal concentration, low
LC ₅₀	lethal concentration, 50% kill
LD _{Lo}	lethal dose, low
LD ₅₀	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	<u>trans,trans</u> -muconic acid
mCi	millicurie
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
NCE	normochromatic erythrocytes
NG	not given
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
ng	nanogram
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration

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PEL	permissible exposure limit
PCE	polychromatic erythrocytes
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short term exposure limit
STORET	STORAGE and RETRIEVAL
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
UMDNJ	University of Medicine and Dentistry New Jersey
U.S.	United States
UF	uncertainty factor
yr	year
WHO	World Health Organization
wk	week
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micrometer
μg	microgram

