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TOXICOLOGICAL PROFILE FOR CRESOLS

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

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DISCLAIMER

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UPDATE STATEMENT

A Toxicological Profile for Cresols, Draft for Public Comment was released in October 2006. This edition supersedes any previously released draft or final profile.

Toxicological profiles are revised and republished as necessary. 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.

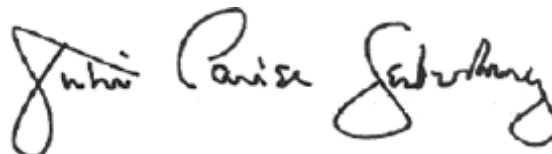
The principal audiences for the toxicological profiles are health professionals at the Federal, State, and local levels; interested private sector organizations and groups; and members of the public.

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 December 7, 2005 (70 FR 72840). For prior versions of the list of substances, see Federal Register notices dated 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); February 28, 1994 (59 FR 9486); April 29, 1996 (61 FR 18744); November 17, 1997 (62 FR 61332); October 21, 1999 (64 FR 56792); October 25, 2001 (66 FR 54014) and November 7, 2003 (68 FR 63098). Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the list.

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@AOEC.ORG • Web Page: <http://www.aoec.org/>.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266.

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THE PROFILE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEWS:

1. Health Effects Review. The Health Effects Review Committee examines the health effects chapter of each profile for consistency and accuracy in interpreting health effects and classifying end points.
2. Minimal Risk Level Review. The Minimal Risk Level Workgroup considers issues relevant to substance-specific Minimal Risk Levels (MRLs), reviews the health effects database of each profile, and makes recommendations for derivation of MRLs.
3. Data Needs Review. The Applied Toxicology Branch reviews data needs sections to assure consistency across profiles and adherence to instructions in the Guidance.
4. Green Border Review. Green Border review assures the consistency with ATSDR policy.

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PEER REVIEW

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

1. David Kalman, Ph.D., Chair and Professor, Department of Environmental and Occupational Health Sciences, University of Washington, Health Sciences Building, F-463, Seattle, Washington;
2. John R. Balmes, M.D., Professor, Pulmonary and Critical Care Division, University of California San Francisco, San Francisco General Hospital, San Francisco, California; and
3. Rolf Hartung, Ph.D., DABT, Consultant in Environmental Toxicology, Professor of Environmental Toxicology (Retired), University of Michigan, 3125 Fernwood Avenue, Ann Arbor, Michigan.

These experts collectively have knowledge of cresol'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.

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 cresols and the effects of exposure to these substances.

The Environmental Protection Agency (EPA) identifies the most serious hazardous waste sites in the nation. These sites are then placed on the National Priorities List (NPL) and are targeted for long-term federal clean-up activities. *o*-Cresol, *m*-cresol, *p*-cresol, and mixed cresols have been identified in at least 210, 22, 310, and 70 of the 1,678 current or former NPL sites, respectively. Although the total number of NPL sites evaluated for these substances is not known, the possibility exists that the number of sites at which cresols are found may increase in the future as more sites are evaluated. This information is important because these sites may be sources of exposure, and exposure to these substances may be harmful.

When a substance is released either from a large area, such as an industrial plant, or from a container, such as a drum or bottle, it enters the environment. Such a release does not always lead to exposure. You can be 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 cresols, many factors will determine whether you will 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 any other chemicals you are exposed to and your age, sex, diet, family traits, lifestyle, and state of health.

1. PUBLIC HEALTH STATEMENT

1.1 WHAT ARE CRESOLS?

Description	<p>Three types (or isomers) of cresols exist: <i>ortho</i>-cresol, <i>meta</i>-cresol, and <i>para</i>-cresol; abbreviated as <i>o</i>-cresol, <i>m</i>-cresol, and <i>p</i>-cresol.</p> <p>Pure cresols are solid, while mixtures tend to be liquid.</p> <p>Cresols have a medicinal smell.</p>
Uses <ul style="list-style-type: none"> • Manufacturing • Consumer products 	<p>Cresols are both manufactured chemicals and natural components in many foods. Large amounts of cresols are produced in the United States.</p> <p>Cresols are used to manufacture other chemicals and as solvents.</p> <p>Cresols kill microorganisms and are added to soaps as disinfectants.</p>

For more information on the physical and chemical properties of cresols, and their production, disposal and use, see Chapters 4 and 5.

1.2 WHAT HAPPENS TO CRESOLS WHEN THEY ENTER THE ENVIRONMENT?

Sources	Cresols are released to the environment during the burning of wood, coal, and fossil fuels, as well as from their manufacture and the use of products containing cresols.
Break down <ul style="list-style-type: none"> • Air • Water • Soil 	<p>Cresols are quickly broken down in the air, usually within 1–2 days. They can also be removed from the air by rain.</p> <p>Cresols in water are degraded within days by microorganisms.</p> <p>Cresols are degraded rapidly in soil by microorganisms, but a portion may move into groundwater.</p>

For more information on cresols in the environment, see Chapter 6.

1. PUBLIC HEALTH STATEMENT

1.3 HOW MIGHT I BE EXPOSED TO CRESOLS?

Air—primary source of exposure	<p>The primary way you can be exposed to cresols is by breathing air containing them. Releases of cresols into the air occur from:</p> <ul style="list-style-type: none"> • industries using or manufacturing cresols • automobile exhaust • cigarette smoke • wood and trash burning <p>A national emissions study conducted from 1990 to 1998 reported an average county-level concentration of 31.7 nanograms per cubic meter (ng/m³) for all cresol isomers combined.</p>
Water	<p>Cresols have been detected in surface waters and groundwater, but generally at low levels (approximately 1 microgram per liter [µg/L] or less).</p> <p>Higher levels have been detected:</p> <ul style="list-style-type: none"> • where petroleum spills have occurred • near hazardous waste sites • in industrial effluents
Workplace	<p>A large number of workers are potentially exposed to cresols. Potential exposures occur in:</p> <ul style="list-style-type: none"> • manufacture of cresols • chemical laboratories • coal gasification facilities • paint and varnish application • application of insulation lacquers to copper wires • wood-preserving facilities <p>Exposure may occur through breathing and dermal contact with contaminated air and/or liquid cresols or products containing cresols.</p>
Food	<p>Low levels of cresols have been found in some foods such as tomatoes, tomato ketchup, asparagus, cheeses, butter, bacon, and smoked foods.</p> <p>Some drinks also contain cresols (coffee, black tea, wine, Scotch whisky, brandy, and rum).</p>
Consumer products	<p>Exposure may occur through accidental or intentional ingestion or contact of the skin with cleaners or disinfectants containing cresols.</p>

For more information on human exposure to cresols, see Chapter 6.

1. PUBLIC HEALTH STATEMENT

1.4 HOW CAN CRESOLS ENTER AND LEAVE MY BODY?

Enter your body <ul style="list-style-type: none"> • Inhalation • Ingestion • Dermal contact 	<p>There is no information to determine whether cresols can enter the bloodstream through your lungs if you breathe air contaminated with these substances.</p> <p>Cresols in food or water may rapidly enter your body through the digestive tract.</p> <p>Cresols may enter through your skin when you come into contact with liquids containing cresols.</p>
Leave your body	<p>Once in your body, cresols are transformed into other chemicals called metabolites. Most of these metabolites leave your body in the urine within 1 day.</p>

For more information on how cresols enter and leave the body, see Chapter 3.

1.5 HOW CAN CRESOLS AFFECT MY HEALTH?

This section looks at studies concerning potential health effects in animal and human studies.

Humans <ul style="list-style-type: none"> • Inhalation • Oral • Dermal 	<p>Brief exposures to 6 mg/m³ <i>o</i>-cresol in the air caused nose and throat irritation.</p> <p>Ingestion of liquid products containing cresols can cause serious gastrointestinal damage and even death.</p> <p>Application of concentrated cresols to the skin can cause severe skin damage and even death.</p>
Laboratory animals <ul style="list-style-type: none"> • Inhalation • Oral • Dermal 	<p>Short-term exposure to cresols in air has caused irritation of the respiratory tract and muscle twitching.</p> <p>Placing cresols in the stomach of animals by means of a feeding tube has caused muscle twitching and loss of coordination.</p> <p>Eating food contaminated mostly with <i>p</i>-cresol or with a mixture of <i>m</i>- and <i>p</i>-cresol for 28 days or longer has caused lesions inside the nose of rats and mice; mice also developed lesions in the lungs and in the thyroid gland.</p> <p>Short-term application of cresols to the skin of animals has produced skin irritation.</p>

1. PUBLIC HEALTH STATEMENT

Cancer	The EPA has determined that cresols are possible human carcinogens. The International Agency for Research on Cancer (IARC) has not classified cresols as to their carcinogenicity.
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Further information on the health effects of cresols in humans and animals can be found in Chapters 2 and 3.

1.6 HOW CAN CRESOLS AFFECT CHILDREN?

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

Effects in children	There are no studies of children exposed to cresols, but it is expected that children exposed to cresols will suffer the same effects observed in exposed adults. There is a report of a baby who suffered serious damage to the skin, liver, and kidneys, went into a coma, and eventually died 4 hours after liquid cresol was accidentally spilled on his head.
Birth defects	Fetal toxicity and birth defects have been reported in animals given cresols. This generally occurred with doses that were also toxic to the mothers.
Breast milk	There is no information on levels of cresols in breast milk.

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

Tobacco smoke	Cresols are components of tobacco smoke. Avoid smoking in enclosed spaces like inside the home or car in order to limit exposure to children and other family members.
Consumer products	Household cleaners and disinfectants containing cresols should be stored out of the reach of young children to prevent accidental poisonings and skin burns and follow manufacturer's directions on the label.

1. PUBLIC HEALTH STATEMENT

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

Detecting exposure	Cresols can be measured in blood and urine. Cresols are normal constituents of human urine.
Measuring exposure	<p>A higher-than-normal concentration of cresols in the urine may suggest recent exposure to these substances or to substances that are converted to cresols in the body.</p> <p>The detection of cresol and/or its metabolites in your urine cannot be used to predict the kind of health effects that might develop from that exposure.</p>

Information about tests for detecting cresols in the body is given in Chapters 3 and 7.

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

Regulations and recommendations can be expressed as “not-to-exceed” levels. These are levels of a toxic substance in air, water, soil, or food that do not exceed a critical value. This critical value is usually based on levels that affect animals; they are then adjusted to levels that will help protect humans. Sometimes these not-to-exceed levels differ among federal organizations because they used different exposure times (an 8-hour workday or a 24-hour day), different animal studies, or other factors.

Recommendations and regulations are also updated periodically as more information becomes available. For the most current information, check with the federal agency or organization that provides it.

1. PUBLIC HEALTH STATEMENT

Some regulations and recommendations for cresols include the following:

Drinking water	EPA has not established drinking water standards and health advisories for cresols.
Workplace air	OSHA set a legal limit of 5 parts per million (ppm) cresols (all isomers) in air averaged over an 8-hour work day.

For more information on regulations and advisories, see Chapter 8.

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 contact ATSDR at the address and phone number below.

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

Toxicological profiles are also available on-line at www.atsdr.cdc.gov and on CD-ROM. You may request a copy of the ATSDR ToxProfiles™ CD-ROM by calling the toll-free information and technical assistance number at 1-800-CDCINFO (1-800-232-4636), by e-mail at cdcinfo@cdc.gov, or by writing to:

Agency for Toxic Substances and Disease Registry
 Division of Toxicology and Environmental Medicine
 1600 Clifton Road NE
 Mailstop F-32
 Atlanta, GA 30333
 Fax: 1-770-488-4178

Organizations for-profit may request copies of final Toxicological Profiles from the following:

National Technical Information Service (NTIS)
 5285 Port Royal Road
 Springfield, VA 22161
 Phone: 1-800-553-6847 or 1-703-605-6000
 Web site: <http://www.ntis.gov/>

1. PUBLIC HEALTH STATEMENT

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2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO CRESOLS IN THE UNITED STATES

Cresols are widely distributed in the environment and the general population may be exposed to low levels of cresols mainly through the inhalation of contaminated air. Cresols are readily degraded in the atmosphere; atmospheric concentrations outside of source-dominated areas are typically low. Since cresols are released via automobile exhaust, areas of high traffic and gas stations are likely to have increased atmospheric levels of cresols. Cresols are also the product of combustion of coal, wood, and municipal solid waste; therefore, residents near coal and petroleum fueled facilities, as well as residents near municipal waste incinerators, may have increased exposure to cresols. There are limited air monitoring data for cresols; a median concentration of $1.5 \mu\text{g}/\text{m}^3$ *o*-cresol was detected in air samples from 3 locations, the range of *p*-cresol at 11 locations was $0.5\text{--}20 \mu\text{g}/\text{m}^3$, and *m*-cresol was not detected in air samples from 2 locations. A national emissions study conducted from 1990 to 1998 reported a county-level estimated ambient average concentration of $31.7 \text{ ng}/\text{m}^3$ for all cresol isomers combined.

Cresol levels in soil and water are usually low. When detected in surface water, cresol levels are typically around $1 \mu\text{g}/\text{L}$ or less. Higher levels are occasionally observed in groundwater or surface water where petroleum spills have occurred or near hazardous waste sites. In a study of public groundwater at superfund sites, *o*-cresol and *p*-cresol were detected at maximum concentrations of 390 and $150 \mu\text{g}/\text{L}$, respectively; however, neither was detected in well fields or finished water from treatment plants (no data were provided for *m*-cresol). Due to their relatively rapid rate of biodegradation, cresols are only occasionally detected in soils, primarily in areas where petroleum products were spilled or produced. *o*-Cresol was detected at maximum concentrations of $12,000\text{--}34,000 \mu\text{g}/\text{kg}$ in soil samples obtained from an abandoned pine tar manufacturing plant in Gainesville, Florida.

Employees in occupations that routinely involve the combustion of coal or wood may be exposed to higher levels of cresols than the general population. Environmental tobacco smoke is also a source of cresol exposure. Depending on the brand and type of cigarette, the average cresol concentration in a 45 cubic meter chamber after six cigarettes had been smoked ranged from 0.17 to $3.9 \mu\text{g}/\text{m}^3$.

Although low levels of cresol have been detected in certain foods and tap water, these do not constitute major sources of exposure for most people. Cresols have been reported in tea leaves, tomatoes, and ketchup as well as butter, oil, and various cheeses, but levels are not available. People with contaminated

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tap water can be exposed from drinking the water or eating foods prepared with it. In addition, inhalation can occur from volatilized cresol during showering, bathing, and cooking activities with contaminated water. Dermal exposure to cresols may also occur due to bathing or showering with contaminated water.

Exposure to children occurs by the same routes that affect adults. There are no known specific sources of exposure to children. Cresol has not been reported in breast milk or baby foods. Children are likely to be exposed to cresols through inhalation of contaminated air from automobile exhaust, waste incineration, and second-hand smoke.

2.2 SUMMARY OF HEALTH EFFECTS

Information about the effects of cresols in humans is derived mainly from case reports of accidental or intentional ingestion of cresol solutions or from accidental contact of cresol with the skin. Cresols produce corrosive damage at sites of contact; therefore, the skin and mucosal membranes are targets for cresols toxicity. In a single study of controlled exposures in volunteers, brief exposures to 6 mg/m^3 *o*-cresol caused 8 out of 10 subjects to complain of respiratory irritation. Fatalities due to ingestion and dermal exposure to cresols have been described. Other effects reported in these acute high oral and/or dermal exposure scenarios include respiratory failure, tachycardia and ventricular fibrillation, abdominal pain, vomiting, and corrosive lesions of the gastrointestinal tract, methemoglobinemia, leukocytosis and hemolysis, hepatocellular injury, renal alterations, skin damage, metabolic acidosis, and unconsciousness. Many of these effects may not have been caused directly by cresols, but may be a result of secondary reactions to shock caused by external and internal burns.

Inhalation or dermal exposure of animals to cresols has produced irritation and corrosion at the site of contact. Animals exposed acutely to cresol vapors and aerosols showed signs of respiratory irritation, although the levels associated with irritation have not been reliably documented. Inflammation and irritation of the upper respiratory tract, pulmonary edema, and hemorrhage and perivascular sclerosis in the lungs were seen in a variety of animal species exposed intermittently to $9\text{--}50 \text{ mg/m}^3$ of *o*-cresol for ≥ 1 month; other isomers were not tested. White mice exposed acutely to commercial mixtures of cresol isomers exhibited irritation and inflammation of the eyes and nose. Also noticed in these inhalation studies were effects on the nervous system (excitation, fatigue, convulsions). Animals that died had fatty degeneration and necrosis of the liver, degeneration of the tubular epithelium in the kidneys, bronchitis, pulmonary hemorrhage, and dystrophic changes in the heart and in nerve cells and glia in the brain. All

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three cresol isomers, either alone or in combination, severely irritated the skin of rabbits, producing visible and irreversible tissue destruction.

From a limited number of intermediate oral studies, nasal epithelial lesions appear to be a particularly sensitive target for cresols' toxicity. Dietary exposure of rats and mice to *p*-cresol or to a mixture of *m/p*-cresol (58.5% *m*-cresol, 40.9% *p*-cresol) for 28 days or 13 weeks induced dose-related alterations in the nasal respiratory epithelium at doses of 95 mg/kg/day and higher. The severity of the lesions also was dose-related. The lesions were located at the most anterior portions of the nasal septum, dorsal arch, and medial aspect of the nasal turbinates. No such lesions were seen with *o*- or *m*-cresol in the 28-day study or with *o*-cresol in the 13-week study (neither *m*-cresol nor *p*-cresol alone were tested in the 13-week study). Nasal lesions were also observed in male rats and female mice exposed to a mixture of *m/p*-cresol in the feed for 2 years; the results suggested that the lesions already had developed by week 13 and did not increase in severity during the remainder of the dosing period. Intermediate-duration oral gavage studies and two multi-generation reproductive dietary studies in mice did not examine the nasal respiratory epithelium of the animals. It is also relevant to note that in the inhalation studies discussed above, there is no specific mention of evaluation of the nasal cavity. Additional studies may be necessary to rule out the possibility that the nasal lesions are due to direct contact of cresol with the nasal epithelium (see Section 2.3 for a more detailed discussion on this particular issue).

The nervous system also appears to be a sensitive target of cresols toxicity in oral studies, although this seems to be limited to oral gavage studies. Rodents administered cresols by oral gavage for acute or intermediate durations showed neurological signs such as hypoactivity, excessive salivation, labored respiration, and tremors, in addition to decreased body weight gain. Some neurological signs were observed in rats dosed by gavage with as low as 50 mg/kg/day of cresol isomers. None of these effects have been seen in dietary studies, or if seen, they have occurred at much higher dose levels than in oral gavage studies. The reason for this difference is unknown, but it probably is related to toxicokinetic differences between the two modes of oral dosing.

Dietary exposure to higher doses of cresols, generally >240 mg/kg/day, caused increases in liver weight; thresholds for these changes in liver weight were comparable among cresol isomers. Kidney weight was only increased in rats dosed with ≥ 861 mg/kg/day *o*-cresol for 28 days. Clinical chemistry tests gave no indication of altered function in these organs and no gross and microscopic alterations were seen, even at the highest doses administered (>1,000 mg/kg/day). Other systemic effects observed in rats and mice treated with relatively high doses of cresols (>1,000 mg/kg/day) in the diet for 13 weeks included

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decreased weight gain (all isomers). A 2-year study also provided evidence of kidney toxicity in rats (720 mg/kg/day *m/p*-cresol) and thyroid gland toxicity in mice (≥ 100 mg/kg/day *m/p*-cresol).

Reproductive effects of cresols isomers administered to rats and mice in the diet were limited to mild to moderate uterine atrophy and lengthening of the estrous cycle, generally at the highest dose levels tested ($>2,000$ mg/kg/day). Dietary multi-generation studies in mice with *o*-cresol and *m/p*-cresol found no significant effects with *o*-cresol; *m/p*-cresol at the highest level tested (1,682 mg/kg/day) caused minor maternal toxicity (reduced body weight gain), decreased number of pups/litter, and increased cumulative days to litter (delay in producing additional F₁ offspring). Developmental studies that treated rats and rabbits by oral gavage during gestation observed fetal effects (skeletal variations and delayed ossification) at dose levels that also caused maternal toxicity.

A 2-year bioassay found equivocal evidence of carcinogenetic activity of *m/p*-cresol (60%/40%) in male Fischer-344 rats based on a nonsignificant increase in the incidence of renal tubule adenoma. The same study found some evidence of carcinogenetic activity in female B6C3F₁ mice based on an increased incidence of forestomach squamous cell papilloma. Cresols gave indications of promotion potential in a dermal skin promotion assay; *p*-cresol was the least potent isomer, *o*-cresol was approximately 3 times more potent than *p*-cresol, and *m*-cresol was in between. The EPA has determined that cresols are possible human carcinogens (Group C) based on inadequate data in humans and limited data in animals (the assessment is dated 10/89). According to EPA's updated criteria for classifying chemicals, cresols fall in the category of chemicals for which there is "inadequate information to assess carcinogenic potential."

The database in animals is insufficient to propose a toxicity ranking for cresol isomers, even though *p*-cresol seemed to be the most potent for induction of the critical effect, nasal respiratory lesions, in rats and mice in the National Toxicology Program (NTP) study. The human database is inadequate to propose a toxicity ranking for cresol isomers.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for cresols. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive

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health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

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

Inhalation MRLs

The available health effects data for humans or animals exposed to cresols by inhalation are inadequate to establish concentration-response relationships, which are needed to identify adverse effects levels. Therefore, inhalation MRLs were not derived for cresols. In an experiment in humans, brief exposures to 6 mg/m³ *o*-cresol caused 8 out of 10 subjects to complain of respiratory irritation (Uzhdavini et al. 1972). No information was provided on how the cresol vapor was generated or sampled. Two animal studies were available in which exposure involved mixtures of vapors and aerosols that provided insufficient information to reliably estimate exposure levels (Campbell 1941; Uzhdavini et al. 1972). *o*-Cresol (9–50 mg/m³) was tested in the studies of Uzhdavini et al. (1972) in a variety of species, whereas Campbell (1941) tested commercial mixtures of cresol isomers in white mice. These studies provided data on lethality, as well as information on effects on the respiratory system (irritation, inflammation, edema, hemorrhage), and nervous system (excitation, fatigue, convulsions). Animals that died had fatty degeneration and necrosis of the liver, degeneration of the tubular epithelium in the kidneys, bronchitis, pulmonary hemorrhage, and dystrophic changes in the heart and in nerve cells and glia in the brain. Because of limitations in study design (mainly in the methodology for generating and monitoring the vapor concentrations) and reporting, these studies are not useful for risk assessment.

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Oral MRLs

As mentioned in Section 2.2, effects of cresol administered by oral gavage are markedly different than those observed in dietary studies. Administration of cresols by oral gavage to animals results in lowest-observed-adverse-effect levels (LOAELs) much lower than LOAELs defined in dietary studies. For example, LD₅₀ values for undiluted cresols in rats ranged from 121 to 242 mg/kg/day (EI du Pont 1969), whereas dietary doses in the range of 1,000–2,000 mg/kg/day for intermediate durations caused little or no toxicity in rats and mice (NTP 1992b). Serious neurological effects (i.e., lethargy, tremors, convulsions) were seen in rats dosed by oral gavage with doses ranging from 450 to 600 mg/kg/day for 90 days (EPA 1988b, 1988c, 1988d; TRL 1986; Tyl 1988a, 1988b), but no such effects were observed in the dietary studies at much higher dose levels (NTP 1992a, 1992b, 1992c, 2008). The reason for this difference is not known, but it is most likely related to differences in toxicokinetics between the two methods of cresol administration. There are no studies that compared the toxicokinetics of cresols following dietary and gavage administration, but there is information for a related chemical, phenol. Phenol toxicity following oral gavage dosing is different than following administration in the drinking water. In the case of phenol, there are data that suggest that toxicity is correlated with peak blood concentration rather than with total dose, such as the area under the blood concentration curve (AUC) following a single gavage dose or repeated daily doses. This is consistent with data from Bray et al. (1950), who observed that *p*-cresol was more toxic when given by stomach tube to fasting rabbits than when the rabbits were given their daily food 1–2 hours before dosing with *p*-cresol; the assumption is that *p*-cresol became mixed with the food, which delayed its absorption. Also relevant is a recent study by Morinaga et al. (2004), which found concentrations of free cresols in liver and spleen from rats given a single oral gavage dose much higher than in blood at all times after dosing (up to 8 hours). Based on these observations and the fact that an oral gavage exposure protocol does not resemble human environmental exposure scenarios to cresols, only dietary studies are considered for MRL derivation, even though some LOAELs by gavage are lower than dietary LOAELs.

No acute-duration oral MRL was derived for cresols due to lack of acute dietary exposure studies.

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

Almost all of the information available on health effects from intermediate-duration oral exposure is derived from a comprehensive study in rats and mice administered *o*-, *m*-, or *p*-cresol or a cresol mixture of *m*- and *p*-cresol for 28 days or 13 weeks (NTP 1992b). There are also two multigeneration

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reproductive toxicity studies in mice dosed with *o*-cresol (NTP 1992a) and a mixture of *m*- and *p*-cresol (NTP 1992c). In the NTP (1992b) study, rats and mice dosed with *p*-cresol or an *m/p*-cresol mixture showed lesions in the nasal respiratory epithelium. The nasal lesions occurred in rats dosed with *p*-cresol for 28 days (≥ 770 mg/kg/day), in rats exposed to *m/p*-cresol for 28 days (≥ 95 mg/kg/day), in mice exposed to *p*-cresol for 28 days (≥ 163 mg/kg/day), in mice exposed to *m/p*-cresol for 28 days (≥ 604 mg/kg/day), in rats exposed to *m/p*-cresol for 13 weeks (≥ 123 mg/kg/day), and in mice exposed to *m/p*-cresol for 13 weeks (≥ 472 mg/kg/day). The lesions were located at the most anterior portions of the nasal septum, dorsal arch, and medial aspect of the nasal turbinates. The hyperplasia was characterized by increased number of goblet cells and pseudogland formation due to the infolding of the hyperplastic cells. The hyperplastic areas were associated with single cell necrosis. The intermediate-duration oral gavage studies (EPA 1988b, 1988d) and two multi-generation reproductive dietary studies in mice (NTP 1992a, 1992c) did not examine the nasal respiratory epithelium of the animals. Small increases in liver weight were observed in rats and mice at higher doses (≥ 242 mg/kg/day) in both the 28-day and 13-week studies; kidney weight was only increased in rats dosed with ≥ 861 mg/kg/day *o*-cresol for 28 days. However, the changes in organ weight were not associated with alterations in clinical tests of liver and kidney function or gross and microscopic alterations (NTP 1992b). Decreased weight gain was also observed in rats and mice at relatively high doses ($>1,000$ mg/kg/day).

In addition to the systemic effects observed in the 28-day and 13-week studies (NTP 1992b), exposure to high doses of cresols has resulted in reproductive and developmental effects. Mild to moderate uterine atrophy and lengthening of the estrous cycle were generally observed at the highest dose levels tested ($>2,000$ mg/kg/day) for all three isomers. Exposure of mice to 1,682 mg/kg/day *m/p*-cresol caused minor maternal toxicity (reduced body weight gain), decreased number of pups/litter, and increased cumulative days to litter (delay in producing additional F₁ offspring). These effects were not observed in mice exposed to 660 mg/kg/day *o*-cresol (NTP 1992a).

Evaluation of the results of the available intermediate-duration dietary studies indicates that the most sensitive end point was the nasal respiratory epithelium of rats and mice dosed with *p*-cresol or a mixture of *m*- and *p*-cresol (NTP 1992b). The effects occurred in male and female rats and mice dosed for 28 days or 13 weeks. The data sets considered for MRL derivation were the 28-day experiment in female rats and the 13-week experiment in male rats based on the lowest effect levels identified in both sets, 95 mg/kg/day in the 28-day experiment and 123 mg/kg/day in the 13-week experiment. In the 28-day study, the incidences of hyperplasia of the nasal respiratory epithelium in female rats dosed with 0, 27, 95, 268, 886, and 2,570 mg/kg/day of *m/p*-cresol were 0/5, 0/5, 3/4, 5/5, 5/5, and 5/5, respectively. In the

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13-week study, the incidences in male rats dosed with 0, 123, 241, 486, 991, and 2,014 mg/kg/day *m/p*-cresol were 0/10, 3/10, 8/10, 10/10, 8/10, and 10/10, respectively. The latter series is preferred because of the longer duration of exposure and because of the increased reliability of a dose-response curve based on 10 rats per group rather than on only 5 rats per group in the 28-day study.

An issue that has to be considered is the possibility that the nasal lesions were caused by evaporation of the cresol from the food (even though cresols have relatively low vapor pressure, particularly *p*-cresol) and thus due to direct contact of the airborne chemical with the nasal respiratory epithelium. The inhalation database consists of a study by Uzhdavini et al. (1972) who exposed various animal species to *o*-cresol (*o*-cresol did not induce nasal lesions in the NTP study) for various periods of time. Acute exposures of mice produced irritation of mucous membranes and higher concentrations induced pulmonary edema and histopathological changes in the lungs. Repeated exposures of mice also induced symptoms of irritation of the respiratory tract, but there is no specific mention of the nasal cavity. Exposures of rats and guinea pigs for 4 months produced symptoms of irritation and inflammation in the upper respiratory tract, local edema, and perivascular sclerosis in the lungs. Because of limitations in study design and reporting, few conclusions can be drawn from the experiments of Uzhdavini et al. (1972) other than that *o*-cresol is a respiratory irritant at the concentrations tested. NTP (1992b) conducted preliminary studies to assess the stability of the various cresol isomer-feed mixtures and detected losses due to evaporation from 10 to 12% after storage for 7 days under simulated cage conditions. Therefore, fresh chemical-diet mixtures were supplied twice weekly during the studies. Estimating the concentration of cresol in the air from such losses from food is virtually impossible due to numerous uncertainties. The threshold for nasal lesions in rats was about 2,000 mg/kg of *m/p*-cresol in the food. A loss of 10% per week represents 200 mg of cresol/kg of food per week or about 1.2 mg/kg feed per hour. However, a concentration of cresol in air cannot be estimated because of many unknown factors such as volume of distribution, air flow speed, etc. A somewhat related possibility is that cresol evaporates inside the mouth of the animal aided by the higher temperature (about 38 °C) and reaches the nasal cavity from inside the mouth. There is also the possibility of nasal exposures due to exhalation of the cresols previously ingested, although there is no indication from toxicokinetics studies that this may occur. Until it can be demonstrated with some certainty that the nasal lesions are not caused by a systemic effect of cresol and in the interest of protecting humans potentially exposed under similar conditions, the MRL was based on the increased incidence of the nasal lesions in rats.

In the principal study for the MRL, groups of Fischer 344 rats (20/sex/group) were administered *m/p*-cresol (58.5% *m*-cresol, 40.9% *p*-cresol) in the diet at levels of 0, 1,880, 3,750, 7,500, 15,000, or

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30,000 ppm for 13 weeks (NTP 1992b). The corresponding doses of test compound estimated by the investigators were 0, 123, 241, 486, 991, and 2,014 mg/kg/day for males and 0, 131, 254, 509, 1,024, and 2,050 mg/kg/day for females. End points evaluated included clinical signs, food consumption, organ weights, clinical chemistry and hematology, and gross and microscopic appearance of organs and tissues. Although the dose groups consisted of 20 rats of each sex, 10 males and 10 females were used for clinical chemistry, hematology, and urinalysis studies and the remaining 10 rats/sex/group were used in gross pathology, organ weight, and histopathological studies. There were no deaths during the study. Final body weight in the 2,014/2,050 mg/kg/day males and females was reduced 17 and 12%, respectively, relative to controls. Food consumption was also reduced (about 10%) in this group during the first week of the study. Additionally, males and females in this group exhibited rough hair coat; females also had a thin appearance. Absolute and relative liver weights were significantly increased (11–12%) in males at 486 mg/kg/day and in females at 1,024 mg/kg/day. Absolute and relative kidney weight was increased in males at 991 mg/kg/day. In general, hematology findings were unremarkable, although there was a tendency to hemoconcentration at 2,014/2,050 mg/kg/day early in the study. Clinical chemistry tests showed an increase in serum alanine aminotransferase (ALT) in males and females exposed to 2,014/2,050 mg/kg/day and in sorbitol dehydrogenase (SDH) in males at 2,014 mg/kg/day only on day 5. Bile acids in serum were increased in females at 2,050 mg/kg/day on day 90 and at 241 and 991 mg/kg/day in males also on day 90. There was no indication of renal injury as judged by the results of urinalyses. Significant histopathological changes included minimal bone marrow hypocellularity in males and females (likely secondary to decreased weight gain) at 2,014/2,050 mg/kg/day, and increased colloid (minimal) in thyroid follicular cells in females at 509 mg/kg/day and in males at 15,000 ppm (991 mg/kg/day). An increased dose-related incidence and severity of hyperplasia and glandular hyperplasia of the nasal respiratory epithelium was observed in male and female rats. Severity was minimal at 123/131 mg/kg/day, mild at 486/509 mg/kg/day, and moderate at 2,014/2,050 mg/kg/day. The lesions were located at the most anterior portions of the nasal septum, dorsal arch, and medial aspect of the nasal turbinates. The hyperplasia was characterized by increased number of goblet cells and pseudogland formation due to the infolding of the hyperplastic cells. The hyperplastic areas were associated with single cell necrosis. The incidences in males dosed with 0, 123, 241, 486, 991, and 2,014 mg/kg/day were 0/10, 3/10, 8/10, 10/10, 8/10, and 10/10, respectively. A similar trend was seen in female rats, but 3/10 control females also exhibited hyperplasia (3/10, 1/10, 5/10, 9/10, 8/10, and 10/10 at 0, 131, 254, 509, 1,024, and 2,050 mg/kg/day, respectively).

Data from the NTP (1992b) were considered adequate for analysis using the benchmark dose approach for MRL derivation. Benchmark dose models in the EPA Benchmark Dose Software (BMDS)

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(version 2.0) were fit to the incidence data for nasal lesions in male and female rats exposed to *m/p*-cresol in the diet for 13 weeks in order to determine potential points of departure for the MRL (details of the modeling are presented in Appendix A). Comparing fits across nine different models, the log-logistic model was determined to be the best-fitting model for the male rat data set, whereas the quantal linear model was the best-fitting model for the female rat data set. Following EPA's Benchmark Dose Guidance (EPA 2000a) to select a point of departure, a benchmark response (BMR) of 10% was selected for the benchmark analysis of nasal lesion incidence data in the 13-week NTP (1992b) study. The benchmark dose (BMD) corresponding to a BMR of 10% extra risk is 55.89 mg/kg/day. BMDL_{10S} (i.e., 95% lower confidence limits on the model-estimated dose associated with a 10% extra risk for nasal lesions) calculated with the best-fitting models for each data set were 13.9 mg/kg/day for males and 30.8 mg/kg/day for females. While this difference in benchmark dose may indicate that male rats are more sensitive than females, it also can be just a statistical artifact in a rather small sample size, only 10 rats per group. The male rat data set was selected for determining the point of departure for MRL derivation in order to be public health protective. Applying an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) to the BMDL₁₀ of 13.9 mg/kg/day yields an intermediate-duration oral MRL of 0.1 mg/kg/day for *m/p*-cresol.

- An MRL of 0.1 mg/kg/day has been derived for chronic-duration oral exposure (365 days or more) to cresols.

The only chronic-duration dietary study with cresols is the NTP (2008) toxicology and carcinogenesis studies in male Fischer-344/N rats and female B6C3F₁ mice. Although the report has not yet been finalized by the NTP, a draft technical report has been reviewed by the NTP Board of Scientific Counselors Technical Reports Review Subcommittee, and a draft abstract, pathology tables, and survival and growth curves are available on the NTP web site. In the study, the male Fischer-344/N rats were fed diets that provided mean time-weighted average (TWA) doses of *m/p*-cresol of approximately 0, 70, 230, or 720 mg/kg/day for 2 years. Survival rates were not affected by treatment with *m/p*-cresol. Inspection of the data shows that the most sensitive end point in rats was the nasal respiratory epithelium, as in the shorter-term studies (NTP 1992b). Other less sensitive effects observed in rats included hyperplasia of the transitional epithelium of the renal pelvis, squamous metaplasia in the nasal respiratory epithelium, inflammation of the nose, and eosinophilic foci in the liver. Incidences of respiratory epithelium hyperplasia of minimal to mild severity were 3/50, 17/50, 31/50, and 47/50 in the control, low-, mid-, and high-dose groups, respectively. During the first 13 weeks of the 2-year study, the mean dose in the low-dose group was 123 mg/kg/day (calculated from weekly averages provided in the report), the same as in the earlier 13-week study (NTP 1992b), and the incidence of respiratory hyperplasia in this

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group at termination was 17/50 (34%), almost the same as in the earlier 13-week study, 3/10 (30%). This suggests that, over the range of doses used in these studies, exposure beyond 13 weeks (i.e., duration of exposure) had little or no effect on the incidence or severity of the lesions, indicating that the intermediate-duration MRL is protective of nasal lesions for a 2-year exposure period. This is supported by the fact that fitting the incidence data for nasal respiratory epithelium hyperplasia from the 2-year study to the same BMDS model (Log-Logistic) that provided the $BMDL_{10}$ used to derive the intermediate-duration oral MRL yields a $BMDL_{10}$ for chronic exposure to *m/p*-cresol of 13.9017 mg/kg/day, essentially the same as the $BMDL_{10}$ of 13.9381 mg/kg/day used to derive the intermediate-duration oral MRL for *m/p*-cresol. Thus, the intermediate-duration oral MRL should be protective of nasal respiratory lesions in rats induced by chronic-duration exposure.

The female B6C3F₁ mice were fed diets that provided TWA doses of approximately 0, 100, 300, or 1,040 mg *m/p*-cresol/kg/day for 2 years. Survival rates were comparable among dose groups. Significant treatment-related, non-neoplastic effects occurred in the lung (bronchiole hyperplasia), nose (respiratory epithelium hyperplasia), thyroid gland (follicular degeneration), and liver (eosinophilic foci). In the lung, the incidences of minimal to moderate bronchiole hyperplasia were 0/50, 42/50, 44/49, and 47/50 in the control, low-, mid-, and high-dose groups, respectively. In the nose, the corresponding incidences of minimal to mild respiratory epithelium hyperplasia were 0/50, 0/50, 28/49, and 45/49. In the thyroid, the corresponding incidences of mild follicular degeneration were 7/48, 24/48, 24/49, and 21/50. The corresponding incidences of eosinophilic foci in the liver were 1/50, 0/50, 2/49, and 12/50. Clearly, the thresholds for thyroid follicular degeneration and bronchiole hyperplasia were lower than those for nasal epithelial hyperplasia and liver foci; therefore, the incidence data for the former two lesions were considered for derivation of a chronic-duration oral MRL for *m/p*-cresol. After inspection of the dose response data, the use of a LOAEL/NOAEL approach for MRL derivation was considered to be more appropriate than the use of benchmark dose analysis because of the steep increase in the response rates between the control groups and the first exposure levels. It should be noted that neither bronchiole hyperplasia nor thyroid follicular degeneration were present in female mice in the 13-week study with *m/p*-cresol (NTP 1992b), suggesting that longer periods of exposure were necessary for these lesions to develop. Applying an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability) to the LOAEL of 100 mg/kg/day for bronchiole hyperplasia of the lung and follicular degeneration of the thyroid gland in female mice, yields a chronic-duration oral MRL of 0.1 mg/kg/day for *m/p*-cresol.

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The most comprehensive study of cresols by dietary exposure is the NTP (1992b) study. In that study, each individual isomer and an *m/p*-cresol mixture were tested in rats and mice for 28 days; in addition, *o*-cresol and *m/p*-cresol were tested in rats and mice for 13 weeks. Assessing the comparative toxicity of the cresol isomers, NTP (1992b) noted that: “In general, there were no significant indications of distinct toxicities between the three isomers.” However, nasal lesions only occurred in rats and mice dosed with *p*-cresol and *m/p*-cresol in the 28-day studies and in rats and mice dosed with *m/p*-cresol in the 13-week studies. Since *m*-cresol alone was not tested in the 13-week studies, it is unknown whether longer dietary exposure to this isomer would produce similar lesions. Thus, it would appear that *p*-cresol is the most toxic of the isomers with regard to inducing nasal lesions and, since no other significant toxicities were observed in these dietary studies, the MRL for *m/p*-cresol should also be protective for exposures to the individual cresol isomers. Therefore, the intermediate- and chronic-duration oral MRLs for *m/p*-cresol also can be adopted for *o*-, *m*-, and *p*-cresol.

3. HEALTH EFFECTS

3.1 INTRODUCTION

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

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

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

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the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

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

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.

3.2.1 Inhalation Exposure

Studies of the inhalation toxicity of cresols have not been adequately detailed. The exposures involved mixtures of vapors and aerosols that were not characterized sufficiently to estimate exposure levels reliably. Furthermore, methods for evaluating the toxicological end points were not adequately described. In addition, it is very likely that dermal exposure, and thus dermal absorption, also occurred. Therefore, no LSE table or figure containing levels of significant exposure was constructed for this route. Nevertheless, certain general conclusions can be drawn from the reports regarding the toxic potential of inhaled cresols. These are discussed below.

3.2.1.1 Death

No studies were located regarding death in humans following inhalation exposure to cresols.

Cresols may be lethal to animals when inhaled (Campbell 1941; Uzhdavini et al. 1972). The inhalation exposure levels and durations that kill animals have not been reliably documented. Lethality has been reported in mice exposed to approximately 178 mg/m³ of *o*-cresol aerosol for an unspecified acute duration, suggesting that the minimal lethal exposure level for cresol aerosols may be <178 mg/m³ (Uzhdavini et al. 1972). For longer-term exposure, the minimal lethal level may exceed 50 mg/m³, since exposure to this concentration of *o*-cresol for 1 month had no effect on mouse mortality (Uzhdavini et al.

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1972). Clinical signs that preceded death in acute experiments included irritation of mucous membranes and neuromuscular excitation that progressed from tremors to clonic convulsions.

3.2.1.2 Systemic Effects

No studies were located regarding gastrointestinal, hematological, musculoskeletal, or dermal effects in humans or animals following inhalation exposure to cresols.

Respiratory Effects. When inhaled as a concentrated aerosol, *o*-cresol is a respiratory irritant in humans; however, the minimal exposure level and duration associated with irritation have not been reliably documented. Following brief exposures to 6 mg/m³, 8 out of 10 subjects complained of mucosal irritation symptoms including dryness, nasal constriction, and throat irritation (Uzhdavini et al. 1972).

Signs of respiratory irritation have been reported in animals acutely exposed to cresol vapors and aerosols, although the levels associated with irritation have not been reliably documented (Campbell 1941; Uzhdavini et al. 1972). Mucosal irritation, as shown by parotid gland secretions, occurred in cats during 30-minute exposures to 5–9 mg/m³ of *o*-cresol (Uzhdavini et al. 1972). An assortment of respiratory effects, including inflammation and irritation of the upper respiratory tract, pulmonary edema, and hemorrhage and perivascular sclerosis in the lungs were seen in animals exposed to 9–50 mg/m³ of *o*-cresol 2–6 hours/day for ≥1 month (Uzhdavini et al. 1972).

Cardiovascular Effects. No studies were located regarding cardiovascular effects in humans following inhalation exposure to cresols.

Heart muscle degeneration was reported in mice exposed to 50 mg/m³ of *o*-cresol 2 hours/day for 1 month (Uzhdavini et al. 1972). Mice were probably exposed to an aerosol. Exposure levels were not reliably documented.

Hepatic Effects. No studies were located regarding hepatic effects in humans following inhalation exposure to cresols.

Fatty degeneration and centrilobular necrosis were observed in the livers of mice that died following acute exposure to *o*-cresol; the mean lethal concentration was 178 mg/m³. Exposure to 9 mg/m³ for

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4 months interfered with liver function in rats, as shown by increased susceptibility to hexanol narcosis (Uzhdavini et al. 1972).

Renal Effects. No studies were located regarding renal effects in humans following inhalation exposure to cresols.

Blood was found in the urine of mice acutely exposed to *o*-cresol; the mean lethal concentration was 178 mg/m³ (Uzhdavini et al. 1972). Necropsy and histopathologic examination of the mice that died following exposure revealed edema and swelling of the glomeruli, degeneration of the tubular epithelium, and perivascular hemorrhage.

Ocular Effects. No studies were located regarding ocular effects in humans following inhalation exposure to cresols.

Eye irritation was noted in mice briefly exposed to highly concentrated cresylic acid (a mixture of cresol isomers and other phenolic solvents that boils above 204 °C) vapors; however, the exact exposure concentrations associated with irritation were not documented (Campbell 1941).

3.2.1.3 Immunological and Lymphoreticular Effects

No studies were located regarding immunological effects in humans or animals following inhalation exposure to cresols.

3.2.1.4 Neurological Effects

No studies were located regarding neurological effects in humans following inhalation exposure to cresols.

Neurologic effects in animals acutely exposed to cresol aerosols have been reported (Uzhdavini et al. 1972). The effects include mild nervous excitation, muscle twitching accompanied by general fatigue, and clonic convulsions. The exposure concentrations associated with these effects have not been reliably documented; however, they may occur at levels approximating 178 mg/m³ during a single exposure. Prolonged exposure (2 hours/day for 1 month) to a lower concentration of *o*-cresol aerosol (50 mg/m³) reportedly produced degeneration of nerve cells and glial elements in mice (Uzhdavini et al. 1972). The

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severity of these changes was not discussed, however, and no further details were provided. The exposure concentration associated with this effect was not reliably documented.

No information was located regarding the following effects of cresols in humans following inhalation exposure:

3.2.1.5 Reproductive Effects

3.2.1.6 Developmental Effects

3.2.1.7 Cancer

3.2.2 Oral Exposure

3.2.2.1 Death

Ingestion of cresols can be fatal to humans. Fatalities were described in several case reports involving ingestion of cresol-containing disinfectants. A 37-year-old woman died 4 days after swallowing about 250 mL of a disinfectant described as 50% cresols in a mixture of linseed oil, potassium hydroxide, and water. Death was caused by acute intravascular hemolysis, which resulted in multiple thrombosis and renal failure (Chan et al. 1971). The lethal dose was roughly 2 g/kg of cresols (only about one-half of which was actually absorbed). The same report described the case of a woman who recovered after drinking a smaller amount of the same disinfectant (approximately 100 mL). The urine of both women contained glucuronides of cresol metabolism. A woman who swallowed between 500 and 750 mL of a concentrated cresol mixture died from cardiac arrest 26 hours later (Labram and Gervais 1968). Among the 52 cases of cresol poisoning reported by Isaacs (1922), two patients died, both within 0.5 hours of drinking a disinfectant purported to contain 25–50% cresols. Similarly, Monma-Ohtaki et al. (2002) reported that ingestion of a large volume of a saponated cresol solution caused the death of a man in about 15 minutes. A woman who drank a disinfectant suspected of containing cresols died 5 days later (Dellal 1931). There was little corrosion in the throat so it is probable that not much disinfectant was swallowed. The cause of death was thought to be acute hemorrhagic degeneration of the pancreas, which may or may not have been related to cresol consumption. Bruce et al. (1976) also described two cases of ingestion of cresols that ended in death; in both cases, there was significant injury to the gastrointestinal tract.

LD₅₀ values in rats were 1,350, 1,800, and 2,020 mg/kg for *o*-, *p*-, and *m*-cresol, respectively, for 10% solutions in olive oil (Deichmann and Witherup 1944). LD₅₀ values of 121, 242, and 207 mg/kg were reported for undiluted *o*-, *m*-, and *p*-cresol, respectively, in rats (EI du Pont 1969). Hypoactivity, tremors,

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convulsions, salivation, and dyspnea were signs commonly seen preceding death (EI du Pont 1969). Acute LD₅₀ values for various cresylic acid formulations in mice ranged from 500 to 2,050 mg/kg (Campbell 1941). Although LD₅₀ values were not determined in other species, minimum lethal values were available for a few species; the small number of animals in these studies, however, limits the reliability of these data. In rabbits, minimum lethal values from ingestion ranged from 620 to 1,400 mg/kg for the three isomers (Deichmann and Witherup 1944). In mink, the minimum lethal value of *o*-cresol by gavage was 200 mg/kg, and in ferrets, it was 400 mg/kg (Hornshaw et al. 1986).

Dietary administration of 4,480 mg/kg/day of *o*-cresol to male mice or 5,000 mg/kg/day to female mice for 10 days resulted in the death of 2/5 males and 1/5 females (NTP 1992b). Doses of 4,710 or 4,940 mg/kg/day of *m*-cresol killed 2/5 males and 2/5 female mice, respectively, in a 6-day period (NTP 1992b). A diet containing 30,000 ppm of *p*-cresol (The National Toxicology Program [NTP] did not estimate doses, but were probably 4,000–5,000 mg/kg/day) caused the death of 4/5 male and 5/5 female mice within 1 week in this diet. In the cases of *o*- and *m*-cresol, necropsy of the dead animals did not reveal any notable histopathological changes. In the case of *p*-cresol, lesions were considered secondary to moribund condition or stress, except for liver and kidney necrosis and bone marrow hypocellularity, which could have been related to *p*-cresol (NTP 1992b). Exposure of male F-344 rats or female B6C3F₁ mice to up to 720 and 1,040 mg/kg/day, respectively, in the diet for 2 years did not affect survival rates (NTP 2008).

Mortality data were also available for pregnant rats (Tyl 1988a) and rabbits (Tyl 1988b) given cresols by gavage repeatedly during gestation in studies of developmental toxicity. Both *o*- and *p*-cresol produced mortality among rats given 450 mg/kg/day, whereas *m*-cresol did not (Tyl 1988a). In rabbits, *p*-cresol appeared to produce a dose-related increase in mortality at 50–100 mg/kg/day. No deaths occurred in rabbits exposed to *o*- or *m*-cresol (Tyl 1988b).

Exposure to *o*-, *p*-, or *m*-cresol at 450 mg/kg/day by oral gavage produced 12–60% mortality in adult male and female rats in two-generation reproduction studies. The elevated mortality occurred in both the F₀ and F₁ generation adults (Neeper-Bradley and Tyl 1989a, 1989b; Tyl and Neeper-Bradley 1989). In 13-week oral gavage studies of systemic toxicity in rats, elevated mortality resulted only from exposure to *o*-cresol at 600 mg/kg/day (EPA 1988b); in these studies, *p*- and *m*-cresol failed to produce mortality at 450–600 mg/kg/day (EPA 1988c, 1988d).

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All reliable LD₅₀ and LOAEL values for death in each species and duration category are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.2 Systemic Effects

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

Respiratory Effects. Diffuse necrosis of the bronchial epithelium was noted in a woman who died after drinking 500–750 mL of a concentrated cresol mixture (Labram and Gervais 1968). This effect was thought to have occurred prior to death. Edema and hemorrhage were also observed, but may have occurred secondary to death. Adhesions and fluid were found in the lungs of a woman who died after drinking a disinfectant suspected of containing cresols (Dellal 1931).

Hyperplastic or metaplastic lesions in the respiratory epithelium have been observed in rats orally exposed to cresols for intermediate durations. Epithelial metaplasia of the trachea has been reported to occur in Sprague-Dawley male and female rats treated by gavage with 600 mg/kg/day of *p*-cresol for 13 weeks (EPA 1988c). Fischer-344 rats exposed to doses of up to approximately 2,600 mg/kg/day of *o*-cresol or *m*-cresol in the diet for 28 days had no noticeable histological alterations in tissues of the respiratory tract, including nasal tissues (NTP 1992b). However, exposure of males to ≥ 835 mg/kg/day or females to ≥ 770 mg/kg/day of *p*-cresol, or of males to ≥ 261 mg/kg/day or females to ≥ 95 mg/kg/day of a mixture of *m*- and *p*-cresol (58/41%) induced dose-related (incidence and severity) hyperplasia of the nasal respiratory epithelium (NTP 1992b). This suggests that *p*-cresol is more potent than the other isomers in inducing this type of lesion. The corresponding NOAELs were 256 and 242 mg/kg/day for *p*-cresol and 90 and 27 mg/kg/day for the mixture. In a 13-week dietary study in rats, similar lesions were seen in males at ≥ 123 mg/kg/day of the cresol mixture and in females at ≥ 254 mg/kg/day (NTP 1992b). A NOAEL for males was not identified; the NOAEL for females was 131 mg/kg/day. Neither *m*-cresol nor *p*-cresol alone was tested in the 13-week study. The lesions were observed at the most anterior portions of the nasal septum, dorsal arch, and medial aspect of the nasal turbinates. The hyperplasia was characterized by increased number of goblet cells and pseudogland formation due to the infolding of the hyperplastic cells. The incidence data for nasal lesions in male and female rats exposed for 13 weeks were analyzed via a benchmark dose approach to derive points of departure for deriving an intermediate-duration oral MRL for cresols.

Table 3-1 Levels of Significant Exposure to Cresols - Oral

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
ACUTE EXPOSURE								
Death								
1	Rat (Wistar)	once (GO)				1350	(LD50, 10% solution in olive oil)	Deichmann and Witherup 1944 ortho
2	Rat (Wistar)	once (GO)				2020	(LD50, 10% solution in olive oil)	Deichmann and Witherup 1944 meta
3	Rat (Wistar)	once (GO)				1800	(LD50, 10% solution in olive oil)	Deichmann and Witherup 1944 para
4	Rat (albino)	once (G)				242	(LD50, undiluted)	El du Pont 1969 meta
5	Rat (albino)	once (G)				121	(LD50, undiluted)	El du Pont 1969 ortho
6	Rat (albino)	once (G)				207	(LD50, undiluted)	El du Pont 1969 para
7	Mouse (NS)	once (GW)				1050	(LD50)	Campbell 1941 mix
8	Mouse (B6C3F1)	2 wk ad lib (F)				4480 M	(2/5 males and 1/5 females died before day 10)	NTP 1992b ortho

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
9	Mouse (B6C3F1)	2 wk ad lib (F)				4710 M (2/5 males and 2/5 females died before day 6)	NTP 1992b meta	
10	Rabbit (New Zealand)	Gd 6-18 (GO)				100 (5/14 deaths; 0/28 in controls)	Tyl 1988b para	
Systemic								
11	Rat (Sprague- Dawley)	Gd 6-15 1 x/d (GO)	Resp	175 F	450 F (audible respiration)		Tyl 1988a ortho	
			Hepatic	450 F				
			Bd Wt	30 F	175 F (12% decreased body weight gain)	450 F (47% decreased body weight gain during treatment)		
			Other		450 F (15% reduced food intake during treatment)			

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
12	Rat (Sprague- Dawley)	Gd 6-15 1 x/d (GO)	Resp	175 F	450 F (labored respiration)		Tyl 1988a meta	
			Hepatic	450 F				
			Bd Wt	175 F	450 F (46% decreased body weight gain during treatment)			
			Other		450 F (13% reduced food intake during treatment)			
13	Rat (Sprague- Dawley)	Gd 6-15 1 x/d (GO)	Resp	175 F	450 F (labored respiration)		Tyl 1988a para	
			Hepatic	450 F				
			Bd Wt	175 F	450 F (40% decreased body weight gain during treatment)			
			Other	175 F	450 F (25% decreased food intake during treatment)			
14	Rabbit (New Zealand)	Gd 6-18 1 x/d (GO)	Resp	5 F	50 F (audible respiration)		Tyl 1988b ortho	
			Hepatic	100 F				
			Ocular	5 F	50 F (ocular discharge)			
			Bd Wt	100 F				

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure	Species ^a (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments	
					Less Serious (mg/kg/day)	Serious (mg/kg/day)			
15	Rabbit (New Zealand)	Gd 6-18 1 x/d (GO)	Resp	5	50	(labored respiration)	Tyl 1988b meta		
			Hepatic	100					
			Ocular	5	50	(ocular discharge)			
			Bd Wt	100					
16	Rabbit (New Zealand)	Gd 6-18 1 x/d (GO)	Resp	5 F	50 F	(labored breathing)	Tyl 1988b para		
			Hepatic	100 F					
			Ocular	5 F	50 F	(ocular discharge)			
			Bd Wt	100 F					
Neurological									
17	Rat (CD)	2 wk 7 d/wk (GO)			50	(CNS stimulation)	600	(convulsions)	TRL 1986 ortho
18	Rat (CD)	2 wk 7 d/wk (GO)			50	(CNS stimulation)	600	(convulsions)	TRL 1986 para
19	Rat (CD)	2 wk 7 d/wk (GO)			50	(CNS stimulation)	450	(convulsions)	TRL 1986 meta
20	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)		175			450	(ataxia, tremors, hypoactivity)	Tyl 1988a ortho

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments	
					Less Serious (mg/kg/day)	Serious (mg/kg/day)			
21	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)		175		450	(ataxia, tremors hypoactivity)	Tyl 1988a meta	
22	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)		175		450	(ataxia, tremors hypoactivity)	Tyl 1988a para	
23	Rabbit (New Zealand)	Gd 6-18 1 x/d (GO)		5	50		(hypoactivity)	Tyl 1988b ortho	
24	Rabbit (New Zealand)	Gd 6-18 1 x/d (GO)		5	50		(hypoactivity)	Tyl 1988b para	
25	Mink (NS)	once (G)		50		100	(incoordination)	Hornshaw et al. 1986 ortho	
26	Ferret (NS)	once (G)				200	(incoordination)	Hornshaw et al. 1986 ortho	
Reproductive									
27	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)		450				Tyl 1988a ortho	NOAEL is for uterine weight and number of corpora lutea.
28	Rat (Sprague-Dawley)	Gd 6-15 1 x/d (GO)		450				Tyl 1988a meta	NOAEL is for uterine weight and number of corpora lutea.

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL		Reference Chemical Form	Comments	
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)			Serious (mg/kg/day)
29	Rat (Sprague- Dawley)	Gd 6-15 1 x/d (GO)		450			Tyl 1988a para	NOAEL is for uterine weight and corpora lutea.
30	Rabbit (New Zealand)	Gd 6-18 1 x/d (GO)		100			Tyl 1988b ortho	NOAEL is for uterine weight and number of corpora lutea.
31	Rabbit (New Zealand)	Gd 6-18 1 x/d (GO)		100			Tyl 1988b meta	NOAEL is for uterine weight and number of corpora lutea.
32	Rabbit (New Zealand)	Gd 6-18 1 x/d (GO)		100			Tyl 1988b para	NOAEL is for uterine weight and number of corpora lutea.
Developmental								
33	Rat (Sprague- Dawley)	Gd 11 once (G)		1000			Kavlock 1990 para	NOAEL is for postimplantation loss, litter size, viability, and postnatal weight.
34	Rat (Sprague- Dawley)	Gd 6-15 1 x/d (GO)		175	450	(increased incidence of skeletal variations)	Tyl 1988a ortho	

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency/ (Route)	System	LOAEL		Reference Chemical Form	Comments			
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)			Serious (mg/kg/day)		
35	Rat (Sprague- Dawley)	Gd 6-15 1 x/d (GO)		450			Tyl 1988a meta	NOAEL is for embryotoxicity and teratogenicity.		
36	Rat (Sprague- Dawley)	Gd 6-15 1 x/d (GO)		175	450	(increased incidence of skeletal variations)		Tyl 1988a para		
37	Rabbit (New Zealand)	Gd 6-18 1 x/d (GO)		50	100	(delayed ossification)		Tyl 1988b ortho		
38	Rabbit (New Zealand)	Gd 6-18 1 x/d (GO)		100				Tyl 1988b meta	NOAEL is for embryotoxicity and teratogenicity.	
39	Rabbit (New Zealand)	Gd 6-18 1 x/d (GO)		100				Tyl 1988b para	NOAEL is for embryotoxicity and teratogenicity.	
INTERMEDIATE EXPOSURE										
Death										
40	Rat (Sprague- Dawley)	13 wk 7 d/wk 1 x/d (GO)					600	(death of 19 females and 9 males out of 30 rats/sex)	EPA 1988b ortho	
41	Rat (CD)	10 wk 5 d/wk (GO)					450	(death of 8/25 males and 5/25 females)	Neeper-Bradley and Tyl 1989a para	

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments	
					Less Serious (mg/kg/day)	Serious (mg/kg/day)			
42	Rat (CD)	10 wk 5 d/wk (GO)				450	(death of 7 males and 5 females out of 25/sex)	Neeper-Bradley and Tyl 1989b meta	
43	Rat (CD)	10-11 wk 5 d/wk (GO)				450	(32-60% mortality in F0 and F1 adults)	Tyl and Neeper-Bradley 1989 ortho	
Systemic									
44	Rat (Sprague-Dawley)	13 wk 7 d/wk 1 x/d (GO)	Resp	600				EPA 1988b ortho	NOAELs are for organ weights and histopathology.
			Cardio	600					
			Gastro	600					
			Hemato	600					
			Musc/skel	600					
			Hepatic	600					
			Renal	600					
			Endocr	600					
			Ocular	600					
			Bd Wt	175 M	600 M (11% decreased body weight gain)				

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
45	Rat (Sprague- Dawley)	13 wk 7 d/wk 1 x/d (GO)	Resp	175	600	(epithelial metaplasia in trachea)	EPA 1988c para	
			Cardio	600				
			Gastro	600				
			Hemato	50 F	175 F	(6-8% decreased red blood cell count and hemoglobin)		
			Musc/skel	600				
			Hepatic	175	600	(increased SGOT, SGPT; inflammation)		
			Renal		50	(nephropathy)		
			Endocr	600				
			Ocular	600				
Bd Wt	175 M			600 M (21% decreased body weight gain)				

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL		Reference Chemical Form	Comments	
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)			Serious (mg/kg/day)
46	Rat (Sprague- Dawley)	13 wk 7 d/wk 1 x/d (GO)	Resp	450			EPA 1988d meta	NOAELs are for organ weights and histopathology.
			Cardio	450				
			Gastro	450				
			Hemato	450				
			Musc/skel	450				
			Hepatic	450				
			Renal	450				
			Endocr	450				
			Ocular	450				
	Bd Wt	50 M		150 M (22% decreased body weight gain)				
47	Rat (Sprague- Dawley)	28 d 1 x/d (GO)	Hemato	1000			Koizumi et al. 2003 meta	NOAELs are for histopathology of liver and kidney and a number of hematology end points.
			Hepatic	1000				
			Renal	1000				
			Bd Wt	300	1000 F (11% reduced final body weight)			

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
48	Rat (CD)	10-11 wk 5 d/wk (GO)	Bd Wt	175 M	450 M (13% reduced final body weight)		Neeper-Bradley and Tyl 1989a para	
49	Rat (CD)	10 wk 5 d/wk (GO)	Bd Wt	175 M	450 M (15% decreased final body weight)		Neeper-Bradley and Tyl 1989b meta	
50	Rat (Fischer- 344) ad lib (F)	28 d	Resp	2610 M			NTP 1992b ortho	NOAELs are for organ weights and histopathology.
			Cardio	2610 M				
			Gastro	2610 M				
			Musc/skel	2610 M				
			Hepatic	266 M	861 M (25% increase absolute liver weight and 23% in relative)			
			Renal	266 M	861 M (15% increase in absolute kidney weight and 13% in relative)			
			Endocr	2610 M				
			Dermal	2610 M				
Bd Wt	881 F	2510 F (12% reduction in final body weight)						

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
51	Rat (Fischer-344)	28 d ad lib (F)	Resp	2470 M			NTP 1992b meta	NOAELs are for organ weights and histopathology.
			Cardio	2470 M				
			Gastro	2470 M				
			Musc/skel	2470 M				
			Hepatic	252 M	870 M (16% increase in absolute and relative liver weight)			
			Renal	2470 M				
			Endocr	2470 M				
			Dermal	2470 M				
			Bd Wt	862 F	2310 F (16% reduced final body weight)			

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
52	Rat (Fischer-344)	28 d ad lib (F)	Resp	242 F	770 F (respiratory nasal epithelium hyperplasia)		NTP 1992b para	NOAELs are for organ weights and histopathology.
			Cardio	2180 M				
			Gastro	2180 M				
			Hemato	770 F	2060 F (bone marrow hypocellularity)			
			Musc/skel	2180 M				
			Hepatic	83 F	242 F (16% increase absolute liver weight)			
			Renal	2180 M				
			Endocr	2180 M				
			Dermal	2180 M				
			Bd Wt	835 M	2060 F (16% reduced final body weight)			

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
53	Rat (Fischer-344)	28 d ad lib (F)	Resp	27 F	95 F (hyperplasia in respiratory nasal epithelium)		NTP 1992b mix	NOAELs are for organ weights and histopathology.
			Cardio	2600 M				
			Gastro	90 M	261 F (hyperplasia and hyperkeratosis of esophageal epithelium)			
			Hemato	886 M	2570 M (bone marrow hypocellularity)			
			Musc/skel	2600 M				
			Hepatic	261 M	877 M (16-20% increase in absolute and relative liver weight)			
			Renal	2600 M				
			Endocr	90 M	261 M (increased colloid in thyroid follicular cell)			
			Dermal	2600 M				
Bd Wt	877 M	2600 M (18% reduced final body weight)						

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
54	Rat (Fischer- 344)	13 wk ad lib (F)	Resp	2028 M			NTP 1992b ortho	NOAELs are for organ weights and histopathology.
			Cardio	2028 M				
			Gastro	2028 M				
			Hemato	513 F	1021 F (bone marrow hypocellularity)			
			Musc/skel	2028 M				
			Hepatic	247 M	510 M (10-12% increase in absolute and relative liver weight)			
			Renal	2028 M				
			Endocr	2028 M				
			Dermal	2028 M				
Bd Wt	1021 F	2024 F (15% reduced final body weight)						

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
55	Rat (Fischer-344)	13 wk ad lib (F)	Resp		123 ^b M (3/10 with minimal hyperplasia in the nasal respiratory epithelium vs. 0/10 in controls)		NTP 1992b mix	NOAELs are for organ weights and histopathology.
			Cardio	2050 F				
			Gastro	2050 F				
			Hemato	991 M	2014 M (bone marrow hypocellularity)			
			Musc/skel	2050 F				
			Hepatic	241 M	486 M (11-12% increase in absolute and relative liver weight)			
			Renal	2050 F				
			Endocr	254 F	509 F (increased colloid in thyroid follicular cells)			
			Dermal	2050 F				
			Bd Wt	991 M	2014 M (17% reduced final body weight)			
56	Rat (CD)	10 wk 5 d/wk (GO)	Bd Wt	175 M	450 M (10% decreased final body weight)		Tyl and Neepser-Bradley 1989 ortho	

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
57	Mouse (B6C3F1)	28 d ad lib (F)	Resp	1650 M	4480 M (rapid breathing)		NTP 1992b ortho	NOAELs are for organ weights and histopathology.
			Cardio	5000 F				
			Gastro	5000 F				
			Musc/skel	5000 F				
			Hepatic	5000 F				
			Renal	5000 F				
			Endocr	5000 F				
			Dermal	5000 F				
			Bd Wt	1650 M	4480 M (28% reduction in final weight)			

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
58	Mouse (B6C3F1)	28 d ad lib (F)	Resp	651 F	2080 F (labored respiration)		NTP 1992b meta	NOAELs are for organ weights and histopathology.
			Cardio	4940 F				
			Gastro	4940 F				
			Musc/skel	4940 F				
			Hepatic	4940 F				
			Renal	4940 F				
			Endocr	4940 F				
			Dermal	4940 F				
			Bd Wt	1730 M	4710 M (21% reduction in final weight)			

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
59	Mouse (B6C3F1)	28 d ad lib (F)	Resp	50 M	163 M (3/5 with minimal hyperplasia of nasal respiratory epithelium vs. 0/5 in controls)		NTP 1992b para	NOAELs are for organ weights and histopathology.
			Cardio	1590 F				
			Gastro	1590 F				
			Hemato	1590 F				
			Musc/skel	1590 F				
			Hepatic	564 F	1590 F (15-20% increase in relative and absolute liver weight)			
			Renal	1590 F				
			Endocr	1590 F				
			Dermal	1590 F				
Bd Wt	469 M	1410 M (17% reduced final body weight)						

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
60	Mouse (B6C3F1)	28 d ad lib (F)	Resp	200 F	604 F (3/5 with minimal hyperplasia of the nasal respiratory epithelium vs. 0/5 in controls)		NTP 1992b mix	NOAELs are for organ weights and histopathology.
			Cardio	4730 F				
			Gastro	4730 F				
			Hemato	1490 M	4530 M (bone marrow hypocellularity)			
			Musc/skel	4730 F				
			Hepatic	604 F	1880 F (30% increase in absolute and relative liver weight)			
			Renal	4730 F				
			Endocr	4730 F				
			Dermal	1490 M	4530 M (alopecia)			
Bd Wt	471 M	1490 M (10% reduced final body weight)	4530 M (27% reduction in final weight)					

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
61	Mouse (B6C3F1)	13 wk ad lib (F)	Resp	3205 F			NTP 1992b ortho	NOAELs are for organ weights and histopathology.
			Cardio	3205 F				
			Gastro	1723 M	2723 M (forestomach epithelial hyperplasia)			
			Hemato	3205 F				
			Musc/skel	3205 F				
			Hepatic	794 M	1723 M (17-19% increase in absolute and relative liver weight)			
			Renal	3205 F				
			Endocr	3205 F				
			Dermal	3205 F				
Bd Wt	1723 M	2723 M (16% reduced final body weight)						

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
62	Mouse (B6C3F1)	13 wk ad lib (F)	Resp	402 M	776 M (4/10 with minimal hyperplasia of the nasal respiratory epithelium vs. 1/10 in controls)		NTP 1992b mix	NOAELs are for organ weights and histopathology.
			Cardio	1693 F				
			Gastro	1693 F				
			Hemato	1693 F				
			Musc/skel	1693 F				
			Hepatic	402 M	776 M (12% increase in absolute and relative liver weight)			
			Renal	1693 F				
			Endocr	1693 F				
			Dermal	1693 F				
Bd Wt	1693 F							
63	Hamster (Golden Syrian)	20 wk ad lib (F)	Gastro		1415 M (mild to moderate forestomach hyperplasia)		Hirose et al. 1986 para	
			Hepatic	1415 M				

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
64	Ferret (NS)	28 d (F)	Resp	400			Hornshaw et al. 1986 ortho	NOAELs are for organ weights and gross necropsy.
			Cardio	400				
			Hemato	400				
			Hepatic	400				
			Renal	400				
			Bd Wt	400				
65	Mink (NS)	28 d (F)	Resp	320			Hornshaw et al. 1986 ortho	NOAELs are for organ weights and gross necropsy.
			Cardio	320				
			Hemato	320				
			Hepatic	320				
			Renal	320				
			Bd Wt		320 F (weight loss)			
66	Rat (Sprague-Dawley)	13 wk 7 d/wk 1 x/d (GO)		600			EPA 1988b ortho	NOAEL is for weight and histopathology of spleen, thymus and lymph nodes.

Immuno/ Lymphoret

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	LOAEL		Reference Chemical Form	Comments	
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)			Serious (mg/kg/day)
67	Rat (Sprague-Dawley)	13 wk 7 d/wk 1 x/d (GO)		600			EPA 1988c para	NOAEL is for changes in histopathology of spleen, thymus, and lymph nodes.
68	Rat (Sprague-Dawley)	13 wk 7 d/wk 1 x/d (GO)		450			EPA 1988d meta	NOAEL is for changes in weight and histopathology of spleen, thymus, and lymph nodes.
69	Rat (Fischer-344)	28 d ad lib (F)		2610 M			NTP 1992b ortho	NOAEL is for weight and histopathology of lymphoreticular organs.
70	Rat (Fischer-344)	28 d ad lib (F)		2470 M			NTP 1992b meta	NOAEL is for lymphoreticular organs weights and histopathology.
71	Rat (Fischer-344)	28 d ad lib (F)		2180 M			NTP 1992b para	NOAEL is for lymphoreticular organs weights and histopathology.
72	Rat (Fischer-344)	13 wk ad lib (F)		2028 M			NTP 1992b ortho	NOAELs are for weight and histopathology of lymphoreticular organs.

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
73	Rat (Fischer- 344)	13 wk ad lib (F)		2050 F			NTP 1992b mix	NOAEL is for weight and histopathology of lymphoreticular organs.
74	Rat (Fischer- 344)	28 d ad lib (F)		2600 M			NTP 1992b mix	NOAEL is for weight and histopathology of lymphoreticular organs.
75	Mouse (B6C3F1)	28 d ad lib (F)		5000 F			NTP 1992b ortho	NOAELs are for weight and histopathology of lymphoreticular organs.
76	Mouse (B6C3F1)	28 d ad lib (F)		4940 F			NTP 1992b meta	NOAELs are for weight and histopathology of lymphoreticular organs.
77	Mouse (B6C3F1)	28 d ad lib (F)		1590 F			NTP 1992b para	NOAEL is for weight and histopathology of lymphoreticular organs.
78	Mouse (B6C3F1)	28 d ad lib (F)		4730 F			NTP 1992b mix	NOAEL is for weights and histopathology of lymphoreticular organs.

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
79	Mouse (B6C3F1)	13 wk ad lib (F)		3205 F			NTP 1992b ortho	NOAEL is for weight and histopathology of lymphoreticular organs.
80	Mouse (B6C3F1)	13 wk ad lib (F)		1693 F			NTP 1992b mix	NOAEL is for weight and histopathology of lymphoreticular organs.
Neurological								
81	Rat (Sprague- Dawley)	13 wk 7 d/wk 1 x/d (GO)		175		600 (coma, convulsions)	EPA 1988b ortho	
82	Rat	13 wk 7 d/wk 1 x/d (GO)		175		600 (convulsions, coma)	EPA 1988c para	
83	Rat	13 wk 7 d/wk 1 x/d (GO)		150		450 (lethargy, tremors)	EPA 1988d meta	
84	Rat (Sprague- Dawley)	28 d 1 x/d (GO)		300		1000 (salivation and tremors)	Koizumi et al. 2003 meta	
85	Rat (CD)	10 wk 5 d/wk (GO)		30	175 (perioral wetness)		Neeper-Bradley and Tyl 1989a para	

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
86	Rat (CD)	10 wk 5 d/wk (GO)		30	175 (perioral wetness)		Neeper-Bradley and Tyl 1989b meta	
87	Rat (Fischer- 344)	28 d ad lib (F)		2610 M			NTP 1992b ortho	NOAEL is for histopathology of the brain and clinical signs.
88	Rat (Fischer- 344)	28 d ad lib (F)		2470 M			NTP 1992b meta	NOAEL is for weight and histopathology of the brain and clinical signs.
89	Rat (Fischer- 344)	28 d ad lib (F)		2180 M			NTP 1992b para	NOAEL is for weight and histopathology of the brain and clinical signs.
90	Rat (Fischer- 344)	13 wk ad lib (F)		2028 M			NTP 1992b ortho	NOAEL is for weight and histopathology of the brain and clinical signs.
91	Rat (Fischer- 344)	13 wk ad lib (F)		2050 F			NTP 1992b mix	NOAEL is for weight and histopathology of the brain and clinical signs.

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
92	Rat (Fischer-344)	28 d ad lib (F)		2600 M			NTP 1992b mix	NOAEL is for histopathology of the brain and clinical signs.
93	Rat (CD)	13 wk 7 d/wk (GO)			50 (CNS stimulation)	450 (convulsions)	TRL 1986 ortho	Behavioral tests done throughout the study had sporadic non dose-related differences with controls.
94	Rat (CD)	13 wk 7 d/wk (GO)			50 (CNS stimulation)	600 (convulsions)	TRL 1986 para	Behavioral tests done throughout the study had sporadic non dose-related differences with controls.
95	Rat (CD)	13 wk 7 d/wk (GO)			50 (hypoactivity)	450 (convulsions)	TRL 1986 meta	Behavioral tests done throughout the study had sporadic non dose-related differences with controls.
96	Rat (CD)	10-11 wk 5 d/wk 6-9 wk 7 d/wk (GO)		30		175 (ataxia, hypoactivity)	Tyl and Neepser-Bradley 1989 ortho	

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
97	Mouse (B6C3F1)	28 d ad lib (F)		1650 M	4480 M (lethargy and tremors)		NTP 1992b ortho	
98	Mouse (B6C3F1)	28 d ad lib (F)		651 F	2080 F (lethargy)		NTP 1992b meta	
99	Mouse (B6C3F1)	28 d ad lib (F)		469 M	1410 ^c M (lethargy) 1590 F		NTP 1992b para	
100	Mouse (B6C3F1)	28 d ad lib (F)		1490 M	4530 M (lethargy)		NTP 1992b mix	
101	Mouse (B6C3F1)	13 wk ad lib (F)		3205 F			NTP 1992b ortho	NOAEL is for weight and histopathology of the brain.
102	Mouse (B6C3F1)	13 wk ad lib (F)		1693 F			NTP 1992b mix	NOAEL is for weight and histopathology of the brain.

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL		Reference Chemical Form	Comments	
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)			Serious (mg/kg/day)
Reproductive								
103	Rat (Sprague- Dawley)	13 wk 7 d/wk 1 x/d (GO)		600			EPA 1988b ortho	NOAEL is for weight and histopathology of reproductive organs. Fertility was not assessed.
104	Rat (Sprague- Dawley)	13 wk 7 d/wk 1 x/d (GO)		600			EPA 1988c para	NOAEL is for histopathology of reproductive organs. Fertility was not assessed.
105	Rat (Sprague- Dawley)	13 wk 7 d/wk 1 x/d (GO)		450			EPA 1988d meta	NOAEL is for changes in weight and histopathology of reproductive organs.
106	Rat (CD)	10 wk 5 d/wk (GO)		450			Neeper-Bradley and Tyl 1989a para	The NOAEL is for reproductive function end points in both sexes.
107	Rat (CD)	10 wk 5 d/wk (GO)		450			Neeper-Bradley and Tyl 1989b meta	The NOAEL is for reproductive function end points in both sexes.

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
108	Rat (Fischer- 344)	28 d ad lib (F)		2610 M			NTP 1992b ortho	NOAEL is for weight and histopathology of reproductive organs; fertility was not assessed.
109	Rat (Fischer- 344)	28 d ad lib (F)		2470 M 862 ^C F	2310 F (mild uterine atrophy in 4/5 females)		NTP 1992b meta	Fertility was not assessed.
110	Rat (Fischer- 344)	28 d ad lib (F)		2180 M 770 ^C F	2060 F (mild to moderate uterine atrophy)		NTP 1992b para	Fertility was not assessed.
111	Rat (Fischer- 344)	13 wk ad lib (F)		2028 M			NTP 1992b ortho	NOAEL is for weight and histopathology of reproductive organs, sperm effects, and estrous cycle length.
112	Rat (Fischer- 344)	13 wk ad lib (F)		2014 M 254 ^C F	509 F (lengthened estrous cycle)		NTP 1992b mix	
113	Rat (Fischer- 344)	28 d ad lib (F)		2600 M			NTP 1992b mix	NOAEL is for histopathology of reproductive organs.

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL		Reference Chemical Form	Comments	
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)			Serious (mg/kg/day)
114	Rat (CD)	10 wk 5 d/wk (GO)		450			Tyl and Neeper-Bradley 1989 ortho	The NOAEL is for reproductive function end points in both sexes.
115	Mouse (CD-1)	14 wk ad lib (F)		660			NTP 1992a ortho	NOAEL is for reproductive functional end points in a study using a continuous breeding protocol.
116	Mouse (B6C3F1)	28 d ad lib (F)		4480 M ^C 763 F	1670 F (mild atrophy of the uterus in 5/5 mice)		NTP 1992b ortho	Fertility was not assessed.
117	Mouse (B6C3F1)	28 d ad lib (F)		4710 M ^C 2080 F		4940 F (mild to moderate atrophy of mammary gland, uterus, and ovaries)	NTP 1992b meta	Fertility was not assessed.
118	Mouse (B6C3F1)	28 d ad lib (F)		1590 F			NTP 1992b para	NOAEL is for weight and histopathology of reproductive organs; fertility was not assessed.

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL		Reference Chemical Form	Comments	
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)			Serious (mg/kg/day)
119	Mouse (B6C3F1)	28 d ad lib (F)		4730 F			NTP 1992b mix	NOAEL is for weight and histopathology of reproductive organs; fertility was not assessed.
120	Mouse (B6C3F1)	13 wk ad lib (F)		2723 M 1663 ^c F	3205 F (lengthened estrous cycle)		NTP 1992b ortho	Fertility was not assessed.
121	Mouse (B6C3F1)	13 wk ad lib (F)		1693 F			NTP 1992b mix	NOAEL is for weight and histopathology of reproductive organs, sperm effects, and estrous cycle length.
122	Mouse (CD-1)	14 wk ad lib (F)		1390	1682 (increased cumulative days to litter)		NTP 1992c mix	No histopathology in reproductive organs from males or females. Fertility of F1 not altered.
123	Mink (NS)	6 mo (F)		105			Hornshaw et al. 1986 ortho	NOAEL is for reproductive function end points in males and females.

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments	
					Less Serious (mg/kg/day)	Serious (mg/kg/day)			
Developmental									
124	Rat (Sprague- Dawley)	18 d 1 x/d pnd 4-21 (GO)		30		100	(tremors under contact stimulus)	Koizumi et al. 2003 meta	Tremors observed in newborn rats but not in 5-week old exposed for 28 days.
125	Rat (CD)	10 wk 5 d/wk (GO)		175		450	(reduced viability of F1 generation)	Neeper-Bradley and Tyl 1989a para	
126	Rat (CD)	10 wk 5 d/wk (GO)		175		450	(reduced viability of F1 generation)	Neeper-Bradley and Tyl 1989b meta	
127	Rat (CD)	10 wk 5 d/wk (GO)		175		450	(reduced viability of F1 generation)	Tyl and Neeper-Bradley 1989 ortho	
128	Mouse (CD-1)	14 wk ad lib (F)		1390		1682	(decreased number of live pups/litter)	NTP 1992c mix	

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
CHRONIC EXPOSURE								
Systemic								
129	Rat (Fischer- 344)	2 yr ad lib (F)	Resp		123 M (17/50 with minimal hyperplasia of the nasal respiratory epithelium, 3/50 in controls)		NTP 2008 mixed	The LOAEL for respiratory is listed as 123 mg/kg/day, which was the mean dose during the first 13 weeks when the nose lesions probably developed.
			Cardio	720 M				
			Gastro	720 M				
			Musc/skel	720 M				
			Hepatic	230 M	720 M (increased incidence of eosinophilic foci)			
			Renal	230 M	720 M (transitional epithelial hyperplasia of the renal pelvis)			
			Endocr	720 M				
			Dermal	720 M				
			Ocular	720 M				
			Bd Wt	230 M	720 M (final body weight reduced 15%)			

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments
					Less Serious (mg/kg/day)	Serious (mg/kg/day)		
130	Mouse (B6C3F1)	2 yr ad lib (F)	Resp		100 ^d F (42/50 with minimal bronchiolar hyperplasia, 0/50 in controls)		NTP 2008 mixed	NOAELs are for histopathology of tissues and organs.
			Cardio	1040 F				
			Gastro	1040 F				
			Musc/skel	1040 F				
			Hepatic	300 F	1040 F (increased eosinophilic foci)			
			Renal	1040 F				
			Endocr		100 F (follicular degeneration in thyroid gland)			
			Dermal	1040 F				
			Ocular	1040 F				
			Bd Wt	100 F	300 F (11% reduction in final body weight)	1040 F (24% reduction in final body weight)		
Immuno/ Lymphoret								
131	Rat (Fischer- 344)	2 yr ad lib (F)		720 M			NTP 2008 mixed	NOAEL is for histopathological alterations of lymphoreticular organs.

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
				NOAEL (mg/kg/day)	Less Serious (mg/kg/day)	Serious (mg/kg/day)		
132	Mouse (B6C3F1)	2 yr ad lib (F)		1040 F			NTP 2008 mixed	NOAEL is for histopathology of lymphoreticular organs.
Neurological								
133	Rat (Fischer- 344)	2 yr ad lib (F)		720 M			NTP 2008 mixed	NOAEL is for histopathology of the brain.
134	Mouse (B6C3F1)	2 yr ad lib (F)		1040 F			NTP 2008 mixed	NOAEL is for histopathology of the brain.
Reproductive								
135	Rat (Fischer- 344)	2 yr ad lib (F)		720 M			NTP 2008 mixed	NOAEL is for histopathology of the reproductive organs.
136	Mouse (B6C3F1)	2 yr ad lib (F)		1040 F			NTP 2008 mixed	NOAEL is for histopathology of reproductive organs.

Table 3-1 Levels of Significant Exposure to Cresols - Oral

(continued)

Key to Figure ^a	Species (Strain)	Exposure/Duration/Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL		Reference Chemical Form	Comments	
					Less Serious (mg/kg/day)	Serious (mg/kg/day)			
Cancer									
137	Mouse (B6C3F1)	2 yr ad lib (F)				1040 F	(CEL: squamous cell papilloma in forestomach, 0/50, 1/50, 1/49, 10/50)	NTP 2008 mixed	

^a The number corresponds to entries in Figure 3-1.

^b Used to derive an intermediate-duration oral minimal risk level (MRL) of 0.1 mg/kg/day; the MRL was derived by dividing the BMDL10 of 13.94 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 to protect sensitive subpopulations).

^c Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-1. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

^d Used to derive a chronic-duration oral minimal risk level (MRL) of 0.1 mg/kg/day; the MRL was derived by dividing the LOAEL of 100 mg/kg/day by an uncertainty factor of 1000 (10 for animal to human extrapolation, 10 for use of a LOAEL, and 10 for human variability).

ad lib = ad libitum; Bd Wt = body weight; BMDL = below minimum detectable limits; Cardio = cardiovascular; CNS = central nervous system; d = day(s); Endocr = endocrine; (F) = feed; F = Female; (G) = gavage; Gastro = gastrointestinal; gd = gestational day; (GO) = gavage in oil; (GW) = gavage in water; hemato = hematological; hr = hour(s); Immuno/Lymphoret = immunological/lymphoreticular; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; mo = month(s); Musc/skel = musculo/skeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; occup = occupational; pnd = post-natal day; Resp = respiratory; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; x = time(s); wk = week(s)

Figure 3-1 Levels of Significant Exposure to Cresols - Oral (Continued)

Acute (≤14 days)

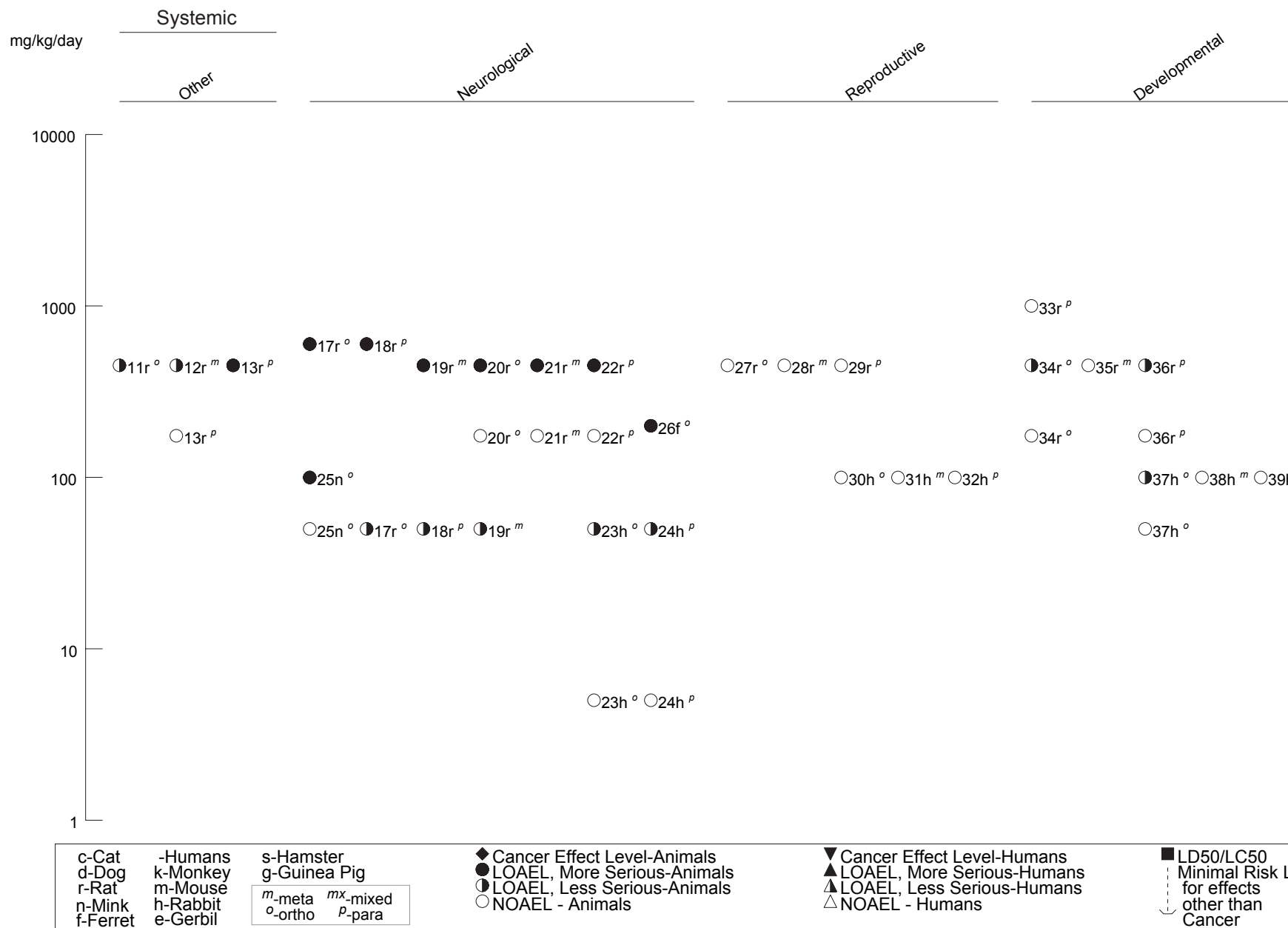
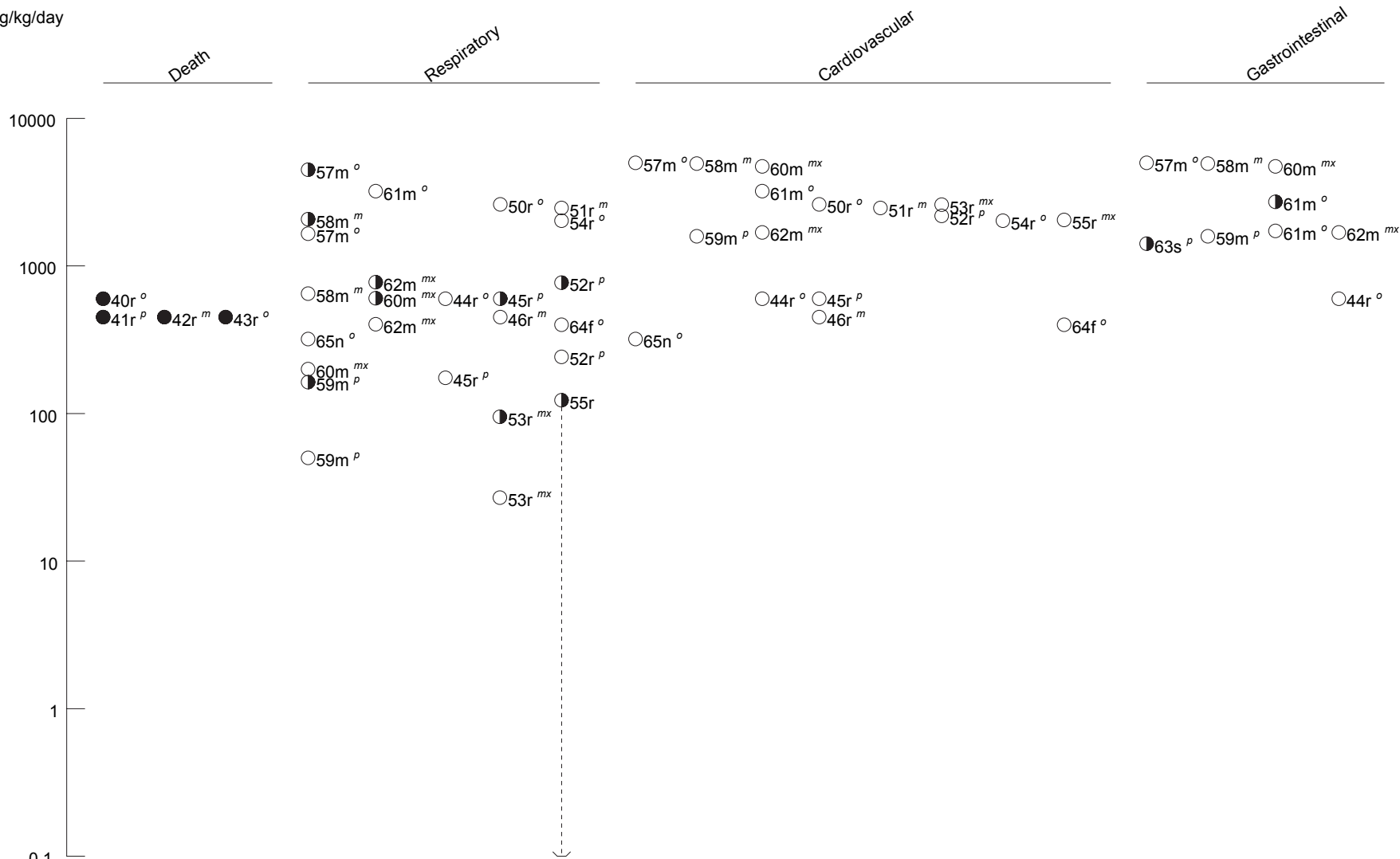


Figure 3-1 Levels of Significant Exposure to Cresols - Oral (Continued)

Intermediate (15-364 days)

Systemic

mg/kg/day



c-Cat	-Humans	s-Hamster	◆ Cancer Effect Level-Animals	▼ Cancer Effect Level-Humans	■ LD50/LC50
d-Dog	k-Monkey	g-Guinea Pig	● LOAEL, More Serious-Animals	▲ LOAEL, More Serious-Humans	⋮ Minimal Risk Level
r-Rat	m-Mouse		◐ LOAEL, Less Serious-Animals	△ LOAEL, Less Serious-Humans	⋮ for effects
n-Mink	h-Rabbit	<i>m</i> -meta <i>mx</i> -mixed	○ NOAEL - Animals	△ NOAEL - Humans	⋮ other than
f-Ferret	e-Gerbil	<i>o</i> -ortho <i>p</i> -para			⋮ Cancer

Figure 3-1 Levels of Significant Exposure to Cresols - Oral (Continued)
Intermediate (15-364 days)

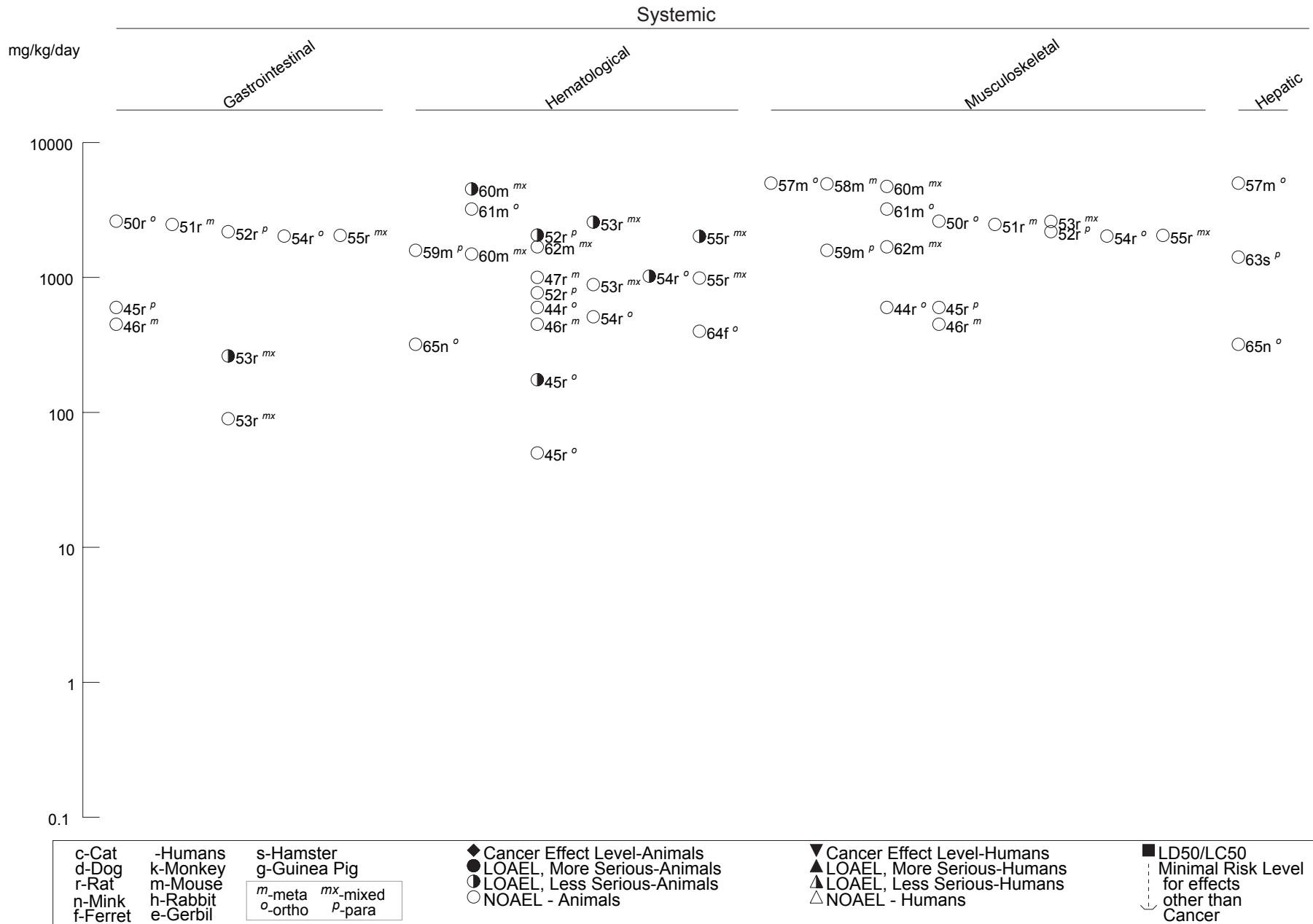


Figure 3-1 Levels of Significant Exposure to Cresols - Oral (Continued)
Intermediate (15-364 days)

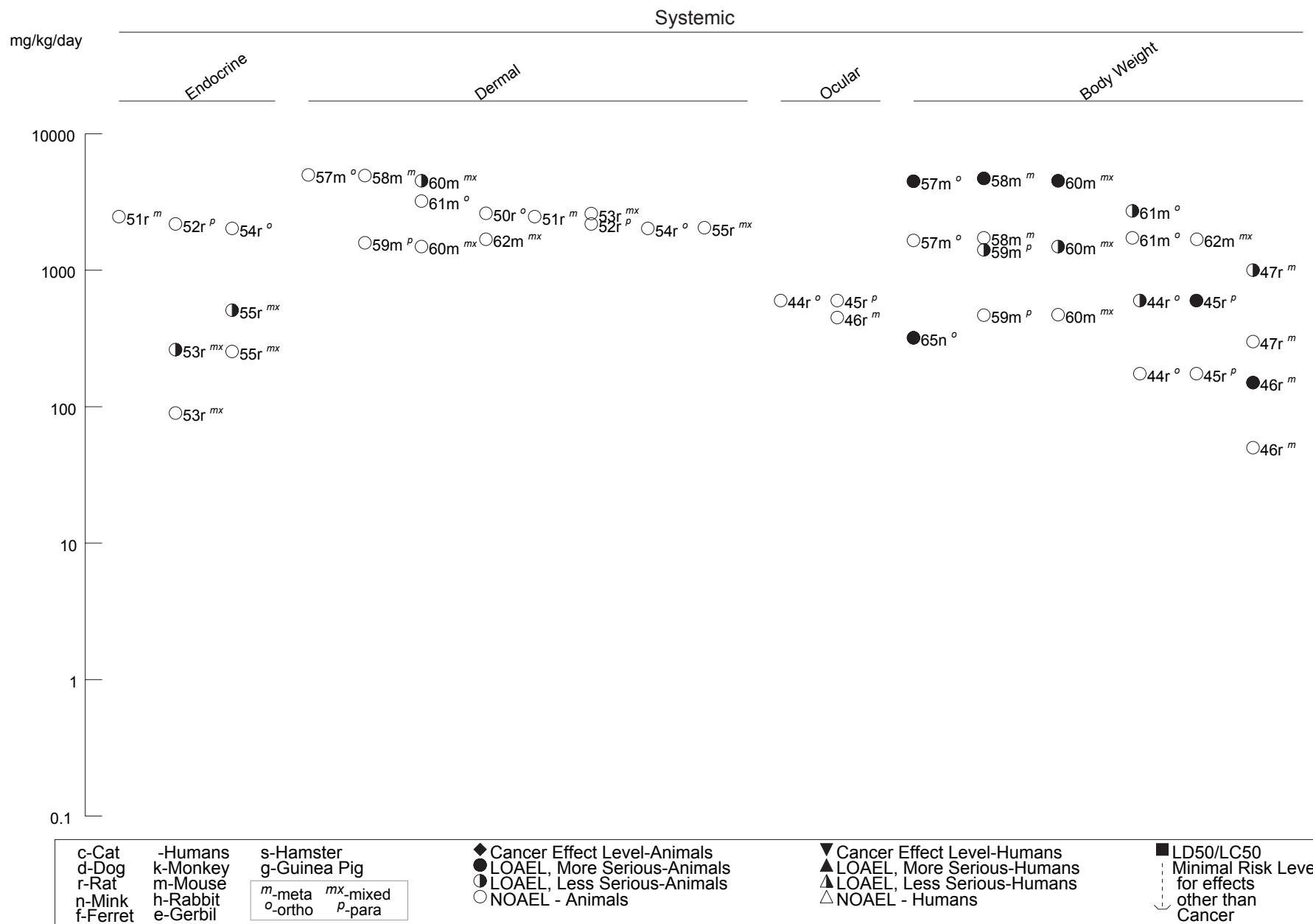


Figure 3-1 Levels of Significant Exposure to Cresols - Oral (Continued)

Intermediate (15-364 days)

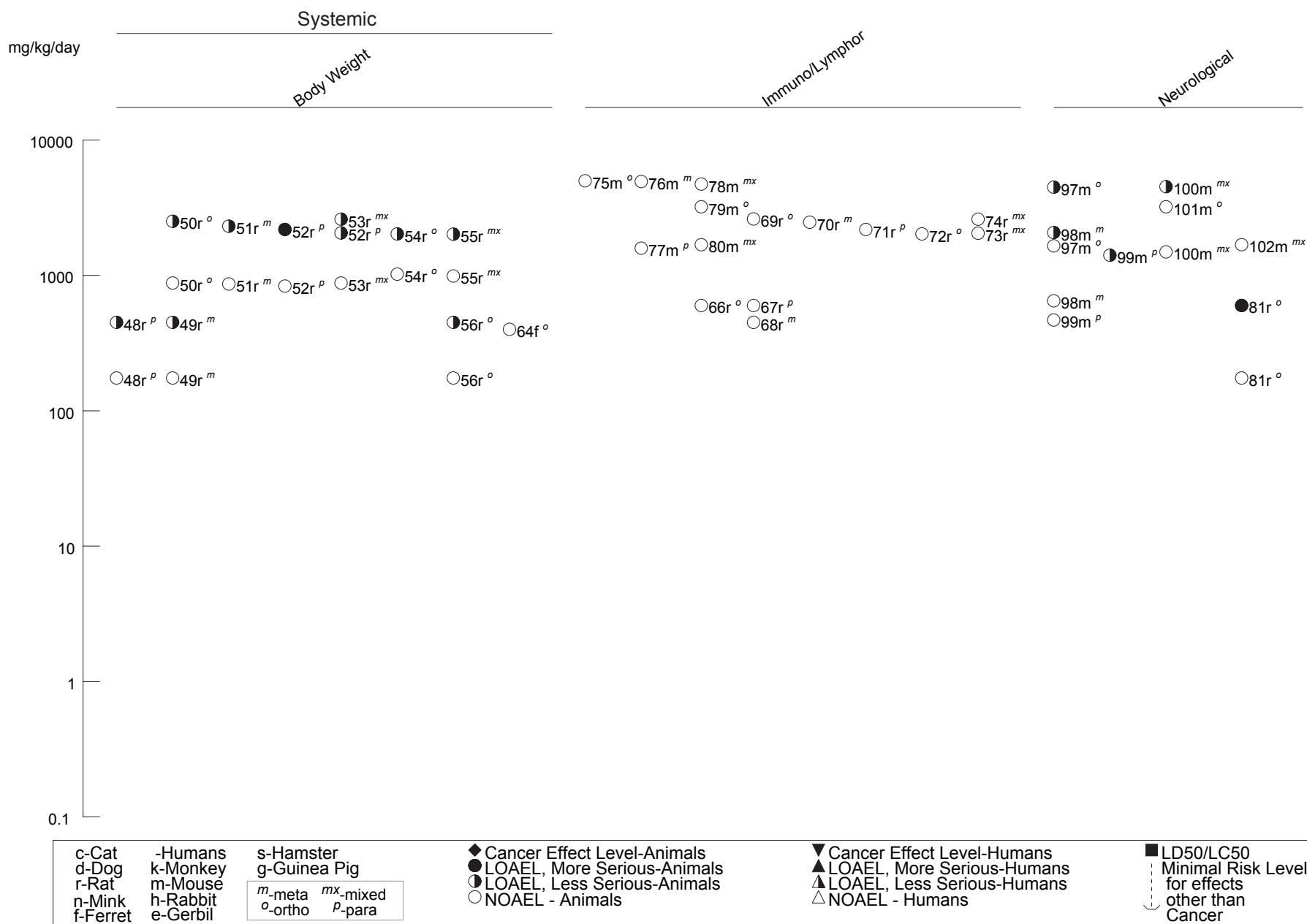


Figure 3-1 Levels of Significant Exposure to Cresols - Oral (Continued)
Intermediate (15-364 days)

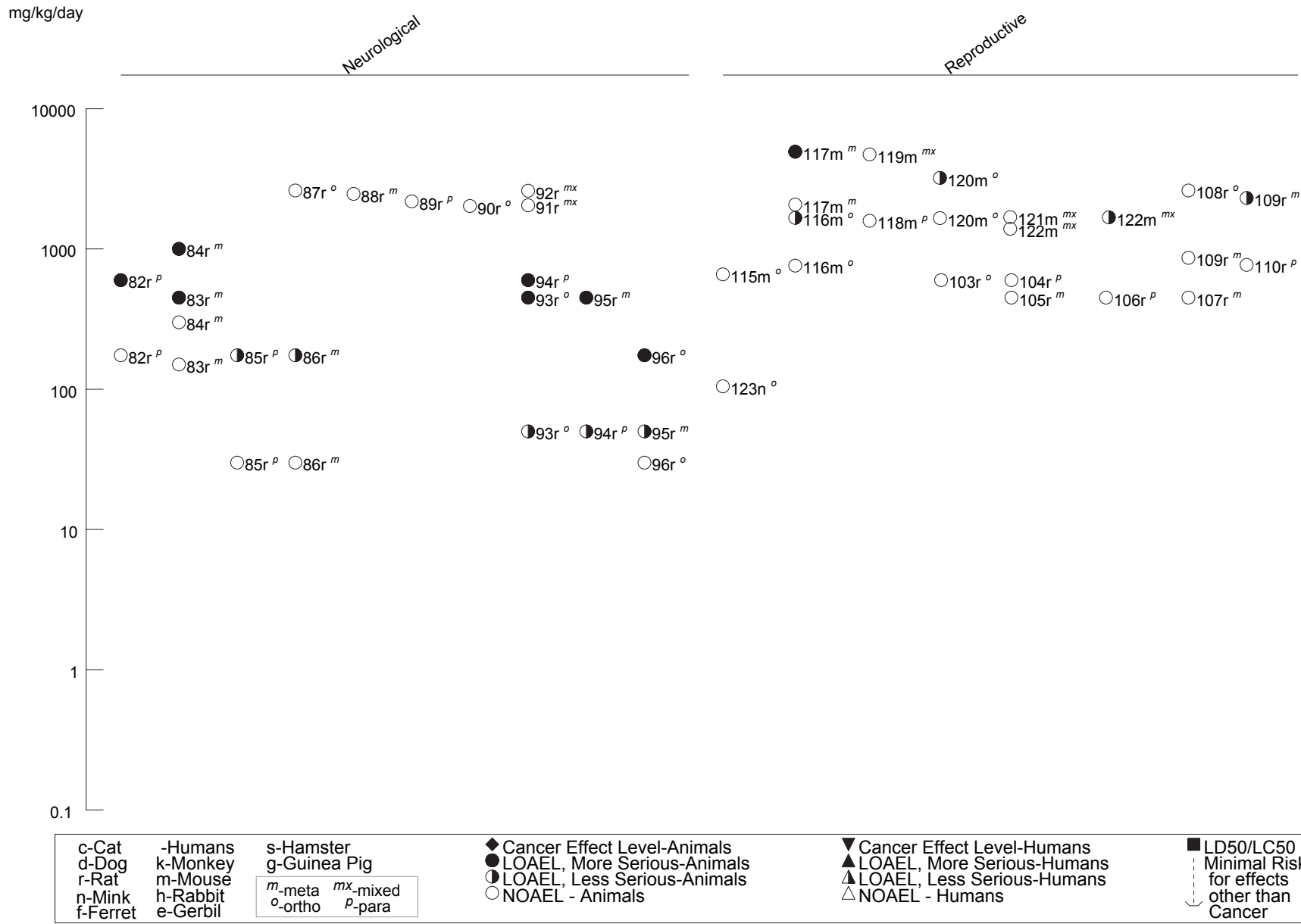
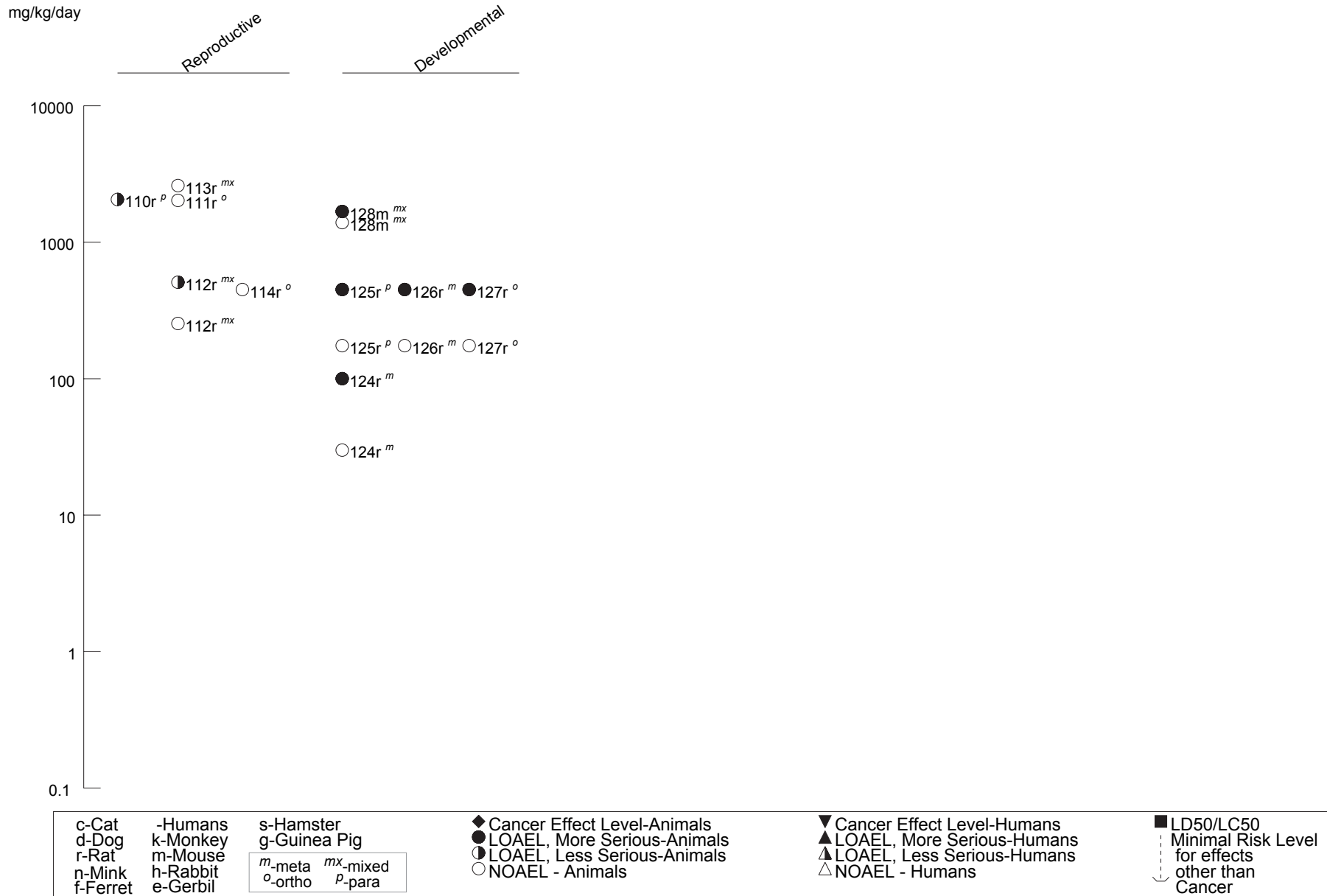


Figure 3-1 Levels of Significant Exposure to Cresols - Oral (Continued)
Intermediate (15-364 days)



3. HEALTH EFFECTS

B6C3F₁ mice also exhibited nasal changes following dietary treatment with *p*-cresol or the *m/p*-cresol mixture for 28 days (NTP 1992b). For *p*-cresol, the LOAEL in males and females was 163 and 207 mg/kg/day, respectively, with corresponding NOAELs of 50 and 60 mg/kg/day. For the mixture, the respective LOAELs in males and females were 4,530 and 604 with corresponding NOAELs of 1,490 and 200 mg/kg/day. Male mice dosed with 4,530 mg/kg/day of the cresol mixture also exhibited a significant increase in bronchiolar hyperplasia. In the 13-week study in mice with *o*-cresol and the cresol mixture, hyperplasia of the respiratory nasal epithelium was seen in males treated with 776 mg/kg/day, but not 402 mg/kg/day, and in females at 1,693 mg/kg/day, but not 923 mg/kg/day of the cresol mixture. No such lesions were seen in mice dosed with *o*-cresol in doses of up to 2,700–3,200 mg/kg/day for 13 weeks.

The respiratory system was also a target for *m/p*-cresol in male Fischer rats (females not tested) and female B6C3F₁ mice (males not tested) in a 2-year dietary study (NTP 2008). In rats, the response with the lowest threshold appeared to be hyperplasia of the respiratory epithelium of the nose, which occurred with an incidence of 3/50, 17/50, 31/50, and 47/50 in rats dosed with mean time-weighted average (TWA) doses of 0, 70, 320, and 720 mg/kg/day, respectively; severity was minimal to mild. The incidence in the low-dose group (17/50, 34%) was very similar to that reported in the 13-week study (NTP 1992b) (3/10, 30%) in male rats that received mean daily doses of 123 mg/kg/day during the 13 weeks of the study. Since the mean dose received by the low-dose rats during the first 13 weeks of the 2-year study was 123 mg/kg/day (from a table in the NTP report providing mean weekly doses during the first 13 weeks), it means that the lesions were already established by week 13 of the 2-year study and did not increase in severity. Therefore, the value listed as a LOAEL in the LSE table is 123 mg/kg/day, the true mean dose during the first 13 weeks, rather than the low TWA dose of 70 mg/kg/day for the entire duration of the chronic study. Other nasal lesions observed in rat included squamous metaplasia of the nasal epithelium, hyperplasia of the goblet cell, and inflammation of the nose. In mice, the most sensitive response was hyperplasia of the bronchiole of the lung, occurring with incidences of 0/50, 42/50, 44/49, and 47/50 in mice dosed with mean TWA doses of 0, 100, 300, and 1,040 mg/kg/day, respectively. Hyperplasia of the bronchiole of the lung was not a lesion reported in mice in the 13-week NTP (1992b) study. Dose-related elevated incidences of respiratory epithelium hyperplasia were also reported at 300 and 1,040 mg/kg/day in mice (NTP 2008). The LOAEL of 100 mg/kg/day for bronchiole hyperplasia in female mice exposed for 2 years was used to derive a chronic-duration oral MRL for cresols.

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Pregnant rats (Tyl 1988b) and rabbits (Tyl 1988a) exposed to *o*-, *p*-, and *m*-cresol were reported to have audible respiration and labored breathing. These effects may be of a neurologic origin, rather than a direct effect on the respiratory system (Section 3.2.2.4).

Cardiovascular Effects. A woman who swallowed 500–750 mL of a concentrated cresol mixture exhibited tachycardia with polymorphic ventricular extra-systoles shortly after exposure (Labram and Gervais 1968). This was followed within 26 hours by ventricular fibrillation and cardiac arrest.

In rats exposed to *o*-cresol (EPA 1988b), *p*-cresol (EPA 1988c), or *m*-cresol (EPA 1988d) at levels up to 600 mg/kg/day for 13 weeks by gavage, histological examination of the heart revealed no changes that indicated an adverse effect on the heart. A 28-day dietary study reported no significant histopathological effects in the heart or aorta of rats dosed with up to approximately 2,600 mg/kg/day of each cresol isomer or with a mixture (58/41%) of *m*- and *p*-cresol (NTP 1992b). A similar lack of effects was reported in rats following 13 weeks of treatment with approximately 2,000 mg/kg/day of *o*-cresol or the cresol mixture in the diet (NTP 1992b).

In mice, treatment for 28 days with up to approximately 5,000 mg/kg/day of *o*-cresol, *m*-cresol, or the *m/p*-cresol mixture or 1,590 mg/kg/day of *p*-cresol had no significant effect on the gross or microscopic appearance of the heart or aorta (NTP 1992b). Similar effects were reported in mice dosed with up to 3,200 mg/kg/day of *o*-cresol or 1,693 mg/kg/day of the *m/p*-cresol mixture for 13 weeks (NTP 1992b). The data available suggest that the cardiovascular system is not a sensitive target for cresol toxicity.

No gross or microscopic alterations were observed in the heart of male rats and female mice administered mean doses of up to 720 and 1,040 mg/kg/day *m/p*-cresol, respectively, via the diet for 2 years (NTP 2008).

Gastrointestinal Effects. Mouth and throat burns, abdominal pain, and vomiting were common symptoms of cresol poisoning among 52 patients who drank between 4 and 120 mL of a disinfectant containing 25–50% mixed cresols (Isaacs 1922). These effects were also seen in a man who swallowed approximately 250 mL of a concentrated cresol mixture in a suicide attempt (Jouglaud et al. 1971). Hemorrhagic degeneration of the pancreas was the cause of death in a woman who swallowed a disinfectant suspected of containing cresols. It was not clear, however, if this effect was actually produced by the disinfectant or was due to a pre-existing condition (little disinfectant was taken) (Dellal 1931). In a man who ingested an unknown amount of cresol, gastrointestinal endoscopy performed

3. HEALTH EFFECTS

10 hours later revealed dark red corrosive injuries on the esophagus and stomach wall (Hayakawa 2002). Diffuse erosions in the gastrointestinal tract have been observed in subjects who drank saponated cresol solutions containing about 50% cresol (Bruce et al. 1976; Kamijo et al. 2003; Wu et al. 1998; Yashiki et al. 1990).

Rats exposed to cresols in doses up to 600 mg/kg/day for 13 weeks by gavage in corn oil did not have gastrointestinal lesions (EPA 1988b, 1988c, 1988d). However, dietary administration of *p*-cresol in doses of approximately 1,415 mg/kg/day for 20 weeks produced an increased incidence of mild and moderate hyperplasia of the forestomach of hamsters (Hirose et al. 1986). Rats treated for 28 days with up to approximately 2,200–2,400 mg/kg/day of each cresol isomer in the diet showed no significant alterations in the gastrointestinal tract. However, doses ≥ 260 mg/kg/day of *m/p*-cresol mixture (58/41%) induced hyperplasia and hyperkeratosis of the esophageal epithelium in male and female rats (NTP 1992b); the NOAEL was 90–95 mg/kg/day. Higher doses (2,500–2,600 mg/kg/day) also induced hyperplasia in the epithelium of the forestomach. Longer treatments (13 weeks) with approximately 2,000 mg/kg/day of *o*-cresol or the cresol mixture had no significant effect on the gastrointestinal tract of rats (NTP 1992b).

In mice, doses of up to near 5,000 mg/kg/day of *o*-, *m*-, or an *m/p*-cresol mixture had no significant effect on the gastrointestinal tract (NTP 1992b). Similarly, no increased incidence of gastrointestinal tract lesions occurred with up to 1,590 mg/kg/day of *p*-cresol; the highest dietary dose of *p*-cresol was not estimated by NTP (1992b) since it killed all the mice, but was probably near 5,000 mg/kg/day. The 13-week studies in mice provided no evidence of gastrointestinal alterations following doses of approximately 1,500–1,700 mg/kg/day of the cresol mixture, but doses of 2,700–3,200 mg/kg/day of *o*-cresol induced minimal forestomach epithelial hyperplasia (NTP 1992b).

No gross or microscopic alterations were observed in the gastrointestinal tract of male rats and female mice administered mean doses of up to 720 and 1,040 mg/kg/day *m/p*-cresol, respectively, via the diet for 2 years (NTP 2008).

Hematological Effects. Hematological effects were described in four people who ingested cresol-containing products. One woman swallowed 100 mL of a disinfectant containing 50% mixed cresols, receiving a dose of approximately 1 g/kg (Chan et al. 1971). Methemoglobin was seen in the blood after 1.5 hours, but was no longer detected after 6 hours. Some Heinz bodies were observed after 6 hours, but these disappeared after 2 days. A second woman who drank 250 mL of disinfectant (roughly 2 g/kg) experienced more serious effects. Methemoglobinemia and markedly reduced glutathione levels were

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seen after 7 hours. After 3 days, the patient developed severe hemoglobinemia and hemoglobinuria, indicating that massive intravascular hemolysis had occurred; extensive Heinz body formation had also taken place. The patient died the next day, apparently from thrombus formation and kidney failure secondary to acute intravascular hemolysis (Chan et al. 1971). A marked increase in methemoglobin also was observed in a man 15 hours after he swallowed a cresol solution of unknown concentration (Minami et al. 1990). Heinz body formation, hemoglobinemia, hemoglobinuria, and hemolytic anemia were also seen in a man who drank 100 mL of penetrating oil containing 12% mixed cresols, receiving a dose of about 170 mg/kg (Cote et al. 1984). In addition, a man who swallowed approximately 250 mL of a concentrated cresol mixture developed severe hemolytic anemia during the second week following ingestion (Jouglard et al. 1971). Isaacs (1922) did not find abnormalities in the blood of any of 52 patients who had ingested cresols, but the specific analyses performed were not reported. Low platelet count, which could have been due to disseminated intravascular congestion, was described in a man who drank an undetermined amount of cresol (Hayakawa 2002). Leukocytosis and hemolysis were reported in a man who drank 300 mL of a 50% saponated solution of cresols (Wu et al. 1998). The hematological effects of cresols appear to be due to both an oxidant effect on the cell contents and a direct effect on the red cell membrane (Chan et al. 1971).

Severe hematological effects, such as those reported in humans, were not observed in animals exposed to cresols possibly because acute high-dose studies in animals did not investigate hematological effects. Mild decreases in red blood cells, blood hemoglobin concentrations, and hematocrit were reported in rats dosed by gavage with 175 mg/kg of *p*-cresol for 13 weeks (EPA 1988c), but the effects were not produced by the other isomers (EPA 1988b, 1988d). Mild and inconsistent changes in red blood cell count seen in mink were of questionable significance (Hornshaw et al. 1986). A study in rats reported increased incidence of moderate bone marrow hypocellularity following 28 days of a diet that provided approximately 2,000–2,200 mg/kg/day of *p*-cresol or 2,500–2,600 mg/kg/day of an *m/p*-cresol mixture (NTP 1992b); the NOAELs were near 800 mg/kg/day. Blood parameters were not monitored in this 28-day study. Bone marrow hypocellularity also was reported in female rats treated with $\geq 1,021$ mg/kg/day of *o*-cresol for 13 weeks and in male and female rats treated with approximately 2,100 mg/kg/day of *m/p*-cresol (NTP 1992b). Hematological parameters in the 13-week studies with both *o*-cresol and *m/p*-cresol were unremarkable, although there was a tendency to hemoconcentration in animals receiving the highest doses ($>2,000$ mg/kg/day) early in the study.

Male mice treated for 28 days with 4,530 mg/kg/day of *m/p*-cresol showed mild to moderate bone marrow hypocellularity, but no such effect was seen at 1,490 mg/kg/day or in females treated with up to

3. HEALTH EFFECTS

4,730 mg/kg/day (NTP 1992b). Bone marrow hypocellularity also was observed in all mice treated with the highest dietary level of *p*-cresol, 30,000 ppm (NTP did not estimate daily doses at this level since all mice died), but not at estimated doses near 1,500 mg/kg/day (NTP 1992b). No significant hematological effects were reported in mice in the 13-week study with *o*-cresol (2,700–3,200 mg/kg/day) or *m/p*-cresol (1,500–1,700 mg/kg/day).

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

Cresols had no effect on the incidence of gross or microscopic lesions in the muscle or bone of rats given doses up to 600 mg/kg/day by gavage for 13 weeks (EPA 1988b, 1988c, 1988d). The NTP (1992b) dietary studies examined sternbrae and femurs of rats and mice and found no significant gross or microscopic alterations in these tissues. Maximal doses of all the cresols tested were approximately 2,000–2,600 mg/kg/day in rats (28-day and 13-week studies), 4,500–5,000 mg/kg/day (28-day study in mice), 2,700–3,200 mg/kg/day (13-week in mice with *o*-cresol), and 1,500–1,600 mg/kg/day (13-week in mice with *m/p*-cresol). Skeletal muscle was not examined in the NTP (1992b) study. No gross or microscopic alterations were observed in bone (not specified) of male rats and female mice administered mean doses of up to 720 and 1,040 mg/kg/day *m/p*-cresol, respectively, via the diet for 2 years (NTP 2008).

Hepatic Effects. Moderate fatty degeneration was found in the liver of a woman who died after drinking 250 mL of a disinfectant, which contained 50% mixed cresols (Chan et al. 1971). The liver appeared normal in another woman who died after ingesting a disinfectant suspected of containing cresols (Dellal 1931). In a more recent case report, a woman who ingested 70 mL of a 50% cresol solution experienced a marked increase in serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) activities (more than 100-fold increase) after a 24-hour asymptomatic period (Hashimoto et al. 1998). The hepatocellular injury was not severe enough to cause liver descompensation and there was no evidence of hepatic encephalopathy. Blood work done 22 days after the poisoning episode revealed normal serum AST and ALT values. Similar results have been reported in other cases of acute oral intoxication with cresols (Bruce et al. 1976; Hayakawa 2002; Kamijo et al. 2003).

Following oral exposure of animals to cresols by gavage, increased relative liver weight and increased serum transaminase levels were reported. Relative liver weights in rats increased following gavage exposure to doses of 450 mg/kg/day of cresols during pregnancy (Tyl 1988a). Longer-term exposure to

3. HEALTH EFFECTS

levels as low as 5 mg/kg/day had the same effect in mink and ferrets (Hornshaw et al. 1986). However, in these studies, changes in liver weight were not accompanied by histological changes and may not have indicated adverse effects. Increased levels of serum AST and ALT were seen in female rats given 600 mg/kg/day of *p*-cresol by gavage for 13 weeks and appeared to be correlated with the presence of hepatic inflammation (EPA 1988c).

Dietary administration of approximately ≥ 700 –800 mg/kg/day of *o*-, *m*-, or *m/p*-cresol to rats for 28 days resulted in increases ($>10\%$) in absolute and relative liver weight (NTP 1992b). The NOAELs were approximately 260–270 mg/kg/day. For *p*-cresol, doses of 242 mg/kg/day caused a 16% increase in absolute liver weight, whereas 83 mg/kg/day produced an increase of only 6%. No significant gross or microscopic changes were seen in the liver in this series of experiments. In the 13-week rat study with *o*-cresol, absolute and relative liver weights were increased in males and females at ≥ 510 mg/kg/day. Clinical chemistry tests showed an increase in serum bile acids in females at $\geq 1,021$ mg/kg/day and in males at 2,028 mg/kg/day. However, there was no indication of liver necrosis or cholestasis, as serum ALT, 5'-nucleosidase, and alkaline phosphatase activities were not significantly affected. Furthermore, there were no gross or histological alterations in the liver even with the highest doses of 2,028 mg/kg/day. Similar results were reported for the *m/p*-cresol mixture. Clinical chemistry tests showed some alterations in enzymes activities, but no clear pattern or dose-relationships. Bile acids in serum were increased at study termination in females at 2,050 mg/kg/day and in males at 241 and 991 mg/kg/day. Gross necropsy and histopathology of the liver did not reveal any significant treatment-related alterations. Administration of mean doses of 720 mg *m/p*-cresol mixture/kg/day for 2 years male Fisher rats produced a significant increase in the incidence of eosinophilic foci in the liver of (NTP 2008). In rats dosed with ≤ 230 mg/kg/day, the incidences were comparable to controls.

In mice, treatment in the diet with up to 5,000 mg/kg/day (the highest dose tested) of *o*- or *m*-cresol for 28 days caused mortality but did not induce significant histopathological effects on the liver (NTP 1992b). Doses of 1,590 mg/kg/day of *p*-cresol increased absolute and relative liver weight (15–20%) in female mice, but caused no histopathology; no significant changes were seen at 564 mg/kg/day. Mice treated with a higher dose level of *p*-cresol (30,000 ppm in food, but doses were not estimated by NTP) that killed 9/10 mice by day 5 showed liver necrosis. The *m/p*-cresol mixture, at $\geq 1,880$ mg/kg/day, increased absolute and relative liver weight in female mice, but there were no histological alterations even at the higher dose level of 4,730 mg/kg/day. In the 13-week study, *o*-cresol increased liver weight in males at $\geq 1,723$ mg/kg/day, whereas the *m/p*-cresol mixture had the same effect at ≥ 776 mg/kg/day (NTP 1992b). There were no treatment-related alterations in liver morphology in the 13-week study or in

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clinical chemistry tests that would have indicated alterations in liver function. The only effect reported in female mice in the 2-year NTP (2008) bioassay with *m/p*-cresol was an increased incidence of eosinophilic foci in the liver at the 1,040 mg/kg/day dose level, but not at ≤ 300 mg/kg/day.

While some hepatic parameters were affected by treatment with some cresol isomers, the overall database does not suggest that the liver is a particularly sensitive target for cresol toxicity.

Renal Effects. Massive eosinophilic necrosis was found in the proximal tubule of a woman who died after drinking 500–750 mL of a concentrated cresol mixture (Labram and Gervais 1968). This effect was considered by the investigators to have occurred before death, and may have been due to the toxic action of cresol. Renal effects in a woman who drank 250 mL of a disinfectant (50% mixed cresols), and later died, consisted of fibrin clumps in the glomeruli and a moderate level of tubular degeneration, which could have been due to intravascular thrombosis (Chan et al. 1971). Mild congestion of the kidney was reported in a second woman who died following consumption of a disinfectant suspected of containing cresols (Dellal 1931). Greatly elevated blood urea nitrogen (BUN) and serum creatinine were reported in another case of ingestion of a saponated cresol solution (Wu et al. 1998). Among 52 patients with diagnosed cresol poisoning, there were signs of renal toxicity, including darkly colored urine, renal irritation, and in a few cases, reduced phenolsulphonephthalein output (Isaacs 1922). Bruce et al. (1976) observed lipofuscin deposits in the cells of many of the proximal convoluted tubules in a woman who died 2 hours after ingestion of an unknown quantity of Lysol®.

Exposure of male rats to 600 mg/kg/day by gavage for 13 weeks induced a slight increase, which did not appear to be dose related, in the incidence of histological changes characteristic of chronic nephropathy (EPA 1988c). No such changes were seen in rats treated with comparable doses of *o*- or *m*-cresol and urinalyses provided no evidence for altered kidney function with any of the cresol isomers. Exposure of rats to *m*-, *p*-, or an *m/p*-cresol mixture in the diet for 28 days in doses of up to 2,200–2,600 mg/kg/day did not induce treatment-related alterations in gross or microscopic appearance of the kidneys (NTP 1992b). Doses of ≥ 861 mg/kg/day of *o*-cresol increased absolute and relative kidney weight (13–15%) in male rats, whereas 266 mg/kg/day produced changes in kidney weight of $\leq 5\%$ relative to controls. Kidney weight in females was not significantly altered. Histological examination of the kidneys did not reveal lesions. The 13-week study found no renal alterations in rats dosed with up to approximately 2,000 mg/kg/day of *o*-cresol or the *m/p*-cresol mixture (NTP 1992b). In both cases, urinalyses provided no evidence of renal injury. Increased incidence of transitional epithelium hyperplasia (minimal to mild severity) of the renal pelvis (8/50 compared with 0/50 in controls) was reported in male rats that received

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mean doses of 720 mg *m/p*-cresol/kg/day for 2 years through the diet (NTP 2008); the NOAEL was 230 mg/kg/day.

Renal effects in mice in the NTP (1992b) studies were limited to kidney necrosis, which was observed in mice that died after being exposed to a diet containing 30,000 ppm *p*-cresol (doses were not calculated by NTP, but were probably in the range of 4,000–5,000 mg/kg/day). *p*-Cresol in doses of 1,590 mg/kg/day had no significant effect on the kidneys in the 28-day study. The other isomers and the *m/p*-cresol mixture did not induce adverse kidney effects in doses of up to 4,000–4,500 mg/kg/day and neither did *o*-cresol (2,700–3,200 mg/kg/day) or *m/p*-cresol (1,500–1,700 mg/kg/day) in the 13-week study. No significant gross or microscopic alterations were reported in the kidneys from female mice dosed with up to 1,040 mg *m/p*-cresol in the diet for 2 years (NTP 2008).

The available studies in animals do not suggest that the kidneys are a sensitive target for cresol toxicity.

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

Studies in animals do not suggest that endocrine organs are susceptible targets for cresol toxicity. A 13-week gavage study with the three cresol isomers reported no treatment-related gross or microscopic alterations in the pituitary, thyroid, adrenals, and pancreas of rats treated with doses of up to 450 mg/kg/day of *m*-cresol or 600 mg/kg/day of *o*- and *p*-cresol (EPA 1988b, 1988c, 1988d).

Both the 28-day and 13-week dietary studies with cresol isomers and a cresol mixture conducted by NTP (1992b) examined the adrenals, pancreas, thyroid, parathyroid, and pituitary of rats and mice. The only treatment-related effect observed was an increase in colloid within the thyroid gland follicles in rats treated with an *m/p*-cresol mixture for 28 days and 13 weeks. The LOAEL and NOAEL in the 28-day were approximately 270 and 90 mg/kg/day, respectively, in males and females. In the 13-week study, the LOAEL for females was 509 mg/kg/day and for males 991 mg/kg/day; the corresponding NOAELs were 254 and 486 mg/kg/day. NTP (1992b) noted that the biological significance of the lesions is uncertain because it was not seen with the individual isomers, nor was it associated with follicular cell hypertrophy and/or hyperplasia. The highest doses of the individual isomers tested in the rats were in the range of 2,000–2,400 mg/kg/day. Mice treated for 28 days received doses of up to 5,000 mg/kg/day of cresols. Mice treated for 13 weeks received up to 3,200 mg/kg/day of *o*-cresol and 1,700 mg/kg/day of *m/p*-cresol. Administration of up to 720 mg *m/p*-cresol/kg/day to male rats via the diet for 2 years did not cause any

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significant alteration in gross or microscopic appearance of the pancreas or of the adrenal, pituitary, parathyroid, and thyroid glands (NTP 2008). In female mice, administration of *m/p*-cresol for 2 years induced a significant increase in the incidence of mild follicular degeneration of the thyroid in all dosed groups (7/48, 24/48, 24/49, and 21/50 in the 0, 100, 300, and 1,040 mg/kg/day dose groups, respectively) (NTP 2008). The LOAEL of 100 mg/kg/day for mild follicular degeneration of the thyroid gland in female mice was used to derive a chronic oral MRL for cresols.

Dermal Effects. No studies were located regarding dermal effects in humans following oral exposure to cresols.

There were no gross or histological alterations in the skin of rats treated with cresol isomers for 28 days or 13 weeks in doses of 2,100–2,600 mg/kg/day (NTP 1992b). In mice, the only significant treatment-related effect was alopecia in males and females treated with 4,530 and 4,730 mg/kg/day, respectively, of *m/p*-cresol for 28 days. No such effect occurred in mice treated with up to 3,205 mg/kg/day of *o*-cresol or 1,693 mg/kg/day of *m/p*-cresol for 13 weeks. No exposure-related histopathological changes in the skin were observed in rats and mice exposed up to 720 or 1,040 mg/kg/day, respectively, *m/p*-cresol in the diet for 2 years (NTP 2008).

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

Pregnant rabbits repeatedly given ≥ 50 mg/kg/day of the cresol isomers during gestation were found to have significant amounts of ocular discharge, some of which may have been due to hemorrhaging (Tyl 1988b), but no gross or microscopic lesions of the eye were found in rats given cresols in doses of up to 450 mg/kg/day of *m*-cresol or 600 mg/kg/day of *o*- or *p*-cresol by oral gavage for 13 weeks (EPA 1988b, 1988c, 1988d; TRL 1986). No exposure-related histopathological changes in the eye were observed in rats and mice exposed up to 720 or 1,040 mg/kg/day, respectively, *m/p*-cresol in the diet for 2 years (NTP 2008).

Body Weight Effects. No studies were located regarding body weight effects in humans following oral exposure to cresols.

In animals, a common response to oral exposure to cresols, particularly in oral gavage studies, was decreased growth, often associated with decreased food consumption (EPA 1988b, 1988c, 1988d;

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Hornshaw et al. 1986; Koizumi et al. 2003; Neeper-Bradley and Tyl 1989a, 1989b; TRL 1986; Tyl 1988a; Tyl and Neeper-Bradley 1989). The effects were usually more pronounced during the early stages of the studies and, in almost all cases, were associated with significant reductions in food consumption. It should be mentioned also that the dose levels that reduced food consumption and body weight gain induced neurological effects such as hypoactivity, incoordination, and tremors. Reduced body weight gain was also observed in the dietary studies in rats and mice, generally at the highest dose levels tested (i.e., $\geq 2,000$ mg/kg/day) and was almost always associated with reduced food consumption (NTP 1992b). Whether the latter is due to poor palatability or other reason is unknown since pair-fed groups were not utilized.

Final body weight in male rats treated with 720 mg *m/p*-cresol/kg/day in the diet for 2 years was 15% lower than in controls (NTP 2008), the NOAEL was 230 mg/kg/day. In the same study, final body weight of female mice dosed with 300 and 1,040 mg *m/p*-cresol/kg/day was reduced 11 and 24%, respectively, relative to controls. Food consumption was not significantly affected in either species throughout the study.

Metabolic Effects. Marked metabolic acidosis (pH 7.058) was reported in a man who drank an undetermined amount of cresol (Hayakawa 2002). Similar observations were made by Kamijo et al. (2003) in a man who drank about 150 mL of a saponated cresol solution containing about 50% cresol. No explicit mention of adverse metabolic effects was made in other reports of ingestion of cresols.

There is no evidence that cresols induced metabolic effects at the doses tested in the animal studies available.

3.2.2.3 Immunological and Lymphoreticular Effects

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

The only immunological end points examined in animal studies were weight and gross and microscopic appearance of the spleen and thymus and occasionally, lymph nodes. Spleen weight was unaffected by 28-day exposure to *o*-cresol in the feed at doses up to 400–720 mg/kg/day in ferrets and 320–480 mg/kg/day in mink (Hornshaw et al. 1986). Similarly, no effect was seen on spleen weight in a reproduction study in which mink were exposed to 105–190 mg/kg/day of *o*-cresol in the feed for 6 months (Hornshaw et al. 1986). Absolute spleen weight was decreased (approximately 18%) in male

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rats given 600 mg/kg/day of *p*-cresol by gavage for 13 weeks, but relative spleen weight was unaffected and no lesions were found; neither weight nor morphological appearance of the thymus or mandibular lymph nodes was significantly altered (EPA 1988c). No significant alterations were seen in these tissues in rats given similar doses of *o*- or *m*-cresol (EPA 1988b, 1988d). Studies in rats and mice exposed to cresol isomers and a mixture of *m*- and *p*-cresol for 28 days or 13 weeks also found no significant histological alterations in lymphoreticular organs and tissues (NTP 1992b). Maximal doses in mice were near 5,000 mg/kg/day and in rats near 2,600 mg/kg/day. Similar results were reported in the 2-year study with maximal doses of *m/p*-cresol of 720 mg/kg/day in male rats and 1,040 mg/kg/day in female mice (NTP 2008). None of the studies mentioned above conducted tests of immunocompetence.

These NOAELs for lymphoreticular effects are presented in Table 3-1 and plotted in Figure 3-1.

3.2.2.4 Neurological Effects

Neurological effects have frequently been noted following oral exposure to cresols. A woman who drank approximately 100 mL of a disinfectant, which consisted of roughly 50% mixed cresols, was semiconscious after 2 hours. A second woman, who swallowed about 250 mL of the same disinfectant, was in a deep coma after 2 hours. She regained consciousness 10 hours later (Chan et al. 1971). A woman who swallowed 500–750 mL of a concentrated cresol mixture fell into a deep coma within 1 hour (Labram and Gervais 1968). Coma was a common feature of cresol poisoning among 52 patients studied by Isaacs (1922). The author noted that unconsciousness could occur very soon after exposure and could last 14 hours or more.

A series of neurological effects, including hypoactivity and lethargy, excess salivation, dyspnea, incoordination, muscle twitches and tremors, convulsions, and coma, have been reported in animals acutely exposed to cresols by gavage (Deichmann and Witherup 1944; Hornshaw et al. 1986; TRL 1986; Tyl 1988a, 1988b). The lowest dose at which neurological effects were reported was 50 mg/kg/day, which produced hypoactivity and labored respiration in pregnant female rabbits repeatedly dosed with *o*- or *p*-cresol during gestation (Tyl 1988b). In rats, effects such as hypoactivity and rapid labored respiration were seen at 50 mg/kg/day for all three isomers (TRL 1986). More serious effects, such as convulsions, were seen at 450 mg/kg/day or higher (TRL 1986).

A detailed oral neurotoxicity study of intermediate duration was performed on rats using all three cresol isomers administered by gavage for 13 weeks (TRL 1986). A host of clinical observations indicative of

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neurotoxicity (including hypoactivity, rapid labored respiration, excessive salivation, and tremors) was reported at doses of 50 mg/kg/day or higher for all three isomers. However, the results of a number of neurobehavioral tests designed to assess demeanor and motor and reflex activity (testing was done 6 times throughout the 13 weeks prior to dosing) showed only sporadic differences with controls and/or alterations were not dose-related. No brain weight changes or histopathologic lesions in the brain or other nervous tissues were found for any isomer. Convulsions were reported at 450 mg/kg/day or higher (TRL 1986). More recently, salivation and tremors were reported in young rats treated by gavage with 1,000 mg/kg/day *m*-cresol, but not 300 mg/kg/day, for 28 days (Koizumi et al. 2003). Other studies of prolonged oral exposure to cresols by gavage had similar findings (EPA 1988b, 1988c, 1988d; Hornshaw et al. 1986; Neeper-Bradley and Tyl 1989a, 1989b; Tyl and Neeper-Bradley 1989). The only intermediate-duration gavage studies to determine NOAEL values for neurological effects were the two-generation reproduction studies in rats (Neeper-Bradley and Tyl 1989a, 1989b; Tyl and Neeper-Bradley 1989). Neurological NOAEL values of 30 mg/kg/day were reported for all three cresol isomers in these studies. However, tests for neurobehavioral effects were not performed. None of the studies mentioned above observed treatment-related gross or microscopic alterations in the brain, spinal cord, or sciatic nerve.

In the intermediate-duration dietary studies in rats and mice conducted by NTP (1992b), the most common adverse clinical signs of neurological impairment observed were lethargy and occasionally tremors, and were seen only in mice. Male and female mice dosed with 4,400–5,000 mg/kg/day of *o*-cresol for 28 days showed lethargy and tremors; these signs were not seen at 1,700 mg/kg/day. Female mice, but not males, exposed to 2,080 mg/kg/day of *m*-cresol for 28 days also exhibited lethargy. Lethargy was also seen in male mice dosed with 1,410 mg/kg/day of *p*-cresol and in male and female mice dosed with 4,530–4,730 mg/kg/day of the *m/p*-cresol mixture. These results indicate that, at least for the end points of lethargy and tremors, mice are more sensitive than rats. Gross and microscopic examination of the brain of rats and mice in the NTP (1992b) study did not reveal any treatment-related lesions. Similar negative observations were reported in male rats and female mice dosed with up to 720 and 1,040 mg/kg/day *m/p*-cresol, respectively, in the diet for 2 years (NTP 2008).

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

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3.2.2.5 Reproductive Effects

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

Developmental toxicity studies in which pregnant rats (Tyl 1988a) and rabbits (Tyl 1988b) were exposed to cresols by gavage during gestation reported no effects on the reproductive parameters investigated (e.g., number of ovarian corpora lutea, number of implantation sites, number of viable fetuses), even at maternally toxic doses. Two-generation reproduction studies in rats (up to 450 mg/kg/day of each isomer by gavage) and mink (up to 105 mg/kg/day dietary *o*-cresol for 6 months) also failed to detect adverse effects on reproductive function or lesions in reproductive tissues (Hornshaw et al. 1986; Neeper-Bradley and Tyl 1989a, 1989b; Tyl and Neeper-Bradley 1989). These studies also included doses producing maternal toxicity. No histopathological lesions and only mild organ weight changes of doubtful significance were reported in the reproductive organs of animals exposed to up to 600 mg/kg/day of cresols by gavage for 13 weeks (EPA 1988b, 1988c, 1988d).

The NTP (1992b) study evaluated changes in weight and histopathology of reproductive organs of males and females, as well as sperm parameters and duration of the estrous cycle, of Fisher-344 rats and B6C3F₁ mice exposed via the diet to cresol isomers and to a mixture of *m*- and *p*-cresol. The only significant effects observed in rats in 28-day experiments included mild to moderate uterine atrophy in females dosed with 2,310 mg/kg/day of *m*-cresol or 2,060 mg/kg/day of *p*-cresol. In the 13-week study, doses of ≥ 509 of *m/p*-cresol lengthened the estrous cycle in females and doses of 1,024 and 2,050 mg/kg/day induced minimal to mild uterine atrophy. No significant effects were seen in male rats dosed with up to 2,200–2,600 mg/kg/day of cresols. In mice, 28 days of dosing with 1,670 mg/kg/day of *o*-cresol produced mild atrophy of the uterus, whereas 4,940 mg/kg/day of *m*-cresol induced mild to moderate atrophy of the mammary glands, uterus, and ovaries. Neither *p*-cresol nor the *m/p*-cresol mixture adversely affected the reproductive end points in mice in the 28-day study. A 13-week regimen of 3,205 mg/kg/day of *o*-cresol lengthened the estrous cycle in mice, and doses of up to 1,500–1,700 mg/kg/day of *m/p*-cresol did not induce any significant alterations in males or females. Treatment of male rats and female mice with up to 720 and 1,040 *m/p*-cresol/kg/day, respectively, in the diet for 2 years did not induce any significant alterations in the gross or microscopic morphology of reproductive organs (NTP 2008).

Two studies have evaluated the effects of *o*-cresol and a mixture of *m/p*-cresol on reproductive function end points in CD-1 mice using a continuous breeding protocol (NTP 1992a, 1992c). End points evaluated

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included fertility, mean number of litters per pair, live litter size, weight and histopathology of reproductive organs, vaginal cytology, and sperm parameters. Both studies started with a 14-week cohabitation period in which males and females received the test material in the diet. The highest doses during this period were 660 mg/kg/day for *o*-cresol and 1,682 mg/kg/day for *m/p*-cresol. No significant alterations were observed with *o*-cresol at any stage of the study. However, the highest dose of *m/p*-cresol significantly decreased the number of live pups/litter and increased the cumulative days to litter; a dose level of 1,390 mg/kg/day was a NOAEL. To determine which sex was the affected sex during the cohabitation period, a 1-week crossover mating trial was conducted, but the results indicated that either sex could have been affected. In neither study was fertility affected. In addition, sperm parameters and gross and microscopic morphology of reproductive organs were not affected by treatment with the cresols.

NOAEL and LOAEL values for reproductive effects derived from these studies are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.6 Developmental Effects

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

Developmental effects have been reported in animals given cresols, but only at maternally toxic doses. Maternal effects in rats dosed by gavage on gestation days 6–15 (audible respiration, reduced body weight gain, reduced food consumption, ataxia, tremors, and hypoactivity) occurred at 450 mg/kg/day (Tyl 1988a). At this dose, both *o*- and *p*-cresol produced slight fetotoxicity (increased incidences of dilated lateral ventricles in the brain and minor skeletal variations, respectively), but had no effect on malformation incidence or gestation parameters (e.g., the number of implantations per litter or fetal body weight per litter). No effects of any kind were seen at lower doses. *m*-Cresol had no effect on gestation parameters, fetotoxicity, or the incidence of malformations, even at maternally toxic doses (Tyl 1988a). An additional study in which rats were dosed only on gestation day 11 with up to 1,000 mg/kg of *p*-cresol reported no significant effects on post-implantation loss, litter size, viability, or postnatal weight of the offspring, even when maternal toxicity was evident at doses ≥ 410 mg/kg (Kavlock 1990). Slight maternal toxicity in the form of decreased weight gain was also observed at the 1,682 mg/kg/day dose level. In rabbits dosed on gestation days 6–18 with up to 100 mg/kg/day of each isomer, maternal effects, such as audible respiration, ocular discharge, and hypoactivity, were seen following exposure to *o*- or *p*-cresol at 50 mg/kg/day (Tyl 1988b). At 100 mg/kg/day, *o*-cresol produced slight fetotoxicity (increased incidences

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of subepidermal hematoma on the head and poorly ossified sternebrae), but no other effects at any dose. Neither *p*- nor *m*-cresol produced any developmental effects in this study (Tyl 1988b).

Fetotoxicity was also observed at parentally-toxic doses in two-generation reproduction studies. Rats treated by gavage with 450 mg/kg/day of *o*- and *p*-cresol for 10 weeks before mating produced F₁ offspring that had reduced body weight 4–6 weeks after birth. This dose also produced overt toxicity in the parents (Neeper-Bradley and Tyl 1989a; Tyl and Neeper-Bradley 1989). In contrast to the results of the developmental toxicity studies discussed above, *m*-cresol was the most potent developmental toxicant among the cresols in the two-generation studies. This isomer reduced pup survival during lactation when administered by gavage at the high dose of 450 mg/kg/day (Neeper-Bradley and Tyl 1989b). Parental toxicity manifested as reduced body weight gain was reported at the low dose of 30 mg/kg/day. Decreased number of live pups/litter (F₁) was reported in a 2-generation reproductive study in mice exposed to 1,682 mg/kg/day of an *m/p*-cresol mixture for 14 weeks, but not at 1,390 mg/kg/day (NTP 1992c).

The comparative susceptibility of newborn and young rats to *m*-cresol was studied by Koizumi et al. (2003). Neonates were treated by gavage with up to 300 mg/kg/day *m*-cresol from postnatal day 4 to 21, whereas 5-week-old rats were dosed with up to 1,000 mg/kg/day for 28 days. Most neonates exhibited deep respiration, hypersensitivity on handling, and tremors under contact stimulus at 300 mg/kg/day. Final body weight also was significantly reduced at this dose level. Tremors also occurred in few neonates at 100 mg/kg/day, but no clinical signs were seen at 30 mg/kg/day. No significant alterations were reported in clinical chemistry, hematology, gross or microscopic pathology (major organs and tissues), or physical development and sexual maturation. In the young rats, clinical signs such as salivation, tremors, and reduced weight gain were observed at 1,000 mg/kg/day, but there were no significant alterations in clinical chemistry, hematology, or histopathological changes at this dose level. A dose level of 300 mg/kg/day *m*-cresol was a NOAEL in 5-week-old rats, whereas 30 mg/kg/day was a NOAEL in neonates.

NOAEL and LOAEL values derived from these studies are recorded in Table 3-1 and plotted in Figure 3-1.

3.2.2.7 Cancer

No studies were located regarding cancer in humans following oral exposure to cresols.

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In an intermediate-duration study, a diet that provided approximately 1,415 mg/kg/day of *p*-cresol for 20 weeks produced an increased incidence of mild to moderate forestomach hyperplasia in hamsters, suggesting that this cresol isomer may have the potential to act as a promoter of forestomach carcinogenesis in this species (Hirose et al. 1986). However, promotion potential was not tested directly. However, *p*-cresol did not produce forestomach hyperplasia in rats treated with the chemical in the diet (2% or approximately 2,140 mg/kg/day) for an unspecified period of time (Altmann et al. 1986), but rats are generally less sensitive than hamsters to inducers of forestomach lesions. In mice, simultaneous administration of 1 mg of *o*-cresol and 1 mg of benzo[a]pyrene twice daily by gavage for up to 30 weeks increased the incidence and malignancy of forestomach tumors and shortened their latency relative to benzo[a]pyrene alone (Yanysheva et al. 1993). However, administration of *o*-cresol before or after benzo[a]pyrene decreased the carcinogenicity of the latter substance.

A recently conducted 2-year feeding study with a mixture of *m*- and *p*-cresol (60%/40%) found no evidence of neoplastic effects in male Fischer-344 rats (females were not tested) that received mean doses of up to 720 mg/kg/day of the test material (NTP 2008). However, NTP (2008) determined that a slight nonstatistically significant increase ($p=0.121$) in the incidence of renal tubule adenoma constituted an equivocal finding. In female B6C3F₁ mice (males were not tested) that received mean doses of approximately 0, 100, 300, or 1,040 mg/kg/day, the incidence of squamous cell papilloma of the forestomach was significantly increased ($p<0.001$) in the high dose group (0/50, 1/50, 1/49, 10/50). No other significant neoplastic effect was reported in mice.

The EPA (IRIS 2008) has classified the three cresol isomers in Group C, “possible human carcinogens,” based on inadequate human data and limited data in animals (the assessment is dated 10/89). The assessment was based on an increased incidence of skin papillomas in mice in an initiation-promotion study and on the fact that the cresol isomers produced positive results in genetic toxicity studies both alone and in combination. Based on updated guidelines for carcinogen assessment (EPA 2005c), cresols fall in the category of chemicals for which there is “inadequate information to assess carcinogenic potential.” EPA did not derive quantitative estimates of carcinogenic risk for cresols (IRIS 2008). EPA’s assessment of cresols’ carcinogenicity was conducted before the results of the NTP (2008) study became available.

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3.2.3 Dermal Exposure**3.2.3.1 Death**

There are two case reports of people who died following dermal exposure to cresols. In one case, a 1-year-old baby had 20 mL of a cresol derivative (90% mixed cresols in water) spilled on his head, covering about 7% of his body surface. The baby died in coma within 4 hours (Green 1975). Assuming the baby weighed approximately 10 kg, the lethal dose in this case can be estimated to have been roughly 2 g/kg if all the cresol was absorbed, but was probably less since the infant's head was washed with soap and water 5 minutes after the spill. In the other case, a man fell into a vat of a cresylic acid derivative (cresol content unknown) and suffered burns on 15% of the body surface. Anuria was evident after 36 hours and blood urea content rose steadily during the following days. The patient fell into a coma on the 9th day, and death occurred on the 10th day (Cason 1959). Dermal absorption of cresol also appears to have been responsible for the death of a man who worked with an antiseptic solution containing concentrated mixed cresols for 2 days prior to becoming ill (Larcan et al. 1974).

In rabbits, dermal LD₅₀ values for cresols were 890, 300, 2,830, and 2,000 mg/kg for *o*-, *p*-, *m*-, and mixed cresols, respectively (Vernot et al. 1977). These values are recorded in Table 3-2. Based on these LD₅₀ values, *p*-cresol appears to be more toxic dermally than *o*-cresol, with *m*-cresol being the least toxic of the three isomers.

3.2.3.2 Systemic Effects

No studies were located regarding cardiovascular or musculoskeletal effects in humans or animals following dermal exposure to cresols.

Respiratory Effects. Hemorrhagic pulmonary edema was found at necropsy in a 1-year-old baby who died after having 20 mL of a cresol-containing product spilled on his head (Green 1975). Liu et al. (1999) reported a case of a woman who suffered acute respiratory failure following chemical burns caused by skin contact with a saponated solution of mixed cresols.

No studies were located regarding respiratory effects in animals following dermal exposure to cresols.

Gastrointestinal Effects. No lesions were found in the gastrointestinal tract of a 1-year-old baby who died after dermal exposure to a cresol-containing product (Green 1975).

Table 3-2 Levels of Significant Exposure to Cresols - Dermal

Species (Strain)	Exposure/Duration/Frequency (Route)	System	LOAEL			Reference Chemical Form	Comments
			NOAEL	Less Serious	Serious		
ACUTE EXPOSURE							
Death							
Rabbit	1 d 24 hr/d				2000 (LD50) mg/kg/day	Vernot et al. 1977 mix	
Rabbit	1 d 24 hr/d				890 (LD50) mg/kg/day	Vernot et al. 1977 ortho	
Rabbit	1 d 24 hr/d				2830 (LD50) mg/kg/day	Vernot et al. 1977 meta	
Rabbit	1 d 24 hr/d				300 (LD50) mg/kg/day	Vernot et al. 1977 para	
Systemic							
Rabbit	1 d 4 hr/d	Dermal			147 (skin corrosion) mg/kg/day	Vernot et al. 1977 mix	
Rabbit	1 d 4 hr/d	Dermal			147 (skin corrosion) mg/kg/day	Vernot et al. 1977 ortho	
Rabbit	1 d 4 hr/d	Dermal			147 (skin corrosion) mg/kg/day	Vernot et al. 1977 meta	
Rabbit	1 d 4 hr/d	Dermal			147 (skin corrosion) mg/kg/day	Vernot et al. 1977 para	

d = day(s); hr = hour(s); LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

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

Hematological Effects. Hematological effects in a man apparently exposed to cresol dermally while working with an antiseptic solution containing concentrated mixed cresols, included methemoglobinemia with massive hemolysis and the presence of numerous large Heinz bodies in the blood (Larcan et al. 1974). Similar effects have been reported following oral exposure to cresols (see Section 3.2.2.2).

No studies were located regarding hematological effects in animals following dermal exposure to cresols.

Hepatic Effects. Necropsy revealed extensive centrilobular to mid-zonal liver necrosis in a 1-year-old baby who had 20 mL of a cresol derivative spilled on his head (Green 1975).

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

Renal Effects. A 1-year-old baby who died after a cresol derivative was spilled on his head had congested and swollen kidneys that were damaged by tubular necrosis (Green 1975). A man who fell into a vat containing a cresylic acid derivative developed anuria after 36 hours and experienced a steady increase in blood urea levels for 10 days until he died (Cason 1959). Anuria was also seen in a man who apparently absorbed cresol through the skin while working with an antiseptic solution containing concentrated mixed cresols (Larcan et al. 1974). Acute polyuric renal failure was described in a man who accidentally spilled with *m*-cresol onto both legs and face (Evers et al. 1994).

No studies were located regarding renal effects in animals following dermal exposure to cresols.

Dermal Effects. Corrosive damage to the skin has been reported in humans dermally exposed to cresols (Cason 1959; Green 1975; Herwick and Treweek 1933; Klinger and Norton 1945; Pegg and Campbell 1985). In one patient, disfiguring scars remained visible 1 year after exposure (Herwick and Treweek 1933). However, no reaction to cresol was noted when it was applied to the skin as a 1% solution in alcohol (Reimann 1933).

Cresols are also strong skin irritants in animals. All three cresol isomers, either alone or in combination, are severely irritating to rabbit skin, producing visible and irreversible tissue destruction (Vernot et al.

3. HEALTH EFFECTS

1977). Some cresylic acids produced induration and discoloration of the skin in rats (Campbell 1941). All reliable LOAEL values for acute dermal effects in rabbits are recorded in Table 3-2.

In a study of intermediate duration, dermal application of 0.5% *p*-cresol for 6 weeks produced permanent depigmentation of the skin and hair of mice (Shelley 1974). A caustic effect on the skin was noted in one strain of mouse, but not another. Neither *o*- nor *m*-cresol produced any color change in the mice. The investigator suggested that only *p*-cresol was active because it mimics the structure of tyrosine, the amino acid present in melanin, so that tyrosinase acts on it, liberating free radicals that damage melanocytes. NOAEL and LOAEL values were not derived from this study because the applied dose was not reported.

3.2.3.3 Immunological and Lymphoreticular Effects

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

3.2.3.4 Neurological Effects

Neurological effects were seen in two people who were accidentally exposed to mixed cresols on the skin and later died. A 1-year-old baby who had 20 mL of a cresol derivative spilled on his head was unconscious within 5 minutes; autopsy revealed swelling and congestion of the brain (Green 1975). A man who fell into a vat containing a cresylic acid derivative and received burns on 15% of his body fell into a coma 9 days later (Cason 1959). A man who survived a 5–6-hour immersion of his hands in a concentrated cresylic acid solution experienced persistent eye watering, followed by pain on the side of his face and, ultimately, marked facial paralysis (Klinger and Norton 1945).

Only one study reported neurological effects in animals following dermal exposure to cresols. Rapid, shallow breathing and convulsions were observed in rats 5–30 minutes after covered dermal application of 1.0–3.5 mL/kg of certain cresylic acid formulations (Campbell 1941). Other formulations had no effect. These convulsions stopped after a few hours in the rats that survived.

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

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

No studies were located regarding cancer in humans following dermal exposure to cresols.

Cresols have not been evaluated for ability to induce cancer when applied to the skin of animals. However, a study of skin tumor promotion by cresols was located (Boutwell and Bosch 1959). Mice were given a single dermal application of 9,10-dimethyl-1,2-benzanthracene (DMBA), a cancer initiator, followed by application of 20% solutions of *o*-, *p*-, or *m*-cresol in benzene twice a week for 12 weeks. This level of cresols exposure proved to be acutely toxic, producing relatively high nontumor-related mortality. Consequently, all tumor results were based on number of survivors (14–20 per group). Promotion with cresols led to increases in the average number of skin papillomas per mouse and the percentage of exposed mice with at least one papilloma. *o*-Cresol was the most potent isomer, and *p*-cresol the least. Carcinomas were not observed following cresols exposure, although the observed papillomas have the potential to develop into carcinomas. A problem with the study was use of benzene, a known carcinogen, as the solvent for the cresols. However, benzene controls in the cresols experiment did not develop papillomas, and neither did benzene controls in four parallel series of experiments (a few papillomas were observed in a fifth benzene control group). Therefore, the results of this study showing that all three cresol isomers are capable of promoting skin tumors initiated by DMBA appear to be valid.

3.3 GENOTOXICITY

The genotoxic effects of cresols have been well studied. *In vitro* genotoxicity assays on *o*-, *p*-, and *m*-cresol are shown in Table 3-3. Results were uniformly negative in *Salmonella* assays with or without metabolic activation (Douglas et al. 1980; Florin et al. 1980; Haworth et al. 1983; Kubo et al. 2002; NTP 1992b; Pepper, Hamilton & Scheetz 1981; Pool and Lin 1982) and mixed in *in vitro* studies using mammalian cells (Brusick 1988a, 1988b, 1988c; Cifone 1988a, 1988b, Gaikwad and Bodell 2001; Hamaguchi and Tsutsui 2000; Hikiba et al. 2005; Li et al. 2005; Miyachi and Tsutsui 2005; Murli 1988, Pepper, Hamilton & Scheetz 1980, 1981). Positive results were reported in assays for chromosomal

3. HEALTH EFFECTS

Table 3-3. Genotoxicity of Cresols *In Vitro*

Species (test system)	End point	Results		References	Isomer
		With activation	Without activation		
Prokaryotic organisms:					
<i>Salmonella typhimurium</i> on plates	Reverse mutation	–	–	Douglas et al. 1980; Florin et al. 1980; Haworth et al. 1983; Kubo et al. 2002; Pepper, Hamilton & Scheetz 1980, 1981; Pool and Lin 1982	<i>o, p, m</i> , 1:1:1 mixture of <i>o, p, m</i>
Eukaryotic organisms:					
Mammalian cells:					
CHO cells	Chromosomal aberrations	+	+	Murli 1988	<i>o, p</i>
CHO cells	Chromosomal aberrations	–	–	Murli 1988	<i>m</i>
CHO cells	Sister chromatid exchange	+	+	Pepper, Hamilton & Scheetz 1980, 1981	<i>o</i> , 1:1:1 mixture of <i>o, p, m</i>
Mouse BALB/C-313 cells	Cell transformation	+	No data	Pepper, Hamilton & Scheetz 1980	1:1:1 mixture of <i>o, p, m</i>
Mouse BALB/C-313 cells	Cell transformation	No data	+	Brusick 1988b	<i>p</i>
Mouse BALB/C-313 cells	Cell transformation	–	–	Brusick 1988a, 1988b, Pepper, Hamilton & Scheetz 1981; Sernav 1989b	<i>o, m</i>
L5178Y mouse lymphoma cells	Forward mutation	+	(+)	Pepper, Hamilton & Scheetz 1980	1:1:1 mixture of <i>o, p, m</i>
L5178Y mouse lymphoma cells	Forward mutation	–	–	Cifone 1988a; Pepper, Hamilton & Scheetz 1981	<i>o, p, m</i>
Mouse spermatid	DNA damage	No data	+	Li et al. 2005	<i>o</i>
Primary rat hepatocytes	Unscheduled DNA synthesis	No data	–	Pepper, Hamilton & Scheetz 1981	<i>o</i>
Rat hepatocytes	DNA adduct formation	–	+	Gaikwad and Bodell 2001	<i>p</i>
Freshly cultured rat hepatocytes	Unscheduled DNA synthesis	No data	–	Cifone 1988b	<i>m</i>
Human peripheral lymphocytes	Semiconservative/repair DNA	No data	(+)	Daugherty and Franks 1986	<i>p</i>
Human peripheral lymphocytes	DNA damage	No data	+	Li et al. 2005	<i>o</i>
HL-60 cells	DNA adduct formation	–	+	Gaikwad and Bodell 2001	<i>p</i>

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Table 3-3. Genotoxicity of Cresols *In Vitro*

Species (test system)	End point	Results		References	Isomer
		With activation	Without activation		
Syrian hamster kidney cells	SV40 induction	No data	(+)	Moore and Coohill 1983	<i>m</i>
SHE cells	Chromosomal aberrations	+	+	Hikiba et al. 2005	<i>m</i>
SHE cells	Unscheduled DNA synthesis	+	–	Hamaguchi and Tsutsui 2000	<i>m</i>
SHE cells	Sister chromatid exchange	No data	+	Miyachi and Tsutsui 2005	<i>m</i>
Cultured human fibroblasts	Sister chromatid exchange	No data	–	Cheng and Kligerman 1984	<i>o, p, m</i>

– = negative result; + = positive result; (+) = weakly positive; CHO = Chinese hamster ovary; DNA = deoxyribonucleic acid; SHE = Syrian hamster embryo

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aberrations for *o*- and *p*- cresol, but not for *m*-cresol in Chinese hamster cells (Murli 1988), while *m*-cresol produced positive results for chromosomal aberrations in Syrian hamster embryo cells (Hikiba et al. 2005). There was a positive result for sister chromatid exchange for *o*-cresol and for a mixture of *o*-, *p*-, and *m*-cresol in Chinese hamster ovary cells (Pepper, Hamilton & Scheetz 1980, 1981), and Syrian hamster embryo cells (Miyachi and Tsutsui 2005), which is in contrast to negative results for sister chromatid exchange in human fibroblasts for the *o*-, *p*-, and *m*-isomers (Cheng and Kligerman 1984). *p*-Cresol, and a mixture of the *o*-, *p*-, and *m*-cresol, also produced cell transformation in mouse BALB/C-3T3 cells (Brusick 1988b; Pepper, Hamilton & Scheetz 1980), while *o*- and *m*-cresol did not (Brusick 1988a, 1988b; Pepper, Hamilton & Scheetz 1981; Sernav 1989b).

A 1:1:1 mixture of the three cresol isomers was positive in tests for forward mutation in mouse lymphoma cells (Pepper, Hamilton & Scheetz 1980), but negative for each isomer tested individually (Cifone 1988a; Pepper, Hamilton & Scheetz 1981). Assays were negative for increased DNA synthesis in rat hepatocytes for *o*- and *m*-cresols (Cifone 1988b; Pepper, Hamilton & Scheetz 1981), and positive in Syrian hamster embryo cells with activation for *m*-cresol (Hamaguchi and Tsutsui 2000) and in human peripheral lymphocytes for *p*-cresol (Daugherty and Franks 1986). DNA damage was found in mouse spermatid and human peripheral lymphocytes in assays testing *o*-cresol (Li et al. 2005), as was DNA adduct formation in rat hepatocytes and HL-60 cells incubated with *p*-cresol (Gaikwad and Bodell 2001). A weak positive result was reported for SV40 induction in Syrian hamster kidney cells (Moore and Coohill 1983). Positive results obtained in some human and animal *in vitro* tests suggest that cresols have some ability to react with DNA, and may be clastogenic under certain circumstances.

Results from *in vivo* genotoxicity assays on *o*-, *p*-, and *m*-cresol are shown in Table 3-4. Studies of the genotoxicity of cresols in animals *in vivo* reported negative results for dominant lethal, chromosomal aberrations and mouse bone marrow, alveolar macrophages, and regenerating liver cells *in vivo* (Cheng and Kligerman 1984; Ivett 1989a, 1989b, 1989c; Sernav 1989a, 1989b). Treatment of male and female B6C3F₁ mice with up to 2,723 or 3,205 mg/kg/day *o*-cresol, respectively, for 13 weeks did not increase the incidence of micronuclei in peripheral blood erythrocytes (NTP 1992b). Similar negative results were reported in male and female mice dosed with up to 1,513 or 1,693 mg/kg/day *m/p*-cresol, respectively (NTP 1992b). However, micronucleus frequency was increased in bone marrow from male mice injected twice intraperitoneally with 20, 40, or 80 mg/kg *o*-cresol (Li et al. 2005). Although *o*-, *p*-, and *m*-cresol and a 1:1:1 mixture of the three cresol isomers gave some indication of genotoxic activity in *in vitro* assays with mammalian cells, most *in vivo* assays were negative, with one exception. Overall, cresols do not seem to pose a genotoxic threat to humans under normal environmental exposure conditions.

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Table 3-4. Genotoxicity of Cresols *In Vivo*

Species (test system)	End point	Results		References	Isomer
		With activation	Without activation		
Eukaryotic organisms (<i>in vivo</i>):					
Mouse	Dominant lethal	No data	–	Ivett 1989a, 1989b	<i>o, p</i>
Mouse	Chromosomal aberrations (bone marrow)	No data	–	Ivett 1989b	<i>m</i>
Mouse	Sister chromatid exchange (bone marrow, alveolar macrophages, and regenerating liver cells)	No data	–	Cheng and Kligerman 1984	<i>o, p, m</i>
Mouse	Micronucleus frequency	No data	+	Li et al. 2005	<i>o</i>
Mouse	Micronucleus frequency	No data	–	NTP 1992b	<i>o, m/p</i>
<i>Drosophila melanogaster</i>	Sex-linked recessive lethal	No data	–	Sernav 1989a, 1989b	<i>o, p</i>

– = negative result; + = positive result

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3.4 TOXICOKINETICS

Cresols can be absorbed following inhalation, oral, and dermal exposure by humans and animals. Most of the evidence of absorption in humans is indirect, derived from cases of accidental dermal contact with these substances or accidental or intentional ingestion. Limited data from workers exposed to airborne cresols provide evidence of absorption by inhalation, although dermal absorption could have also occurred. Quantitative data are not available. Little is known about distribution of cresols in humans. In a fatal case of dermal intoxication, cresols were found in the brain and liver. Studies in animals dosed by oral gavage with a single dose of *m*- or *p*-cresol indicate that cresols can distribute rapidly into many organs and tissues. Cresols undergo oxidative metabolism in the liver and are rapidly eliminated, mostly in the urine, as sulfate or glucuronide conjugates. A study showed that human and rat liver microsomes *in vitro* metabolized *p*-cresol in a similar manner. However, the relevance of the available toxicokinetics information in animals to toxicokinetics of cresols in humans is unknown.

3.4.1 Absorption

p-Cresol is normally found in the body where it is generated from protein breakdown. *p*-Cresol is one of the metabolites of the amino acid tyrosine and of phenylalanine. Tyrosine and phenylalanine are converted to 4-hydroxyphenylacetic acid by intestinal bacteria. 4-Hydroxyphenylacetic acid is further decarboxylated to *p*-cresol, which is absorbed from the intestine and excreted in the urine as conjugates (De Smet et al. 1997; Vanholder et al. 1999). De Smet et al. (1998a) reported a mean concentration of 8.6 µmol/L of *p*-cresol (0.93 mg/L) in serum from healthy subjects.

3.4.1.1 Inhalation Exposure

No studies were located regarding the rate and extent of absorption in humans following inhalation exposure to cresols.

The absorption of cresols following inhalation exposure in animals has not been quantified, but can be assumed to occur, since mortality and other effects have been reported in animals following exposure (Campbell 1941; Kurlyandskiy et al. 1975; Uzhdavini et al. 1972).

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3.4.1.2 Oral Exposure

No studies were located regarding the rate and extent of absorption in humans following oral exposure to cresols. However, it can be assumed that cresol are absorbed orally based on the many reports of adverse effects in subjects who ingested cresols accidentally or intentionally (i.e., Chan et al. 1971; Hashimoto et al. 1998; Kamijo et al. 2003; Labram and Gervais 1968).

In a study in rabbits administered all three cresol isomers by oral gavage under fasting conditions, from 65 to 84% of the administered dose was recovered in the urine within 24 hours, indicating that at least that amount had been absorbed (Bray et al. 1950). When *p*-cresol was administered 1–2 hours after the rabbits were fed, the rabbits exhibited less toxic effects than when given the compound under fasting conditions, indicating that the gastrointestinal contents retarded the absorption of *p*-cresol (Bray et al. 1950). A recent study showed that after a single gavage dose of a cresol soap solution (*p*- and *m*-cresol) to rats, 50% of the administered dose disappeared from the gastric contents in 15 minutes, and almost all of the administered cresol disappeared within 8 hours (Morinaga et al. 2004). In blood, the unconjugated concentrations of *p*- and *m*-cresol decreased rapidly for 2 hours after peaking 30 minutes after dosing. No unconjugated cresols could be detected after 4 hours. The *p*-cresol glucuronide in blood was always higher than the *p*-cresol sulfate, whereas the concentration of *m*-cresol sulfate was consistently higher than the *m*-cresol glucuronide. Based on the fact that the concentrations of the unconjugated cresols in liver and spleen were much higher than those in blood over a monitoring period of 8 hours, Morinaga et al. (2004) suggested that cresol administered by oral gavage diffuses directly through the gastric and small intestinal walls.

3.4.1.3 Dermal Exposure

The occurrence of coma, death, and systemic effects in two humans dermally exposed to cresols (Cason 1959; Green 1975) indicates that these compounds can be absorbed through the skin. In another case of accidental dermal exposure to cresols, Fuke et al. (1998) reported that the concentrations of unconjugated *p*-cresol, sulfate, and glucuronide in the serum collected 2 hours after exposure were 15.7, 21.3, and 38.6 µg/mL, respectively. The respective concentrations of *m*-cresol were 31.4, 17.0, and 82.9 µg/mL; the exposure amount was unknown so that the extent of absorption could not be estimated. An *in vitro* study of the permeability of human skin to cresols found that these substances had permeability coefficients greater than that for phenol, which is known to be readily absorbed across the skin in humans (Roberts et al. 1977).

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No studies were located regarding the rate and extent of absorption in animals following dermal exposure to cresols.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No studies were located regarding the extent of distribution in humans or animals following inhalation exposure to cresols.

3.4.2.2 Oral Exposure

No studies were located regarding the distribution of cresols in humans following oral exposure.

The distribution of *m*- and *p*-cresol has been studied in rats (Morinaga et al. 2004). Rats received a single gavage dose of a mixture of *m*- and *p*-cresol soap solution (100 mg *p*-cresol, 160 mg *m*-cresol/kg) and conjugated and unconjugated cresols were determined in tissues at various times up to 8 hours after dosing. The concentrations of unconjugated *m*- and *p*-cresol in liver and spleen were always much higher than in blood and higher than the sulfate or glucuronide metabolites in those organs. The unconjugated concentrations of both cresols in brain, lung, and muscle were similar to those in blood. The concentration of glucuronidated cresols were always highest in the kidney followed by the liver. Comparison of the concentration of glucuronide and sulfate conjugates in tissues showed that the glucuronide was always higher than the sulfate for both *p*- and *m*-cresol, particularly in the liver and kidneys. In all tissues, *m*-cresol sulfate was always higher than *p*-cresol sulfate, suggesting a slightly different metabolic disposition for these two isomers.

3.4.2.3 Dermal Exposure

Cresols were identified in the blood (12 mg/100 mL), liver, and brain of a 1-year-old baby who died 4 hours after 20 mL of a cresol derivative was spilled on his head (Green 1975).

No studies were located regarding the extent of distribution in animals following dermal exposure to cresols.

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3.4.2.4 Other Routes of Exposure

In rats administered a single intravenous dose of 3 mg/kg of *p*-cresol, the concentration of *p*-cresol in blood 5 minutes after dosing was 6.7 mg/L and decreased gradually to 0.6 mg/L near 240 minutes after dosing (Lesaffer et al. 2001). The half-life of *p*-cresol in serum was 1.5 hours (twice as long as creatinine) and its total clearance was 23.2 mL/minute/kg (3 times that of creatinine). Also, the volume of distribution of *p*-cresol was 5 times that of creatinine; however, renal clearance of *p*-cresol (4.8 mL/minute/kg) was about half that of creatinine. Similar results were reported in a subsequent paper from the same group of investigators (Lesaffer et al. 2003a).

3.4.3 Metabolism

No studies were located regarding metabolism in humans following exposure to cresols.

A few studies reported on the metabolism of cresols in animals. Cresols in the urine are found primarily as sulfate and glucuronide conjugates. In the urine of rabbits, 60–72% of the orally administered dose was recovered as ether glucuronide, and 10–15% was recovered as ethereal sulfate (Bray et al. 1950). A similar result was obtained in an earlier study in rabbits in which 14.5–23.5% of the orally administered dose was found conjugated with sulfate in the urine (Williams 1938). For simple phenols such as cresols, the proportions of the conjugates are known to vary with dose and to differ from one species to the next. In the study by Bray et al. (1950), hydroxylation of a small percentage (3%) of the administered dose to 2,5-dihydroxytoluene (conjugated) occurred for both *o*- and *m*-cresol. No hydroxylation occurred for *p*-cresol, but *p*-hydroxybenzoic acid (both free and conjugated) was detected in the urine. Only 1–2% of the administered dose was found as unconjugated free cresol in the urine. A study in rats showed that *m*-cresol is preferentially metabolized to sulfate, and *p*-cresol to glucuronide (Morinaga et al. 2004).

Studies by Thompson and coworkers (Thompson et al. 1994, 1995, 1996) and Yan et al. (2005) have provided more detailed information on the metabolism of cresols and the role of metabolism in hepatotoxicity (the role of metabolism on hepatotoxicity is discussed in Section 3.5.2). Using rat liver microsomes and precision-cut liver slices, Thompson et al. (1995) demonstrated that *p*-cresol formed monogluthathione conjugates with a structure consistent with the formation of a quinone methide intermediate. The latter may be formed in two successive one electron oxidation steps by cytochrome P-450 (Koymans et al. 1993). Using human liver microsomes Yan et al. (2005) confirmed that the activation of *p*-cresol by oxidation forms a reactive quinone methide which formed a conjugate,

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glutathionyl-4-methylphenol. In addition, a new pathway was identified consisting of aromatic oxidation leading to the formation of 4-methyl-*o*-hydroquinone which is further oxidized to 4-methyl[1,2]benzoquinone. The latter formed three adducts with glutathione, but the predominant was found to be 3-(glutathione-*S*-yl)-5-methyl *o*-hydroquinone. It was also found that 4-hydroxybenzylalcohol, a major metabolite formed by oxidation of the methyl group in liver microsomes, was further converted to 4-hydroxybenzaldehyde. Experiments with recombinant P-450s demonstrated that the formation of the quinone methide intermediate was mediated by several P-450s including CYP2D6, 2C19, 1A2, 1A1, and 2E1. The ring oxidation pathway was found to be mediated primarily by the CYP2E1 and to a lesser extent by CYP1A1, 1A2, and 2D6. Formation of 4-hydroxybenzaldehyde was catalyzed by 1A2 and also 1A1 and 2D6. Human liver microsomes formed the same adducts as rat liver microsomes suggesting that the metabolism of *p*-cresol is similar in humans and rats. The metabolic pathway for *p*-cresol proposed by Yan et al. (2005) is shown in Figure-3-2.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

Studies of subjects occupationally exposed to cresols have demonstrated that cresols are eliminated in the urine. Workers employed in the distillation of the high temperature phenolic fraction of tar excreted *p*- and *o*-cresol in the urine at rates of 2.4 and 3.3 mg/hour, respectively (Bieniek 1994). The highest concentrations in urine were found during the first 2 hours after the end of the work shift. A study of 76 men working at a coke plant where the geometric mean concentrations of *o*-, *m*-, and *p*-cresol in the breathing zone air were 0.09, 0.13, and 0.13 mg/m³, respectively, reported that the corresponding concentrations in hydrolyzed urine were 16.74, 16.74, and 0.53 mg/g creatinine (Bieniek 1997).

3.4.4.2 Oral Exposure

No studies were located regarding excretion in humans following oral exposure to cresols.

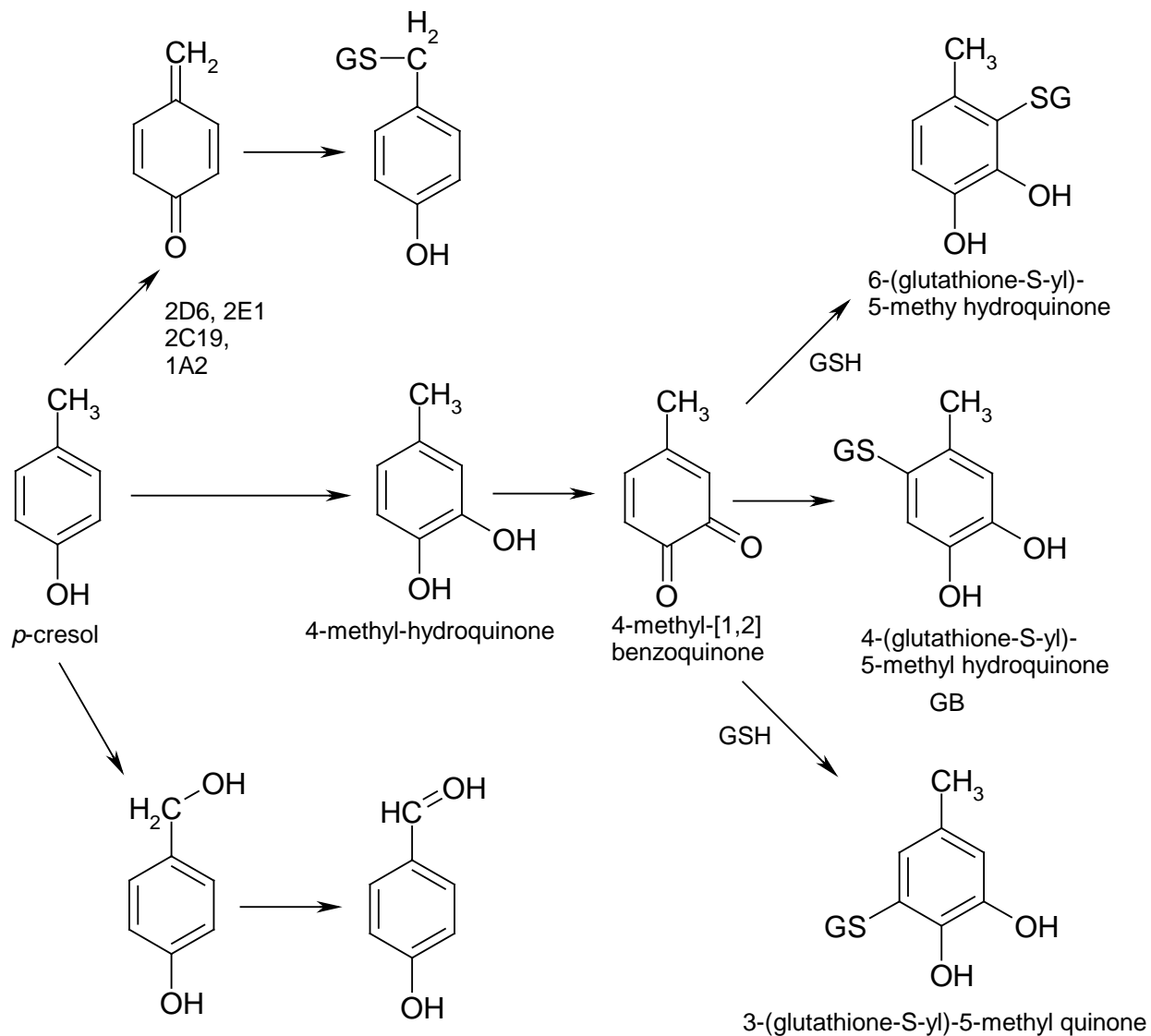
Following oral exposure to cresols in rabbits, 65–84% of the dose was excreted in the urine within 24 hours, mostly as ethereal glucuronides and sulfates (Bray et al. 1950).

3.4.4.3 Dermal Exposure

No studies were located regarding excretion in humans or animals following dermal exposure to cresols.

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Figure 3-2. Bioactivation Pathways of *p*-Cresol in Human Liver Microsomes



Source: adapted from Yan et al. 2005

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3.4.4.4 Other Routes of Exposure

Intravenous injection of a single dose of *p*-cresol to rats resulted in approximately 23% of the injected dose being excreted in the urine as parent compound within 240 minutes, the duration of the experiment (Lesaffer et al. 2001). As indicated in Section 3.4.2.4, the total clearance of *p*-cresol largely exceeded its renal clearance, which led Lesaffer et al. (2001) to suggest the presence of extra-renal elimination routes for *p*-cresol, namely, exsorption from the blood compartment into the gastrointestinal tract, biotransformation, or excretion via the bile. A subsequent study from the same group of investigators showed that in rats, 64% of an intravenous dose of *p*-cresol (9.6 mg/kg) was excreted as *p*-cresylglucuronide (Lesaffer et al. 2003b). When the glucuronide and the unconjugated *p*-cresol were combined, approximately 85% of the injected dose was recovered in the urine.

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

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

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

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The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (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) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

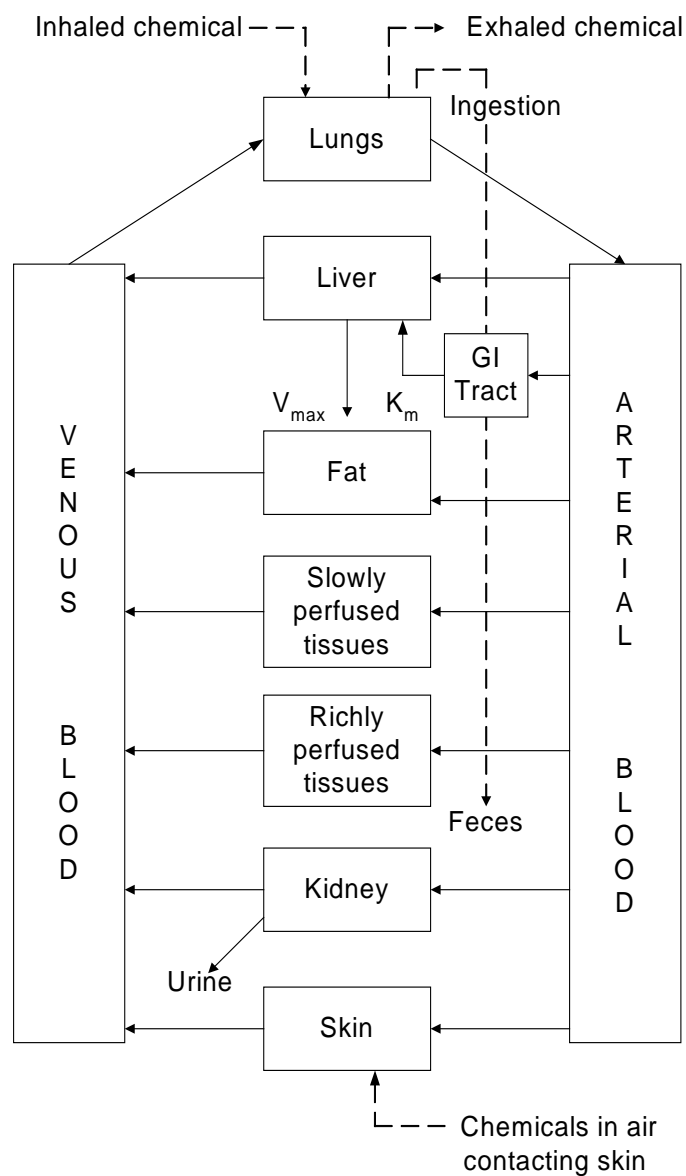
PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in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

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

No PBPK models have been developed for cresols.

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



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

Source: adapted from Krishnan et al. 1994

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3.5 MECHANISMS OF ACTION**3.5.1 Pharmacokinetic Mechanisms**

Absorption. No specific information was located regarding the mechanism of absorption of cresols. However, in a study in rats administered a cresol soap solution (*m*- and *p*-cresol) via a gastric tube, the concentration of free cresols in liver and spleen were much higher than those in blood at all times after dosing (up to 8 hours) (Morinaga et al. 2004). This led the investigators to suggest that cresol administered via a stomach tube diffuses directly through the gastric and small intestinal walls, which according to Morinaga et al. (2004), would explain the very high concentration of unconjugated cresols found in the liver and also in the spleen, which is adjacent to the stomach. Whether this also happens following ingestion of cresols mixed in food or in water is not known.

Distribution. No specific information was located regarding how cresols are transported in blood, but it is reasonable to assume that they may be bound to albumin, the most important binding protein for many acidic and basic drugs (Mabuchi and Nakahashi 1988). In a study of healthy subjects and patients with chronic renal failure, no free *p*-cresol could be detected in the blood of healthy subjects, 100% was protein-bound (De Smet et al. 1998a). No information was located for *o*- or *m*-cresol.

Metabolism. The limited information available summarized in Section 3.4.3 indicates that cresols undergo conjugation with sulfate and glucuronic acid and also form oxidative metabolites. However, there is virtually no information on possible shifts between these reactions that could be dose-dependent, dependent on the availability of co-substrates in the conjugation reactions, or related to different enzyme activity levels across areas of the liver, as occurs with structurally similar chemicals (i.e., phenol). The role of metabolism on the toxicity of cresols is discussed in Section 3.5.2.

Excretion. Cresols are excreted in the urine as glucuronides and sulfates. However, based on the observation that the total clearance of *p*-cresol largely exceeded its renal clearance in rats administered *p*-cresol intravenously, Lesaffer et al. (2001) suggested the presence of extra-renal elimination routes for *p*-cresol, namely, exsorption (reverse absorption or secretion) from the blood compartment into the gastrointestinal tract, biotransformation, or excretion via the bile. Exsorption from the blood compartment into the gastrointestinal tract may be plausible for unbound *p*-cresol, a relatively small molecule, but not for protein-bound *p*-cresol, which is how 100% of *p*-cresol is normally found in the blood (De Smet et al. 1998a). No pertinent information was located for *o*- or *m*-cresol.

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3.5.2 Mechanisms of Toxicity

Limited information is available regarding the mechanism(s) of toxicity of cresols. Cresols are irritant and corrosive at high concentrations as evidenced by numerous cases of accidental dermal exposure or accidental or intentional ingestion of cresols. Much like phenol, cresols impair the stratum corneum and produce coagulation necrosis by denaturing and precipitating proteins.

The role of metabolism in the toxicity of cresol has been studied by Thompson and coworkers (Thompson et al. 1994, 1995, 1996). Using lactate dehydrogenase (LDH) leakage or intracellular potassium as indices of toxicity in precision-cut rat liver slices as a test system, they showed that *p*-cresol was the most toxic of the three isomers. Similar results were obtained in liver slices from rats pretreated with phenobarbital, an inducer of cytochrome P-450; however, in this case, the toxicity of each isomer relative to control was increased compared to untreated slices. On a molar basis, *p*-cresol was 5–10 times more toxic than *o*- or *m*-cresol in the LDH leakage test. Incubation with the thiol precursor N-acetylcysteine or inhibition of cytochrome P-450 with metyrapone inhibited the toxicity of *p*-cresol, whereas depletion of glutathione increased the toxicity of *p*-cresol. These treatments had little effect on the toxicity of *o*- or *m*-cresol, suggesting a somewhat different mechanism of action, at least in the test system used. Furthermore, *p*-cresol rapidly depleted intracellular levels of glutathione, while the other isomers did it to a lesser extent. In the absence of glutathione, the major metabolite of *p*-cresol was *p*-hydroxybenzyl alcohol, which caused no observable toxicity to the liver slices. In the presence of glutathione, the amount of *p*-hydroxybenzyl alcohol was reduced by about 30% and the new product formed was confirmed to be a glutathione conjugate formed via the formation of a reactive quinone methide intermediate. The reactive intermediate bound covalently to protein in slices and in microsomal preparations. A metabolic pathway for *p*-cresol proposed by Yan et al. (2005) is shown in Figure 3-2.

A study by Kitagawa (2001) suggested that liver mitochondria may be a target for the liver toxicity of cresols based on results that indicated that these compounds inhibited mitochondrial respiration and induced or accelerated swelling of the mitochondria. However, it is difficult to relate the results from these studies *in vitro* to the observations of little or no alterations in the liver of animals dosed with cresols for extended periods of time (NTP 1992b).

Many studies in which the animals were dosed with cresols by oral gavage reported adverse neurological signs ranging from lethargy to tremors and convulsions (EPA 1988b, 1988c; TRL 1986; Tyl 1988a, 1988b). Dietary studies reported occasional tremors only at the highest doses administered. The

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mechanism by which cresols induced these effects is unknown. Studies in rats have reported that cresols induce changes in neurotransmitter levels in the brain (Calderón-Guzmán et al. 2005) and in activities of some enzymes (DeWolf et al. 1988; Savolainen 1979). Calderón-Guzmán et al. (2005) also suggested that cresols may increase lipid peroxidation and change membrane fluidity in rat brain. Studies have also reported neurophysiological changes in animals exposed to cresols. Mattsson et al. (1989) observed excitation of somatosensory evoked potentials and changes in the EEG in rats following intravenous administration of *o*-cresol. Mohammadi et al. (2001) reported that *o*-cresol, but not *m*-cresol, activated GABA_A receptors expressed in transformed human embryonic kidney cells. If such an effect were to occur in the intact animal, it may result in decreased activity and sedation since GABA normally mediates inhibitory neural activity. Whether any of these putative mechanisms of neurological effects are involved in the effects observed following oral dosing of animals, particularly by gavage, is unknown. Cresols could be acting at multiple sites including sites at the periphery.

3.5.3 Animal-to-Human Extrapolations

Cresols are irritants and corrosive in high concentrations and will produce similar effects on the skin and mucosal surfaces of humans and animals. Other than death and neurological effects, which have been reported both in humans and animals exposed to high amounts of cresols, it is difficult to predict other health outcomes in humans based on observations in animals. The metabolism of cresols seems to be similar in humans and rats based on the fact that both species excrete sulfate and glucuronide conjugation products in the urine. Furthermore, Yan et al. (2005) showed that bioactivation patterns for *p*-cresol in human and rat liver microsomes lead to the same reactive intermediates and glutathione adducts. While this and other studies (Thompson et al. 1994, 1995) served to construct a toxicity ranking for cresol isomers in hepatocytes *in vitro*, extrapolation to other toxicities would be pure speculation and inappropriate.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a

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naturally occurring estrogen, or other such endocrine effect[s]...”. To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavonoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

Based on the available information, there is no evidence that cresols are endocrine disruptors in humans and little evidence in animals. A 28-day dietary study reported mild uterine atrophy in female rats dosed with 2,310 mg/kg/day of *m*-cresol or 2,060 mg/kg/day of *p*-cresol (NTP 1992b). Comparable doses of *o*-cresol or an *m/p*-cresol mixture were without significant effect. A 13-week treatment with the ≥ 509 mg/kg/day *m/p*-cresol in the diet significantly lengthened the estrous cycle of rats, and doses of 1,024 and 2,050 mg/kg/day induced minimal to mild uterine atrophy (NTP 1992b). In mice, exposure to $\geq 1,670$ mg/kg/day of *o*-cresol for 28 days also induced mild atrophy of the uterus, and 4,940 mg/kg/day of *m*-cresol induced mild to moderate atrophy of the mammary gland, uterus, and ovaries (NTP 1992b). In addition, doses of 3,205 mg/kg/day of *o*-cresol for 13 weeks lengthened the estrous cycle in female mice. In these studies, there was no biologically significant effect on males’ reproductive organs or on sperm parameters. In the 2-year bioassay, doses of up to 720 and 1,040 mg/kg/day *m/p*-cresol, respectively, did not induce and significant alterations in gross or microscopic morphology of reproductive organs (NTP 2008).

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Multiple-generation reproductive studies that administered cresols by oral gavage (Neeper-Bradley and Tyl 1989a, 1989b; Tyl and Neeper-Bradley 1989) or through the diet (NTP 1992a, 1992c) have provided no evidence of endocrine-mediated alterations on reproduction or development.

In standard developmental toxicity studies in rats and rabbits, cresols have induced slight fetotoxicity, but only at maternally toxic doses (Tyl 1988a, 1988b). A study that treated newborn rats with *m*-cresol by gavage from postnatal day 4 through 21 reported noticeable clinical signs (tremors, hypersensitivity) with the highest dose tested, 300 mg/kg/day, but there were no alterations in the physical development or sexual maturation of the pups (Koizumi et al. 2003).

A study in which embryos of rats were incubated *in vitro* with *p*-cresol observed increased incidence of structural abnormalities such as hind limb bud absence and tail defects, but there is no evidence that this was endocrine-mediated (Oglesby et al. 1992). Additional information from studies *in vitro* is limited. Nishihara et al. (2000) reported that *p*-cresol tested positive and *o*-cresol negative for estrogenic activity in a reporter gene expression assay using yeast cells (Nishihara et al. 2000). A substance was considered positive when its activity was more than 10% of the activity of 10^{-7} M 17β -estradiol. Neither *o*-cresol nor *p*-cresol showed androgenic activity (agonist or antagonist) in stably transfected CHO-K1 cell lines, which expressed the androgen receptor (AR) and a AR-responsive luciferase gene reporter (Araki et al. 2005; Satoh et al. 2005).

Collectively, the available evidence does not suggest that cresols represent a hazard due to properties of endocrine disrupters, although a few cases of mild atrophy of female reproductive organs and lengthening of estrous cycle in rats and mice were reported for cresols, but generally at relatively high doses.

3.7 CHILDREN'S SUSCEPTIBILITY

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

Relevant animal and *in vitro* models are also discussed.

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

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their

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alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

There are no studies that specifically address the health effects of exposure to cresols in children; therefore, it is unknown whether children differ from adults in their susceptibility to health effects from cresols. Only one study was located that compared the effects of *m*-cresol administered by gavage in newborn rats and young rats (Koizumi et al. 2003). Newborn rats exhibited adverse neurological signs at approximately one third the doses that affected young rats. It is unknown whether this reflects differences in pharmacokinetics or on other aspects of *m*-cresol action. Data on the effects of cresols in adults are derived almost exclusively from cases of accidental or intentional ingestion of cresol solutions (i.e., Chan et al. 1971; Hayakawa 2002; Isaacs 1922; Jouglard et al. 1971; Kamijo et al. 2003; Minami et al. 1990; Wu et al. 1998) or accidental dermal exposure (i.e., Cason 1959; Pegg and Campbell 1985). In some of these cases, death occurred. Exposure to these amounts of cresols produced corrosion at the points of contact including the skin and gastrointestinal tract. Similar effects would be expected in children exposed to high amounts of cresols. In fact, Green (1975) reported the death of a child after a cresol mixture was spilled on his head.

There is no information regarding possible adverse developmental effects in humans exposed to cresols. Some studies in animals have reported fetotoxicity at dose levels that also produced maternal toxicity (Neeper-Bradley and Tyl 1989a, 1989b; Tyl 1988a, 1988b; Tyl and Neeper-Bradley 1989). For the most part, cresols have been negative in genotoxicity tests *in vivo*. Therefore, it is unlikely that parental exposure would result in adverse childhood development or cancer development as a result of cresol exposures to parental germ cells.

There is no information regarding pharmacokinetics of cresols in children. A study of the metabolism of *p*-cresol in human liver microsomes showed that both phase I and phase II metabolic enzymes are involved in the biotransformation of *p*-cresol and that the metabolism of *p*-cresol in humans and rats is similar (Yan et al. 2005). That study and others (Thompson et al. 1994, 1995) have provided evidence that, at least in rats, phase I enzymes increase the liver toxicity of *p*-cresol *in vitro*, whereas conjugation reactions decreased the toxicity. To the extent that some of these enzymes are developmentally regulated, the metabolism, and consequently the toxicity of cresols in immature humans may be different than in adults. However, since the causative agent of cresols toxicity is still unknown, trying to predict how immature enzymatic systems could affect the toxicity of cresols in developing humans would be pure

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speculation at this time. It is not known whether cresols can cross the placenta and there are no reports on levels of cresols in maternal milk.

There are no biomarkers of exposure or effect for cresols that have been validated in children or in adults exposed as children. No relevant studies were located regarding interactions of cresols with other chemicals in children or adults.

No information was located regarding pediatric-specific methods for reducing peak absorption following exposure to cresols, reducing body burden, or interfering with the mechanism of action for toxic effects.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target 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, 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 cresols are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of

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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 cresols are discussed in Section 3.8.2.

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

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Cresols

No biomarkers that uniquely implicate exposure to cresols have been identified in humans or animals. Cresols are formed from the commonly found amino acid tyrosine, and occur naturally in human and animal tissues, fluids, and urine. Cresols are also formed as minor metabolites of toluene, and an increased presence of *o*-cresol in the body could be due to exposure to this substance, although toluene or hippuric acid in the urine seem to be more reliable indicators of occupational exposure to toluene than *o*-cresol (De Rosa et al. 1987; Fustinoni et al. 2007). The use of cresols as a biomarker of exposure to cresol would require a considerable elevation to exceed biological background levels and potential confounding from conversion of other environmental agents. There is some evidence that the presence of *o*-cresol in urine can be used as a biomarker for phenol exposure. A study of workers at a coke plant involved in the tar-distillation process found a statistically significant correlation ($p < 0.001$) between low concentrations of *o*-cresol in breathing-zone air and end-of-shift urine samples (Bieniek 1997). Urinary levels of *o*-cresol were also found to be significantly higher in the urine of workers employed in the distillation of carbolic oil than in nonexposed workers (Bieniek 1994).

p-Cresol has been found to form adducts with DNA in *in vitro* systems and it has been suggested that this property might provide a biomarker to assess occupational exposure to toluene (Gaikwad and Bodell 2001, 2003).

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3.8.2 Biomarkers Used to Characterize Effects Caused by Cresols

No biomarkers of effects caused by cresols have been identified in humans or animals. Data on human exposure to cresols are derived mainly from cases of acute accidental or intentional exposure to high amounts of cresol, which usually caused external burns and corrosive necrosis of the gastrointestinal tract. Generally, these types of exposures also involved liver and kidney alterations as well as other nonspecific pathologies.

3.9 INTERACTIONS WITH OTHER CHEMICALS

Cresols are irritant and corrosive by impairing the stratum corneum and producing coagulation necrosis by denaturing and precipitating proteins, which explains the toxic effects at the sites of contact (i.e., skin, mucosal surfaces). However, there is no information on other mechanisms of toxicity for cresols. Studies with liver cells *in vitro* suggested that metabolic activation of cresols by microsomal enzymes might produce toxic reactive intermediates (Thompson et al. 1994). It is plausible that exposure to substances that induce P-450 isozymes involved in the metabolism of cresols may increase the toxicity of cresols. Similar outcomes could occur by simultaneous exposure to cresols and substances that decrease phase II metabolic reactions. However, there is no experimental evidence to support these assumptions.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

Some groups have been identified that might exhibit increased vulnerability to the effects of cresols. There is very limited evidence that individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency may have increased susceptibility to hematological effects of cresols; the increase in methemoglobin formation and decrease in glutathione levels were more pronounced in blood taken from subjects with G6PD deficiency than in blood taken from normal subjects following exposure of the blood to a disinfectant containing 50% cresols *in vitro* (Chan et al. 1971).

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Patients with chronic renal failure constitute another group with increased susceptibility to *p*-cresol. In these patients, the concentration of *p*-cresol in the blood is 10 times higher than in healthy subjects due to both overgrowth of intestinal bacteria responsible for *p*-cresol production and reduced renal clearance. Free serum concentrations of *p*-cresol were shown to predict mortality in hemodialysis patients (Bammens et al. 2006). It has also been suggested that *p*-cresol decreases endothelial proliferation and wound repair in uremic patients, thus contributing to the immune defect in these patients (Dou et al. 2002, 2004). In a prospective longitudinal study, the concentrations of *p*-cresol were higher in hypoalbuminemic individuals than in those with normal albumin, and free *p*-cresol was related to hospitalization for infection (De Smet et al. 2003b).

3.11 METHODS FOR REDUCING TOXIC EFFECTS

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

Ellenhorn MJ, ed. 1997. *Ellenhorn's medical toxicology. Diagnosis and treatment of human poisoning.* 2nd ed. Baltimore, MD: Williams and Wilkins.

Haddad LM, Shannon MW, Winchester JF. 1998. *Clinical management of poisoning and drug overdose.* 3rd ed. Philadelphia, PA: W.B. Saunders Company.

Leikin JB, Paloucek FP. 2002. *Leikin and Paloucek's poisoning and toxicology handbook.* 3rd ed. Hudson, OH: Lexi-Comp, Inc.

3.11.1 Reducing Peak Absorption Following Exposure

For ingestion exposure, water or milk should be given if the patient is alert and has an intact gag reflex. Activated charcoal and a cathartic can then be administered orally or by gastric tube. Because cresol is corrosive and may cause seizures, emesis should not be induced. If the eyes have been exposed, they should be thoroughly irrigated as soon as possible with running water or saline. If the skin has been exposed, it should be flushed promptly with copious amounts of water or undiluted polyethylene glycol

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followed by thorough washing with soap or mild detergent and water (Bronstein and Currence 1988; Haddad et al. 1998; HSDB 2008; Leikin and Paloucek 2002; Stutz and Janusz 1988).

3.11.2 Reducing Body Burden

Procedures that might decrease the toxicity of cresols present in the bloodstream have not been identified. Although supporting data were not located, it is possible that elimination of cresols from the blood would be enhanced by alkaline diuresis, which would increase the proportion of cresols existing in the ionized state, thereby reducing reabsorption of cresols by the kidney tubules.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

No specific procedures have been developed to interfere with the mechanism of action of cresols. Treatment of individuals intoxicated with cresols is mainly supportive. Exposed individuals with evidence of central nervous system depression or seizures should be evaluated for the presence of some other underlying disorder. Diazepam or phenobarbital may be administered to alleviate seizures. Supplemental oxygen can also be administered. If pulmonary edema occurs, conventional therapy should be given. Methylene blue may be administered for treatment of methemoglobinemia. Additional information regarding the treatment of individuals exposed to cresols may be obtained from Bronstein and Currence 1988; Haddad et al. 1998; HSDB 2008; Leikin and Paloucek 2002; and Stutz and Janusz 1988.

3.12 ADEQUACY OF THE DATABASE

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

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

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

3.12.1 Existing Information on Health Effects of Cresols

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to cresols are summarized in Figure 3-4. The purpose of this figure is to illustrate the existing information concerning the health effects of cresols. 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* (Agency for Toxic Substances and Disease Registry 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.

In the following discussion, the various forms of cresol are considered together, due to the similarity of their effects and the levels at which these effects occur.

Cresols are irritants and have corrosive properties following exposure to high concentrations by any route of exposure. Therefore, the skin and mucosal membranes are targets for cresol toxicity. The existing information on the health effects of cresols in humans comes almost entirely from case reports of people who accidentally or intentionally swallowed cresol-containing substances or had these substances spilled on them. The single exception was an inhalation study of mucosal irritation in humans. Acute oral or dermal exposure to high amounts of cresol caused serious systemic effects and even death in humans.

A limited number of studies of inhalation exposure in animals tried to determine lethal levels or evaluated systemic and neurologic end points. A much greater number of studies in animals have been conducted by the oral route. Evaluation of the oral database suggests that a distinction should be made between studies by oral gavage and dietary studies based on differences on end points affected and threshold levels. Cresols are much more toxic when administered by oral gavage than when given in the diet. The difference is most likely related to differences in pharmacokinetics between the two means of administration. Animals exposed to cresols by gavage often showed adverse neurological signs and decreased weight gain associated with decreased food consumption. Oral gavage studies evaluated

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Figure 3-4. Existing Information on Health Effects of Cresols

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

Human

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

Animal

● Existing Studies

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reproductive, developmental, and neurological end points. Longer-term dietary studies examined systemic end points as well as reproductive, developmental, and carcinogenic effects. Studies of dermal exposure to cresols in animals generally looked at levels of lethality and irritation to the skin and eyes. One study of intermediate duration investigated dermal effects. A cancer-promotion study was also performed using dermally applied cresols.

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Case reports of humans exposed to high doses of cresols, either orally or dermally, have provided acute toxicity information. Fatalities due to ingestion and dermal exposure have been described (Bruce et al. 1976; Cason 1959; Chan et al. 1971; Green 1975; Isaacs 1922; Labram and Gervais 1968; Monma-Ohtaki et al. 2002). Other effects reported in these acute high exposure scenarios include respiratory failure (Liu et al. 1999), tachycardia and ventricular fibrillation (Labram and Gervais 1968), abdominal pain, vomiting, and corrosive lesions of the gastrointestinal tract (Hayakawa 2002; Isaacs 1922; Jouglard et al. 1971; Kamiyo et al. 2003; Wu et al. 1998; Yashiki et al. 1990), methemoglobinemia (Chan et al. 1971; Minami et al. 1990), leukocytosis and hemolysis (Cote et al. 1984; Wu et al. 1998), hepatocellular injury (Chan et al. 1971; Hashimoto et al. 1998; Hayakawa 2002; Kamiyo et al. 2003), renal alterations (Chan et al. 1971; Isaacs 1922; Labram and Gervais 1968; Wu et al. 1998), skin damage (Cason 1959; Green 1975; Herwick and Treweek 1933; Klinger and Norton 1945; Pegg and Campbell 1985), metabolic acidosis (Hayakawa 2002; Kamiyo et al. 2003), and unconsciousness (Chan et al. 1971; Isaacs 1922; Labram and Gervais 1968). Many of these effects may not have been caused directly by cresols, but represent secondary reactions to shock caused by external and internal burns. A single study in volunteers reported that brief exposures to 6 mg/m³ of *o*-cresol in the air caused respiratory tract irritation (Uzhdavini et al. 1972).

Limited data on acute inhalation effects were available from only two studies (Campbell 1941; Uzhdavini et al. 1972) in which exposure involved mixtures of vapors and aerosols that provided insufficient information to estimate exposure levels reliably; therefore, an acute-duration inhalation MRL for cresols was not derived. Still, these studies provided some data on lethality of airborne cresols as well as information on the respiratory system (irritation), liver (fatty degeneration and necrosis), renal (tubular degeneration), and nervous system (excitation, fatigue, convulsions). Inhalation studies that use modern methodology to generate and control exposure atmospheres and that evaluate a wide range of end points may be considered in order to construct dose-response curves for acute inhalation exposure. However, under normal circumstances, acute inhalation exposure is generally not considered hazardous due to

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cresols' low vapor pressure and a distinct odor at <1 ppm (NTP 1992b). A study of acute dermal exposure of animals to cresols determined exposure levels that produce skin irritation and death (Vernot et al. 1977); it is unclear what new key information would be provided by additional dermal studies. All acute-duration oral studies in animals administered cresols by oral gavage, a dosing mode that, as discussed in Section 2.3, induces different effects than those observed in dietary studies and is not considered relevant for risk assessment. Oral gavage studies showed reduced body weight, neurotoxicity, fetotoxicity, and death in exposed animals (EPA 1988b, 1988c, 1988d; TRL 1986; Tyl 1988a, 1988b). No acute dietary or drinking water studies were located for cresols, and for that reason, no acute-duration oral MRLs were derived. Although drinking water studies would mimic exposure to contaminated water at or near a waste site, the solubility of cresols would limit the high doses to be around 2%. In addition, the odor and taste of cresols may pose potential palatability problems. Therefore, acute-duration dietary studies are needed for defining targets and generating dose-response relationships for this exposure duration.

Intermediate-Duration Exposure. No information is available regarding humans exposed to cresols for an extended period of time. One of the studies that provided acute-duration inhalation data also provided intermediate-duration inhalation data (Uzhdavini et al. 1972). Rodents exposed to cresols showed adverse respiratory, cardiovascular, hepatic, renal, and neurological effects, but the methods used at the time to generate and monitor the exposure atmospheres were inadequate to estimate exposure concentrations with any precision. Modern studies are needed to define targets of toxicity and to establish dose-response relationships. It would be important to determine whether the nasal lesions observed in rats and mice in the dietary study conducted by NTP (1992b) also appear in animals exposed by inhalation. If so, the intermediate-duration oral MRL for cresols (see below) may have to be revisited (this also applies for chronic-duration exposure).

Oral gavage studies of intermediate duration in animals have been performed for all three cresol isomers, and have helped to identify the levels at which cresols produce neurological, respiratory, hepatic, renal, hematological, and body weight changes in orally exposed animals (EPA 1988b, 1988c, 1988d; TRL 1986). However, gavage administration of cresols induces different effects than those observed in dietary studies and do not resemble human environmental exposure scenarios to cresols. Therefore, only dietary studies were considered for MRL derivation even though some LOAELs by gavage are lower than dietary LOAELs. NTP (1992b) tested the cresol isomers and a mixture of *m*- and *p*-cresol in 28-day and 13-week dietary studies in rats and mice. A comprehensive number of end points were examined and the critical effect was nasal lesions in both species exposed to *p*-cresol and *m/p*-cresol. The data from the 13-week

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study in rats exposed to *m/p*-cresol were used to derive an intermediate-duration oral MRL for cresols. Additional intermediate oral studies do not seem necessary at this time since the NTP (1992b) study evaluated a comprehensive number of end points and cresols exhibited relatively little toxicity. Only one intermediate-duration dermal study in animals was located (Shelley 1974). People living near waste sites may be exposed to cresols in soil or dermally through water contaminated with cresols. Therefore, additional intermediate-duration dermal exposure studies are needed.

Chronic-Duration Exposure and Cancer. No studies of chronic duration were found in humans. Information regarding chronic toxicity is important because people living near hazardous waste sites might be exposed to cresols for many years. A mixture of *m/p*-cresol was tested in male Fischer-344 rats and female B6C3F₁ mice in a 2-year toxicity and carcinogenicity bioassay sponsored by NTP (NTP 2008). Although the study is yet to be finalized, preliminary results confirmed the presence of nasal lesions reported in the 28-day and 13-week studies (NTP 1992b) and also observed increased incidences of bronchiolar hyperplasia and follicular degeneration of the thyroid gland in treated mice (0, 100, 300, and 1,040 mg/kg/day). The data for bronchiole hyperplasia and follicular degeneration of the thyroid gland in female mice exposed for 2 years were used to derive a chronic-duration oral MRL for cresols. Additional long-term studies do not seem necessary at this time.

No studies were located regarding the carcinogenicity of cresols in humans. In a 2-year NTP-sponsored bioassay, an *m/p*-cresol mixture administered in the diet to male Fischer-344 rats and female B6C3F₁ mice induced a nonsignificant increase in the incidence of renal tubule adenoma in rats at 720 mg/kg/day, which was considered an equivocal finding of carcinogenicity by NTP (2008); no other neoplastic effects were reported in rats. In mice, treatment with 1,040 mg/kg/day *m/p*-cresol induced a significant increase in the incidence of squamous cell papilloma in the forestomach. Additional carcinogenicity bioassays do not seem necessary at this time.

Genotoxicity. No data were located regarding the genotoxicity of cresols in humans *in vivo*. *In vitro* studies using cultured human cells were negative for sister chromatid exchange for all three isomers (Cheng and Kligerman 1984) and positive for unscheduled DNA synthesis for *p*-cresol (Daugherty and Franks 1986). Studies of the genotoxicity of cresols in animals *in vivo* reported negative results (Cheng and Kligerman 1984; Ivett 1989a, 1989b, 1989c; NTP 1992b; Sernav 1989a, 1989b) with the exception of one study (Li et al. 2005). Results were mixed in *in vitro* studies using mammalian cells (Brusick 1988a, 1988b, 1988c; Cifone 1988a, 1988b; Murli 1988; Pepper, Hamilton & Scheetz 1980, 1981), and uniformly negative in *Salmonella* assays (Douglas et al. 1980; Florin et al. 1980; Haworth et al. 1983;

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Kubo et al. 2002; NTP 1992b; Pepper, Hamilton & Scheetz 1981; Pool and Lin 1982). The positive results obtained in some human and animal *in vitro* tests suggest that cresols have some ability to react with DNA. It is unlikely that additional tests will provide new key information regarding the genotoxicity of cresols.

Reproductive Toxicity. There are no data available regarding the reproductive effects of cresols in humans. Studies in animals do not suggest that reproductive end points are sensitive targets for cresols toxicity (EPA 1988b, 1988c, 1988d; Hornshaw et al. 1986; Neeper-Bradley and Tyl 1989a, 1989b; NTP 1992a, 1992b, 1992c, 2008; Tyl and Neeper-Bradley 1989). The well-conducted dietary continuous breeding protocol studies in mice with *o*-cresol and *m/p*-cresol found no evidence of reproductive toxicity for *o*-cresol (NTP 1992a); *m/p*-cresol, at a dose that caused minor maternal toxicity, produced a decrease in the number of pups/litter and increased the cumulative days to litter, but did not affect other reproductive function end points (NTP 1992c). In the intermediate-duration dietary studies in rats and mice conducted by NTP (1992b), effects were limited to mild to moderate uterine atrophy and lengthening of the estrous cycle, generally at the highest dose levels tested. In the 2-year bioassay in male rats and female mice dosed with up to 720 and 1.040 mg *m/p*-cresol/kg/day, respectively, there were no gross or microscopic alterations in the reproductive organs (NTP 2008). There is no reason to believe that potential reproductive effects might be route-dependent. Additional studies do not seem warranted at this time.

Developmental Toxicity. There are no data available regarding the developmental effects of cresols in humans. The developmental toxicity of cresols in animals was evaluated in a series of studies in which pregnant rats and rabbits were exposed by oral gavage to each cresol isomer (Neeper-Bradley and Tyl 1989a, 1989b; Tyl 1988a, 1988b; Tyl and Neeper-Bradley 1989) and in pregnant mice exposed to *o*-cresol or *m/p*-cresol in the diet in continuous breeding protocol studies (NTP 1992a, 1992c). These studies generally reported mild fetotoxicity only at maternally toxic doses. Additional information was provided by a comparative study that observed tremors in newborn mice exposed to 100 mg/kg/day *m*-cresol on postnatal days 4–21, but none in adults exposed to up to 300 mg/kg/day for 28 days (Koizumi et al. 2003). The reason why this occurs is not known, but it is likely related to differences in the metabolic disposition of *m*-cresol between the two age groups. There is no indication that potential developmental effects of cresols could be route-dependent. Since the data from gestation exposure studies in animals indicate that developmental effects occur only at dose levels that affect the mother, further studies examining the potential developmental toxicity of cresols do not seem necessary at this time.

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Immunotoxicity. No immunological effects were reported in case studies of human exposure. No significant alterations in weight or histology of lymphoreticular organs have been observed in animals following cresol exposure (EPA 1988b, 1988c, 1988d; Hornshaw et al. 1986; NTP 1992b, 2008). The information available does not suggest that the immune system is a target for cresol toxicity, but immunocompetence has not been evaluated.

Neurotoxicity. A common feature of oral poisoning with cresols in humans is coma (Chan et al. 1971; Isaacs 1922; Labram and Gervais 1968). Accidental dermal exposure of a cresol derivative was fatal to a child (Green 1975) and produced facial paralysis in a man who spilled cresol on his face (Klinger and Norton 1945). Oral gavage studies in rodents often induced adverse clinical signs indicative of neurological impairment such as hypoactivity, excessive salivation, labored respiration, and tremors (Neeper-Bradley and Tyl 1989a, 1989b; TRL 1986; Tyl and Neeper-Bradley 1989). In no cases have gross or microscopic alterations of the brain, spinal cord, or sciatic nerve been observed. None of the clinical signs seen in oral gavage studies have been seen in dietary studies (NTP 1992b, 2008), or if seen, they have occurred at much higher dose levels than in oral gavage studies. This difference is probably related to the different disposition of cresols and metabolites between the two modes of oral dosing. The mechanism(s) by which cresols induce these effects is not known, but could include actions at both central and peripheral sites of the nervous system. There is no reason to believe that the neurotoxic effects of cresols are route-dependent. Studies aimed at elucidating these mechanisms of action would be informative, but from the point of view of hazard identification, the nervous system is not a sensitive target for cresols administered at environmentally relevant levels by relevant routes of exposure.

Epidemiological and Human Dosimetry Studies. As previously mentioned, information about the effects of cresols in humans is derived mainly from case reports of accidental or intentional ingestion of cresol solutions or from accidental contact of cresol with the skin. Specific effects and references are mentioned under *Acute-Duration Exposure*. Doses were generally not available in the acute oral case reports, but Chan et al. (1971) estimated that roughly 2 g/kg may have caused the death of a woman. No group of the general population has been identified as having being exposed exclusively or predominantly to low levels of cresols for a long time. Based on data from long-term dietary studies in animals, it would be difficult to determine what specific end points to monitor in humans exposed to cresols since cresols caused relatively little systemic toxicity in the animal studies; hyperplastic or metaplastic lesions in the nasal respiratory epithelium were the most sensitive effects identified in rats and mice.

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Biomarkers of Exposure and Effect.

Exposure. No biomarkers of exposure to cresols have been identified. In fact, even the cresols themselves cannot be considered specific biomarkers for cresol exposure because they are also formed as breakdown products of toluene and tyrosine. However, if toluene exposure could be ruled out, then a high level of cresols or metabolites in the blood or urine would strongly suggest cresol exposure. *p*-Cresol was found to form adducts with DNA in *in vitro* systems (Gaikwad and Bodell 2001, 2003); however, even if it does the same *in vivo*, identification of adducts would not necessarily indicate exposure to cresols for the same reasons mentioned above.

Effect. No specific biomarkers of effect have been identified for cresols. Since cresols are irritants and corrosive at high concentration, their main effects are at sites of contact (i.e., skin, respiratory, and gastrointestinal tract). Other effects observed in subjects exposed acutely to relatively high amounts of cresols (i.e., hepatic, renal, hematological, and metabolic) may be secondary to the external and internal injuries (burns) caused by cresols. It seems unlikely that specific biomarkers of effect will be identified for cresols.

Absorption, Distribution, Metabolism, and Excretion. Case reports and a limited number of studies in animals suggest that cresols are well absorbed by all routes of exposure, although quantitative data are lacking. Only one study was located that provided information on the distribution of *m*- and *p*-cresol in rats following an oral gavage dose (Morinaga et al. 2004). Cresols were found to distribute widely among tissues and no specific organ seemed to preferentially accumulate cresols. The intermediate-duration oral MRL for cresols is based on nasal effects in rats administered the test material in the diet (NTP 1992b). Since there is the possibility that the lesions may be caused by inhalation of vapors of cresol from the food, a particularly valuable study would be to administer radiolabeled cresols by gavage and determine whether cresol-derived radioactivity appears disproportionately in the nasal epithelium.

The basic metabolic reactions for cresols are known (Bray et al. 1950; Morinaga et al. 2004; Williams 1938). The metabolism of *p*-cresol has been examined in more detail in rat liver microsomes and liver slices (Thompson et al. 1994, 1995, 1996; Yan et al. 2005). These studies suggested that a reactive intermediate plays a role in the toxicity of *p*-cresol on liver cells *in vitro*, but the relevance of this finding to studies *in vivo* is unknown since cresols exhibited little or no liver toxicity in dietary studies in rats and mice (NTP 1992b).

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Lacking from the cresol database are studies comparing the pharmacokinetics of cresols administered by oral gavage and in the diet. This is important because the effects of cresols administered by gavage are different than those seen following dietary administration. Based on information on a similar chemical, phenol, it is likely that the toxicity of cresols correlate with peak blood concentration rather than with total dose, but this has not been experimentally demonstrated for cresols. Information on possible dose dependency of the phase II metabolism is also lacking. It would be valuable to know for the various isomers which conjugation reaction, with sulfate or glutathione, predominates at low and high doses, and at what level each reaction might become saturated. No PBPK models have been developed for cresols. Such models are needed for addressing interspecies issues related to saturable pathways associated with various dosing parameters such as ingestion from food or water, issues related to gavage dosing, and inhalation and dermal absorption.

Comparative Toxicokinetics. The limited information available suggests that the metabolism of cresols is similar in humans and rats based on the fact that both species excrete sulfate and glutathione conjugation products in the urine. In addition, a recent study showed that bioactivation patterns for *p*-cresol in human and rat liver microsomes led to the same reactive intermediates and glutathione adducts (Yan et al. 2005). This information is insufficient to predict whether humans and animals will exhibit similar effects under similar exposure conditions, with the exception of portal-of-entry effects. However, it is unclear what practical information would provide additional comparative toxicokinetics studies given that cresols showed little systemic toxicity in animal studies when administered by an environmentally relevant route of exposure (other than nasal lesions) and no reports were found on humans exposed to cresols for long periods of time.

Methods for Reducing Toxic Effects. Cresols are strong irritants and corrosive at high concentrations and, therefore, their main effects are on surfaces with which they come in contact, such as the skin, and respiratory and gastrointestinal epithelia. Cresols exhibited little systemic toxicity in a limited number of intermediate-duration dietary studies in animals; therefore, attempts to suggest studies to counteract a yet unknown mechanism of action seem impractical at this time. The treatment for high dermal or oral exposures to cresols is standard for chemical burns and mainly supportive. Development of new therapies for the treatment of skin burns will help subjects accidentally exposure to cresols and similar chemicals.

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Children's Susceptibility. Data needs relating to both prenatal and childhood exposures, and developmental effects expressed either prenatally or during childhood, are discussed in detail in the Developmental Toxicity subsection above.

There are no studies that specifically addressed exposure to cresols in children. Data on the effects of cresols in adults are derived almost exclusively from cases of accidental or intentional ingestion of cresol solutions (see above *Acute-Duration Exposure* for specific references). Exposure to these high amounts of cresols produced corrosion at the points of contact including the skin and gastrointestinal tract. Similar effects would be expected in children exposed to high amounts of cresols. There is no information on whether the developmental process is altered in humans exposed to cresols. Studies in animals suggest that fetotoxicity occurs only with doses of cresols that are also toxic to the mother (Neeper-Bradley and Tyl 1989a, 1989b; Tyl 1988a, 1988b; Tyl and Neeper-Bradley 1989) and further standard developmental toxicity studies do not appear necessary at this time. A study showed that newborn rats (exposed daily on postnatal days 4–21) were more sensitive to the neurological effects of bolus doses of cresols than young rats (exposed daily for 28 days) (Koizumi et al. 2003). This may be due to age-related differences in toxicokinetics.

There are no data to evaluate whether toxicokinetics of cresols in children are different from adults. There is no information on whether cresols can cross the placenta and there are no studies on whether cresols can be transferred from mother to offspring through maternal milk. Research into the development of biomarkers of exposure for cresols would be valuable for both adults and children. There are no data on the interactions of cresols with other chemicals in children. There are no pediatric-specific methods to mitigate the effects of exposure to high amounts of cresols. Based on the information available, it is reasonable to assume that the supportive methods recommended for maintaining vital functions in adults, will also be applicable to children.

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

3.12.3 Ongoing Studies

No ongoing studies pertaining to cresols were identified in the Federal Research in Progress database (FEDRIP 2008).

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4. CHEMICAL AND PHYSICAL INFORMATION

4.1 CHEMICAL IDENTITY

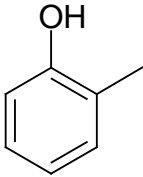
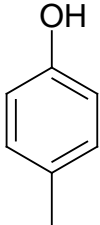
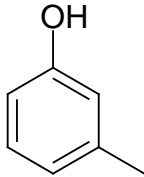
Data pertaining to the chemical identity of cresols are listed in Table 4-1.

4.2 PHYSICAL AND CHEMICAL PROPERTIES

The physical and chemical properties of cresols are presented in Table 4-2.

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-1. Chemical Identity of Cresols

Characteristics	<i>o</i> -Cresol	<i>p</i> -Cresol	<i>m</i> -Cresol	<i>o</i> -, <i>m</i> -, <i>p</i> -Cresol	References
Chemical name	<i>o</i> -Cresol	<i>p</i> -Cresol	<i>m</i> -Cresol	(<i>o</i> , <i>m</i> , <i>p</i>)-Cresol	ChemID 2008
Synonyms	2-Methylphenol; 2-hydroxy- toluene; <i>o</i> -cresylic acid	4-Methylphenol; 4-hydroxy- toluene; <i>p</i> -cresylic acid	3-Methylphenol 3-hydroxy- toluene; <i>m</i> -cresylic acid	Methylphenol; hydroxytoluene; cresylic acid	ChemID 2008; HSDB 2008; SANSS 1989
Trade names	No data	No data	No data	No data	
Chemical formula	C ₇ H ₈ O	C ₇ H ₈ O	C ₇ H ₈ O	C ₇ H ₈ O	ChemID 2008
Chemical structure				Mixture of three previous isomers	
Identification numbers:					
CAS registry	95-48-7	106-44-5	108-39-4	1319-77-3	ChemID 2008
NIOSH RTECS	GO6300000	GO6475000	GO61250000	GO5950000	SANSS 1989
EPA hazardous waste	F004; U052	F004; U052	F004; U052	F004; U052	HSDB 2008
DOT/UN/NA/IMCO shipping	UN 2022; UN 3455; UN 2076; IMO 6.1	UN 2022; UN 3455; UN 2076; IMO 6.1	UN 2022; UN 3455; UN 2076; IMO 6.1	UN 2022; UN 3455; UN 2076; IMO 6.1	HSDB 2008
HSDB	1813	1814	1815	250	HSDB 2008
NCI	No data	No data	No data	No data	

CAS = Chemical Abstracts Service; DOT/UN/NA/IMCO = Department of Transportation/United Nations/North America/Intergovernmental Maritime Consultive Organization; EPA = Environmental Protection Agency; HSDB = Hazardous Substance Data Bank; NCI = National Cancer Institute; NIOSH = National Institute for Occupational Safety and Health; RTECS = Registry of Toxic Effects of Chemical Substances

4. CHEMICAL AND PHYSICAL INFORMATION

Table 4-2. Physical and Chemical Properties of Cresols

Property	<i>o</i> -Cresol	<i>m</i> -Cresol	<i>p</i> -Cresol	Mixture of <i>o</i> -, <i>p</i> -, and <i>m</i> -cresol	References
Molecular weight	108.14	108.14	108.14	108.14	O'Neil et al. 2001
Color	White crystals darken with age	Colorless to yellowish	No data	Colorless, yellowish, brownish-yellow, or pinkish	O'Neil et al. 2001
Physical state	Solid	Liquid	Solid	Liquid	O'Neil et al. 2001
Melting point	30.944 °C	12.22 °C	34.739 °C	11–35 °C	Lewis 2001; Riddick et al. 1986
Boiling point					
1 atm	191.004 °C	202.32 °C	201.94 °C	191–203 °C	Riddick et al. 1986
10 mmHg	74.9 °C	86 °C	85.7 °C	No data	Lewis 2001; Lide 2005
Density (20 °C)	1.047 g/mL	1.034 g/mL	1.0341 g/mL	1.030–1.038 g/mL	O'Neil et al. 2001
Odor	Phenol-like	Phenol-like	Phenol-like	Phenol-like	O'Neil et al. 2001
Odor threshold					
Water	No data	0.037 ppm	No data	No data	Amoore and Hautala 1983
Air	No data	0.00028 ppm	No data	No data	Amoore and Hautala 1983
Solubility					
Water at 25 °C	25,950 ppm	22,700 ppm	21,520 ppm	No data	Yalkowsky et al. 1987
Organic solvents	Alcohol, ether, acetone, benzene, chloroform, alkali hydroxides (aqueous)	Alcohol, ether, acetone, benzene, chloroform, alkali hydroxides (aqueous)	Alcohol, ether, acetone, benzene, chloroform, alkali hydroxides (aqueous)	Alcohol, glycol, base	Lewis 2001; Lide 2005; O'Neil et al. 2001
Partition coefficients					
Log octanol/water	1.95	1.96	1.94	No data	Hansch and Leo 1985
Log K _{oc}	1.03	1.54	1.69	No data	Artiola-Fortuny and Fuller 1982; Boyd 1982
Vapor pressure					
25 °C	0.299 mmHg	0.138 mmHg	0.11 mmHg	No data	AIChE 1989,2000, Chao et al. 1983

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Table 4-2. Physical and Chemical Properties of Cresols

Property	<i>o</i> -Cresol	<i>m</i> -Cresol	<i>p</i> -Cresol	Mixture of <i>o</i> -, <i>p</i> -, and <i>m</i> -cresol	References
Henry's law constant atm/m ³ -molecule at 25 °C	1.2x10 ⁻⁶	8.65x10 ⁻⁷ (calculated from vapor pressure and water solubility)	7.92x10 ⁻⁷	No data	Gaffney et al. 1987; Hine and Mookerjee 1975
Flashpoint (closed cup)	81 °C	85 °C	86 °C	82 °C	Lewis 2001
Flammability limits	1.4% (lower)	1.1% (lower)	1.1% (lower)		HSDB 2008
Conversion factors					
ppm (v/v) to mg/m ³ in air (20 °C)	4.50	4.50	4.50	4.50	Verschueren 1983
mg/m ³ to ppm (v/v) in air (20 °C)	0.22	0.22	0.22	0.22	Verschueren 1983
Bioconcentration factor					
Log BCF	1.25 (calculated from K _{ow})	1.30	1.24 (calculated from K _{ow})	No data	Freitag et al. 1985; Thomas 1982
Explosive limits	No data	No data	No data	No data	

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

5.1 PRODUCTION

Prior to World War II, multimillion pound quantities of cresols were produced annually in the United States, and domestic production and sales of cresols have steadily increased over the past several decades. In 1987, the national capacity for producing cresolics (compounds relating to cresols) was 208 million pounds per year (CMR 2004). More recent data indicate that the total U.S. production capacity for cresols, xylenols, and cresylics is approximately 470 million pounds (CMR 2004). Overall demand for cresols, xylenols, and cresylics was 340 million pounds in 2002, 365 million pounds in 2003, and is projected to increase to 385 million pounds by 2007 (CMR 2004). Information regarding the production levels of individual isomers and specific mixtures was unavailable. These production totals include data on the manufacture of cresylic acid and exclude information on cresol production by coke and gas-retort ovens. The commercial mixture of cresol isomers, in which the *m*-isomer predominates and contains <5% phenol, is sometimes referred to as cresylic acid (Windholz et al. 1983). However, cresylic acids generally are composed of cresols, phenols, and xylenols; they are defined as those mixtures in which over 50% will boil at temperatures above 204 °C (Lewis 2001).

Cresols are used widely by industry. Information from the EPA's Toxic Release Inventory (TRI) on facilities that either manufactured or processed *o*-, *m*-, *p*-, or mixed isomers of cresols in 2004 is outlined in Tables 5-1 through 5-4, respectively. The TRI data should be used with caution since only certain types of facilities were required to report. This is not an exhaustive list. According to the 2005 Directory of Chemical Producers (SRI 2005), cresols are currently produced by five manufacturers in New York, Pennsylvania, Illinois, and Texas. Stanford Research Institute (SRI 2005) data for individual isomers and the mixture *o*-, *p*-, and *m*-isomers are included in Table 5-5.

The oldest cresol production method used in the United States is through the recovery of fractional distillates from coal tars. Most domestic cresols are formed via catalytic and thermal cracking of naphtha fractions during petroleum distillation. Since 1965, quantities of coal tar and petroleum isolates have been insufficient to meet the rising demand. Consequently, several processes for the manufacture of the various isomers have been developed. One General Electric facility produces *o*-cresol at an annual capacity of 10,000 tons by the methylation of phenol in the presence of catalysts. The Sherman-Williams Company uses the toluene sulfonation process and maintains an annual capacity for *p*-cresol of 15,000 tons. The Hercules Powder Company produced *p*-cresol until 1972 by the cymene-cresol process.

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

Table 5-1. Facilities that Produce, Process, or Use o-Cresol

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
AL	4	0	999,999	1, 6, 9, 12, 13, 14
AR	1	1,000	9,999	12
CA	8	1,000	999,999	2, 3, 6, 7
DE	1	10,000	99,999	6
GA	4	100	99,999	2, 3, 6, 7, 8
IL	12	100	9,999,999	1, 2, 3, 4, 6, 7, 12
IN	9	100	99,999	1, 5, 7, 8, 10, 11, 12
KS	1	100	999	12
KY	11	0	999,999	2, 3, 6, 7, 8, 10, 11, 12
LA	7	1,000	9,999,999	1, 2, 3, 6, 12, 13
MI	1	1,000	9,999	7
MO	4	100	99,999	9, 12
MS	1	10,000	99,999	1, 3, 6
NE	2	1,000	99,999	12
NJ	6	1,000	999,999	6, 7, 9, 12
NY	9	1,000	999,999	1, 5, 6, 7, 13
OH	9	0	999,999	1, 3, 6, 7, 8, 12
OK	2	100	999	6, 7
PA	6	1,000	999,999	1, 4, 8, 9, 13
RI	4	1,000	99,999	6, 7, 8
SC	1	10,000	99,999	12
TN	8	100	9,999,999	2, 3, 6, 8, 9, 11, 12
TX	28	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13
UT	2	10,000	999,999	1, 3, 4, 5, 6
WI	4	1,000	999,999	6, 7
AL	4	0	999,999	1, 6, 9, 12, 13, 14
AR	1	1,000	9,999	12

^aPost office state abbreviations used^bAmounts on site reported by facilities in each state^cActivities/Uses:

- | | | |
|--------------------------|--------------------------|-----------------------------|
| 1. Produce | 6. Impurity | 11. Chemical Processing Aid |
| 2. Import | 7. Reactant | 12. Manufacturing Aid |
| 3. Onsite use/processing | 8. Formulation Component | 13. Ancillary/Other Uses |
| 4. Sale/Distribution | 9. Article Component | 14. Process Impurity |
| 5. Byproduct | 10. Repackaging | |

Source: TRI05 2007 (Data are from 2005)

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

Table 5-2. Facilities that Produce, Process, or Use m-Cresol

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
AR	2	100	9,999	12
CA	3	0	999,999	4, 7
FL	1	1,000	9,999	7, 8
GA	3	10,000	999,999	2, 3, 6, 7, 10, 11
IL	6	100	99,999	1, 5, 6, 10, 12, 13
IN	16	100	999,999	2, 3, 6, 7, 8, 10, 11, 12
KS	3	1,000	99,999	6, 12
KY	10	1,000	999,999	1, 2, 3, 6, 8, 10, 11, 12
LA	1	1,000	9,999	6
MA	2	1,000	99,999	6, 11
MI	2	10,000	99,999	6
MO	8	100	999,999	1, 4, 8, 9, 10, 11, 12
MS	4	100	999,999	6, 10
NC	3	0	99,999	6, 10, 11, 12
NJ	1	1,000	9,999	12
NY	6	10,000	999,999	1, 5, 6, 9, 10, 13
OH	6	100	999,999	1, 3, 5, 6, 7, 12
OK	4	100	99,999	6, 7, 10
PA	8	1,000	999,999	1, 4, 6, 8, 9, 13
RI	3	10,000	99,999	6, 7, 8
SC	4	10,000	9,999,999	6, 12
TN	9	0	9,999,999	6, 7, 8, 9, 11, 12
TX	19	0	9,999,999	1, 2, 3, 4, 5, 6, 8, 11, 12, 13, 14
WI	1	10,000	99,999	7
WV	1	100,000	999,999	6

^aPost office state abbreviations used^bAmounts on site reported by facilities in each state^cActivities/Uses:

- | | | |
|--------------------------|--------------------------|-----------------------------|
| 1. Produce | 6. Impurity | 11. Chemical Processing Aid |
| 2. Import | 7. Reactant | 12. Manufacturing Aid |
| 3. Onsite use/processing | 8. Formulation Component | 13. Ancillary/Other Uses |
| 4. Sale/Distribution | 9. Article Component | 14. Process Impurity |
| 5. Byproduct | 10. Repackaging | |

Source: TRI05 2007 (Data are from 2005)

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

Table 5-3. Facilities that Produce, Process, or Use p-Cresol

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
AL	5	100	999,999	1, 2, 6, 12, 13, 14
AR	3	0	9,999	12
AZ	1	1,000	9,999	7
CA	3	1,000	9,999,999	1, 3, 6, 7
CT	2	10,000	999,999	6
GA	1	10,000	99,999	2, 3, 6, 7
IL	7	1,000	9,999,999	1, 3, 4, 6, 7, 10, 12
IN	13	0	999,999	2, 3, 7, 8, 10, 11, 12
KS	5	100	999,999	2, 3, 6, 8, 12
KY	9	1,000	999,999	2, 3, 6, 8, 10, 11, 12
LA	12	0	999,999	1, 2, 3, 4, 5, 6, 12
MO	9	100	999,999	1, 4, 8, 9, 10, 11, 12
MS	1	1,000	9,999	10
NC	4	1,000	99,999	6, 8, 10, 12
NE	2	1,000	99,999	12
NJ	6	1,000	999,999	2, 3, 6, 12
NY	4	100	999,999	1, 5, 6, 12, 13
OH	5	1,000	999,999	6, 12
OK	3	100	99,999	6, 7, 10
PA	8	100	999,999	1, 4, 6, 8, 9, 12, 13
RI	2	10,000	99,999	6, 8
SC	3	10,000	999,999	6, 12
TN	8	0	49,999,999	7, 8, 9, 11, 12
TX	17	0	9,999,999	1, 2, 4, 5, 6, 8, 11, 12, 13, 14
WV	1	100,000	999,999	6

^aPost office state abbreviations used

^bAmounts on site reported by facilities in each state

^cActivities/Uses:

- | | | |
|--------------------------|--------------------------|-----------------------------|
| 1. Produce | 6. Impurity | 11. Chemical Processing Aid |
| 2. Import | 7. Reactant | 12. Manufacturing Aid |
| 3. Onsite use/processing | 8. Formulation Component | 13. Ancillary/Other Uses |
| 4. Sale/Distribution | 9. Article Component | 14. Process Impurity |
| 5. Byproduct | 10. Repackaging | |

Source: TRI05 2007 (Data are from 2005)

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

Table 5-4. Facilities that Produce, Process, or Use Cresol (Mixed Isomers)

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
AL	25	0	999,999	1, 2, 3, 4, 5, 6, 7, 8, 12, 13, 14
AR	17	0	99,999	1, 2, 3, 5, 6, 7, 8, 9, 12, 13
CA	43	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14
CT	6	100	9,999	1, 5, 7, 10, 11
DE	5	10,000	99,999	1, 3, 5, 6, 7, 12
FL	8	0	99,999	1, 5, 7, 8, 11, 12, 13
GA	25	0	999,999	1, 2, 3, 5, 6, 7, 8, 10, 11, 12, 13
IA	1	100	999	7
ID	5	0	999	1, 5, 13
IL	36	1,000	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 13, 14
IN	47	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13
KS	9	1,000	999,999	1, 4, 5, 7, 10, 12, 13
KY	27	0	9,999,999	1, 2, 3, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
LA	48	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14
MA	3	1,000	99,999	2, 3, 6, 10, 11
MD	7	0	999,999	1, 5, 12, 13
ME	2	0	99	1, 5, 13
MI	16	0	999,999	1, 4, 5, 6, 7, 12, 13
MN	6	100	99,999	1, 2, 3, 4, 5, 6, 9, 11, 12, 13
MO	24	0	999,999	2, 3, 4, 6, 7, 8, 9, 10, 11, 12, 14
MS	23	0	999,999	1, 2, 3, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14
NC	18	0	999,999	1, 2, 3, 5, 6, 7, 10, 11, 12, 13
NE	2	1,000	99,999	12
NH	6	1,000	999,999	2, 3, 7, 10, 11
NJ	17	1,000	999,999	2, 3, 4, 6, 7, 9, 12
NM	3	10,000	999,999	1, 2, 3, 7, 10, 12, 13
NV	1	10,000	99,999	12
NY	21	100	9,999,999	1, 2, 4, 5, 6, 7, 8, 9, 10, 12, 13
OH	30	0	9,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
OK	6	1,000	999,999	1, 3, 4, 5, 6, 7, 9, 10, 13, 14
OR	7	0	9,999,999	1, 2, 3, 5, 7, 9, 12, 13
PA	27	0	9,999,999	1, 4, 5, 6, 7, 9, 10, 11, 12, 13, 14
PR	1	100	999	2, 3, 4, 7, 9
RI	1	10,000	99,999	6
SC	13	0	999,999	1, 2, 3, 5, 6, 7, 12, 13
TN	14	0	999,999	1, 5, 6, 7, 9, 10, 11, 12, 13, 14
TX	68	0	49,999,999	1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14
UT	12	1,000	999,999	1, 3, 4, 5, 6, 7, 9, 10, 12, 13

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

Table 5-4. Facilities that Produce, Process, or Use Cresol (Mixed Isomers)

State ^a	Number of facilities	Minimum amount on site in pounds ^b	Maximum amount on site in pounds ^b	Activities and uses ^c
VA	10	0	999,999	1, 5, 10, 11, 12
VI	1	100	999	2, 3, 4, 7, 9
WA	24	0	9,999,999	1, 2, 3, 4, 5, 7, 12, 13, 14
WI	6	0	999,999	1, 5, 6, 13
WV	12	0	9,999,999	1, 2, 3, 4, 5, 6, 8, 12, 13
WY	5	0	99,999	1, 4, 5, 6, 13

^aPost office state abbreviations used

^bAmounts on site reported by facilities in each state

^cActivities/Uses:

- | | | |
|--------------------------|--------------------------|-----------------------------|
| 1. Produce | 6. Impurity | 11. Chemical Processing Aid |
| 2. Import | 7. Reactant | 12. Manufacturing Aid |
| 3. Onsite use/processing | 8. Formulation Component | 13. Ancillary/Other Uses |
| 4. Sale/Distribution | 9. Article Component | 14. Process Impurity |
| 5. Byproduct | 10. Repackaging | |

Source: TRI05 2007 (Data are from 2005)

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

Table 5-5. Current U.S. Producers of Cresol

Company	Location ^a	Isomer
Merisol Antioxidants, LLC	Oil City, Pennsylvania	<i>m</i> -cresol
Merisol USA, LLC	Houston, Texas	<i>m</i> -cresol <i>m/p</i> -cresol <i>o</i> -cresol <i>p</i> -cresol (<i>o,m,p</i>)-cresol
General Electric Company	Selkirk, New York	<i>o</i> -cresol
PMC Specialties Group, Inc.	Chicago, Illinois	<i>o</i> -cresol
Bell Flavors and Fragrances, Inc.	Northbrook, Illinois	<i>p</i> -cresol

Source: Derived from SRI 2005

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

This method is capable of producing *p*- or *m*-cresol from the corresponding cymene (isopropyltoluene). Alkaline chlorotoluene hydrolysis is used to formulate a cresol mixture with a high *m*-cresol content. However, information pertaining to domestic use of this process was unavailable (Fiege and Bayer 1987).

5.2 IMPORT/EXPORT

In 2007, 548,446 kg of cresol and cresol salts were imported from other countries netting \$1,895,164 (OSITC 2008). The largest exporters of cresol and cresol salts to the United States were Spain and the United Kingdom with export amounts for 2005 of 165,040 and 822,170 kg, respectively. Money spent on the import of cresols and their salts to the United States has increased from \$698,000 in 2003 to \$1,363,000 in 2004 and \$2,754,000 in 2005 (USITC 2006).

In 2007, 26,100,350 kg of cresol and cresol salts were exported to other countries netting \$62,558,544 (OSITC 2008). The largest importers of cresol and cresol salts from the United States were China, Japan, the Netherlands, and the United Kingdom with export values for 2005 of 3,200,351; 2,436,843; 6,317,298; and 6,140,655 kg, respectively. Money from export of cresols and their salts from the United States has increased from \$29,736,000 in 2003 to \$38,534,000 in 2004 and \$47,280,000 in 2005 (USITC 2006).

5.3 USE

A considerable amount of *o*-cresol is used directly as either a solvent or disinfectant. *o*-Cresol is also used as a chemical intermediate for a wide variety of products. *o*-Cresol is hydrogenated to 2-methylcyclohexanol or 2-methylcyclohexanone, which are also solvents. Coumarin is made from the carbonate ester of *o*-cresol and is a deodorizing and odor-enhancing agent that also has pharmaceutical applications (Lewis 2001). Alkylation of *o*-cresol with propene gives 3-isopropyl-6-methylphenol (carvacrol). Carvacrol is used as an antiseptic and in fragrances (Windholz et al. 1983). *o*-Cresol also serves as an intermediate for the production of various antioxidants. Several dye intermediates are manufactured from *o*-cresol. *o*-Cresotinic acid, produced from *o*-cresol via the Kolbe synthesis, is used as a dye, a dye intermediate, and a pharmaceutical intermediate. Recently, an increasing proportion of *o*-cresol has been devoted to the formulation of epoxy-*o*-cresol novolak (ECN) resins. ECN resins are sealing materials for integrated circuits (silicon chips). *o*-Cresol is also used as an additive to phenol-formaldehyde resins. The manufacture of certain herbicides and pesticides, including 4-chloro-2-methylphenoxyacetic acid (MCPA), 2-(4-chloro-2-methylphenoxy)-propionic acid (MCPPE), γ (4-chloro-

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

2-methylphenoxy)-butyric acid (MCPB), and 4,6-dinitro-*o*-cresol (DNOC), is also dependent upon *o*-cresol (Fiege and Bayer 1987).

p-Cresol is used largely in the formulation of antioxidants such as 2,6-di-*tert*-butyl-*p*-cresol (BHT), 2,6-dicyclopentyl-*p*-cresol, 2,2'-methylene- or 2,2'-thiodiphenols, and Tinuvin 326. Tinuvin 326 absorbs ultraviolet (UV) light and is added to polyethylene and polypropylene films and coatings for protection against photodegradation. *p*-Cresol also has many applications in the fragrance and dye industries (O'Neil et al. 2001). Synthetic food flavors also contain *p*-cresol (Lewis 2001). *p*-Cresol carboxylic acid esters and anisaldehyde are used in perfumes (Lewis 2001). The latter is made from *p*-cresol methyl ether (Fiege and Bayer 1987).

m-Cresol, either pure or mixed with *p*-cresol, is important in the production of contact herbicides such as O,O-dimethyl-O-(3-methyl-4-nitrophenyl)thionophosphoric acid (fenitrothion, Follithion, and Sumithion) and O,O-dimethyl-O-(3-methyl-4-methylthiophenyl)thionophosphoric acid ester (fenthion, Baytex, and Lebaycid) (Fiege and Bayer 1987). *m*-Cresol is also a precursor to the pyrethroid insecticides. Furthermore, many flavor and fragrance compounds, such as (-)-methanol and musk ambrette, are derived from *m*-cresol. Several important antioxidants are produced from *m*-cresol. *m*-Cresol is also used to manufacture an explosive, 2,4,6-nitro-*m*-cresol.

Mixtures of *m*- and *p*-cresol often serve as disinfectants and preservatives (O'Neil et al. 2001). Because cresols are bactericides and fungicides, they are added to soaps as disinfectants. Crude cresols are used as wood preservatives. Tricresyl phosphate and diphenyl cresyl phosphate are produced from *m*- and *p*-cresol mixtures. These neutral phosphoric acid esters are used as flame-retardant plasticizers for polyvinylchloride (PVC) and other plastics, fire-resistant hydraulic fluids, additives for lubricants, and air filter oils. Cresol mixtures condensed with formaldehyde are important for modifying phenolic resins. However, the *m*-isomer content is critical to the mixture because *m*-cresol is the most reactive of the three isomers. Cresols are also used in paints and textiles. Mixtures of cresols are used as solvents for synthetic resin coatings such as wire enamels, metal degreasers, cutting oils, and agents to remove carbon deposits from combustion engines. Other uses of cresol mixtures include ore flotation and fiber treatment (Fiege and Bayer 1987; Windholz et al. 1983).

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

5.4 DISPOSAL

Cresols may be disposed of by landfill, land applications, biological waste water treatment, or incineration. In an activated sludge system, cresols exhibit a 96% reduction of the chemical oxygen demand and a biodegradation rate of 55 mg of oxygen/g/hour. Cresols may be disposed of in a rotary kiln incinerator with a temperature range of 820–1,600 °C and a residence time of seconds. Cresols may also be disposed of in a fluidized bed incinerator with a temperature range of 450–980 °C and a residence time of seconds (HSDB 2008).

6. POTENTIAL FOR HUMAN EXPOSURE

6.1 OVERVIEW

o-Cresol, *m*-cresol, *p*-cresol, and mixed cresols have been identified in at least 210, 22, 310, and 70 of the 1,678 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL), respectively (HazDat 2006). However, the number of sites evaluated for cresols is not known. The frequency of these sites for *o*-, *m*-, *p*-, and mixed cresols can be seen in Figures 6-1, 6-2, 6-3, and 6-4, respectively.

Cresols are widely occurring natural and anthropogenic products. Although cresols appear to be ubiquitous in the environment, their concentrations probably remain low due to their rapid removal rates in most environmental media. In air, cresols degrade rapidly because of reactions with photochemically produced hydroxyl radicals. Biodegradation is the dominant mechanism responsible for the fast breakdown of cresols in soil and water. Nevertheless, cresols may persist in extremely oligotrophic waters, in those with limited microbial communities, and/or those under anaerobic conditions, such as in some sediments and groundwater aquifers.

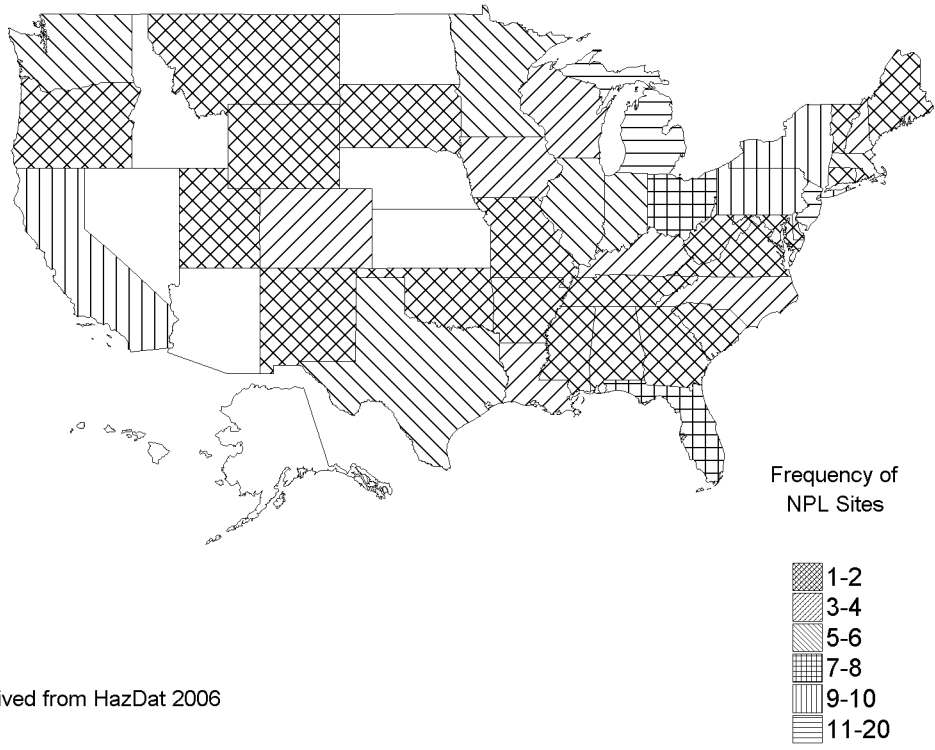
Based on the available information, the most common route of exposure for the general population is inhalation. Cresols are constantly emitted to air via automobile exhaust; consequently, people who live in urban and suburban settings may be constantly exposed to low levels of cresols in the atmosphere. Cresols are also emitted to ambient air during the combustion of coal, wood, and municipal solid waste. Therefore, residents near coal- and petroleum-fueled electricity-generating facilities, municipal solid waste incinerators, and industries with conventional furnace operations or large-scale incinerators may be exposed to cresols in air. People in residential areas where homes are heated with coal, oil, or wood may also be exposed to cresols in air. High levels of cresol exposure can result from active and passive inhalation of cigarette smoke (Wynder and Hoffmann 1967). Therefore, people who smoke or live with smokers are exposed to higher concentrations of cresol in the air.

6.2 RELEASES TO THE ENVIRONMENT

The Toxics Release Inventory (TRI) data should be used with caution because only certain types of facilities are required to report (EPA 2005). This is not an exhaustive list. Manufacturing and processing facilities are required to report information to the TRI only if they employ 10 or more full-time employees; if their facility is included in Standard Industrial Classification (SIC) Codes 10 (except 1011,

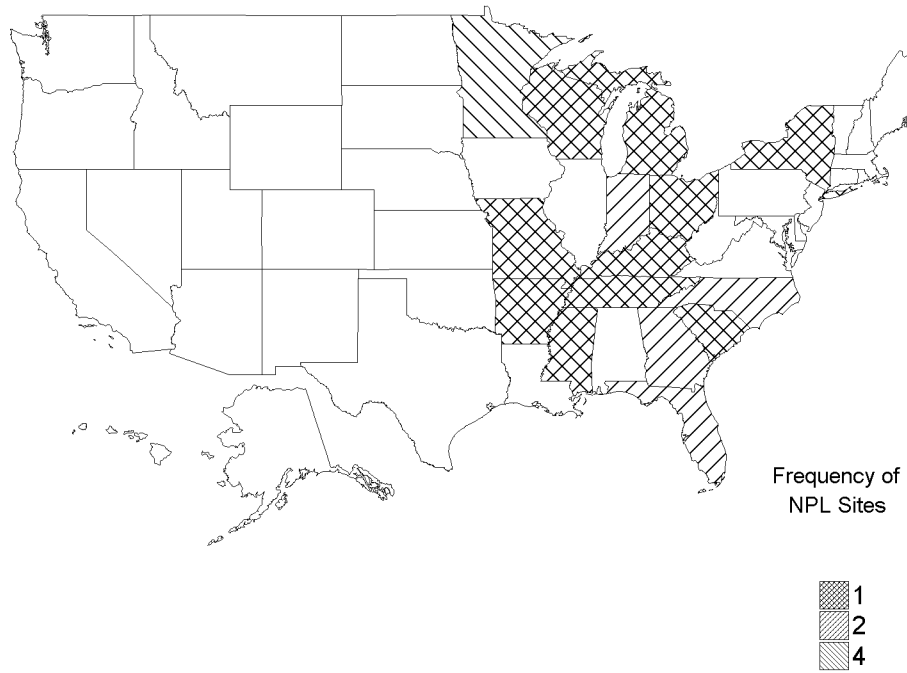
6. POTENTIAL FOR HUMAN EXPOSURE

Figure 6-1. Frequency of NPL Sites with o-Cresol Contamination



6. POTENTIAL FOR HUMAN EXPOSURE

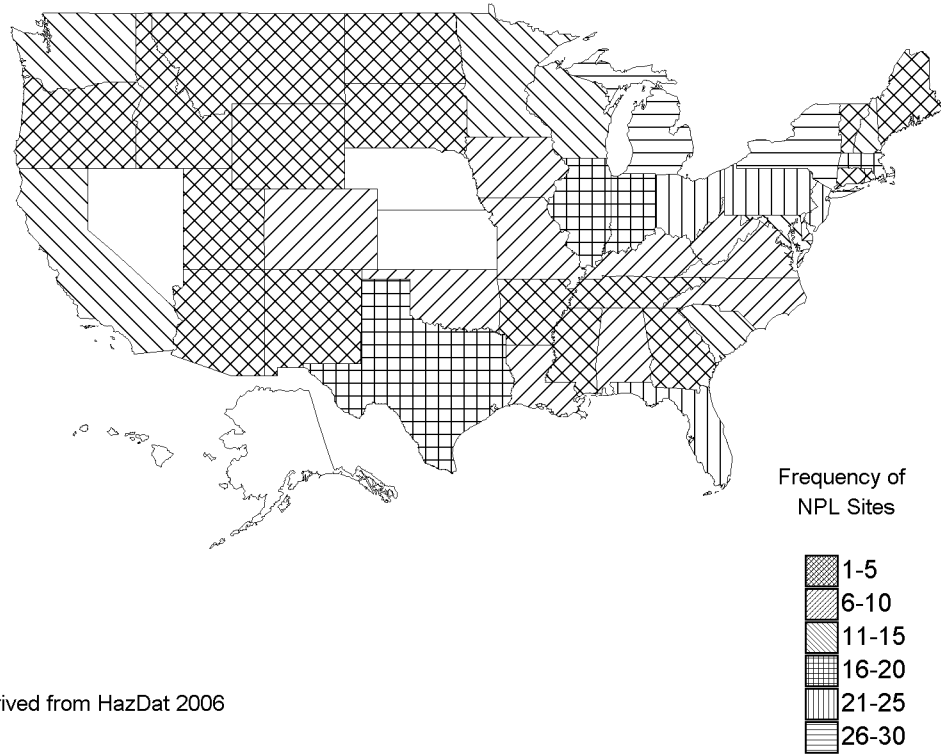
Figure 6-2. Frequency of NPL Sites with *m*-Cresol Contamination



Derived from HazDat 2006

6. POTENTIAL FOR HUMAN EXPOSURE

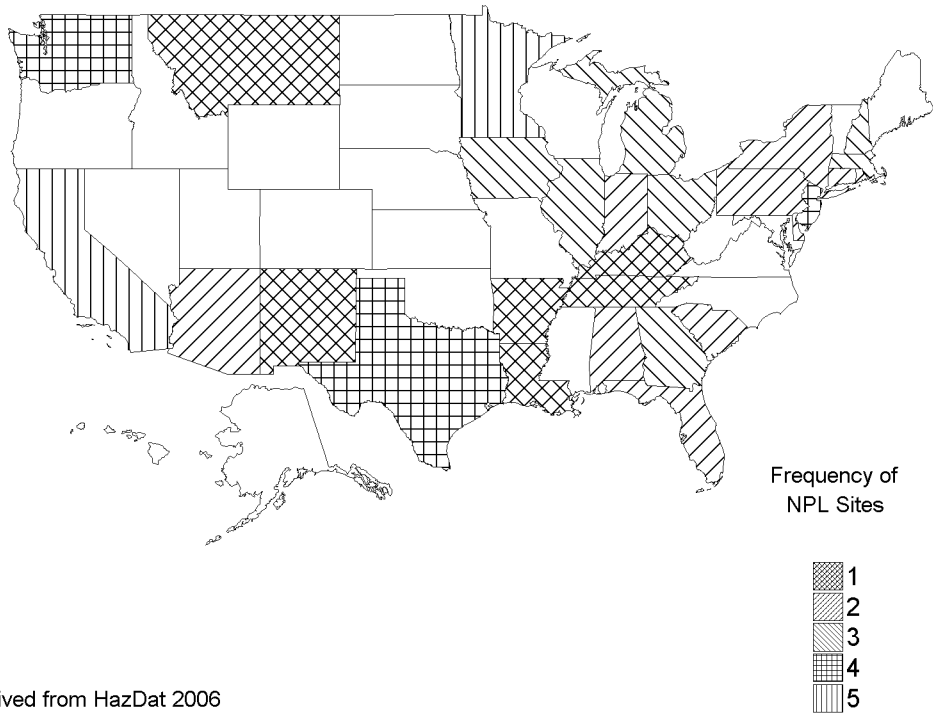
Figure 6-3. Frequency of NPL Sites with *p*-Cresol Contamination



Derived from HazDat 2006

6. POTENTIAL FOR HUMAN EXPOSURE

Figure 6-4. Frequency of NPL Sites with Cresols (Mixed Isomers) Contamination



Derived from HazDat 2006

6. POTENTIAL FOR HUMAN EXPOSURE

1081, and 1094), 12 (except 1241), 20–39, 4911 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4931 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4939 (limited to facilities that combust coal and/or oil for the purpose of generating electricity for distribution in commerce), 4953 (limited to facilities regulated under RCRA Subtitle C, 42 U.S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited S.C. section 6921 et seq.), 5169, 5171, and 7389 (limited to facilities primarily engaged in solvents recovery services on a contract or fee basis); and if their facility produces, imports, or processes $\geq 25,000$ pounds of any TRI chemical or otherwise uses $>10,000$ pounds of a TRI chemical in a calendar year (EPA 2005).

6.2.1 Air

Estimated releases of 3,313 pounds (~1.5 metric tons) of *o*-cresol, 41,496 pounds (~19 metric tons) of *m*-cresol, 31,393 pounds (~14 metric tons) of *p*-cresol, and 932,106 pounds (~423 metric tons) of mixed isomers of cresol, to the atmosphere from 23, 28, 27, and 157 domestic manufacturing and processing facilities in 2005, accounted for about <1, 21, 21 and 72% of the estimated total environmental releases of *o*-cresol, *m*-cresol, *p*-cresol, and cresol mixed isomer from facilities required to report to the TRI (TRI05 2007), respectively. These releases are summarized in Tables 6-1 through 6-4.

A national emissions study conducted from 1990 to 1998 reported an estimated 11,000 tons/year released throughout the United States for all combined isomers of cresol (EPA 2000d). The emissions of total cresol isomers were 6,000 and 5,000 tons/year for urban and rural locations, respectively (EPA 2000d).

Cresols are a group of widely distributed natural compounds formed as metabolites of microbial activity and excreted in the urine of mammals (Fiege and Bayer 1987). Cresols occur in various plant lipid constituents, including oils from jasmine, cassia, Easter lily, ylang ylang, and *Yucca gloriosa* flowers, peppermint, eucalyptus, and camphor. Oils from conifers, oaks, and sandalwood trees also contain cresols (Fiege and Bayer 1987). Volatilization of natural cresols from urine and transpiration of plants may release cresols to the air. Cresols are also a product of combustion and can be released to the atmosphere from natural fires associated with lightning, spontaneous combustion, and volcanic activity (McKnight et al. 1982).

Cresols are natural components of crude oil and coal tar, from which they are recovered as fractional distillates. Cresols are also produced synthetically. The dominant anthropogenic sources for the release

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-1. Releases to the Environment from Facilities that Produce, Process, or Use o-Cresol^a

State ^c	RF ^d	Reported amounts released in pounds per year ^b							Total release	
		Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	On-site ^j	Off-site ^k	On- and off-site	
AR	1	0	No data	0	0	0	0	0	0	0
IL	2	10	No data	0	5	250	10	255	265	
KY	2	478	No data	0	0	0	478	0	478	
LA	2	4	0	0	0	0	4	0	4	
MO	1	10	No data	0	0	0	10	0	10	
NY	3	1,000	5	0	0	0	1,005	0	1,005	
OH	3	103	0	0	255	0	103	255	358	
TX	7	1,695	118	182,006	10	1	182,358	1,472	183,830	
WI	2	12	0	0	0	0	12	0	12	
Total	23	3,313	123	182,006	270	251	183,981	1,982	185,963	

^aThe TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.

^bData in TRI are maximum amounts released by each facility.

^cPost office state abbreviations are used.

^dNumber of reporting facilities.

^eThe sum of fugitive and point source releases are included in releases to air by a given facility.

^fSurface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).

^gClass I wells, Class II-V wells, and underground injection.

^hResource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.

ⁱStorage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown

^jThe sum of all releases of the chemical to air, land, water, and underground injection wells.

^kTotal amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI05 2007 (Data are from 2005)

6. POTENTIAL FOR HUMAN EXPOSURE

Table 6-2. Releases to the Environment from Facilities that Produce, Process, or Use *m*-Cresol^a

State ^c	RF ^d	Reported amounts released in pounds per year ^b					Total release		
		Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	On-site ^j	Off-site ^k	On- and off-site
IL	2	10	No data	0	5	250	10	255	265
IN	6	28,159	No data	0	0	0	28,159	0	28,159
KS	1	3	No data	0	0	0	3	0	3
KY	1	785	No data	0	0	0	785	0	785
MI	1	3	No data	0	0	0	3	0	3
MO	2	270	0	0	0	0	270	0	270
MS	1	2,400	No data	0	0	0	2,400	0	2,400
NC	1	3	No data	0	0	0	3	0	3
NY	1	255	5	0	0	0	260	0	260
OH	1	1,144	0	0	500	0	1,144	500	1,644
OK	1	0	No data	0	0	0	0	0	0
SC	3	207	No data	0	0	0	207	0	207
TN	1	1,414	No data	0	0	0	1,414	0	1,414
TX	5	6,820	497	153,332	274	13	160,786	150	160,936
WV	1	23	42	0	1	0	65	1	66
Total	28	41,496	544	153,332	780	263	195,509	906	196,415

^aThe TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.

^bData in TRI are maximum amounts released by each facility.

^cPost office state abbreviations are used.

^dNumber of reporting facilities.

^eThe sum of fugitive and point source releases are included in releases to air by a given facility.

^fSurface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).

^gClass I wells, Class II-V wells, and underground injection.

^hResource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.

ⁱStorage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown

^jThe sum of all releases of the chemical to air, land, water, and underground injection wells.

^kTotal amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI05 2007 (Data are from 2005)

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Table 6-3. Releases to the Environment from Facilities that Produce, Process, or Use *p*-Cresol^a

State ^c	RF ^d	Reported amounts released in pounds per year ^b							
		Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	Total release		
							On-site ^j	Off-site ^k	On- and off-site
AR	1	0	No data	0	0	0	0	0	0
IL	2	10	No data	0	5	250	10	255	265
IN	6	19,942	No data	0	0	0	19,942	0	19,942
KY	1	478	No data	0	0	0	478	0	478
LA	3	4,798	0	2,282	0	0	7,080	0	7,080
MO	1	255	No data	0	0	0	255	0	255
MS	1	1,500	No data	0	0	0	1,500	0	1,500
NC	1	3	No data	0	0	0	3	0	3
NJ	1	8	0	0	23	0	31	0	31
NY	1	10	5	0	0	0	15	0	15
OH	1	0	0	0	500	0	0	500	500
OK	1	0	No data	0	0	0	0	0	0
SC	1	16	No data	0	0	0	16	0	16
TN	1	879	No data	0	0	0	879	0	879
TX	5	3,494	249	114,939	138	3	118,751	72	118,823
Total	27	31,393	254	117,221	666	253	148,960	827	149,787

^aThe TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.

^bData in TRI are maximum amounts released by each facility.

^cPost office state abbreviations are used.

^dNumber of reporting facilities.

^eThe sum of fugitive and point source releases are included in releases to air by a given facility.

^fSurface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).

^gClass I wells, Class II-V wells, and underground injection.

^hResource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.

ⁱStorage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown

^jThe sum of all releases of the chemical to air, land, water, and underground injection wells.

^kTotal amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI05 2007 (Data are from 2005)

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Table 6-4. Releases to the Environment from Facilities that Produce, Process, or Use Cresol (Mixed Isomers)^a

State ^c	RF ^d	Reported amounts released in pounds per year ^b							
		Air ^e	Water ^f	UI ^g	Land ^h	Other ⁱ	Total release		On- and off-site
							On-site ^j	Off-site ^k	
AL	7	95,823	24	0	6	0	95,853	0	95,853
AR	4	48,000	44	0	29	0	48,047	26	48,073
CA	11	424	877	0	22	0	1,301	22	1,323
DE	1	3	55,312	0	5	0	55,315	5	55,320
FL	3	47,346	7	0	18	0	47,371	0	47,371
GA	6	101,614	11	0	2	0	101,627	0	101,627
ID	1	30,000	5	0	0	0	30,005	0	30,005
IL	8	1,051	151	0	1,479	253	1,202	1,732	2,934
IN	9	13,914	0	0	193	0	13,914	193	14,107
KS	1	311	0	0	0	0	311	0	311
KY	5	103,854	0	0	0	0	103,854	0	103,854
LA	16	39,749	2,072	0	555	250	41,852	774	42,626
MD	1	35,000	No data	0	0	0	35,000	0	35,000
ME	2	73,719	14	0	1	0	73,734	0	73,734
MI	2	28,073	517	0	2	21,202	28,592	21,202	49,794
MN	1	797	No data	0	12	5	797	17	814
MO	4	510	0	0	0	0	510	0	510
MS	3	68,209	258	0	0	0	68,467	0	68,467
NC	3	41,818	9	0	343	0	41,830	340	42,170
NH	1	2,320	No data	0	0	0	2,320	0	2,320
NJ	3	1,007	14	0	480	0	1,501	0	1,501
NM	2	422	No data	0	0	529	422	529	951
NY	5	5,650	385	0	0	7	6,035	7	6,042
OH	7	557	0	0	752	18	557	770	1,327
OK	2	500	0	0	0	8,669	500	8,669	9,169
OR	1	0	No data	0	0	0	0	0	0
PA	4	9,437	3	2,400	15	3,100	9,450	5,505	14,955
SC	6	76,282	7	2	492	0	76,779	4	76,783
TN	2	21,834	20	0	5	0	21,854	5	21,859
TX	19	57,824	233	241,664	24	2	297,466	2,281	299,747
UT	3	500	500	0	6,000	0	7,000	0	7,000
VA	2	4,602	1	0	531	0	5,133	1	5,134
WA	7	19,905	256	0	6	0	20,167	0	20,167
WI	3	707	No data	0	0	0	707	0	707
WV	1	93	No data	0	0	0	93	0	93

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Table 6-4. Releases to the Environment from Facilities that Produce, Process, or Use Cresol (Mixed Isomers)^a

State ^c	RF ^d	Air ^e	Reported amounts released in pounds per year ^b						
			Water ^f	UI ^g	Land ^h	Other ⁱ	Total release		On- and off-site
							On-site ^j	Off-site ^k	
WY	1	250	No data	0	0	0	250	0	250
Total	157	932,106	60,721	244,066	10,971	34,035	1,239,817	42,082	1,281,899

^aThe TRI data should be used with caution since only certain types of facilities are required to report. This is not an exhaustive list. Data are rounded to nearest whole number.

^bData in TRI are maximum amounts released by each facility.

^cPost office state abbreviations are used.

^dNumber of reporting facilities.

^eThe sum of fugitive and point source releases are included in releases to air by a given facility.

^fSurface water discharges, waste water treatment-(metals only), and publicly owned treatment works (POTWs) (metal and metal compounds).

^gClass I wells, Class II-V wells, and underground injection.

^hResource Conservation and Recovery Act (RCRA) subtitle C landfills; other on-site landfills, land treatment, surface impoundments, other land disposal, other landfills.

ⁱStorage only, solidification/stabilization (metals only), other off-site management, transfers to waste broker for disposal, unknown

^jThe sum of all releases of the chemical to air, land, water, and underground injection wells.

^kTotal amount of chemical transferred off-site, including to POTWs.

RF = reporting facilities; UI = underground injection

Source: TRI05 2007 (Data are from 2005)

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of cresols to the atmosphere are fugitive or accidental emissions during the manufacture, use, transport, and storage of cresols or associated products of the coal tar and petroleum industries.

Low levels of cresols are constantly emitted to the atmosphere in the exhaust from motor vehicle engines using petroleum based-fuels (Fraser et al. 1998; Hampton et al. 1982; Johnson et al. 1989; Seizinger and Dimitriades 1972). Using data collected from 7,060 vehicles entering a tunnel in Southern California, the emission rates (calculated as μg cresol emitted per liter of fuel consumed) of *o*-cresol, and *m/p*-cresol were calculated as 756.6 and 4,449.1 $\mu\text{g/L}$, respectively (Fraser et al. 1998). Cresols have been identified in stack emissions from municipal waste incinerators (Assmuth and Kalevi 1992; James et al. 1984; Jin et al. 1999; Junk and Ford 1980) and in emissions from the incineration of vegetable materials (Liberti et al. 1983). Cresols have also been identified as a component of fly ash from coal combustion (Junk and Ford 1980). Therefore, coal- and petroleum-fueled electricity-generating facilities are likely to emit cresols to the air. The combustion of wood (Hawthorne et al. 1988, 1989; Schauer et al. 2001) and cigarettes (Arrendale et al. 1982; Novotny et al. 1982) also emits cresols to the ambient air. Cresols are also formed in the atmosphere as a result of reactions between toluene and photochemically generated hydroxy radicals (Leone et al. 1985).

6.2.2 Water

Estimated releases of 123 pounds (~0.6 metric tons) of *o*-cresol, 544 pounds (~0.2 metric tons) of *m*-cresol, 254 pounds (~0.1 metric tons) of *p*-cresol, and 60,721 pounds (~28 metric tons) of mixed isomers of cresols to surface water from 23, 28, 27, and 157 domestic manufacturing and processing facilities in 2005, accounted for about 0.06, 0.2, 0.1, and 4.7% of the estimated total environmental releases of *o*-cresol, *m*-cresol, *p*-cresol, and cresol mixed isomer from facilities required to report to the TRI (TRI05 2007), respectively. These releases are summarized in Tables 6-1 through 6-4.

Cresols are widely distributed natural compounds. As discussed above, they are formed as metabolites of microbial activity and are excreted in the urine of humans (Needham et al. 1984) as well as other mammals (Fiege and Bayer 1987). Cresols from human urine are biodegraded at municipal sewage treatment facilities prior to release to ambient waters. However, for combined septic and storm sewage systems, cresols may be released to surface waters during periods of precipitation when influent volumes exceed treatment plant capacities. Also, in rural and suburban areas where septic tanks are used (*o*- and *m*-cresols can resist anaerobic digestion), human excrement may be a nonpoint source release of cresols to groundwater.

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Low levels of cresols are constantly emitted in the exhaust from motor vehicle engines using petroleum-based fuels (Hampton et al. 1982; Johnson et al. 1989; Seizinger and Dimitriades 1972). Therefore, waterways used for transportation and recreation are likely to receive cresols from ship and motorboat traffic. Waste water effluents from coal gasification (Giabbai et al. 1985; Neufeld et al. 1985) and liquefaction facilities (Fedorak and Hrudey 1986), shale oil production sites (Dobson et al. 1985; Hawthorne and Sievers 1984), refineries (Cardwell et al. 1986; Snider and Manning 1982), and a poultry processing plant (Andelman et al. 1984) also may release cresols to surface waters.

In general, cresols will degrade in surface waters very rapidly. However, cresols may persist in groundwater due to a lack of microbes and/or anaerobic conditions. Cresols are largely released to groundwater via landfills and hazardous waste sites. Tables 6-5 through 6-8 include monitoring data for these sources.

Coal liquefaction and other waste water may contain elevated levels of cresols. Effluent from coal gasification facilities contained *o*-cresol at a concentration of 586 mg/L (Fedorak and Hrudey 1986). Waste water effluents from coal gasification facilities contained *p*-cresol at concentrations of 880 mg/L (Neufeld et al. 1985) and 5.12 mg/L (Pellizzari et al. 1979). A coal liquefaction and a shale oil waste water effluent contained *p*-cresol at concentrations of 420 mg/L (Fedorak and Hrudey 1986) and 0.779 mg/L (Pellizzari et al. 1979), respectively. *p*-Cresol was emitted with the waste water of a poultry processing plant at concentrations ranging from 0.00214 to 0.0225 mg/L (Andelman et al. 1984). Waste water effluents from coal gasification facilities contained *m*-cresol at concentrations of 950 mg/L (Neufeld et al. 1985) and 2.67 mg/L (Pellizzari et al. 1979). A coal liquefaction and a shale oil waste water effluent contained *m*-cresol at concentrations of 1,230 mg/L (Fedorak and Hrudey 1986) and 0.561 mg/L (Pellizzari et al. 1979), respectively. Waste water effluents from coal gasification plants located in North Dakota contained *p*- and *m*-cresol at a combined concentration of 1,840 mg/L (Giabbai et al. 1985).

p- and *m*-Cresol were detected at a combined average concentration of 1.0 mg/L for three samples of retort water from a shale oil production facility (Hawthorne and Sievers 1984). *o*-Cresol was detected at an average concentration of 1.1 mg/L for three samples of retort water from a shale oil production facility (Hawthorne and Sievers 1984).

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Table 6-5. Detection of o-Cresol in the Groundwater of Hazardous Waste Sites and Landfills

Type/location	Sampling dates	Number of samples	Number positive	Concentration	Reference
<i>Waste sites, groundwater</i>					
Hazardous waste/ Buffalo, New York	No data	No data	No data	2.3 mg/L	Weber and Matsumoto 1987
Pine tar manufacturing/ Gainesville, Florida	No data	No data	No data	3.08 mg/L	Drinkwater et al. 1986
Wood preserving/ Pensacola, Florida	March 1984	19	6	0.04–7.10 mg/L	Goerlitz et al. 1985
Coal gasification/Hoe Creek, Wyoming	No data	3	3	63–6,600 µg/L	Stuermer et al. 1982
Gas works Park/Seattle, Washington	December 1986	10	2	1–10 µg/L	Turney and Goerlitz 1990
American Creosote Works Facility/ Pensacola, Florida	March 1990	No data	No data	4.2 mg/L	Middaugh et al. 1991
Coal gasification/ Denmark	No data	12	8	10–77 µg/L	Johansen et al. 1997
Samara River/Ukraine (mine water)	1987–1990	No data	No data	1–10 µg/L	Goncharuk and Milyukin 1999
American Creosote Works Facility/ Pensacola, Florida (stream)	March 1990	No data	No data	0.0047 mg/L	Middaugh et al. 1991
Abandoned pine tar manufacturing plant/ Gainesville, Florida	No data	11	11	0.3–5,200 mg/L	McCreary et al. 1983
<i>Effluent water</i>					
American Creosote Works Facility/ Pensacola, Florida (feed water)	March 1990	No data	No data	10.95 mg/L	Middaugh et al. 1991
American Creosote Works Facility/ Pensacola, Florida (permeate water)	March 1990	No data	No data	0.157 mg/L	Middaugh et al. 1991
Industrial effluent/ Managua, Nicaragua	No data	4	1	418 µg/L	Bethune et al. 1996

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Table 6-6. Detection of *m*-Cresol in the Groundwater of Hazardous Waste Sites and Landfills

Type/location	Sampling dates	Number of samples	Number positive	Concentration	Reference
<i>Waste sites, groundwater</i>					
Wood preserving/ Pensacola, Florida	March 1984	19	4	0.05–13.73 mg/L	Goerlitz et al. 1985
<i>Infiltration of waste water, groundwater</i>					
Municipal, secondary/ Port Devens, Massachusetts	No data	2	1	0.02 µg/L	Bedient et al. 1983; Hutchins et al. 1984
Samara River/Ukraine (mine water)	1987–1990	No data	No data	2.5–4 µg/L	Goncharuk and Milyukin 1999
<i>Landfill, Groundwater</i>					
Municipal/Southington, Connecticut	1982–1983	No data	No data	0.6 mg/L	Sawhney and Kozloski 1984
Gas works Park/Seattle, Washington	December 1986	10	1	1.5 mg/L	Turney and Goerlitz 1990
American Creosote Works Facility/ Pensacola, Florida	March 1990	No data	No data	2.5 mg/L	Middaugh et al. 1991
American Creosote Works Facility/ Pensacola, Florida (stream)	March 1990	No data	No data	0.0031 mg/L	Middaugh et al. 1991
American Creosote Works Facility/ Pensacola, Florida (feed water)	March 1990	No data	No data	11.3 mg/L	Middaugh et al. 1991
American Creosote Works Facility/ Pensacola, Florida (permeate water)	March 1990	No data	No data	0.271 mg/L	Middaugh et al. 1991
Industrial effluent/ Managua, Nicaragua	No data	4	1	349 µg/L	Bethune et al. 1996

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Table 6-7. Detection of *p*-Cresol in the Groundwater of Hazardous Waste Sites and Landfills

Type/location	Sampling dates	Number of samples	Number positive	Concentration	Reference
<i>Waste sites, groundwater</i>					
Hazardous waste/ Buffalo, New York	No data	No data	No data	15 mg/L	Weber and Matsumoto 1987
Wood preserving/ Pensacola, Florida	March 1984	19	3	0.02–6.17 mg/L	Goerlitz et al. 1985
Gas Works Park/Seattle, Washington	December 1986	10	2	0.6 and 1.6 mg/L	Turney and Goerlitz 1990
American Creosote Works Facility/ Pensacola, Florida	March 1990	No data	No data	2 mg/L	Middaugh et al. 1991
<i>Landfill, groundwater</i>					
Municipal/Southington, Connecticut	1982–1983	No data	No data	1.5 mg/L	Sawhney and Kozloski 1984
<i>Waste sites/surface water</i>					
American Creosote Works Facility/ Pensacola, Florida (stream)	March 1990	No data	No data	0.0022 mg/L	Middaugh et al. 1991
<i>Effluent water</i>					
American Creosote Works Facility/ Pensacola, Florida (feed water)	March 1990	No data	No data	8.5 mg/L	Middaugh et al. 1991
American Creosote Works Facility/ Pensacola, Florida (permeate water)	March 1990	No data	No data	0.75 mg/L	Middaugh et al. 1991
Industrial effluent/ Managua, Nicaragua	No data	4	2	166 µg/L	Bethune et al. 1996

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Table 6-8. Detection of *p*- and *m*-Cresol in the Groundwater of Hazardous Waste Sites and Landfills

Type/location	Sampling dates	Number of samples	Number positive	Concentration	Reference
<i>Waste sites, groundwater</i>					
Pine tar, manufacturing/ Gainesville, Florida	No data	No data	No data	5.17 mg/L	Drinkwater et al. 1986
Coal gasification/Hoe Creek, Wyoming	No data	3	3	9.6–16.000 µg/L	Stuermer et al. 1982
Abandoned pine tar manufacturing plant/ Gainesville, Florida	No data	11	<0.3	0.3–2,900 µg/L	McCreary et al. 1983
Coal gasification/ Denmark	No data	12	7	5–77 µg/L	Johansen et al. 1997
Landfill leachate/Sweden	No data	3	3	34 µg/L	Oman and Hynning 1993

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6.2.3 Soil

Estimated releases of 270 pounds (~0.1 metric tons) of *o*-cresol, 780 pounds (~0.4 metric tons) of *m*-cresol, 666 pounds (~0.3 metric tons) of *p*-cresol, and 10,971 pounds (~5 metric tons) of mixed isomers of cresol to soils from 23, 28, 27, and 157 domestic manufacturing and processing facilities in 2005, accounted for about 0.1, 0.4, 0.4, and 0.9% of the estimated total environmental releases of *o*-cresol, *m*-cresol, *p*-cresol, and mixed isomers respectively, from facilities required to report to the TRI (TRIO5 2007). An additional 182,006 pounds (~83 metric tons) of *o*-cresol, 153,332 pounds (~70 metric tons) of *m*-cresol, 117,221 pounds (~53 metric tons) of *p*-cresol, and 244,066 pounds (~111 metric tons) of mixed isomers of cresols constituting about 98, 78, 78, and 19% of the total environmental emissions for *o*-cresol, *m*-cresol, *p*-cresol, and mixed isomers respectively, were released via underground injection (TRIO5 2007). These releases are summarized in Tables 6-1 through 6-4.

Cresols can enter soil from the same types of natural sources as described above. In fact, microbial activity may be an important contributor of cresols to soil. Poultry manure reportedly contained *p*-cresol at an average concentration of 11.7 mg/kg (Yasuhara 1987). Consequently, natural cresols are constantly released to soils via excrement, exocellular secretions, and necromass of living and former living organisms, where they are expected to degrade rapidly (Section 6.3.2.3). Also, rural and suburban septic tanks and grazing animals on pasture lands may contribute relatively large amounts of cresols to soil.

Cresols are released to soil at landfills and hazardous waste sites. In general, cresols will degrade in soil very rapidly. However, cresols may persist in soil under anaerobic conditions or due to the toxic effects of high concentrations of cresols or other associated compounds. Tables 6-5 through 6-8 include monitoring data for these sources. The land application of municipal sewage sludges that contain cresols may also release cresols to soil (Demirjian et al. 1984, 1987).

6.3 ENVIRONMENTAL FATE**6.3.1 Transport and Partitioning**

The transport and partitioning of an organic compound in the environment is a function of the physical and chemical properties of that compound and the site-specific characteristics of the environment (e.g., percentage soil organic matter). Based on the environmental correlations with physical properties (Thomas 1982), the physical and chemical properties of the three isomeric cresols are sufficiently similar to indicate that similar transport and partitioning processes will be important for each isomer in the

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environment. Therefore, their potential for partitioning between the various environmental compartments will be discussed collectively.

In the atmosphere, the vapor pressure of the isomeric cresols, 0.11 ± 0.30 mmHg at 25.5 °C (AIChE 1989, 2000; Chao et al. 1983), suggests that these compounds will exist predominantly in the vapor phase (Eisenreich et al. 1981) rather than being bonded to atmospheric particles. This is consistent with experimental studies that found all three isomers in the gas phase of urban air samples, but they were not present in the particulate samples collected at the same time (Cautreels and Van Cauwenberghe 1978) when the droplets are present, gas-phase creosote will predominantly be taken up. The relatively high water solubility of the cresol isomers, 21,520–25,950 mg/L (Yalkowsky et al. 1987), indicates that wet deposition may remove them from the atmosphere. This is confirmed by the detection of cresols in rain water (Section 6.4.2). The short atmospheric residence time expected for the cresols (Section 6.3.2.1) suggests that cresols will not be transported long distances from their initial point of release.

Calculated soil adsorption coefficients (K_{oc}) of 17.5–117 have been determined for the three isomeric cresols, and compare favorably with experimentally determined values ranging from 22 to 158 (Boyd 1982; Koch and Nagel 1988). The estimated values were derived by regression analysis based on the inherent hydrophobicity (octanol/water partition coefficient [K_{ow}]) of an organic compound. For the soils studied in these adsorption studies, this type of regression analysis successfully predicted the potential for the movement of cresols through soil, suggesting high to very high mobility in soil (Swann et al. 1983).

The mobility of the isomeric cresols cannot be adequately described by considering their tendency to partition from water. The hydroxyl function of cresol is capable of forming relatively strong hydrogen bonds with active sites in the soil, and its mobility will depend on the degree in which these bonds are formed (Artiola-Fortuny and Fuller 1982; Boyd 1982; Southworth and Keller 1986). This was the rationale presented to explain large values obtained in laboratory experiments, which obtained K_{oc} values for isomeric cresol ranging from 115 to 3,420 in a study of three different soils (Southworth and Keller 1986). A K_{oc} value near 3,000 would suggest only slight mobility in soil (Swann et al. 1983). The amount of hydrogen bonding to sites in the soil will be strongly influenced by the pH of the surrounding medium, the type of soil, its iron oxide content, anion exchange capacity, and amount of organic matter present. From the literature, one cannot make generalized trends as to which soils provide active bonding sites for the cresol isomers. For example, *m*-cresol adsorbed strongly to a high-clay-content soil (Southworth and Keller 1986), but not to two others (Luh and Baker 1970).

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In water, the isomeric cresols may eventually volatilize to the atmosphere, but volatilization is expected to be a slow process. Based on their Henry's law constants, which range from 1.2×10^{-6} to 8.65×10^{-7} atm·m³/molecule (Gaffney et al. 1987; Hine and Mookerjee 1975), the volatilization half-life from a model river 1 m deep, flowing at 1 m/sec, with a wind velocity of 3 m/sec can be estimated to range from approximately 30 to 41 days (Thomas 1982).

Experimental bioconcentration factors (BCFs) of 14.1 for *o*-cresol (Sabljić 1987) and 19.9 for *m*-cresol (Freitag et al. 1982) indicate that the isomers of cresol will not bioconcentrate in fish and aquatic organisms to any significant extent. Also, cresols are not likely to bioconcentrate in humans. Similar to their behavior in soil, the isomeric cresols are not expected to adsorb to sediment and suspended organic matter, although the potential for this process exists.

6.3.2 Transformation and Degradation

All cresol isomers can be rapidly removed from environmental media. The dominant removal mechanism in air appears to be oxidation by hydroxyl radical during the day and nitrate radical at night, with half-lives on the order of a day. In water under aerobic conditions, biodegradation will be the dominant removal mechanism; half-lives will be on the order of a day to a week. Under anaerobic conditions, biodegradation should still be important, but half-lives should be on the order of weeks to months. In soil under aerobic conditions, biodegradation is also important, with half-lives on the order of a week or less.

6.3.2.1 Air

Cresols degrade rapidly in air. Removal during the day is dominated by the reaction with hydroxyl radical (HO•), while nighttime removal is dominated by the nitrate radical. Reaction with other oxidants in air (e.g., ozone) will be much slower than reactions with hydroxyl or nitrate radical (Atkinson and Carter 1984).

Hydroxyl radicals react with cresols by attacking the carbon bearing the hydroxyl group. Degradation products from this reaction include nitrocresols and products of ring opening such as pyruvic acid, acetaldehyde, formaldehyde, peroxyacetylnitrate, and nitrocresol (Atkinson et al. 1980; Grosjean 1984, 1985). Products may vary, depending on whether the reaction takes place in the gas or particle phase (Grosjean 1984). Second-order rate constants for *o*-, *p*-, and *m*-cresol of 4.0×10^{-11} , 4.4×10^{-11} , and 5.7×10^{-11} cm³ molecule⁻¹ sec⁻¹, respectively, were determined (Atkinson 1985). Using 5×10^5 molecules

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cm³ as an average tropospheric hydroxyl radical concentration (Atkinson 1985) and the reaction rate constants presented above, the atmospheric half-lives for *o*-, *p*-, and *m*-cresol were calculated to be 9.63, 8.75, and 6.76 hours, respectively.

At night, hydroxyl radical concentrations decrease and nitrate radical concentrations increase (Platt et al. 1984), making nitrate radical reactions more important than hydroxyl radical reactions. Nitrate radicals attack cresols by removing the hydroxyl hydrogen, yielding a phenoxy radical. The average second-order rate constants for the reactions of *o*-, *p*-, and *m*-cresol and the nitrate radical are 1.01×10^{-11} , 0.70×10^{-11} , and 1.08×10^{-11} cm³ molecule⁻¹ sec⁻¹, respectively (Atkinson et al. 1984; Carter et al. 1981). The half-lives for these reactions, assuming an average night-time nitrate radical concentration of 2.4×10^8 molecules cm³, are 4.8, 4.5, and 6.9 minutes for *o*-, *m*-, and *p*-cresols, respectively (Atkinson et al. 1984; Carter et al. 1981).

In addition to degradation by hydroxyl and nitrate radicals, all three cresol molecules absorb small amounts of UV light with wavelengths above 290 nm (Sadtler 1960a, 1960b, 1966). Therefore, direct photolysis is also possible; however, the photolysis rate is slow compared to the rate of reaction with atmospheric radicals.

6.3.2.2 Water

Dilute cresols have been tested for biodegradability in numerous screening tests and sewage treatment plant simulation tests, as well as in surface water, groundwater, estuarine water, and sea water. Most tests indicate that the cresol isomers rapidly and completely degrade to simpler molecules under aerobic conditions in fresh water. Degradation is slower in salt water and under anaerobic conditions.

All cresol isomers were found to degrade rapidly in biodegradation screening and sewage treatment plant simulation studies with half-lives between <24 hours and <7 days (Alexander and Lustigman 1966; Babeu and Vaishnav 1987; Baird et al. 1974; Chambers et al. 1963; EPA 1979; Heukelekian and Rand 1955; Ludzack and Ettinger 1960; Lund and Rodriguez 1984; Malaney 1960; Malaney and McKinney 1966; McKinney et al. 1956; Pauli and Franke 1972; Pitter 1976; Tabak et al. 1964; Young et al. 1968). In these studies, degradation was rapid with both acclimated and unacclimated inocula; initial concentrations ranged from 0.5 to >500 ppm. Degradation generally was slower at the higher concentrations; however, under sewage treatment plant conditions, high cresol concentrations can be degraded (e.g., Chudoba et al. [1968] reported >99% removal of starting material [4,448 ppm of *p*-cresol])

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in 3 days under sewage treatment plant conditions). The available screening tests indicate that the cresols are readily degraded by microorganisms and activated sludge.

Very little information is available concerning the differences in the biodegradability of the cresol isomers. Based on the results of one study (Visser et al. 1977), biodegradability of their isomers appears to exist in the order: *p*-cresol > *o*-cresol > *m*-cresol. Aerobic degradation under these conditions appears to be fast, with the initial step being the rate-limiting step. No intermediate products have been reported using grab samples and the inoculum (EPA 1978; Spain and van Veld 1983).

Aerobic biodegradation in salt water (estuarine and sea water) appears to be slower than in fresh water; insufficient information is available to estimate anaerobic degradation in salt water. Factors governing biodegradation of *m*- and *p*-cresol in salt water include spatial and temporal variations (e.g., salinity and temperature) (Bartholomew and Pfaender 1983; Palumbo et al. 1988; Pfaender and Bartholomew 1982a, 1982b; Spain and van Veld 1983; van Veld and Spain 1983), substrate concentration (Palumbo et al. 1988; Spain and van Veld 1983), and the presence or absence of sediment (van Veld and Spain 1983). Almost no information is available for *o*-cresol, although one biological oxygen demand (BOD) test in saline water suggested rapid degradation (Takemoto et al. 1981).

In contrast to aerobic conditions, cresols do not appear to degrade rapidly in anaerobic fresh water sediments, although very little information is available. Horowitz et al. (1982) reported that the cresol isomers in anoxic sediments from Wintergreen Lake in Kalamazoo County, Michigan, had degradation times in excess of 29 weeks. The authors also stated that, as described above for anaerobic sludges, the *m*- and *p*-cresol isomers showed the most degradation, while *o*-cresol resisted degradation.

In anaerobic groundwater samples and groundwater samples with aquifer materials, cresol isomers display the same pattern of degradation *p*-cresol > *m*-cresol > *o*-cresol, where *p*-cresol is the most readily biodegradable of the three isomers, seen in anaerobic sewage sludge experiments. Thomas et al. (1989) reported that *o*-cresol concentrations decreased, then increased, in a groundwater sample from a creosote-contaminated site. The authors suggested that *o*-cresol may be a metabolite of some other chemical present during the multi-component study.

The degradation pathway of *p*-cresol in groundwater appears to proceed by oxidation of the methyl group to first give the corresponding benzaldehyde, then benzoic acid (Kuhn et al. 1988; Smolenski and Suflita

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1987; Suflita et al. 1988, 1989). The hydroxybenzoic acid then can be either decarboxylated or dehydroxylated to phenol or benzoic acid, respectively.

There are no hydrolyzable functional groups on cresol, so hydrolysis is not an important environmental fate process. In addition to biodegradation, chemical oxidation (including by superoxide, singlet oxygen, hydroxyl radical, and organic peroxy radicals) and photolysis may be removal pathways in the environment, but do not appear to be as fast as biodegradation under most conditions. Faust and Holgné (1987) reported that the irradiation of water containing fulvic acid produced a transient oxidant that oxidized *o*- and *p*-cresol. The transient radical was suggested to be an organic peroxy species. Irradiation of water without fulvic acid produced almost no degradation of *p*-cresol in 3 hours; the addition of fulvic acids caused rapid disappearance with half-times of about 50 minutes (EPA 1978). In water from Greifensee (a polluted, eutrophic, pre-alpine Swiss lake) at pH 8, calculated half-lives for the top meter of water (where light of the necessary wavelength is present) are 11 and 4.4 days for *o*- and *p*-cresol, respectively. Singlet oxygen is also produced by solar irradiation on natural waters and can react with cresols. A rate constant of $3.7 \times 10^{-8} \text{ M}^{-1} \text{ sec}^{-1}$ for *p*-cresol reaction with singlet oxygen was produced in the laboratory by irradiation of water containing rose bengal (Scully and Hoigne 1987). Using a singlet oxygen concentration of $4 \times 10^{-14} \text{ M}$ (corresponding to the concentration in water at noon on a summer day), these authors calculated a half-life of 500 hours. EPA (1978) studied the direct photolysis of *p*-cresol in water. In pure water and using solar irradiation in April, EPA (1978) reported half-lives of approximately 35 days.

While the above data indicate that oxidative and photolytic processes occur during degradation of cresols in water, it is difficult to estimate the half-lives for these under environmental conditions. Since environmental waters vary significantly in clarity (and hence, in their ability to transmit light), as well as their concentration of fulvic substances, half-lives are expected to vary considerably. Additionally, the absorbance of cresols changes with the pH of the water (EPA 1978). Thus, the amount of light absorbed at a specific wavelength by cresols will change with pH, as will the degradation rates. EPA (1978) estimated a half-life of *p*-cresol in environmental waters from direct photolysis of 300–400 days under summer light conditions. This, with the other estimates presented above, suggests that chemical oxidation from light-produced radicals and direct photolysis will not be a significant removal mechanism under most environmental conditions.

In addition to oxidants generated by light, Stone (1987) reported that ferric iron [Fe(III)] and manganese [Mn(III/IV)] oxides are capable of oxidizing *p*-cresol. Fe(III) and Mn(III/IV) oxides are common species

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found in surface water particulate and soils, as well as in dust and ash. Rate constants for *p*-cresol ranged from 10^{-9} to 10^{-6} mol/L-min for pH of 7.8–4.2, respectively. In the environment and at low pH values, these species may oxidize cresols with half-lives on the order of several hours.

6.3.2.3 Sediment and Soil

Cresol degradation in soil has been reported by Medvedev and Davidov (1981a, 1981b), Namkoong et al. (1988), and Dobbins and Pfaender (1988). Dobbins and Pfaender (1988) and Namkoong et al. (1988) found that the data for cresol degradation fit first-order kinetics, but with very different rates. Dobbins and Pfaender (1988) found that CO₂ from *m*-cresol degradation evolved slowly when *m*-cresol was incubated in water slurries of surface and subsurface soils from a pristine location. Degradation was followed by trapping radioactive carbon dioxide, and overall mass balances were performed by comparing radioactivity remaining in the soil with the trapped CO₂. In surface soils, first-order rate constants based on CO₂ evolution were 7.55×10^{-5} – 6.31×10^{-4} hour⁻¹, which yields half-lives from 46 days to about 1 year.

By contrast, Namkoong et al. (1988) reported a rapid degradation of all cresol isomers in surface soils from an uncultivated grassland site. Degradation was followed by analyzing for the parent substance, and first-order kinetics were followed. *o*-Cresol reportedly had a half-life of about 1.6 days, while *p*-cresol degraded too fast to allow measurement of a rate constant. *m*-Cresol reportedly had a half-life of about 0.6 days. Medvedev and Davidov (1981a, 1981b) reported the same relative rates for the three isomers in a soil from the Soviet Union but did not report absolute rates. Times to disappearance in the soil were reportedly 16, 9, and 27 days for *o*-, *p*-, and *m*-cresol, respectively. These authors were unable to detect any secondary products from cresol metabolism. The differences in the rates reported by Namkoong et al. (1988) and Dobbins and Pfaender (1988) appear to be the result of the different analytical methods used. Namkoong et al. (1988) used gas chromatography to determine the rate of cresol disappearance, while Dobbins and Pfaender (1988) used CO₂ evolution to determine the rate of carbon dioxide appearance. Thus, based on the available information, cresols degrade rapidly in soils, possibly becoming incorporated into soil microorganisms, but they mineralize slowly. Indeed, Dobbins and Pfaender (1988) noted that significant amounts of radioactivity were bound to the soil, which supports the explanation that cresols or cresol metabolites are incorporated.

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6.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

Reliable evaluation of the potential for human exposure to cresols depends in part on the reliability of supporting analytical data from environmental samples and biological specimens. Concentrations of cresols in unpolluted atmospheres and in pristine surface waters are often so low as to be near the limits of current analytical methods. In reviewing data on cresol 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. The analytical methods available for monitoring cresols in a variety of environmental media are detailed in Chapter 7.

6.4.1 Air

Monitoring data have not shown cresols to be widely occurring atmospheric pollutants. A national emissions study conducted from 1990 to 1998 reported an estimated ambient concentration average of 31.7 ng/m³ (EPA 2000d). In an analysis of contaminants of the air in southern California in August 1987, background levels of *p*-cresol and *o*-cresol were found in concentrations of 0.02–0.07 and 0.09–0.30 ppb (Harley and Cass 1994). The National Ambient Volatile Organic Compounds (VOCs) Database, a compilation of published and unpublished air monitoring data from 1970 to 1987, contained very little information on the cresols (EPA 1988e). The database contained only information for *o*-cresol in source-dominated atmospheres (air surrounding a facility or known release of the chemical in question). The median air concentration of *o*-cresol at source-dominated sites is 1.62 µg/m³ for 32 samples (EPA 1988e). The median atmospheric concentration of *o*-cresol (10 samples collected at three unspecified sites in the United States) was 1.5 µg/m³, a range of 0.5–20 µg/m³ was reported for *p*-cresol (62 samples collected at 11 unspecified sites in the United States), and *m*-cresol was not detected in any of the three samples studied (Kelly et al. 1994). On September 8–9, 1993, 46.77 and 90.53 ng/m³ of *o*-cresol and a mixture of *p*- and *m*-cresol, respectively, were detected in vapor-phase semivolatile organics over Southern California during a major photochemical smog event (Fraser et al. 1998). Cresol was detected in the ambient air of Upland, California; however, specific isomers were not identified (Kolber et al. 1981).

All three isomers of cresol have been identified, but not quantified, in gas samples taken from various municipal landfills in southern Finland (Assmuth and Kalevi 1992). In coal gas effluent, *p*- and *m*-cresol were found in concentrations of 11.6 and 7.09 mg/L, respectively (Jin et al. 1999). *p*-Cresol was detected in the emissions at waste incineration plants in Germany at a concentration of 0.43 µg/m³ (Jay and Stieglitz 1995). *p*-Cresol was identified in the air adjacent to municipal incinerators, waste collection

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centers, and sewage treatment plants around Southampton, England in concentrations ranging from <0.1 to 24.5 $\mu\text{g}/\text{m}^3$ (Leach et al. 1999).

In a study of air emissions from burning pine, oak, and eucalyptus, *o*-cresol was detected in the gas phase for all three samples at concentrations of 89.6, 47.7, and 37.8 mg/kg wood burned, respectively, and in the particle phase of oak and eucalyptus at concentrations of 0.018 and 0.006 mg/kg wood burned, respectively. A mixture of *p*- and *m*-cresol was detected in the gas phase for pine, oak, and eucalyptus in concentrations of 380, 179, and 110 mg/kg wood burned, respectively, and in the particle phase of all three wood types at concentrations of 0.5, 0.21, and 0.055 mg/kg wood burned, respectively (Schauer et al. 2001).

The absence of data does not necessarily indicate a lack of cresol emissions into ambient air. In general, cresols are highly reactive with hydroxyl and nitrate radicals in the day and night, respectively, and atmospheric half-lives for cresols are short. Scavenging by water may further reduce the atmospheric residence time of cresols (see Section 6.3.2.1).

6.4.2 Water

In a national study of organic contaminants in 139 U.S. streams located in 30 states from 1999 to 2000, *p*-cresol was detected in 24.7% of the samples taken with a maximum concentration of 0.54 $\mu\text{g}/\text{L}$ and a mean concentration of 0.05 $\mu\text{g}/\text{L}$ (Kolpin et al. 2002). In a study of public groundwater at superfund sites, *o*-cresol and *p*-cresol were detected with maximum concentrations of 390 and 150 $\mu\text{g}/\text{L}$, respectively; however, neither was detected in well fields or finished water from treatment plants (Canter and Sabatini 1994).

o-Cresol was detected in fresh water samples from Spirit Lake, Washington, on August 7, 1980 and from South Fork Castle Lake and Smith Creek, Washington, on September 11, 1980 at unreported concentrations (McKnight et al. 1982). The presence of cresols attributed to the Mount St. Helens eruption on May 18, 1980 was most likely a result of incomplete combustion of plant materials (McKnight et al. 1982). Whether or not the cresols originated from wood fires or the actual eruption was not clarified.

p-Cresol was detected in surface water with a frequency of occurrence of 1.5% and with a geometric mean concentration of 11 $\mu\text{g}/\text{L}$ for positive samples (CLPSD 1988). *p*-Cresol was identified as a

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contaminant of mixed water and sediment samples from the Tennessee River (Gordon and Goodley 1971) at a concentration of 200 µg/L (Goodley and Gordon 1976). *p*-Cresol also was detected in fresh water samples from Spirit Lake, Washington, on August 7, 1980 at unreported concentrations (McKnight et al. 1982).

m-Cresol was detected with a frequency of occurrence of 0.9% in surface water (CLPSD 1988). In addition, *m*-cresol was listed as a contaminant of the St. Joseph River in the Lake Michigan Basin (Great Lakes Water Quality Board 1983). *m*-Cresol was detected in fresh water samples from Spirit Lake, Washington, on August 7, 1980 at unreported concentrations (McKnight et al. 1982).

Industrial effluents are a source of groundwater exposure to cresols. While human exposure to these waters is unlikely, it is important to note these releases to groundwater. Unspecified isomers of cresol were detected from one of seven sample sites along the Delaware River at a concentration of 20 µg/L. This was a result of industrial waste water effluent discharged by the Philadelphia Northeast Sewage Treatment Plant, which discharges secondary effluent into the river (Hites 1979; Sheldon and Hites 1979). For Delaware River water from August 1976 to March 1977, the summer and winter average concentrations of unspecified isomers of cresols that were not traceable to any source were "not detected" and 2 µg/L, respectively; this suggested that rapid biodegradation prevents cresol detection during the warmer months (Sheldon and Hites 1978).

Tables 6-5 through 6-8 summarize the literature data on cresols found in groundwater and their respective anthropogenic sources.

Rain water at Portland, Oregon, contained *o*-cresol at concentrations ranging from 0.240 to 2.80 µg/L, with an average concentration of 1.02 µg/L for seven rainfalls between February 12, 1984 and April 12, 1984. In addition to this study, combined *p*- and *m*-cresol was detected in rain in Portland, Oregon at concentrations >1.1 µg/L (Grosjean 1991). Combined *p*- and *m*-cresol concentrations ranged from 0.380 to 2.00 µg/L, with an average concentration of >1.10 µg/L (Leuenberger et al. 1985). *o*-Cresol was detected in rain water from a rural site (Grepden, Switzerland) on April 3, 1986, at concentrations ranging from not detected to 1.3 µg/L. Combined *p*- and *m*-cresol concentrations ranged from 0.65 to 9.3 µg/L (Czuczwa et al. 1987). Combined *p*- and *m*-cresol were detected in rain and cloud water in Vosges Mountains in France at concentrations ranging from 0.47 to 2.23 µg/L (Levsen et al. 1993). *p*- and *m*-Cresol were also detected in concentrations ranging from 0.6 to 3.6 µg/L in cloud water samples taken from Mt. Brocken in Germany during June 1994 (Luttke et al. 1999). *p*-Cresol was found

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in snow samples from Finland, Moscow, and Siberia at concentrations 0.04, 0.004–0.06, and 0.29 µg/kg (Poliakova et al. 2000). *o*-Cresol was found in snow samples from Finland and Moscow in concentration of 0.07 and 0.03 µg/kg, respectively (Poliakova et al. 2000).

Cresols are formed when various aromatic compounds are metabolized. Therefore, cresols are expected to be in municipal waste water. *p*-Cresol was detected in five of nine municipal waste water plants in western Virginia with concentrations ranging from 0.18 to 0.86 µg/sample (Dietrich et al. 1993).

The absence of monitoring data does not necessarily indicate a lack of cresols in the environment. Cresols are widely occurring natural and anthropogenic products. However, biodegradation is probably the dominant mechanism responsible for the rapid removal of cresols from surface waters (see Section 6.3.2.2). Nevertheless, cresols may persist in extremely oligotrophic waters, in waters with limited microbial communities, and/or under anaerobic conditions such as in some sediments and groundwater aquifers.

6.4.3 Sediment and Soil

o-Cresol was detected in 3.7% of the soil samples in the Contract Laboratory Program Statistical Database (CLPSD) (CLPSD 1988). *p*- and *m*-Cresol were also detected with frequencies of occurrence of 4.4 and 0.9%, and geometric mean concentrations of 257 and 1,105 µg/kg for the positive samples, respectively (CLPSD 1988). *o*-Cresol was detected at maximum concentrations of 12,000, 21,000, 34,000, and 55,000 µg/kg in the soil of an abandoned pine tar manufacturing plant in Gainesville, Florida at four separate sites (McCreary et al. 1983).

Cresols are an excretory product of mammals and an intermediate biotransformation product of natural aromatics such as lignin constituents (Fiege and Bayer 1987). Soil microorganisms are capable of metabolizing cresols, and any anthropogenic release of cresol, other than massive spills, is likely to be rapidly degraded in soil (Section 6.3.2.3).

Cresols have been detected in various sediment samples. In Roane County, Tennessee, *p*-cresol was detected in two sediment samples at concentrations of 1,233 and 127 ppb. In a study of streambed sediment in 20 major river basins of the United States from 1992 to 1995, *p*-cresol was identified in 37.8% of the sites with a maximum value of 4,800 µg/kg dry weight; however, 90% of the positive samples contained ≤430 µg/kg dry weight (Lopes and Furlong 2001). *o*- and *p*-Cresol were identified, but not

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quantified, in sediment samples obtained from the Elbe River of the German Bight (Schwarzbauer et al. 2000).

6.4.4 Other Environmental Media

As discussed above, cresols are widely distributed natural compounds. They are formed as metabolites of microbial activity and are excreted in the urine of animals. Various plant lipid constituents, including many oils, contain cresols. Cresols have also been detected in certain foods and beverages such as tomatoes, tomato ketchup, cooked asparagus, various cheeses, butter, oil, red wine, distilled spirits, raw and roasted coffee, black tea, smoked foods, tobacco, and tobacco smoke (Fiege and Bayer 1987). However, very few monitoring data for cresols in food were found in the literature. *p*-Cresol has been detected in fermented soybean curds at concentrations ranging from 52.0 to 67.3 µg/kg (Chung 1999) and *o*-cresol has been detected in big eyed herring fermented fish at a mean concentration of 18.6 µg/kg (Cha and Cadwallader 1995).

Both *o*-cresol and *p*-cresol have been detected in eggs of birds of the Selenga river estuary in Lake Baikal, Russia, one of the largest fresh natural water sources in the world. Concentrations ranged from 208 to <10 µg/kg dry weight and from 540 to <10 µg/kg dry weight for *o*- and *p*-cresol, respectively (Lebedev et al. 1998).

All three cresol isomers were identified as volatile emissions of fried bacon (Ho et al. 1983). Various brands of Scotch whiskey, whiskeys made outside of Scotland, cognac, armagnac, brandy other than cognac and armagnac, and white and dark rums contained cresol at concentrations of 0.01–0.20 ppm, 0.01–0.07 ppm, trace to 0.02 ppm, trace to 0.02 ppm, trace to 0.02 ppm, and trace to 0.20 ppm, respectively (Lehtonen 1983).

Cresols are emitted in cigarette smoke. The total concentration of *o*-cresol and combined *m*-cresol and *p*-cresol in cigarette smoke was reported to range from approximately 14 to 26 µg/cigarette and from 41 to 82 µg/cigarette, respectively (Wynder and Hoffmann 1967). Depending upon the rate of ventilation, *o*-cresol was detected in cigarette smoke at levels of 7.1–37 µg/cigarette, while combined *m*-cresol and *p*-cresol isomers were emitted at a rate of 12.3–68 µg/cigarette (Singer et al. 2002). The average cresol concentration in a 45 cubic meter chamber after six cigarettes had been smoked ranged from 0.17 to 3.9 µg/m³ depending on the brand and type of cigarette (Nelson et al. 1998). In another study, *o*-, *m*-, and *p*-cresol were emitted from mainstream cigarette smoke at mean rates of 3.31, 2.55, and 6.36 µg/cigarette,

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respectively (Rustemeier et al. 2002). Under steady-state conditions in a furnished 50 cubic meter room, the exposure relevant emission factors (EREFs) of *o*-, *m*-, and *p*-cresol were 22–41, 16–35, and 32–72 µg/cigarette, respectively, depending upon the ventilation of the building (Singer et al. 2003). These EREFs measure not only the initial exposure to environmental tobacco smoke, but also the potential for exposure from the re-emission of chemicals from absorbing surfaces such as wallboard, carpeting, and other room furnishings.

6.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

Inhalation exposure is likely to be the most common route of exposure for the general population to cresols. However, since cresols have a short residence time in both day- and night-time air; atmospheric levels are probably low despite their ubiquitous nature.

Cresols have been identified as components of automobile exhaust (Hampton et al. 1982; Johnson et al. 1989; Seizinger and Dimitriadis 1972), and may volatilize from gasoline and diesel fuels used to power motor vehicles. Vehicular traffic in urban and suburban settings provides a constant source of cresols to the atmosphere. Hence, urban and suburban populations may be constantly exposed to atmospheric cresols. Cresols are also emitted to ambient air during the combustion of coal (Junk and Ford 1980), wood (Hawthorne et al. 1988, 1989), municipal solid waste (James et al. 1984; Junk and Ford 1980), and cigarettes (Arrendale et al. 1982; Novotny et al. 1982). Therefore, residents near coal- and petroleum-fueled electricity-generating facilities, municipal solid waste incinerators, and industries with conventional furnace operations or large-scale incinerators may be exposed to cresols in air. People in residential areas where homes are heated with coal, oil, or wood may also be exposed to cresols in air.

Exposure to cresol may occur in atmospheres containing toluene. Cresols are formed in the atmosphere during photochemical reactions between toluene and photochemically generated hydroxy radicals (Leone et al. 1985).

Cigarette smoke is also a source of cresol exposure. One estimate indicated that an individual who smokes two packs of cigarettes a day may inhale 3 µg/day of total cresol (Wynder and Hoffmann 1967). Other estimates are somewhat higher; for instance, Nazaroff and Singer (2004) estimated that nonsmokers who live with a person who smokes nine cigarettes/day may inhale 2–5 µg/day of cresols through inhalation of second-hand smoke.

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Ingestion of certain foods may be as prevalent or more prevalent a route of exposure than inhalation. However, more quantitative data on the occurrence of cresols in food would be required to make a comparison. Cresols have been detected in tomatoes and tomato ketchup, cooked asparagus, various cheeses, butter, and oil (Fiege and Bayer 1987). Beverages such as red wine and distilled spirits (Lehtonen 1983), raw and roasted coffee, and black tea contain cresols (Fiege and Bayer 1987). Fried (Ho et al. 1983), smoked, and barbecued foods also may contain cresols (Fiege and Bayer 1987). For people with groundwater wells near landfills or hazardous waste sites, drinking water may be an important source of exposure; individuals living near hazardous waste sites or cresol production facilities may also be exposed. Quantitative information for both foods and drinking water was lacking, and the respective average daily intakes were not calculated.

Dermal contact to cresols may occur during recreational activities at natural waterways containing either naturally or anthropogenically generated cresols. However, cresols are expected to degrade rapidly in surface water and this is not likely to be a major source of exposure.

According to the National Occupational Exposure Survey (NOES) conducted by NIOSH in the workplace between 1981 and 1983, 10,985 (483 are female), 21,313 (16,798 are female), 5,615 (1,174 are female), and 132,742 (28,184 are female) workers were potentially exposed to *o*-, *p*-, *m*-, and the mixture of isomers, respectively (NIOSH 1989). The NOES database does not contain information on the frequency, concentration, or duration of exposure of workers to any of the chemicals listed therein. These surveys provide estimates of the number of workers potentially exposed to the chemicals in the workplace. The most probable routes of occupational exposure are inhalation and dermal contact at places where cresols and/or cresol-containing compounds are produced or used.

Very little information pertaining to occupational exposure to cresols was located in the literature. Occupational exposure to cresols has been documented in laboratories and coal gasification facilities (Needham et al. 1984), during paint and varnish application (Angerer and Wulf 1985), during application of insulation lacquers to copper wires, and in wood-preserving facilities (Nieminen and Heikkila 1986). During the creosote impregnation of wood, workers were exposed to cresol concentrations $<0.1 \text{ mg/m}^3$ (Heikkila et al. 1987). Workers of a bench scale coal conversion process were exposed to atmospheric levels of cresols $<0.1 \text{ ppm}$ in 1981 and 1982 (Dreibelbis et al. 1985).

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6.6 EXPOSURES OF CHILDREN

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

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

No data regarding environmental cresol exposure in children were found. No reports or studies of cresol in baby food or breast milk were found. The most likely route of exposure to cresols for children is through inhalation of ambient air. Children who live in areas of high traffic or with adults who smoke are more likely to be exposed to cresols through inhalation.

6.7 POPULATIONS WITH POTENTIALLY HIGH EXPOSURES

High levels of exposure to cresols are most likely to occur in occupational settings where cresols are either produced or used. Intake by inhalation or dermal contact is the most probable route of high exposure to cresols. Cigarette smokers or persons who reside with smokers are likely to be exposed to higher amounts of cresols than the nonsmoking general population

People who work at manufacturing facilities that process coal or coal tar may have an increased risk for cresol exposure. In a study of 76 male workers aged 22–58 years of age employed at a coke plant in Poland, slightly elevated levels of *o*-cresol and *m/p*-cresol were detected in the urine of employees when compared to a group of 34 nonoccupationally exposed individuals (Bieniek 1997). The concentrations of *o*-cresol and *m/p*-cresol in the urine of subjects working in the high temperature tar distillation process were 0.54 and 18.14 mg/L, respectively, while the nonexposed control group had levels of 0.041 and 14.38 mg/L for *o*-cresol and *m/p*-cresol, respectively (Bieniek 1997). The time-weighted geometric mean concentrations of *o*-cresol and *m/p*-cresol in the breathing zone at the plant were reported as 0.09 and 0.13 mg/m³, respectively (Bieniek 1997).

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Workers at gas stations, or those involved in distillation of crude tar, oil, and other plants that produce cresols as side-products are likely to have increased exposure to cresols. However, there are no monitoring data to give the exact exposure.

Cresols are metabolites of other aromatic compounds. *o*-Cresol is a metabolite of toluene and therefore, exposure to toluene may increase exposure to *o*-cresol. Toluene is a major component of glue. In a Japanese study, people who sniffed glue as a form of intoxication had a mean value of 7.31 mg *o*-cresol/g creatinine in their urine as opposed to 0.095 and 0.016 mg *o*-cresol/g creatinine for industrial workers and those who did not sniff glue (Yamazaki et al. 1992). Workers who were occupationally exposed to toluene at a median concentration of 284.4 mg/m³ in workplace air had a median urinary *o*-cresol level of 2.1 mg/g creatinine (Angerer and Kramer 1997). Workers at a rotogravure printing plant, who were exposed to toluene at levels ranging from 8 to 496 mg/m³ in workplace air, had mean *o*-cresol urinary excretion levels ranging from 0.080 to 2.37 mmol *o*-cresol/mol creatinine (0.076–2.26 mg *o*-cresol/g creatinine) (Nise 1992). These *o*-cresol excretory levels were correlated with toluene exposure levels and smoking habits of the employees.

6.8 ADEQUACY OF THE DATABASE

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

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

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6.8.1 Identification of Data Needs

Physical and Chemical Properties. The physical and chemical properties necessary to estimate the fate and transport of cresols in the environment have been described for all isomers (AIChE 1989, 2000; Amore and Hautala 1983; Artiola-Fortuny and Fuller 1982; Boyd 1982; Chao et al. 1983; Freitag et al. 1985; Gaffney et al. 1987; Hansch and Leo 1985; Hine and Mookerjee 1975; Lewis 2001; Lide 2005; Riddick et al. 1986; Verschueren 1983; Windholz et al. 1983; Yalkowsky et al. 1987). Knowledge of some of these properties was required to describe the fate and transport of cresols because adequate experimental data were not available. The database was sufficient to perform the necessary estimates (Thomas 1982).

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 substance release and off-site transfer information to the EPA. The TRI, which contains this information for 2005, became available in May of 2007. This database is updated yearly and should provide a list of industrial production facilities and emissions.

Current production volumes and demand for cresolics are available (CMR 2004; USITC 2006), as are historical and predictive production volume information (CMR 2004; USITC 2006). Information on the uses of cresols is available, including the use as a chemical intermediate and wood preservative. Information on the release of cresols to the environment (Andelman et al. 1984; Arrendale et al. 1982; Cardwell et al. 1986; Dobson et al. 1985; Fedorak and Hrudey 1986; Giabbai et al. 1985; Hampton et al. 1982; Hawthorne and Sievers 1984; Hawthorne et al. 1988, 1989; James et al. 1984; Johnson et al. 1989; Junk and Ford 1980; Leone et al. 1985; Liberti et al. 1983; Neufeld et al. 1985; Novotny et al. 1982; Pellizzari et al. 1979; Seizinger and Dimitriadis 1972; Snider and Manning 1982) from manufacturing, production, and use (TRI05 2007) and to the workplace, as well as their presence in foods and other natural sources, is available (Fiege and Bayer 1987; McKnight et al. 1982; Needham et al. 1984). Disposal methods are also well described.

Environmental Fate. Information concerning the partitioning of cresols in the environment is available; cresols occur in all environmental media. Information on the transport of cresols in environmental media is also available; however, the confounding influence of pH on soil transport makes assessing soil leaching difficult. An extensive database is available describing the aerobic (Alexander and Lustigman 1966; Babeu and Vaishnav 1987; Baird et al. 1974; Chambers et al. 1963; EPA 1979;

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Heukelekian and Rand 1955; Ludzack and Ettinger 1960; Lund and Rodriguez 1984; Malaney 1960; Malaney and McKinney 1966; McKinney et al. 1956; Pauli and Franke 1972; Pitter 1976; Tabak et al. 1964; Young et al. 1968) and anaerobic (Battersby and Wilson 1988, 1989; Boyd et al. 1983; EPA 1981; Fedorak and Hrudey 1984; Horowitz et al. 1982; Wang et al. 1988, 1989) degradation of cresols in water. Data exist regarding the biodegradation of cresols in soils (Dobbins and Pfaender 1988; Medvedev and Davidov 1981a, 1981b; Namkoong et al. 1988). The atmospheric fate of cresol isomers is well described and suggests that cresols are rapidly degraded in air (Atkinson 1985; Atkinson et al. 1980, 1984; Carter et al. 1981; Grosjean 1984, 1985; Platt et al. 1984). No data needs are identified at this time.

Bioavailability from Environmental Media. Case reports of people who have experienced cresol poisoning following oral and dermal exposure indicate that all cresols can be absorbed by these routes (Cason 1959; Chan et al. 1971; Green 1975). However, no information is available regarding oral or dermal absorption of cresols in water and soil matrices, or plant material. Studies in animals have shown that cresols can be absorbed from contaminated air by inhalation but have not attempted to quantify this absorption. Studies of absorption of cresols from air, water, soil, and plant material are required to determine the rate and extent of absorption from each of these media and comparison of the potential hazard posed by cresols contained in each.

Food Chain Bioaccumulation. Few data are available describing the food chain bioaccumulation of cresols. The available experimental data (Freitag et al. 1985) are consistent with estimated values obtained from regression equations which suggest that it will not bioconcentrate to any significant extent (Thomas 1982). Information concerning the potential for biomagnification has not been described, although the log K_{ow} values are small and biomagnification is expected to be insignificant. Therefore, no data needs exist at this time.

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

Cresol levels in groundwater (Bedient et al. 1983; Drinkwater et al. 1986; Goerlitz et al. 1985; Oliveira and Sitar 1985; Sawhney and Kozloski 1984; Stuermer et al. 1982; Weber and Matsumoto 1987) and surface water (CLPSD 1988; Great Lakes Water Quality Board 1983; Kolpin et al. 2002) are available. Data exist regarding the level of cresols in atmospheric samples including rain water and clouds (Fraser et

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al. 1998; Grosjean 1991; Kelly et al. 1994; Leuenberger et al. 1985; Levsen et al. 1993; Luttko et al. 1999). Cresols have infrequently been identified in foods (Chung 1999; Fiege and Bayer 1987), as well as in soil and sediment samples (Lopes and Furlong 2001; McCreary et al. 1983). Continued monitoring data in air, water, soil, and foods is necessary in order to assess the potential for human exposure from environmental media. Of particular value would be more quantitative data on the cresol levels in various foods.

Exposure Levels in Humans. Cresols are naturally occurring substances that are widely distributed in the environment. Humans excrete, on average, 87 mg of *p*-cresol per day in urine (Fiege and Bayer 1987). Cresols may also be present as a result of the metabolic breakdown of other organic compounds, such as toluene (Needham et al. 1984). As such, positive detections of cresols in human biological samples do not necessarily indicate exposure solely to cresol. Information concerning the number of persons potentially exposed to cresols near waste sites and manufacturing, production, and use facilities, however, is not available. High production and widespread use make the potential for human exposure high. A data need exists to rigorously establish cresol exposure levels in humans. There are insufficient data regarding body burden of cresol, partially due to the rapid metabolism and lack of bioaccumulation.

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

Exposures of Children. There are limited, if any, data relating to exposures of children to cresols. Some of the factors that would increase the risk of children exposure include living with a smoker, and living near gas stations, heavy traffic areas, and companies that use and/or produce cresol. A data need exists to establish cresol exposure in children.

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

Exposure Registries. No exposure registries for cresols were located. This substance is not currently one of the compounds for which a sub-registry has been established in the National Exposure Registry. The substance will be considered in the future when chemical selection is made for sub-registries 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.

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6.8.2 Ongoing Studies

The Federal Research in Progress (FEDRIP 2008) database provided no additional information of ongoing studies that may fill in some of the data needs identified in Section 6.8.1.

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7. ANALYTICAL METHODS

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

7.1 BIOLOGICAL MATERIALS

Numerous methods for the determination of *o*-, *m*-, and *p*-cresol in urine have appeared in the literature. *o*-Cresol in urine is often measured to determine exposure to toluene or other aromatic compounds, of which cresol is a metabolite (DeRosa et al. 1987). The analytical methods summarized in Table 7-1 are sufficiently sensitive to detect the individual isomers of cresol at a concentration that may cause concern for human health. Humans normally excrete 16–29 mg of *p*-cresol daily as a result of the breakdown of tyrosine (Needham et al. 1984).

The isomers of cresol are excreted in the urine as their glucuronides and sulfates (Bieniek and Wilczok 1986). To analyze for cresols directly, they must first be separated from the biological carrier. This is usually accomplished by heating a urine sample with a concentrated mineral acid for 30 minutes to 1 hour (Angerer and Wulf 1985; DeRosa et al. 1987; Needham et al. 1984; Yoshikawa et al. 1986). The transfer of cresol from the aqueous hydrolysate to an organic solvent is accomplished by simple extraction with a volatile organic solvent such as methylene chloride or ethyl ether. Concentration of the extract by gentle removal of the solvent prepares the sample for the analysis stage.

The amount of cresol in the concentrated extract can then be determined by high performance liquid chromatography (HPLC) (DeRosa et al. 1987; Yoshikawa et al. 1986) or gas chromatography (GC) coupled to either a flame ionization detector (FID) or a mass spectrometer detection system (Angerer and Wulf 1985; Needham et al. 1984). Separation of the cresol isomers by GC is readily accomplished, and the use of an appropriate internal standard allows the determination of their concentrations. Although

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Table 7-1. Analytical Methods for Determining Cresols in Biological Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference	Isomer
Blood	Acidification with HCl followed by centrifugation at 3,000 rpm, filter to isolate free cresol	GC/MS	0.14 µg/mL	95.4	De Smet et al. 1998	<i>p</i>
Blood	Deprotonization with 2 mL acetonitrile, vortex, centrifugation at 1,000 rpm	GC/MS	0.016 µg/mL	>95	Boatto et al. 2004	<i>o</i>
Urine	Hydrolyze with sulfuric acid; extract with ethyl acetate	GC/FID	No data	78–97	Needham et al. 1984	<i>o, m, p</i>
Urine	Hydrolyze with HCl extract with isopropyl ether; remove solvent; dissolve residue in water; add B-cyclodextrin	HPLC/UV	1 ppm	97–102	Yoshikawa et al. 1986	<i>o, m, p</i>
Urine	Acidify; steam distill; extract with methylene chloride	GC/MS	No data	No data	Angerer and Wulf 1985	<i>o</i>
Urine	Hydrolyze with sulfuric acid; extract with CH ₂ Cl ₂ ; concentrate	HPLC/UV	No data	No data	DeRosa et al. 1987	<i>o</i>
Urine	Collect sample with thymol; hydrolyze with HCl; extract with ethyl ether	GC/FID	2 µg/mL	94%	NIOSH 1994b	<i>o</i>
Expired air	Breath collected in Teflon bag; concentration on Tenax GC adsorbent; thermal desorption	GC/MS	No data	No data	Krotoszynski and O'Neill 1982	Not specified

FID = flame ionization detector; GC = gas chromatography; HPLC = high performance liquid chromatography; MS = mass spectrometry; UV = ultraviolet spectroscopy

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exact detection limits were not given for the above GC methods, a concentration of 10 ppm appears to be readily determined.

Reversed-phase chromatography columns have been used for the analysis of cresols with limited success. A reversed-phase support has been developed that allows complete separation of the three cresol isomers (Bassler and Hartwick 1989). Inclusion complexes of the cresols with β -cyclodextrin cleanly separate the three isomers on commercially available columns (Yoshikawa et al. 1986). Detection limits down to 1 ppm can be obtained by this method.

In cases involving acute cresol poisoning, cresol levels in biological tissues or blood levels are occasionally determined (Boatto et al. 2004). Methods have been described that can determine the level of free (nonprotein bound) *p*-cresol (De Smet et al. 1998) and *o*-cresol (Boatto et al. 2004) in blood. These methods typically involve hydrolysis with hydrochloric acid or acetonitrile to separate cresol from proteins followed by centrifugation, solvent extraction, and analysis by GC/mass spectrometry (MS).

The detection of cresol in the expired air of humans has been accomplished by techniques used routinely for the analysis of other organic compounds in this sample matrix (Krotoszynski and O'Neill 1982). In this technique, the subject's breath is collected in a bag made of inert material. The sample is then concentrated by pumping the expired air through a sorbent tube that collects the organic compounds. The organics are liberated from the adsorbent tube by thermal desorption, which flushes the components of the mixture directly onto a GC. The amount of each cresol isomer is quantified by comparison of the signal strength to that of a suitable internal standard using a FID, and identification is accomplished by interpretation of the data provided by a mass spectrometer. No detection limits were given for this method.

7.2 ENVIRONMENTAL SAMPLES

Methods for determining cresols in environmental media are summarized in Table 7-2. Procedures for the determination of *o*- and *p*-cresol in water, soil, and sediment samples at hazardous waste sites are outlined by EPA (2005a). The required quantitation limits for each of the isomeric cresols are 10 ppb for water samples and 330 ppb for soil and sediment samples in this monitoring program.

For the determination of cresol in water, good laboratory practice (GLP) guidelines state that the aqueous sample be brought to pH 11 by the addition of sodium hydroxide (NaOH). The basic mixture is then

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Table 7-2. Analytical Methods for Determining Cresols in Environmental Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference	Isomer
Air	Pump air through adsorbent tube, desorb with methanol	HPLC/UV	0.3 ppt	90–110	Kuwata and Tanaka 1988	<i>o, m, p</i>
Air	Aerodispersive enrichment into water	HPLC/ED	No data	No data	Vecera and Janák 1987	<i>o</i>
Air	Samples collected on solid sorbent tube. Desorb with methanol	HPLC/UV	No data	No data	NIOSH 1994a	<i>o, m, p</i>
Air	Sample collected on solid sorbent tube, desorb with methanol	GC/FID	No data	No data	NIOSH 1994b	<i>o, m, p</i>
Air	Ambient air drawn through impingers containing 15 mL of 0.1M NaOH Phenolates solution adjusted to pH <4 with 5% sulfuric acid and diluted with water	HPLC/UV	1–5 ppbv	>80	EPA 1986	<i>o, m, p</i>
Water	Adjust pH to 2, extract with CH ₂ Cl ₂ , concentrate	GC/MS	No data	No data	EPA 2005a	<i>o, p</i>
Water	Solvent extraction, liquid chromatography prefractionation	GC/MS	No data	No data	Hites 1979	Not specified
Rain water	None; direct injection onto ion exchange column	HPLC/CD	No data	No data	DOE 1985	<i>o, m, p</i>
Rain water	Acidify, extract with CH ₂ Cl ₂ , concentrate. methylate	GC/MS	No data	>50	Kawamura and Kaplan 1986	<i>o, m, p</i>
Drinking water	1-L sample is extracted using a solid phase extraction cartridge	GC/MS	0.026 µg/L	85	EPA 2000b Method 528	<i>o</i>
Soil, air, water,	Samples are prepared for analysis by GC/MS	GC/MS	Not applicable	Not applicable	EPA 1998 Method 8270D	<i>o, m, p</i>
Water or leachate	Aqueous liquid waste or leachate is directly injected into a reverse phase HPLC column	HPLC/UV	2.6 mg/L (<i>o</i> -cresol) 0.9 mg/L (<i>m</i> -cresol) 2.1 mg/L (<i>p</i> -cresol)	89	DOE 1997a Method OH100R	<i>o, m, p</i>

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Table 7-2. Analytical Methods for Determining Cresols in Environmental Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference	Isomer
Water	The sample is extracted at pH 12–13, then at pH <2 with methylene chloride using continuous extraction techniques; the extract is dried over sodium sulfate and concentrated to a volume of 1 mL	GC/MS	Not applicable	Not applicable	EPA 2001 Method 1625	<i>o</i>
Drinking water	Water samples are collected and analyzed via GC/MS	GC/MS	27 µg/L <i>o</i> -cresol 42 µg/L <i>p</i> -cresol	96	DOE 1997b Method OM100R	<i>o, p</i>
Aqueous samples	Samples are extracted and cleaned up (according to sample matrix) and the solvent appropriately exchanged; the phenols are then determined with or without derivatization	GC/MS	Not applicable	Not applicable	EPA 2000c Method 8041A	<i>o, m, p</i>
Effluent Water	The sample is extracted at pH 12–13, then at pH <2 with methylene chloride using continuous extraction techniques; the extract is dried over sodium sulfate and concentrated to a volume of 1 mL	GC-MS (Method 1625)	Not applicable	Not applicable	EPA 2001b	<i>o, m, p</i>
Soil, sediment	Extract sample with CH ₂ Cl ₂ using ultra sonic probe	GC/MS	330 ppb	No data	EPA 2005a	<i>o, p</i>
Bottom sediment	Wet sediment samples were dried and compounds were extracted using dichloromethane	GC/MS	41.2 µg/Lkg	86	USGS 1995 Method 0-5130-95	<i>p</i>
Water	Water samples were filtered using glass fiber filters; samples were extracted using SPE cartridges	GC/MS	0.27 µg/L	36	USGS 2002 Method 0-1433-01	<i>p</i>

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Table 7-2. Analytical Methods for Determining Cresols in Environmental Materials

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference	Isomer
Sediment	Extract rapidly stirred sediment slurry with CH ₂ Cl ₂ or ether, concentrate	GC/MS	No data	No data	Goodley and Gordon 1976	Not specified
Breathing air	Draw air through XAD-s adsorbent tube, acetonitrile desorption	HPLC/ED	8 µg/m ³	No data	Nieminen and Heikkila 1986	<i>o, m, p</i>

CD = conductivity detector; ED = electrochemical detector; GC = gas chromatography; HPLC = high performance liquid chromatography; MS = mass spectrometry; SPE = solid phase extraction; UV = ultraviolet detector

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extracted with methylene chloride either in a separatory funnel or a continuous liquid-liquid extractor. The aqueous phase is then acidified to pH 2 and reextracted with methylene chloride. This second extract is concentrated by evaporation and subjected to GC/mass spectrometry (MS) analysis for identification and quantification.

In sediment and soil samples, the isomers of cresol are determined by transferring a small portion of the solid sample (1 g) to a vial and adding methylene chloride. The contaminants are extracted from the sample with the aid of an ultrasonic probe. The methylene chloride extract is filtered, concentrated, and subjected to GC/MS analysis for quantitation.

No other standardized methods for the determination of the three isomers of cresol were located (EPA 1988a). However, numerous methods for their determination have appeared in the open literature. Methods for the determination of cresols in ambient air (Kolber et al. 1981; Kuwata and Tanaka 1988; Vecera and Janák 1987), breathing air (Heikkila et al. 1987; Leuenberger et al. 1985; Nieminen and Heikkila 1986), surface water (Goodley and Gordon 1976; Hites 1979; McKnight et al. 1982; Sheldon and Hites 1979), groundwater (Goerlitz et al. 1985; Hutchins et al. 1984; Sawhney and Kozloski 1984; Stuermer et al. 1982) rain water (DOE 1985; Kawamura and Kaplan 1986; Leuenberger et al. 1985), and sediment samples (Goodley and Gordon 1976; Hites and Lopez-Avila 1980) are available.

The greatest difference between these methods is the procedure used in the sample preparation step. This step of the analysis varies widely between experimental techniques and may involve the use of highly specialized equipment. After the sample preparation step, however, the consensus is that separation of the isomers is best accomplished by using either GC or HPLC.

Cresols degrade rapidly in the environment (see Section 6.3.2). The degradation products are also removed rapidly. The products resulting from the degradation of the three isomers of cresol in the environment are not unique to these compounds.

7.3 ADEQUACY OF THE DATABASE

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

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

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

7.3.1 Identification of Data Needs

Methods for Determining Biomarkers of Exposure and Effect.

Exposure. There are no known biomarkers of exposure that are unique to cresols. In addition, *o*-cresol has been used as a biomarker of toluene exposure, and the isomers of cresol may appear as a result of exposure to other aromatic compounds (Needham et al. 1984). The methods presently available are capable of determining low levels of the cresol isomers in biological media, and background levels in the population could be established using existing techniques (Angerer and Wulf 1985; DeRosa et al. 1987; Krotoszynski and O'Neill 1982; Needham et al. 1984; Yoshikawa et al. 1986). Before a complete discussion on determining biomarkers of exposure for cresol can be undertaken, biomarkers unique to this compound must first be established.

Effect. Correlations of exposure and resulting biological effects are confounded by the metabolic formation of cresol after exposure to other organic compounds. Although the analytical methods for determining cresol in biological materials appear to provide the necessary precision and accuracy, their reliability in determining biomarkers of exposure and effect cannot, at this time, be ascertained. Before a complete discussion on determining biomarkers of effect for cresol can be undertaken, biomarkers unique to this compound must first be established.

Methods for Determining Parent Compounds and Degradation Products in Environmental

Media. Numerous methods for the determination of cresol in environmental matrices have appeared in the literature (DOE 1985; EPA 2005a; Goodley and Gordon 1976; Hites 1979; Kawamura and Kaplan 1986; Kuwata and Tanaka 1988; Nieminen and Heikkila 1986; Vecera and Janák 1987). These procedures are capable of both identifying areas that have been contaminated with cresol and determining

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if the contaminated areas constitute a concern for human health. Human exposure to cresol is likely to occur by inhalation or ingestion of contaminated water. Standardized methods for the determination of the isomeric cresols exist for both of these matrices. These methods are both reproducible and sensitive. In addition, acceptable methods for the determination of cresol in other environmental media have appeared in the literature. No data needs are identified at this time.

Although the isomeric cresols degrade readily in the environment, their degradation products (Bayly and Wigmore 1973; Masunaga et al. 1983, 1986) are not unique to these compounds (see Section 6.3.2). As a result, the determination of these intermediates cannot be accurately extrapolated back to levels of cresol contamination in the environment.

7.3.2 Ongoing Studies

No information regarding ongoing studies was found as a result of a search of the Federal Research in Progress database (FEDRIP 2008).

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 cresols and other volatile organic compounds in blood. These methods use purge and trap methodology, high-resolution gas chromatography, and magnetic sector mass spectrometry, which give detection limits in the low parts per trillion (ppt) range.

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 cresols and other phenolic compounds in urine. These methods use high-resolution gas chromatography and magnetic sector mass spectrometry, which give detection limits in the low parts per trillion (ppt) range.

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8. REGULATIONS AND ADVISORIES

International and national regulations and guidelines pertinent to human exposure to cresols are summarized in Table 8-1.

ATSDR has derived an intermediate-duration oral MRL of 0.1 mg/kg/day for cresols based on an increase in incidence of nasal lesions in male rats administered *m/p*-cresol in the diet for 13 weeks (NTP 1992b).

The MRL was derived using benchmark modeling of incidence data for nasal lesions in male rats. Following EPA's Benchmark Dose Guidance (EPA 2000a) to select a point of departure, a BMR of 10% was selected for the benchmark analysis of nasal lesion incidence data in male rats in the 13-week NTP (1992b) study. The BMD corresponding to a BMR of 10% extra risk is 55.89 mg/kg/day; the corresponding BMDL₁₀ is 13.94 mg/kg/day. An uncertainty factor of 100 (10 for interspecies extrapolation and 10 for human variability) was applied to the BMDL₁₀.

ATSDR has derived a chronic-duration oral MRL of 0.1 mg/kg/day for cresols based on increased incidences of bronchiole hyperplasia of the lung and follicular degeneration of the thyroid gland in female mice administered *m/p*-cresol in the diet for 2 years. The MRL was derived using a LOAEL of 100 mg/kg/day divided by an uncertainty factor of 1,000 (10 for use of a LOAEL, 10 for extrapolation from animals to humans, and 10 for human variability).

EPA (IRIS 2008) has derived oral reference doses of 0.05 mg/kg/day for *m*- and *o*-cresol based on NOAELs of 50 mg/kg/day for decreased body weights and neurotoxicity (myoclonus, tremors, labored respiration) observed in Sprague-Dawley rats exposed by gavage for 90 days (TRL 1986) in an assessment conducted in 1989. An uncertainty factor of 100 (10 for interspecies and 10 for intraspecies variability) was applied to the NOAEL.

The EPA (IRIS 2008) has classified *m*-cresol, *o*-cresol, and *p*-cresol as possible human carcinogens (Group C) based on inadequate human data and limited data in animals. The assessment was based on an increased incidence of skin papillomas in mice in an initiation-promotion study and on the fact that the cresol isomers produced positive results in genetic toxicity studies both alone and in combination. According to EPA's updated criteria for assessing carcinogenicity of chemicals (EPA 2005c), cresols fall in the category of chemicals for which there is "inadequate information to assess carcinogenic potential." The American Conference of Governmental Industrial Hygienists (ACGIH), International Agency for

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Table 8-1. Regulations and Guidelines Applicable to Cresols

Agency	Description	Information	Reference
<u>INTERNATIONAL</u>			
Guidelines:			
IARC	Carcinogenicity classification	No data	IARC 2004
WHO	Air quality guidelines	No data	WHO 2000
	Drinking water quality guidelines	No data	WHO 2004
<u>NATIONAL</u>			
Regulations and Guidelines:			
a. Air			
ACGIH	TLV (8-hour TWA), all isomers ^a	5 ppm	ACGIH 2005
EPA	AEGL	No data	EPA 2006a
	Hazardous air pollutant, all isomers	Yes	EPA 2006c 42 USC 7412
NIOSH	REL (10-hour TWA), all isomers	2.3 ppm	NIOSH 2005
	IDLH, all isomers	250 ppm	
OSHA	PEL (8-hour TWA) for general industry, all isomers ^b	5 ppm	OSHA 2005c 29 CFR 1910.1000
	PEL (8-hour TWA) for construction industry, all isomers ^b	5 ppm	OSHA 2005b 29 CFR 1926.55, Appendix A
	PEL (8-hour TWA) for shipyard industry, all isomers ^b	5 ppm	OSHA 2005a 29 CFR 1915.1000
b. Water			
EPA	Designated as hazardous substances in accordance with Section 311(b)(2)(A) of the Clean Water Act, all isomers	Yes	EPA 2006b 40 CFR 116.4
	Drinking water standards and health advisories	No data	EPA 2004
	Reportable quantities of hazardous substances designated pursuant to Section 311 of the Clean Water Act, mixed cresols	Yes	EPA 2006f 40 CFR 117.3
	Water quality criteria for human health	No data	EPA 2006e
c. Food			
FDA	Bottled drinking water	No data	FDA 2005 21 CFR 165.110
d. Other			
ACGIH	Carcinogenicity classification	No data	ACGIH 2005
EPA	Carcinogenicity classification		IRIS 2008
	Cresol	No data	
	<i>m</i> -Cresol	Group C ^c	
	<i>o</i> -Cresol	Group C ^c	
	<i>p</i> -Cresol	Group C ^c	

8. REGULATIONS AND ADVISORIES

Table 8-1. Regulations and Guidelines Applicable to Cresols

Agency	Description	Information	Reference
NATIONAL (cont.)			
EPA	RfC		IRIS 2008
	Cresol	No data ^d	
	<i>m</i> -Cresol	No data ^d	
	<i>o</i> -Cresol	No data ^d	
	<i>p</i> -Cresol	No data ^d	
	RfD		
	Cresol	No data	
	<i>m</i> -Cresol	0.05 mg/kg/day	
	<i>o</i> -Cresol	0.05 mg/kg/day	
	<i>p</i> -Cresol	Withdrawn	
	Identification and listing of hazardous waste, mixed cresols	U052	EPA 2006d 40 CFR 261, Appendix VIII
	Superfund, emergency planning, and community right-to-know		EPA 2006g 40 CFR 302.4
	Designated CERCLA hazardous substance, all isomers	Yes	
	Reportable quantity	100 pounds	
	Effective date of toxic chemical release reporting, all isomers	01/01/87	EPA 2006i 40 CFR 372.65
	Extremely hazardous substances and their threshold planning quantities, <i>o</i> -cresol only	1,000/10,000 pounds	EPA 2006h 40 CFR 355, Appendix A
NTP	Carcinogenicity classification	No data	NTP 2004

^aSkin notation: refers to the potential significant contribution to the overall exposure by the cutaneous route, including mucous membranes and the eyes, either by contact with vapors, liquids, and solids.

^bSkin designation

^cGroup C: possible human carcinogen

^dThe health effects data for cresol, *m*-cresol, *o*-cresol, and *p*-cresol were reviewed by the U.S. EPA RfD/RfC Work Group and determined to be inadequate for the derivation of an inhalation RfC.

ACGIH = American Conference of Governmental Industrial Hygienists; AEGL = Acute Exposure Guideline Level; CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act; CFR = Code of Federal Regulations; EPA = Environmental Protection Agency; FDA = Food and Drug Administration; IARC = International Agency for Research on Cancer; IDLH = immediately dangerous to life or health; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PEL = permissible exposure limit; REL = recommended exposure limit; RfC = inhalation reference concentration; RfD = oral reference dose; TLV = threshold limit values; TWA = time-weighted average; USC = United States Code; WHO = World Health Organization

8. REGULATIONS AND ADVISORIES

Research on Cancer (IARC), and the National Toxicology Program (NTP) have not classified cresols for human carcinogenicity (ACGIH 2005; IARC 2004; NTP 2004).

OSHA requires employers of workers who are occupationally exposed to cresol to institute engineering controls and work practices to reduce and maintain employee exposure at or below permissible exposure limit time-weighted average (PEL-TWA). The employer must use engineering and work practice controls to reduce exposures to or below an 8-hour TWA of 5 ppm for cresol and its isomers (OSHA 2006). Both NIOSH and ACGIH and have established guideline values that range from 2.3 to 5 ppm for cresol and its isomers (ACGIH 2005; NIOSH 2005).

EPA regulates cresols and its isomers under the Clean Air Act (CAA) and the Clean Water Act (CWA) and has designated them as hazardous air pollutants (HAPs) and hazardous substances, respectively (EPA 2006b, 2006c). EPA has established a reportable quantity (RQ) of 100 pounds (EPA 2006i).

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10. GLOSSARY

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

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

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

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

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

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

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

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

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

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

Carcinogen—A chemical capable of inducing cancer.

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

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

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

10. GLOSSARY

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

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

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

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

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

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

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

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

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

Epidemiology—Refers to the investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

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

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

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

Immunologic Toxicity—The occurrence of adverse effects on the immune system that may result from exposure to environmental agents such as chemicals.

10. GLOSSARY

Immunological Effects—Functional changes in the immune response.

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

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

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

In Vivo—Occurring within the living organism.

Lethal Concentration_(LO) (LC_{LO})—The lowest concentration of a chemical in air that 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_(LO) (LD_{LO})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose₍₅₀₎ (LD₅₀)—The dose of a chemical that 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 exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

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

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

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

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

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

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

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

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

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

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

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

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

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

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) allowable exposure level in workplace air averaged over an 8-hour shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests.

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

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

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

10. GLOSSARY

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

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

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

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

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

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

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

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

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

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

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

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

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

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

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

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

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

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

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

Toxic Dose₍₅₀₎ (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.

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

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

Xenobiotic—Any chemical that is foreign to the biological system

APPENDIX A. ATSDR MINIMAL RISK LEVELS AND WORKSHEETS

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

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

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

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

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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 100-fold 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 and Environmental Medicine, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop F-32, Atlanta, Georgia 30333.

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Cresols
CAS Numbers: 95-48-7, 108-39-4, 106-44-5, 1319-77-3
Date: July 2008
Profile Status: Final Draft Post-Public Comment
Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Graph Key: 55
Species: Rat

Minimal Risk Level: 0.1 mg/kg/day ppm

Reference: NTP. 1992b. NTP report on the toxicity studies of cresols (CAS Nos. 95-48-7, 108-39-4, 106-44-5) in F344/N rats and B6C3F1 mice (feed studies). Research Triangle Park, NC: National Toxicology Program. NIH Publication No. 92-3128. NTP Tox 9.

Experimental design: Groups of Fischer 344 rats (20/sex/group) were administered *m/p*-cresol (58.5% *m*-cresol, 40.9% *p*-cresol) in the diet at levels of 0, 1,880, 3,750, 7,500, 15,000, or 30,000 ppm for 13 weeks (NTP 1992b). The corresponding doses of test compound estimated by the investigators were 0, 123, 241, 486, 991, and 2,014 mg/kg/day for males and 0, 131, 254, 509, 1,024, and 2,050 mg/kg/day for females. End points evaluated included clinical signs, food consumption, organ weights, clinical chemistry and hematology, and gross and microscopic appearance of organs and tissues. Although the dose groups consisted of 20 rats of each sex, 10 males and 10 females were used for clinical chemistry, hematology, and urinalysis studies and the remaining 10 rats/sex/group were used in gross pathology, organ weight, and histopathological studies.

Effect noted in study and corresponding doses: There were no deaths during the study. Final body weight in the 2,014/2,050 mg/kg/day males and females was reduced 17 and 12%, respectively, relative to controls. Food consumption was also reduced (about 10%) in this group during the first week of the study. Additionally, males and females in this group exhibited rough hair coat; females also had a thin appearance. Absolute and relative liver weights were significantly increased (11–12%) in males at 486 mg/kg/day and in females at 1,024 mg/kg/day. Absolute and relative kidney weight were increased in males at 991 mg/kg/day. In general, hematology findings were unremarkable, although there was a tendency to hemoconcentration at 2,014/2,050 mg/kg/day early in the study. Clinical chemistry tests showed an increase in serum alanine aminotransferase (ALT) in males and females exposed to 2,014/2,050 mg/kg/day and in sorbitol dehydrogenase (SDH) in males at 2,014 mg/kg/day only on day 5. Bile acids in serum were increased in females at 2,050 mg/kg/day on day 90 and at 241 and 991 mg/kg/day in males also on day 90. There was no indication of renal injury as judged by the results of urinalyses. Significant histopathological changes included minimal bone marrow hypocellularity in males and females at 2,014/2,050 mg/kg/day, and increased colloid (minimal) in thyroid follicular cells in females at 509 mg/kg/day and in males at 15,000 ppm (991 mg/kg/day). An increased dose-related incidence and severity of hyperplasia and glandular hyperplasia of the nasal respiratory epithelium was observed in male and female rats. Severity was minimal at 123/131 mg/kg/day, mild at 486/509 mg/kg/day, and moderate at 2,014/2,050 mg/kg/day. The lesions were located at the most anterior portions of the nasal septum, dorsal arch, and medial aspect of the nasal turbinates. The hyperplasia was characterized by increased number of goblet cells and pseudogland formation due to the infolding of the hyperplastic cells. The hyperplastic areas were associated with single cell necrosis. The incidences in males dosed with 0, 123, 241, 486, 991, and 2,014 mg/kg/day were 0/10, 3/10, 8/10, 10/10, 8/10, and 10/10, respectively. A similar trend was seen in female rats, but 3/10 control females also exhibited hyperplasia (3/10, 1/10, 5/10, 9/10, 8/10, and 10/10 at 0, 131, 254, 509, 1,024, and

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2,050 mg/kg/day, respectively). The LOAELs for nasal lesions in male and female rats were 123 and 254 mg/kg/day, respectively. The NOAEL in females was 131 mg/kg/day and no NOAEL was established in males.

In the 28-day study with *m/p*-cresol in rats, the incidences of hyperplasia of the nasal respiratory epithelium in females dosed with 0, 27, 95, 268, 886, and 2,570 mg/kg/day were 0/5, 0/5, 3/4, 5/5, 5/5, and 5/5, respectively. However, data from the 13-week study are preferred for MRL derivation because of the longer duration and because only five rats/group were examined in the 28-day study.

Data from the NTP (1992b) were considered adequate for analysis using the benchmark dose approach for MRL derivation. Benchmark dose models in the EPA Benchmark Dose Software (BMDS) (version 2.0) were fit to the incidence data for nasal lesions in male and female rats exposed to *m/p*-cresol in the diet for 13 weeks in order to determine potential points of departure for the MRL (details of the modeling are presented below).

Dose and end point used for MRL derivation: BMDL₁₀ of 13.94 mg/kg/day for nasal lesions in male rats.

NOAEL LOAEL BMDL₁₀

Uncertainty Factors used in MRL derivation:

- 10 for extrapolation from animals to humans
- 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Conversion from diet to dose was done by the investigators.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: Almost all of the information available on health effects from intermediate-duration oral exposure is derived from a comprehensive study in rats and mice administered the three cresol isomers and a cresol mixture for 28 days and 13 weeks (NTP 1992b). There are also two multigeneration reproductive studies in mice dosed with *o*-cresol (NTP 1992a) and a cresol mixture (NTP 1992c). Evaluation of the results of these studies indicates that the most sensitive end point was the nasal respiratory epithelium of rats and mice dosed with *p*-cresol or an *m/p*-cresol mixture. No clear target of toxicity emerged for *o*- or *m*-cresol. The nasal lesions occurred in rats dosed with *p*-cresol for 28 days (≥ 770 mg/kg/day), in rats exposed to *m/p*-cresol for 28 days (≥ 95 mg/kg/day), in mice exposed to *p*-cresol for 28 days (≥ 163 mg/kg/day), in mice exposed to *m/p*-cresol for 28 days (≥ 604 mg/kg/day), in rats exposed to *m/p*-cresol for 13 weeks (≥ 123 mg/kg/day), and in mice exposed to *m/p*-cresol for 13 weeks (≥ 472 mg/kg/day). Other effects that occurred at higher doses included increases in liver and kidneys weights (≥ 240 mg/kg/day), bone marrow hypocellularity ($\geq 2,000$ mg/kg/day), and mild uterine atrophy ($\geq 1,000$ mg/kg/day) (NTP 1992b). Clinical tests of liver and kidney function were generally unremarkable and gross and microscopic evaluation of the liver and kidney showed no significant alterations (NTP 1992b). None of the intermediate-duration oral gavage studies examined the nasal respiratory epithelium of the animals, and neither did the two multigeneration reproductive dietary studies in mice (NTP 1992a, 1992c).

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BENCHMARK MODELING OF NASAL RESPIRATORY LESIONS IN RATS

Benchmark dose models in the EPA Benchmark Dose Software (BMDS version 2.0) were fit to the incidence data for nasal lesions in male and female rats exposed to *m/p*-cresol in the diet for 13 weeks in order to determine potential points of departure for the MRL. BMDL_{10S} (i.e., 95% lower confidence limits on the model-estimated dose associated with a 10% extra risk for nasal lesions) calculated with the best-fitting models for each data set (see Tables A-1, A-2, and, A-3 and Figures A-1 and A-2) were 13.9 mg/kg/day for males and 30.8 mg/kg/day for females. While this difference in benchmark dose may indicate that male rats are more sensitive than females, it also can be a statistical artifact of a rather small sample size, only 10 rats per group. The male rat data set was selected for determining the point of departure for MRL derivation in order to be public health protective.

Table A-1. Incidence Data for Respiratory Epithelium Glandular Hyperplasia or Hyperplasia in Rats Exposed to *m/p*-Cresol in the Diet for 13 Weeks

	Dietary concentration (ppm)	Dose (mg/kg/day)	Incidence of nasal lesions
Male	0	0	0/10
	1,880	123	3/10
	3,750	241	8/10
	7,500	486	10/10
	15,000	991	9/10
	30,000	2,014	10/10
Female	0	0	3/10
	1,880	131	2/10
	3,750	254	6/10
	7,500	509	10/10
	15,000	1,024	8/10
	30,000	2,050	10/10

Source: NTP 1992b

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Table A-2. Goodness-of-Fit Statistics and BMD₁₀s and BMDL₁₀s from Models Fit to Incidence Data for Nasal Lesions in Male Rats Exposed to *m/p*-Cresol in the Diet for 13 Weeks

Model	AIC	X ² p value ^a	BMD ₁₀ (mg/kg/day)	BMDL ₁₀ (mg/kg/day)
Gamma	37.3167	0.1221	24.1138	16.7698
Logistic	46.7819	0.0000	63.9362	42.8254
Log-Logistic^b	36.8962	0.2605	55.8863	13.9381
Multistage	37.3167	0.1221	24.1138	16.7698
Probit	49.738	0.0002	71.306	50.8541
Log-probit	37.6831	0.2511	46.1987	26.6915
Quantal-linear	37.3167	0.1221	24.1138	16.7698
Weibull	37.3167	0.1221	24.1138	16.7698

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

^bBest-fitting model

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; p = p value from the Chi-squared test

Source: NTP 1992b

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Table A-3. Goodness-of-Fit Statistics and BMD₁₀s and BMDL₁₀s from Models Fit to Incidence Data for Nasal Lesions in Female Rats Exposed to *m/p*-Cresol in the Diet for 13 Weeks

Model	AIC	X ² p value ^a	BMD ₁₀ (mg/kg/day)	BMDL ₁₀ (mg/kg/day)
Gamma	61.5191	0.0477	64.2166	30.9781
Logistic	60.7552	0.0557	89.5533	60.4852
Log-Logistic	60.0961	0.0487	98.7921	28.7889
Multistage^b	59.5988	0.1020	48.0244	30.7916
Probit	61.2978	0.0600	98.0573	69.3757
Log-probit	60.351	0.0591	99.9316	51.3824
Quantal-linear^b	59.5988	0.1020	48.0246	30.7916
Weibull	61.5874	0.0505	52.5879	30.8181

^aValues <0.1 fail to meet conventional goodness-of-fit criteria.

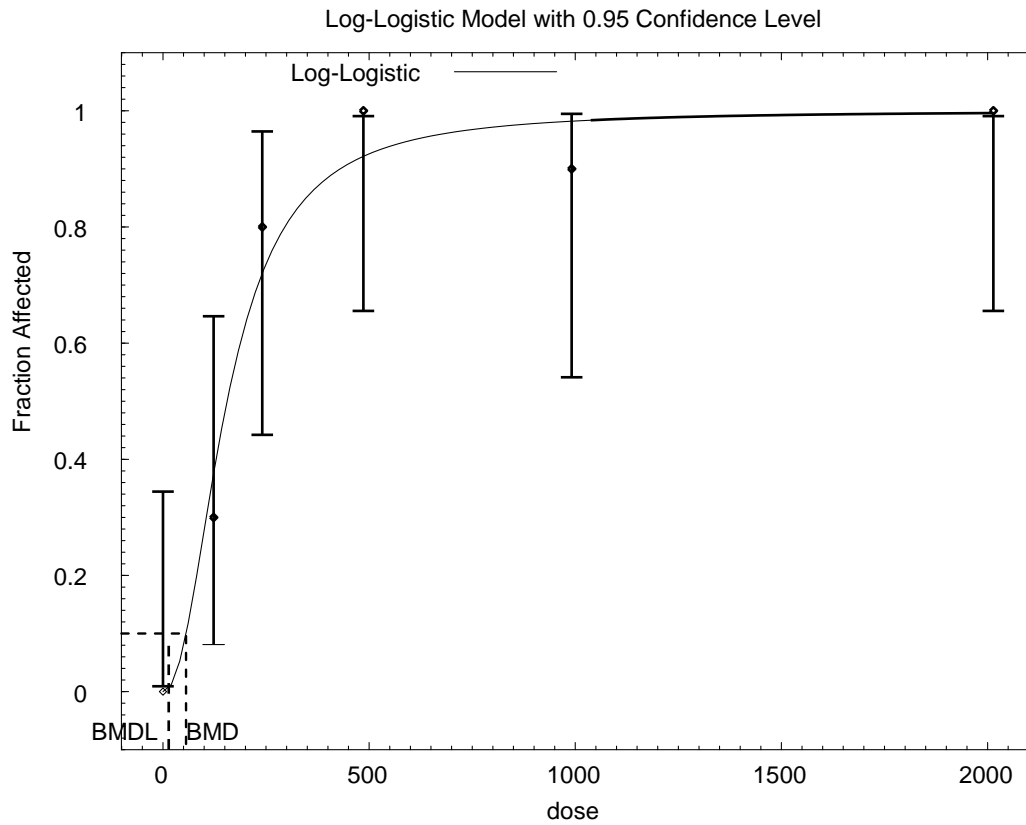
^bBest-fitting model

AIC = Akaike's Information Criteria; BMD = benchmark dose; BMDL = lower confidence limit (95%) on the benchmark dose; p = p value from the Chi-squared test

Source: NTP 1992b

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Figure A-1. Observed and Predicted Incidences of Nasal Lesions in Male Rats Exposed to *m/p*-Cresol in the Diet for 13 Weeks*



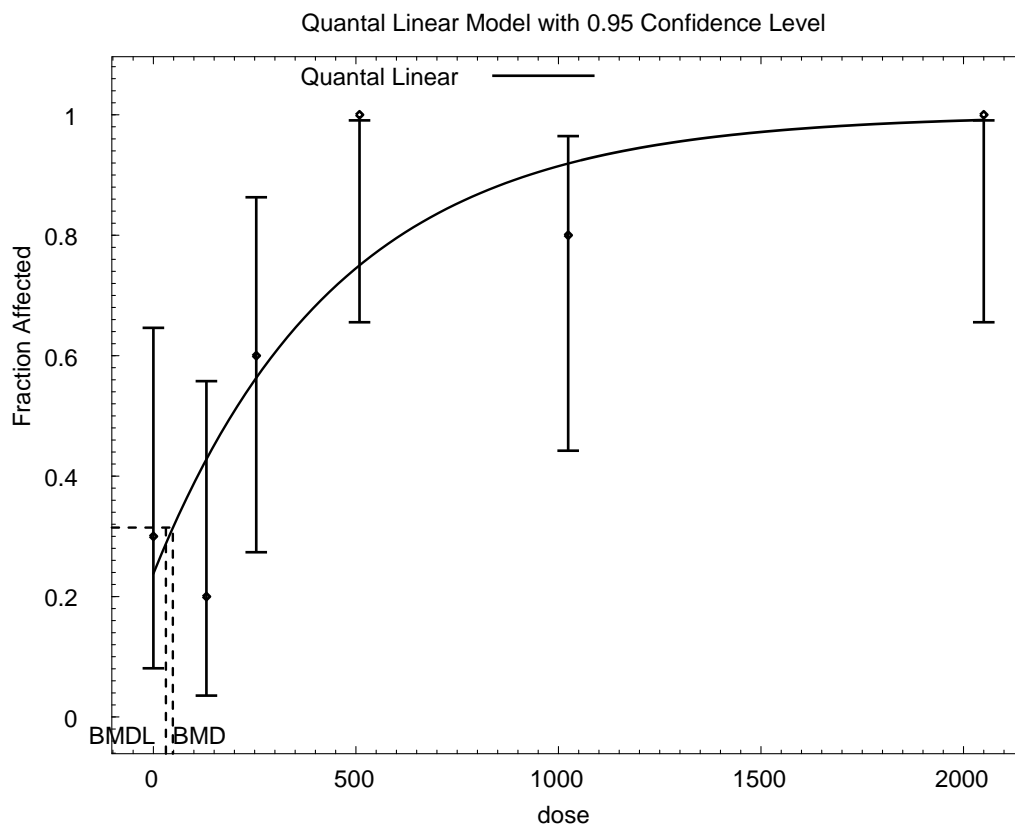
10:36 07/16 2008

*BMDs and BMDLs indicated are for a 10% extra risk and are in units of mg/kg/day.

Source: NTP 1992b

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Figure A-2. Observed and Predicted Incidences of Nasal Lesions in Female Rats Exposed to *m/p*-Cresol in the Diet for 13 Weeks*



*BMDs and BMDLs Indicated are for a 10% extra risk and are in units of mg/kg/day.

Source: NTP 1992b

BMDs and BMDLs associated with 1, 5, 10, 20, and 30% extra risk were calculated with the best-fitting model of the male rat nasal lesion incidence data (see Table A-4). Following EPA's Benchmark Dose Guidance (EPA 2000a) to select a point of departure, a benchmark response (BMR) of 10% was selected for the benchmark analysis of nasal lesion incidence data in male rats in the 13-week NTP (1992b) study. The BMD corresponding to a BMR of 10% extra risk is 55.89 mg/kg/day; the corresponding BMDL₁₀ is 13.94 mg/kg/day (see Table A-4). Applying an uncertainty factor of 100 (10 each for intra- and interspecies extrapolation) to the BMDL₁₀ yields an intermediate-duration oral MRL of 0.1 mg/kg/day for *m/p*-cresol.

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Table A-4. Best-fitting Model Predictions for 1, 5, 10, 20, and 30% Extra Risk for Incidence of Nasal Lesions Observed in Rats Exposed to *m/p*-Cresol in the Feed for 13 Weeks

Best fitting model	BMR (% extra risk)	BMD (mg/kg/day)	BMDL (mg/kg/day)
Male: Log-Logistic	1	18.38	1.70
	5	39.52	7.26
	10	55.89	13.94
	20	81.41	28.08
	30	104.53	44.35
Female: Quantal Linear	1	4.58	2.94
	5	23.38	14.99
	10	48.02	30.79
	20	101.71	65.21
	30	162.58	104.24

Source: NTP 1992b

All available dichotomous models in the EPA BMDS (version 2.0) were fit to the incidence data for nasal lesions (respiratory epithelium glandular hyperplasia or hyperplasia) in male and female rats exposed to *m/p*-cresol in the diet for 13 weeks (NTP 1992b) (Table A-1). Predicted doses associated with 30, 20, 10, 5, and 1% extra risks were calculated.

Male Rats

As assessed by the chi-square goodness-of-fit test, several models in the software provided adequate fits to the data for the incidence of nasal lesions in male rats (χ^2 p value ≥ 0.1) (Table 2). Comparing across models, a better fit is indicated by a lower Aikake's Information Criteria value (AIC) (EPA 2000a). The log-logistic model was determined to be the best-fitting model, as indicated by the AIC (Table A-2). Benchmark doses (BMDs and BMDLs) associated with an extra risk of 30, 20, 10, 5, and 1, calculated from the best fitting model, are shown in Table A-4.

The form and parameters of the log-logistic model for the male rat data are as follows:

$P[\text{response}] = \text{background} + (1 - \text{background}) / [1 + \text{EXP}(-\text{intercept} - \text{slope} * \text{Log}(\text{dose}))]$
background = 0;
intercept = -5.78913;
slope = 1.21882.

Female Rats

As assessed by the chi-square goodness-of-fit test, only the quantal linear model (which was the similar to the 1-degree polynomial model) provided an adequate fit to the data for the incidence of nasal lesions in female rats (χ^2 p value ≥ 0.1). Therefore, the quantal linear model was determined to be the best-fitting model (Table 3). Benchmark doses (BMDs and BMDLs) associated with an extra risk of 30, 20, 10, 5, and 1%, calculated from the quantal linear model, are shown in Table A-4.

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The form and parameters of the quantal linear model for the female rat data are as follows:

$$P[\text{response}] = \text{background} + (1 - \text{background}) * [1 - \text{EXP}(-\text{slope} * \text{dose})]$$

background = 0.318182;

slope = 0.001321;

Power = 1 (Specified)

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MINIMAL RISK LEVEL (MRL) WORKSHEET

Chemical Name: Cresols
CAS Numbers: 95-48-7, 108-39-4, 106-44-5, 1319-77-3
Date: July 2008
Profile Status: Final Draft Post-Public Comment
Route: Inhalation Oral
Duration: Acute Intermediate Chronic
Graph Key: 130
Species: Mice

Minimal Risk Level: 0.1 mg/kg/day ppm

Reference: NTP. 2008. Toxicology and carcinogenesis studies of cresols (CAS No. 1319-77-3) in male F344/N rats and female B6C3F₁ mice (feed studies). Research Triangle Park, NC: National Toxicology Program. TR-550. Draft technical report.

Although the report has not yet been finalized by the NTP, a draft technical report has been reviewed by the NTP Board of Scientific Counselors Technical Reports Review Subcommittee, and a draft abstract, pathology tables, and survival and growth curves are available in the NTP web site (<http://ntp.niehs.nih.gov/index.cfm?objectid=9B58ADF7-F1F6-975E-78A23152B1596409>).

Experimental design: Groups of female B6C3F₁ mice (50/group) were administered *m/p*-cresol (60% *m*-cresol, 40% *p*-cresol) in the diet at levels of 0, 1,000, 3,000, or 10,000 ppm for 2 years (NTP 2008). The corresponding doses of test compound estimated by the investigators were approximately 0, 100, 300, and 1,040 mg/kg/day. End points evaluated included clinical signs, food consumption, organ weights, and gross and microscopic appearance of organs and tissues at termination.

Effect noted in study and corresponding doses: Dosing with *m/p*-cresol did not affect survival rate. Food consumption did not appear to vary significantly throughout the study. No significant treatment-related clinical signs were reported. At termination, body weight in the mid- and high-dose groups was significantly lower than controls (11 and 24%, respectively). Significant treatment-related, non-neoplastic effects included: minimal to moderate bronchiolar hyperplasia in the lung (0/50, 42/50, 44/49, 47/50); minimal to mild hyperplasia of the nasal respiratory epithelium (0/50, 0/50, 28/49, 21/50); mild follicular degeneration of the thyroid gland (7/48, 24/48, 24/49, 21/50); and increased eosinophilic foci in the liver (1/50, 0/50, 2/49, 12/50). NOAELs for bronchiolar hyperplasia and thyroid follicular degeneration were not established, and in both cases, the LOAEL was 100 mg/kg/day.

Since the incidence data indicate that bronchiolar hyperplasia of the lung and follicular degeneration of the thyroid gland had lower thresholds than the liver or nasal effects, the former two responses were considered for analysis using the benchmark dose approach for MRL derivation. After inspection of the dose response data, the use of a LOAEL/NOAEL approach for MRL derivation was considered to be more appropriate than the use of benchmark dose analysis because of the steep increase in the response rates between the control group and the first exposure level.

Dose and end point used for MRL derivation: LOAEL of 100 mg/kg/day for bronchiole hyperplasia of the lung and follicular degeneration of the thyroid gland in female mice.

NOAEL LOAEL BMDL₁₀

APPENDIX A

Uncertainty Factors used in MRL derivation:

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

Was a conversion factor used from ppm in food or water to a mg/body weight dose? Conversion from diet to dose was done by the investigators.

If an inhalation study in animals, list conversion factors used in determining human equivalent dose: Not applicable.

Was a conversion used from intermittent to continuous exposure? No.

Other additional studies or pertinent information that lend support to this MRL: The NTP (2008) is the only chronic-duration study with cresols available. The NTP (2008) also tested male F-344/N rats and the results showed that the most sensitive end point was the nasal respiratory epithelium, as in the shorter-term studies (NTP 1992b). Other less sensitive effects observed in rats included hyperplasia of the transitional epithelium of the renal pelvis, squamous metaplasia in the nasal respiratory epithelium, inflammation of the nose, and eosinophilic foci in the liver. The incidence of respiratory epithelium hyperplasia of minimal to mild severity was 3/50, 17/50, 31/50, and 47/50 in the control, low-, mid-, and high-dose groups, respectively. As discussed in Section 2.3, the data suggest that, over the range of doses used in the NTP (1992b, 2008) studies, exposure beyond 13 weeks had little or no effect on the incidence or severity of the nasal respiratory hyperplasia, indicating that the intermediate-duration MRL, which is based on incidence data for this lesion, should be protective of nasal lesions induced by chronic-duration exposure. This is supported by the fact that fitting the incidence data for nasal respiratory epithelium hyperplasia from the 2-year study to the same BMDS model (Log-Logistic) that provided the BMDL₁₀ used to derive the intermediate-duration oral MRL yields a BMDL₁₀ for chronic exposure to *m/p*-cresol of 13.9017 mg/kg/day, essentially the same as the BMDL₁₀ of 13.9381 mg/kg/day used to derive the intermediate-duration oral MRL for *m/p*-cresol.

Agency Contacts (Chemical Managers): Malcolm Williams, Ph.D.; John Risher, Ph.D.; Mike Fay, Ph.D.

APPENDIX A

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APPENDIX B. USER'S GUIDE

Chapter 1

Public Health Statement

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

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

Chapter 2

Relevance to Public Health

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

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

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

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

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Chapter 3 Data Needs section.

Interpretation of Minimal Risk Levels

Where sufficient toxicologic information is available, ATSDR has derived 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.

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MRLs should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as Chapter 3 Section 3.9, "Interactions with Other Substances," and Section 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

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

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables.

Chapter 3

Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures 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, 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 NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

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LEGEND**See Sample LSE Table 3-1 (page B-6)**

- (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. Typically when sufficient data exist, 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 Tables 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures.
- (2) Exposure Period. Three exposure periods—acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more)—are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.
- (3) Health Effect. The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).
- (4) Key to Figure. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in sample Figure 3-1).
- (5) Species. The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.
- (6) Exposure Frequency/Duration. The duration of the study and the weekly and daily exposure regimens 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 "Chemical x" via inhalation for 6 hours/day, 5 days/week, for 13 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, one systemic effect (respiratory) was investigated.
- (8) NOAEL. A NOAEL is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system, which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

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- (9) LOAEL. A LOAEL is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific end point used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less Serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.
- (10) Reference. The complete reference citation is given in Chapter 9 of the profile.
- (11) CEL. A 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 that the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

LEGEND**See Sample Figure 3-1 (page B-7)**

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 acute and intermediate 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, the open circle designated 18r identifies a NOAEL critical end point in the rat upon which an intermediate inhalation exposure MRL is based. 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 38m is one of three studies for which CELs were derived. The diamond symbol refers to a CEL for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

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- (18) Estimated Upper-Bound Human Cancer Risk Levels. This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels (q_1^*).
- (19) Key to LSE Figure. The Key explains the abbreviations and symbols used in the figure.

SAMPLE

1 →

Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation

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

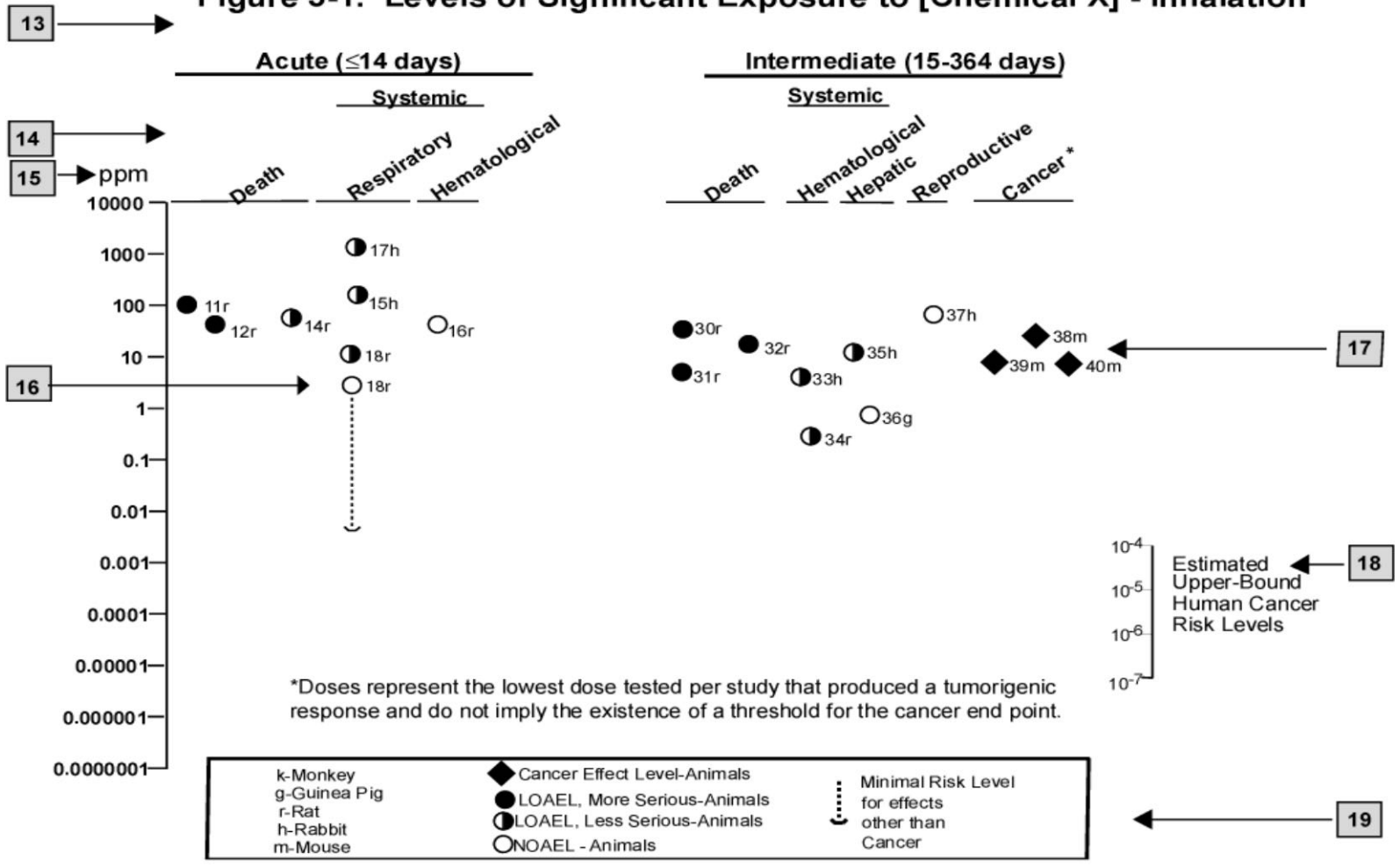
12 →

^a The number corresponds to entries in Figure 3-1.

^b Used to derive an intermediate inhalation Minimal Risk Level (MRL) of 5×10^{-3} ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE

Figure 3-1. Levels of Significant Exposure to [Chemical X] - Inhalation



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APPENDIX C. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AED	atomic emission detection
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
ALT	alanine aminotransferase
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
APHA	American Public Health Association
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	best available technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BMD	benchmark dose
BMR	benchmark response
BSC	Board of Scientific Counselors
C	centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/	Department of Transportation/United Nations/
NA/IMCO	North America/Intergovernmental Maritime Dangerous Goods Code

APPENDIX C

DWEL	drinking water exposure level
ECD	electron capture detection
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F ₁	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
FR	Federal Register
FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
ILO	International Labor Organization
IRIS	Integrated Risk Information System
K _d	adsorption ratio
kg	kilogram
kgg	metric ton
K _{oc}	organic carbon partition coefficient
K _{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC ₅₀	lethal concentration, 50% kill
LC _{Lo}	lethal concentration, low
LD ₅₀	lethal dose, 50% kill
LD _{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
LT ₅₀	lethal time, 50% kill
m	meter
MA	<i>trans,trans</i> -muconic acid
MAL	maximum allowable level
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor

APPENDIX C

MFO	mixed function oxidase
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCEH	National Center for Environmental Health
NCI	National Cancer Institute
ND	not detected
NFPA	National Fire Protection Association
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OR	odds ratio
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	polycyclic aromatic hydrocarbon

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PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
pg	picogram
PHS	Public Health Service
PID	photo ionization detector
pmol	picomole
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	pretreatment standards for new sources
RBC	red blood cell
REL	recommended exposure level/limit
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
RQ	reportable quantity
RTECS	Registry of Toxic Effects of Chemical Substances
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SGOT	serum glutamic oxaloacetic transaminase
SGPT	serum glutamic pyruvic transaminase
SIC	standard industrial classification
SIM	selected ion monitoring
SMCL	secondary maximum contaminant level
SMR	standardized mortality ratio
SNARL	suggested no adverse response level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short term exposure limit
STORET	Storage and Retrieval
TD ₅₀	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	total organic carbon
TPQ	threshold planning quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization

APPENDIX C

>	greater than
\geq	greater than or equal to
=	equal to
<	less than
\leq	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
-	negative
+	positive
(+)	weakly positive result
(-)	weakly negative result

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