

TOXICOLOGICAL PROFILE FOR  
CRESOLS

Agency for Toxic Substances and Disease Registry  
U.S. Public Health Service

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## FOREWORD

The Superfund Amendments and Reauthorization Act (SARA) of 1986 (Public Law 99-499) extended and amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). This public law directed the Agency for Toxic Substances and Disease Registry (ATSDR) to prepare toxicological profiles for hazardous substances which are most commonly found at facilities on the CERCLA National Priorities List and which pose the most significant potential threat to human health, as determined by ATSDR and the Environmental Protection Agency (EPA). The lists of the 250 most significant hazardous substances were published in the Federal Register on April 17, 1987; on October 20, 1988; on October 26, 1989; and on October 17, 1990. A revised list of 275 substances was published on October 17, 1991.

Section 104(i)(3) of CERCLA, as amended, directs the Administrator of ATSDR to prepare a toxicological profile for each substance on the lists. Each profile must include the following content:

- (A) An examination, summary, and interpretation of available toxicological information and epidemiological evaluations on the hazardous substance in order 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 which present a significant risk to human health of acute, subacute, and chronic health effects.
- (C) Where appropriate, an identification of toxicological testing needed to identify the types or levels of exposure that may present significant risk of adverse health effects in humans.

This toxicological profile is prepared in accordance with guidelines developed by ATSDR and 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 is intended to characterize succinctly the toxicological and adverse health effects information for the hazardous substance being described. Each profile identifies and reviews the key literature (that has been peer-reviewed) that describes a hazardous substance's toxicological properties. Other pertinent literature is also presented but 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.

*Foreword*

Each toxicological profile begins with a public health statement, which 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 will be identified by ATSDR, the National Toxicology Program (NTP) of the Public Health Service, and EPA. The focus of the profiles is on health and toxicological information; therefore, we have included this information in the beginning of the document.

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 our assessment of all relevant toxicological testing and information that has been peer reviewed. It has been reviewed by scientists from ATSDR, the Centers for Disease Control, the NTP, and other federal agencies. It has also been reviewed by a panel of nongovernment peer reviewers. Final responsibility for the contents and views expressed in this toxicological profile resides with ATSDR.



William L. Roper, M.D., M.P.H.  
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Disease Registry

## CONTENTS

FOREWORD . . . . .	iii
LIST OF FIGURES . . . . .	ix
LIST OF TABLES . . . . .	xi
1. PUBLIC HEALTH STATEMENT . . . . .	1
1.1 WHAT ARE CRESOLS? . . . . .	1
1.2 HOW MIGHT I BE EXPOSED TO CRESOLS? . . . . .	2
1.3 HOW CAN CRESOLS ENTER AND LEAVE MY BODY? . . . . .	2
1.4 HOW CAN CRESOLS AFFECT MY HEALTH? . . . . .	3
1.5 IS THERE A MEDICAL TEST TO DETERMINE WHETHER I HAVE BEEN EXPOSED TO CRESOLS? . . . . .	3
1.6 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO PROTECT HUMAN HEALTH? . . . . .	4
1.7 WHERE CAN I GET MORE INFORMATION? . . . . .	4
2. HEALTH EFFECTS . . . . .	5
2.1 INTRODUCTION . . . . .	5
2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE . . . . .	5
2.2.1 Inhalation Exposure . . . . .	6
2.2.1.1 Death . . . . .	6
2.2.1.2 Systemic Effects . . . . .	7
2.2.1.3 Immunological Effects . . . . .	8
2.2.1.4 Neurological Effects . . . . .	8
2.2.1.5 Developmental Effects . . . . .	8
2.2.1.6 Reproductive Effects . . . . .	8
2.2.1.7 Genotoxic Effects . . . . .	8
2.2.1.8 Cancer . . . . .	8
2.2.2 Oral Exposure . . . . .	9
2.2.2.1 Death . . . . .	9
2.2.2.2 Systemic Effects . . . . .	10
2.2.2.3 Immunological Effects . . . . .	29
2.2.2.4 Neurological Effects . . . . .	30
2.2.2.5 Developmental Effects . . . . .	31
2.2.2.6 Reproductive Effects . . . . .	32
2.2.2.7 Genotoxic Effects . . . . .	32
2.2.2.8 Cancer . . . . .	32
2.2.3 Dermal Exposure . . . . .	33
2.2.3.1 Death . . . . .	33
2.2.3.2 Systemic Effects . . . . .	33
2.2.3.3 Immunological Effects . . . . .	36
2.2.3.4 Neurological Effects . . . . .	36
2.2.3.5 Developmental Effects . . . . .	36
2.2.3.6 Reproductive Effects . . . . .	36
2.2.3.7 Genotoxic Effects . . . . .	36
2.2.3.8 Cancer . . . . .	37

2.3	TOXICOKINETICS . . . . .	37
2.3.1	Absorption . . . . .	37
2.3.1.1	Inhalation Exposure . . . . .	37
2.3.1.2	Oral Exposure . . . . .	37
2.3.1.3	Dermal Exposure . . . . .	38
2.3.2	Distribution . . . . .	38
2.3.2.1	Inhalation Exposure . . . . .	38
2.3.2.2	Oral Exposure . . . . .	38
2.3.2.3	Dermal Exposure . . . . .	38
2.3.3	Metabolism . . . . .	38
2.3.4	Excretion . . . . .	39
2.3.4.1	Inhalation Exposure . . . . .	39
2.3.4.2	Oral Exposure . . . . .	39
2.3.4.3	Dermal Exposure . . . . .	39
2.4	RELEVANCE TO PUBLIC HEALTH . . . . .	39
2.5	BIOMARKERS OF EXPOSURE AND EFFECT . . . . .	46
2.5.1	Biomarkers Used to Identify and/or Quantify Exposure to Cresols . . . . .	48
2.5.2	Biomarkers Used to Characterize Effects Caused by Cresols . . . . .	48
2.6	INTERACTIONS WITH OTHER CHEMICALS . . . . .	48
2.7	POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE . . . . .	49
2.8	MITIGATION OF EFFECTS . . . . .	49
2.9	ADEQUACY OF THE DATABASE . . . . .	50
2.9.1	Existing Information on Health Effects of Cresols . . . . .	50
2.9.2	Data Needs . . . . .	52
2.9.3	On-going Studies . . . . .	57
3.	CHEMICAL AND PHYSICAL INFORMATION . . . . .	59
3.1	CHEMICAL IDENTITY . . . . .	59
3.2	PHYSICAL AND CHEMICAL PROPERTIES . . . . .	59
4.	PRODUCTION, IMPORT, USE, AND DISPOSAL . . . . .	63
4.1	PRODUCTION . . . . .	63
4.2	IMPORT/EXPORT . . . . .	73
4.3	USE . . . . .	73
4.4	DISPOSAL . . . . .	75
5.	POTENTIAL FOR HUMAN EXPOSURE . . . . .	77
5.1	OVERVIEW . . . . .	77
5.2	RELEASES TO THE ENVIRONMENT . . . . .	77
5.2.1	Air . . . . .	77
5.2.2	Water . . . . .	79
5.2.3	Soil . . . . .	92
5.3	ENVIRONMENTAL FATE . . . . .	93
5.3.1	Transport and Partitioning . . . . .	93
5.3.2	Transformation and Degradation . . . . .	94
5.3.2.1	Air . . . . .	94
5.3.2.2	Water . . . . .	95
5.3.2.3	Soil . . . . .	100
5.4	LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT . . . . .	101
5.4.1	Air . . . . .	101

5.4.2	Water . . . . .	102
5.4.3	Soil . . . . .	103
5.4.4	Other Environmental Media . . . . .	104
5.5	GENERAL POPULATION AND OCCUPATIONAL EXPOSURE . . . . .	104
5.6	POPULATIONS WITH POTENTIALLY HIGH EXPOSURES . . . . .	106
5.7	ADEQUACY OF THE DATABASE . . . . .	106
5.7.1	Data Needs . . . . .	106
5.7.2	On-going Studies . . . . .	108
6.	ANALYTICAL METHODS . . . . .	111
6.1	BIOLOGICAL MATERIALS . . . . .	111
6.2	ENVIRONMENTAL SAMPLES . . . . .	113
6.3	ADEQUACY OF THE DATABASE . . . . .	115
6.3.1	Data Needs . . . . .	115
6.3.2	On-going Studies . . . . .	116
7.	REGULATIONS AND ADVISORIES . . . . .	117
8.	REFERENCES . . . . .	119
9.	GLOSSARY . . . . .	145
APPENDICES		
A.	USER'S GUIDE . . . . .	A-1
B.	ACRONYMS, ABBREVIATIONS, AND SYMBOLS . . . . .	B-1
C.	PEER REVIEW . . . . .	C-1



**LIST OF FIGURES**

2-1a	Levels of Significant Exposure to o-cresol-Oral	.	.	.	.	21
2-1b	Levels of Significant Exposure to p-cresol-Oral	.	.	.	.	23
2-1c	Levels of Significant Exposure to m-cresol-Oral	.	.	.	.	25
2-2	Existing Information on Health Effects of Cresols	.	.	.	.	51
5-1	Frequency of NPL Sites with Cresols Contamination	.	.	.	.	78



## LIST OF TABLES

2-1a	Levels of Significant Exposure to o-Cresol - Oral . . . . .	11
2-1b	Levels of Significant Exposure to p-Cresol - Oral . . . . .	15
2-1c	Levels of Significant Exposure to m-Cresol - Oral . . . . .	18
2-2	Levels of Significant Exposure to Cresols - Dermal . . . . .	34
2-3a	Genotoxicity of o-Cresol . . . . .	43
2-3b	Genotoxicity of p-Cresol . . . . .	44
2-3c	Genotoxicity of m-Cresol . . . . .	45
2-3d	Genotoxicity of a 1:1:1 Mixture of o-, p-, and m-Cresol . . . . .	47
3-1	Chemical Identity of Cresols . . . . .	60
3-2	Physical and Chemical Properties of Cresols . . . . .	61
4-1	Facilities that Manufacture or Process Cresols . . . . .	64
4-2a	Current U.S. Producers of o-Cresol . . . . .	69
4-2b	Current U.S. Producers of p-Cresol . . . . .	70
4-2c	Current U.S. Producers of m-Cresol . . . . .	71
4-2d	Current U.S. Producers of the Mixture of o-, p-, and m-Cresol . . . . .	72
4-3	Recent U.S. Imports of Cresols . . . . .	74
5-1	Releases to the Environment from Facilities that Manufacture or Process Cresols . . . . .	80
5-2a	Detection of o-Cresol in the Groundwater of Hazardous Waste Sites and Landfills . . . . .	87
5-2b	Detection of p-Cresol in the Groundwater of Hazardous Waste Sites and Landfills . . . . .	88
5-2c	Detection of m-Cresol in the Groundwater of Hazardous Waste Sites and Landfills . . . . .	89
5-2d	Detection of p- and m-Cresol in the Groundwater of Hazardous Waste Sites and Landfills . . . . .	90

LIST OF TABLES (Continued)

5-2e	Detection of Unspecified Isomers of Cresol in the Groundwater of Hazardous Waste Sites and Landfills . . . . .	91
6-1	Analytical Methods for Determining Cresols in Biological Materials . . . . .	112
6-2	Analytical Methods for Determining Cresols in Environmental Samples . . . . .	114
7-1	Regulations and Guidelines Applicable to Cresols . . . . .	118



## **1. PUBLIC HEALTH STATEMENT**

This Statement was prepared to give you information about cresols and to emphasize the human health effects that may result from exposure to it. The Environmental Protection Agency (EPA) has identified 1,177 sites on its National Priorities List (NPL). Cresols have been found at 25 of these sites. However, we do not know how many of the 1,177 NPL sites have been evaluated for cresols. As EPA evaluates more sites, the number of sites at which cresols are found may change. The information is important for you because cresols may cause harmful effects and because these sites are potential or actual sources of human exposure to cresols.

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

If you are exposed to a hazardous substance such as cresols, several factors will determine whether harmful health effects will occur and what the type and severity of those health effects will be. These factors include the dose (how much), the duration (how long), the route or pathway by which you are exposed (breathing, eating, drinking, or skin contact), the other chemicals to which you are exposed, and your individual characteristics such as age, sex, nutritional status, family traits, life style, and state of health.

### **1.1 WHAT ARE CRESOLS?**

Three types of closely related cresols exist: ortho-cresol (o-cresol), meta-cresol (m-cresol), and para-cresol (p-cresol). Pure cresols are colorless chemicals, but they may be found in brown mixtures such as creosote and cresylic acids (e.g., wood preservatives). Because these three types of cresols are manufactured separately and as mixtures, they can be found both separately and together. Cresols can be either solid or liquid, depending on how pure they are; pure cresols are solid, while mixtures tend to be liquid. Cresols have a medicinal smell (odor) and when dissolved in water, they give it a medicinal smell and taste. Cresols do not evaporate quickly from water, but in rivers and lakes, they can be removed quickly by bacteria. Dissolved cresols can pass through soil into underground water sources. This may be a problem at hazardous waste sites where cresols are buried. Once cresols are in the water table, they may stay there for months without changing. Cresols in air quickly change and break down into smaller chemicals, some of which irritate the eyes. Cresols can also irritate the eyes.

Cresols are natural products that are present in many foods and in animal and human urine. They are also present in wood and tobacco smoke,

## 1. PUBLIC HEALTH STATEMENT

crude oil, and coal tar. In addition, cresols also are man-made and used as disinfectants and deodorizers, to dissolve substances, and as starting chemicals for making other chemicals.

You will find more information on the chemical properties of cresols in Chapter 3. The uses of cresols are given in Chapter 4. More information on how cresols will behave in the environment is found in Chapter 5.

### 1.2 HOW MIGHT I BE EXPOSED TO CRESOLS?

People are most likely to be exposed to cresols by breathing, eating, or drinking them. You can breathe cresols from the air. We do not have enough information to know the background levels of cresols in air, water, or soil, but we do know where they are released. Cresols in the air can come from car exhaust. People are likely to be exposed to cresols in cities and crowded neighborhoods where traffic is heavy. Houses that are heated with coal or wood also may send cresols into the air through chimneys. People who live near factories that burn trash and garbage may breathe cresols from the smokestacks. Smokestacks of factories, electrical power plants, and oil refineries may send cresols into the air, and people who live close to these places may breathe in cresols. People who work in places that use or make cresols may breathe cresols in the air or get cresols on their skin. Cigarette smoke contains cresols, so people who smoke cigarettes are likely to breathe in more cresols than people who do not smoke. Nonsmokers may also breathe in cresols from the cigarette smoke of nearby smokers.

You may eat cresols in your food. Some foods that contain cresols are tomatoes, tomato ketchup, asparagus, cheeses, butter, bacon, and smoked foods. Drinks can also contain cresols. Coffee, black tea, wine, Scotch whiskey, whiskey, brandy, and rum can contain small amounts of cresols. People who live near garbage dumps or places where chemicals are stored or were buried, including hazardous waste sites, may have large amounts of cresols in their well water. They may drink some cresols in the tap water. At work places where cresols are produced or used, people may be exposed to large amounts of cresols. You can find more information on how much cresol is in the environment and how you can be exposed to it in Chapter 5.

### 1.3 HOW CAN CRESOLS ENTER AND LEAVE MY BODY?

Cresols can enter your body tissues quickly if you breathe air containing cresol gas or mist (droplets of cresol-containing liquid in the air), drink water or eat food that contains cresols, or allow your skin to come into contact with substances that contain cresols. If you live near a hazardous waste site, you might come into contact with cresols by drinking water, touching substances, or breathing in air that contains cresols. Cresols may also be formed in your body from other compounds, such as toluene and the amino acid tyrosine, which is present in most proteins. Most of the cresols that enter your body are quickly changed to other substances and leave

## 1. PUBLIC HEALTH STATEMENT

your body in the urine within 1 day. More information on how cresols enter and leave your body can be found in Chapter 2.

### 1.4 HOW CAN CRESOLS AFFECT MY HEALTH?

If you were to eat food or drink water contaminated with very high levels of cresols, you might feel a burning in the mouth and throat as well as stomach pains. If your skin were in contact with a substance containing high cresol levels, you might develop a rash or severe irritation. In some cases, a severe chemical burn might result. If you came into contact with high enough levels of cresols, for example, by drinking or spilling on your skin a substance containing large amounts of cresols, you might become anemic, experience kidney problems, become unconscious, or even die.

Studies in animals have not found any additional effects that would occur after long-term exposure to lower levels of cresols. It is possible that some of the effects in humans listed above, such as kidney problems and anemia, might occur at lower levels if exposure occurs over a longer time period. Effects on the nervous system, such as loss of coordination and twitching of muscles, are produced by low levels of cresols in animals, but we do not know whether low levels also cause such effects in humans. Cresols may enhance the ability of carcinogenic chemicals to produce tumors in animals, and they have some ability to interact with mammalian genetic material in the test tube, but they have not been shown to produce cancer in humans or animals. The EPA has determined that cresols are possible human carcinogens. Animal studies suggest that cresols probably would not produce birth defects or affect reproduction in humans.

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

Samples of your urine can be tested for the presence of cresols, although this test is not routinely available in hospitals and clinics. This test will not tell you whether or not you will have any adverse health effects. The urine sample would have to be taken within 1 day of your exposure to be valid. Because cresols occur naturally in people, and at levels that vary from one individual to the next, results from tests for cresol exposure should be compared to values obtained from the same individual either before exposure or several days after exposure. Small changes might be caused by variation in daily diet. You should also be aware that an increased presence of cresols in the urine could indicate exposure to toluene, a related compound, rather than cresols. However, toluene exposure would also result in elevated urinary levels of hippuric acid; cresol exposure would not. See Chapters 2 and 6 for more information about tests for exposure to cresols.

## 1. PUBLIC HEALTH STATEMENT

### **1.6 WHAT RECOMMENDATIONS HAS THE FEDERAL GOVERNMENT MADE TO HEALTH?**

The Occupational Safety and Health Administration (OSHA) sets rules for cresol levels in the workplace. The occupational exposure limit for 8-hour workdays over a 40-hour work week is 22 milligrams of cresols per cubic meter of air (22 mg/m<sup>3</sup>), which is equivalent to 5 ppm. See Chapter 7 for more information on regulations and guidelines for cresols.

### **1.7 WHERE CAN I GET MORE INFORMATION?**

If you have any more questions or concerns not covered here, please contact your state health or environmental department or:

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

This agency can also provide you with information on the location of the nearest occupational and environmental health clinic. These clinics specialize in recognizing, evaluating, and treating illnesses resulting from exposure to hazardous substances.

## 2. HEALTH EFFECTS

### 2.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective of the toxicology of cresols and a depiction of significant exposure levels associated with various adverse health effects. It contains descriptions and evaluations of studies and presents levels of significant exposure for cresols based on toxicological studies and epidemiological investigations.

There are three isomers of cresol: o-cresol, p-cresol, and m-cresol. These are described in detail in Chapter 3. In the following discussion, the effects of o-cresol and p-cresol, which have similar toxicities, are generally described prior to those of m-cresol, which is somewhat less toxic. Occasionally, data were available regarding the effects of cresol mixtures (containing the three isomers in varying proportions) and cresylic acids (technical mixtures containing other substances in addition to the three cresol isomers). These are generally discussed after the individual isomers.

### 2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals 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, developmental, reproductive, genotoxic, and carcinogenic effects. These data are discussed in terms of three exposure periods--acute (less than 15 days), 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 noobserved-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. These distinctions are intended to help the users of the document identify the levels of exposure at which adverse health effects start to appear. They should also help to determine whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the tables and figures may differ depending on the user's perspective. For example, physicians concerned with the interpretation of clinical findings in exposed persons may be interested in levels of exposure associated with "serious" effects. Public health officials and project managers concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAEL) or exposure

## 2. HEALTH EFFECTS

levels below which no adverse effects (NOAEL) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels, MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made, where data were believed reliable, for the most sensitive noncancer effect for each exposure duration. MRLs include adjustments to reflect human variability from laboratory animal data to humans.

Although methods have been established to derive these levels (Barnes et al. 1988; EPA 1989), 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.

### 2.2.1 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. 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.

#### 2.2.1.1 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/m<sup>3</sup> of o-cresol aerosol for an unspecified acute duration, suggesting that the minimal lethal exposure level for cresol aerosols may be less than 178 mg/m<sup>3</sup> (Uzhdavini et al. 1972). For longer-term exposure, the minimal lethal level may exceed 50 mg/m<sup>3</sup>, since exposure to this concentration of o-cresol for 1 month had no effect on mouse mortality (Uzhdavini et al. 1972).

## 2. HEALTH EFFECTS

### 2.2.1.2 Systemic Effects

No studies were located regarding gastrointestinal, hematological, or musculoskeletal 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  $6 \text{ mg/m}^3$ , 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  $5\text{-}9 \text{ mg/m}^3$  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  $9\text{-}50 \text{ mg/m}^3$  of o-cresol 2-6 hours/day for 1 month or more (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  $50 \text{ mg/m}^3$  of o-cresol 2 hours/day for 1 month (Uzhdavini et al. 1972). The cresol was probably given as 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  $178 \text{ mg/m}^3$ . Exposure to  $9 \text{ mg/m}^3$  for 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  $178 \text{ mg/m}^3$  (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.

## 2. HEALTH EFFECTS

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

Eye irritation was noted in mice briefly exposed to highly concentrated cresylic acid vapors; however, the exact exposure concentrations associated with irritation were not documented (Campbell 1941).

### 2.2.1.3 Immunological Effects

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

### 2.2.1.4 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  $178 \text{ mg/m}^3$  during a single exposure. Prolonged exposure (2 hours/day for 1 month) to a lower concentration of o-cresol aerosol ( $50 \text{ mg/m}^3$ ) reportedly produced degeneration of nerve cells and glial elements in mice (Uzhdavini et al. 1972). The 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 studies were located regarding the following health effects in humans or animals after inhalation exposure to cresols:

### 2.2.1.5 Developmental Effects

### 2.2.1.6 Reproductive Effects

### 2.2.1.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

### 2.2.1.8 Cancer

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

## 2. HEALTH EFFECTS

### 2.2.2 Oral Exposure

#### 2.2.2.1 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 after 26 hours (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. A woman who drank a disinfectant suspected of containing cresols died 5 days later (Della 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.

There are few reliable studies of the acute lethality of cresols in animals following oral exposure. LD<sub>50</sub> values (doses lethal to 50% of test animals) in rats were 1,350, 1,800, and 2,020 mg/kg for o-, p-, and m-cresol, respectively (Deichmann and Witherup 1944). Acute LD<sub>50</sub> values for various cresylic acid formulations in mice ranged from 500 to 2,050 mg/kg (Campbell 1941). Although LD<sub>50</sub> 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 was 200 mg/kg, and in ferrets, it was 400 mg/kg (Hornshaw et al. 1986).

Mortality data were also available for pregnant rats (BRRC 1988a) and rabbits (BRRC 1988b) given cresols 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 (BRRC 1988a). In rabbits, p-cresol appeared to produce a dose-related increase in mortality at 50-100 mg/kg/day. Rabbit mortality was not affected by exposure to o- or m-cresol (BRRC 1988b).

Exposure to o-, p-, or m-cresol at 450 mg/kg/day produced 12%-60% mortality in adult male and female rats exposed to these compounds in

## 2. HEALTH EFFECTS

two-generation reproduction studies. The elevated mortality occurred in both the F<sub>0</sub> and F<sub>1</sub> generation adults (BRRC 1989a, 1989b, 1989c). In 13-week studies of systemic toxicity in rats, elevated mortality resulted only from exposure to o-cresol at 600 mg/kg/day (MBA 1988a); in these studies, p- and m-cresol failed to produce mortality at 450-600 mg/kg/day (1988b, 1988c).

The highest NOAEL values and all reliable LD<sub>50</sub> and LOAEL values for death in each species and duration category are recorded in Tables 2-1a, 2-1b, and 2-1c and plotted in Figures 2-1a, 2-1b, and 2-1c.

### 2.2.2.2 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 2-1a, 2-1b, and 2-1c and plotted in Figures 2-1a, 2-1b, and 2-1c.

**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 (Della, 1931).

Pregnant rats (BRRC 1988b) and rabbits (BRRC 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 2.2.2.4). Based on the NOAEL of 5 mg/kg/day for m-cresol for audible respiration in pregnant rabbits (BRRC 1988a), an acute oral MRL of 0.05 mg/kg/day was calculated for this isomer, as described in footnote b in Table 2-1c. Although o- and p-cresol also had NOAEL values of 5 mg/kg/day, MRLs for these isomers were based primarily on more explicit neurological effects and are described in Section 2.2.2.4. Epithelial metaplasia of the trachea has been reported to occur in rats subjected to prolonged exposures to p-cresol (MBA 1988b). Other histopathological changes attributable to oral exposure to cresols in animals have not been reported.

**Cardiovascular Effects.** A woman who swallowed 500-750 mL of a concentrated cresol mixture exhibited tachycardia with polymorphic ventricular extrasystoles 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 (MBA 1988a), p-cresol (MBA 1988b), or m-cresol (MBA 1988c) at levels up to 600 mg/kg/day for 13 weeks, histological examination of the heart revealed no changes that indicated an adverse effect on the heart. Mild increases in relative heart weight (approximately 10%)

TABLE 2-1a. Levels of Significant Exposure to o-Cresol - Oral

Key to figure <sup>a</sup>	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
						Less serious (mg/kg/day)	Serious (mg/kg/day)	
<b>ACUTE EXPOSURE</b>								
<b>Death</b>								
1	Rat	(GO)	1x				1,350 (LD <sub>50</sub> )	Deichmann and Witherup 1944
<b>Systemic</b>								
2	Rat	(GO)	2 wk 7d/wk 1x/d	Other	50	175 (decreased body weight gain)		MBA 1988a
3	Rat	(GO)	2 wk 7d/wk 1x/d	Other		600 (decreased food intake)		TRL 1986
4	Rat	(GO)	Gd6-15	Resp Hepatic Other	175 450	450 (audible respiration) 450 (decreased body weight gain, food intake)		BRRC 1988b
5	Rabbit	(GO)	Gd6-18	Resp Hepatic Derm/oc Other	5 100 5 100	50 (audible respiration) 50 (ocular discharge)		BRRC 1988a
<b>Neurological</b>								
6	Rat	(GO)	2 wk 7d/wk 1x/d				600 (convulsions, coma)	MBA 1988a
7	Rat	(GO)	2 wk 7d/wk 1x/d			50 (CNS stimulation)	600 (convulsions)	TRL 1986
8	Rat	(GO)	Gd6-15			450 (ataxia, tremors, hypoactivity)		BRRC 1988a
9	Rabbit	(GO)	Gd6-18		5 <sup>b</sup>	50 (hypoactivity)		BRRC 1988b

TABLE 2-1a (Continued)

Key to figure <sup>a</sup>	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
						Less serious (mg/kg/day)	Serious (mg/kg/day)	
10	Ferret	(G)	1x			200 (incoordination)	300 (unconsciousness)	Hornshaw et al. 1986
11	Mink	(G)	1x		50	100 (incoordination)	300 (unconsciousness)	Hornshaw et al. 1986
Developmental								
12	Rat	(GO)	Gd6-15		175		450 (slight fetotoxicity)	BRRC 1988a
13	Rabbit	(GO)	Gd6-18		50		100 (slight fetotoxicity)	BRRC 1988b
Reproductive								
14	Rat	(GO)	Gd6-15		450			BRRC 1988a
15	Rabbit	(GO)	Gd6-18		100			BRRC 1988b
INTERMEDIATE EXPOSURE								
Death								
16	Rat	(GO)	13 wk 7d/wk 1x/d		175		600 (death)	MBA 1988a
17	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d				450 (death)	BRRC 1989a
18	Ferret	(F)	28 d		400			Hornshaw et al. 1986
19	Mink	(F)	28 d		320			Hornshaw et al. 1986

TABLE 2-1a (Continued)

Key to figure <sup>a</sup>	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
						Less serious (mg/kg/day)	Serious (mg/kg/day)	
Systemic								
20	Rat	(GO)	13 wk 7d/wk 1x/d	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Derm/oc Other	600 600 600 600 600 600 600 600 175	600 (decreased body weight gain)		MBA 1988a
21	rat	(GO)	16-20 wk 5-7 wk 1x/d	Other		450 (decreased body weight gain)		BRRC 1989a
22	Ferret	(F)	28 d	Resp Cardio Hemato Hepatic Renal Other	400 400 400 400 400 400			Hornshaw et al. 1986
23	Mink	(F)	28 d	Resp Cardio Hemato Hepatic Renal Other	320 320 320 320 320	320 (decreased body weight gain)		Hornshaw et al. 1986
24	Mink	(F)	6 mo	Other	25	105 (decreased body weight gain)		Hornshaw et al. 1986
Neurological								
25	Rat	(GO)	13 wk 7d/wk 1x/d			175 (tremors)	600 (coma, convulsions)	MBA 1988a

TABLE 2-1a (Continued)

Key to figure <sup>a</sup>	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
						Less serious (mg/kg/day)	Serious (mg/kg/day)	
26	Rat	(GO)	13 wk 7d/wk 1x/d			50 (CNS stimulation)	450 (convulsions)	TRL 1986
27	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d		30	175 (ataxia, hypoactivity)		BRRC 1989a
Developmental								
28	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d		175	450 (decreased body weight of offspring)		BRRC 1989a
29	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d		450			BRRC 1989a
Reproductive								
30	Mink	(F)	6 mo		105			Hornshaw et al. 1986

<sup>a</sup>The number corresponds to entries in Figure 2-1a.

<sup>b</sup>Used to derive an acute oral Minimum Risk Level (MRL) of 0.05 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Cardio = cardiovascular; CNS = central nervous system; d = day; Derm/oc = dermal/ocular; (F) = feed; (G) = gavage; Gastro = gastrointestinal; Gd = gestation day; (GO) = gavage - oil; Hemato = hematological; LD<sub>50</sub> = lethal dose 50% kill; LOAEL = lowest-observed-adverse-effect level; mo = month; Musc/skel = muscular/skeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week; x = time

TABLE 2-1b. Levels of Significant Exposure to p-Cresol - Oral

Key to figure <sup>a</sup>	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
						Less serious (mg/kg/day)	Serious (mg/kg/day)	
<b>ACUTE EXPOSURE</b>								
<b>Death</b>								
1	Rat	(GO)	1x				1,800 (LD <sub>50</sub> )	Deichmann and Witherup 1944
<b>Systemic</b>								
2	Rat	(GO)	2 wk 7d/wk 1x/d	Other		50 (decreased body weight gain)		MBA 1988b
3	Rat	(GO)	2 wk 7d/wk 1x/d	Other		600 (decreased body weight gain, food intake)		TRL 1986
4	Rat	(GO)	Gd6-15	Resp Hepatic Other	175 450	450 (audible respiration) 450 (decreased body weight gain, food intake)		BRRC 1988a
5	Rabbit	(GO)	Gd6-18	Resp  Hepatic Derm/oc Other	5  100 5 100	50 (difficulty breathing)  50 (ocular discharge)		BRRC 1988b
<b>Neurological</b>								
6	Rat	(GO)	2 wk 7d/wk 1x/d				600 (convulsions, coma)	MBA 1988b
7	Rat	(GO)	2 wk 7d/wk 1x/d			50 (CNS stimulation)	600 (convulsions)	TRL 1986
8	Rat	(GO)	Gd6-15			450 (ataxia, tremors, hypoactivity)		BRRC 1988a
9	Rabbit	(GO)	Gd6-18		5 <sup>b</sup>	50 (hypoactivity)		BRRC 1988b

TABLE 2-1b (Continued)

Key to figure <sup>a</sup>	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
						Less serious (mg/kg/day)	Serious (mg/kg/day)	
<b>Developmental</b>								
10	Rat	(GO)	Gd6-15		175		450 (slight fetotoxicity)	BRRC 1988a
11	Rabbit	(GO)	Gd6-18		100			BRRC 1988b
<b>Reproductive</b>								
12	Rat	(GO)	Gd6-15		450			BRRC 1988a
13	Rabbit	(GO)	Gd6-18		100			BRRC 1988b
<b>INTERMEDIATE EXPOSURE</b>								
<b>Death</b>								
14	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d		175		450 (death)	BRRC 1989b
<b>Systemic</b>								
15	Rat	(GO)	13 wk 7d/wk 1x/d	Resp	175	600 (epithelial metaplasia in trachea)		MBA 1988b
				Cardio	600			
				Gastro	600			
				Hemato	50	175 (decreased red blood cell count, hemoglobin)		
				Musc/skel	600			
				Hepatic	175	600 (increased SGOT, SGPT; inflammation)		
				Renal		50 (nephropathy)		
				Derm/oc	600			
				Other	175	600 (decreased body weight gain)		
16	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d	Other		450 (decreased body weight gain)		BRRC 1989b

TABLE 2-1b (Continued)

Key to figure <sup>a</sup>	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
						Less serious (mg/kg/day)	Serious (mg/kg/day)	
Neurological								
17	Rat	(GO)	13 wk 7d/wk 1x/d				600 (convulsions, coma)	MBA 1988b
18	Rat	(GO)	13 wk 7d/wk 1x/d			50 (CNS stimulation)	600 (convulsions)	TRL 1986
19	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d		30	175 (perioral wetness)		BRRC 1989b
Developmental								
20	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d		175	450 (decreased body weight of offspring)		BRRC 1989b
Reproductive								
21	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d		450			BRRC 1989b

<sup>a</sup>The number corresponds to entries in Figure 2-1b.

<sup>b</sup>Used to derive an acute oral Minimum Risk Level (MRL) of 0.05 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Cardio = cardiovascular; CNS = central nervous system; d = day; Derm/oc = dermal/ocular; Gastro = gastrointestinal; Gd = gestation day; (GO) = gavage - oil; Hemato = hematological; LD<sub>50</sub> = lethal dose 50% kill; LOAEL = lowest-observed-adverse-effect level; Musc/skel = muscular/skeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; wk = week; x = time

TABLE 2-1c. Levels of Significant Exposure to m-Cresol - Oral

Key to figure <sup>a</sup>	Species	Route	Exposure frequency/duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
						Less serious (mg/kg/day)	Serious (mg/kg/day)	
<b>ACUTE EXPOSURE</b>								
<b>Death</b>								
1	Rat	(GO)	1x				2,020 (LD <sub>50</sub> )	Deichmann and Witherup 1944
<b>Systemic</b>								
2	Rat	(GO)	2 wk 7d/wk 1x/d	Other		450 (decreased food intake)		TRL 1986
3	Rat	(GO)	Gd6-15	Resp Hepatic Other	175 450 175	450 (audible respiration) 450 (decreased body weight gain, food intake)		BRRC 1988a
4	Rabbit	(GO)	Gd6-18	Resp Hepatic Derm/oc Other	5 <sup>b</sup> 100 5 100	50 (audible respiration) 50 (ocular discharge)		BRRC 1988b
<b>Neurological</b>								
5	Rat	(GO)	2 wk 7d/wk 1x/d			450 (lethargy, tremors)		MBA 1988c
6	Rat	(GO)	2 wk 7d/wk 1x/d			50 (CNS stimulation)	450 (convulsions)	TRL 1986
7	Rat	(GO)	Gd6-15			450 (ataxia, tremors, hypoactivity)		BRRC 1988a
<b>Developmental</b>								
8	Rat	(GO)	Gd6-15		450			BRRC 1988a
9	Rabbit	(GO)	Gd6-18		100			BRRC 1988b

TABLE 2-1c (Continued)

Key to figure <sup>a</sup>	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
						Less serious (mg/kg/day)	Serious (mg/kg/day)	
Reproductive								
10	Rat	(GO)	Gd6-15		450			BRRC 1988a
11	Rabbit	(GO)	Gd6-18		100			BRRC 1988b
INTERMEDIATE EXPOSURE								
Death								
12	Rat	(GO)	16-20 wk 5-7d/wk 1x/d		175		450 (death)	BRRC 1988c
Systemic								
13	Rat	(GO)	13 wk 7d/wk 1x/d	Resp Cardio Gastro Hemato Musc/skel Hepatic Renal Derm/oc Other	450 450 450 450 450 450 450 450	150 (decreased body weight gain)		MBA 1988c
14	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d	Other		450 (decreased body weight gain)		BRRC 1989c
Neurological								
15	Rat	(GO)	13 wk 7d/wk 1x/d			450 (lethargy, tremors)		MBA 1988c
16	Rat	(GO)	13 wk 7d/wk 1x/d			50 (CNS stimulation)	450 (convulsions)	TRL 1986

TABLE 2-1c (Continued)

Key to figure <sup>a</sup>	Species	Route	Exposure frequency/ duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference
						Less serious (mg/kg/day)	Serious (mg/kg/day)	
17	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d		30	175 (perioral wetness)		BRRC 1989c
Developmental								
18	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d		175	450 (reduced pup survival)		BRRC 1989c
Reproductive								
19	Rat	(GO)	16-20 wk 5-7 d/wk 1x/d		450			BRRC 1989c

<sup>a</sup>The number corresponds to entries in Figure 2-1c.

<sup>b</sup>Used to derive an acute oral Minimum Risk Level (MRL) of 0.05 mg/kg/day; dose divided by an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Cardio = cardiovascular; CNS = central nervous system; d = day; Derm/oc = dermal/ocular; Gastro = gastrointestinal; Gd = gestation day; (GO) = gavage - oil; Hemato = hematological; LD<sub>50</sub> = lethal dose 50% kill; LOAEL = lowest-observed-adverse-effect level; Musc/skel = muscular/skeletal; NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week; x = time

FIGURE 2-1a. Levels of Significant Exposure to o-Cresol - Oral

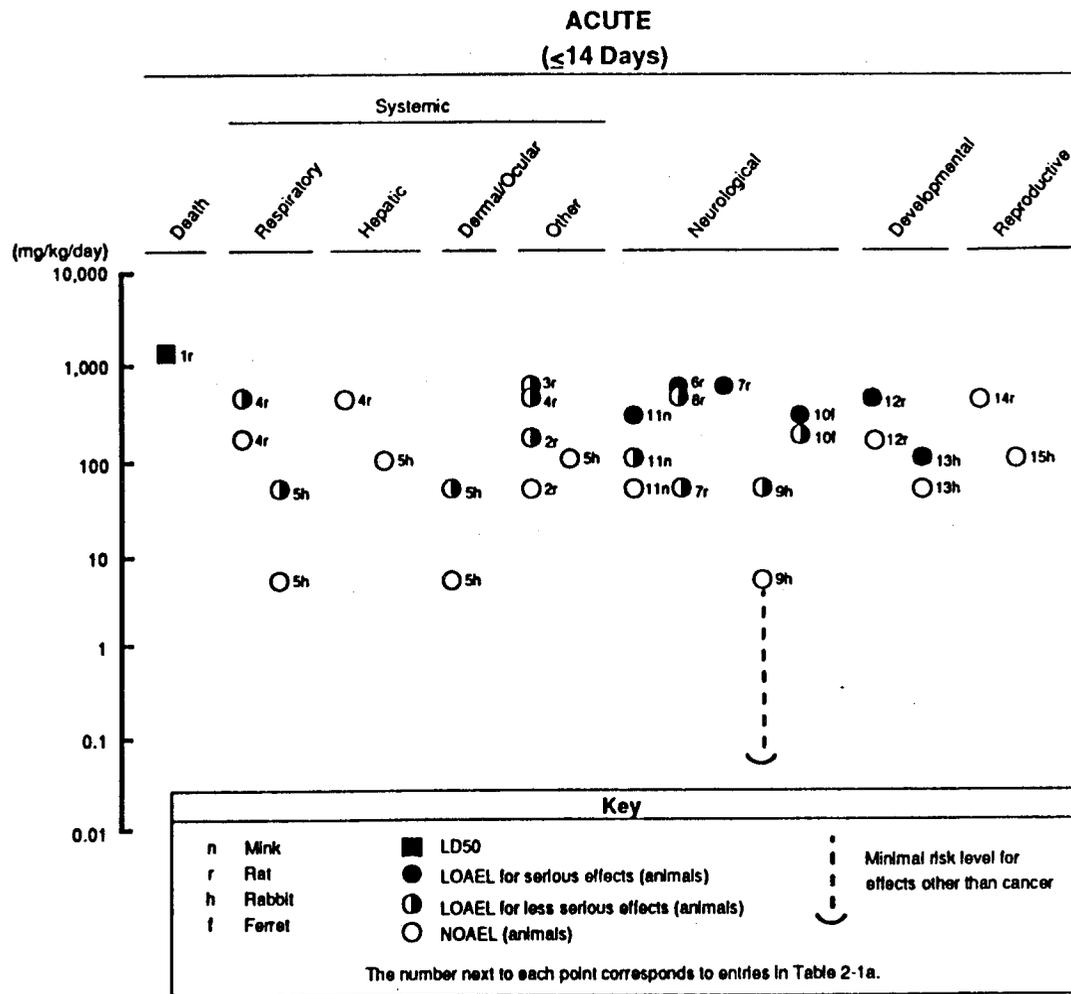


FIGURE 2-1a (Continued)

INTERMEDIATE  
(15-364 Days)

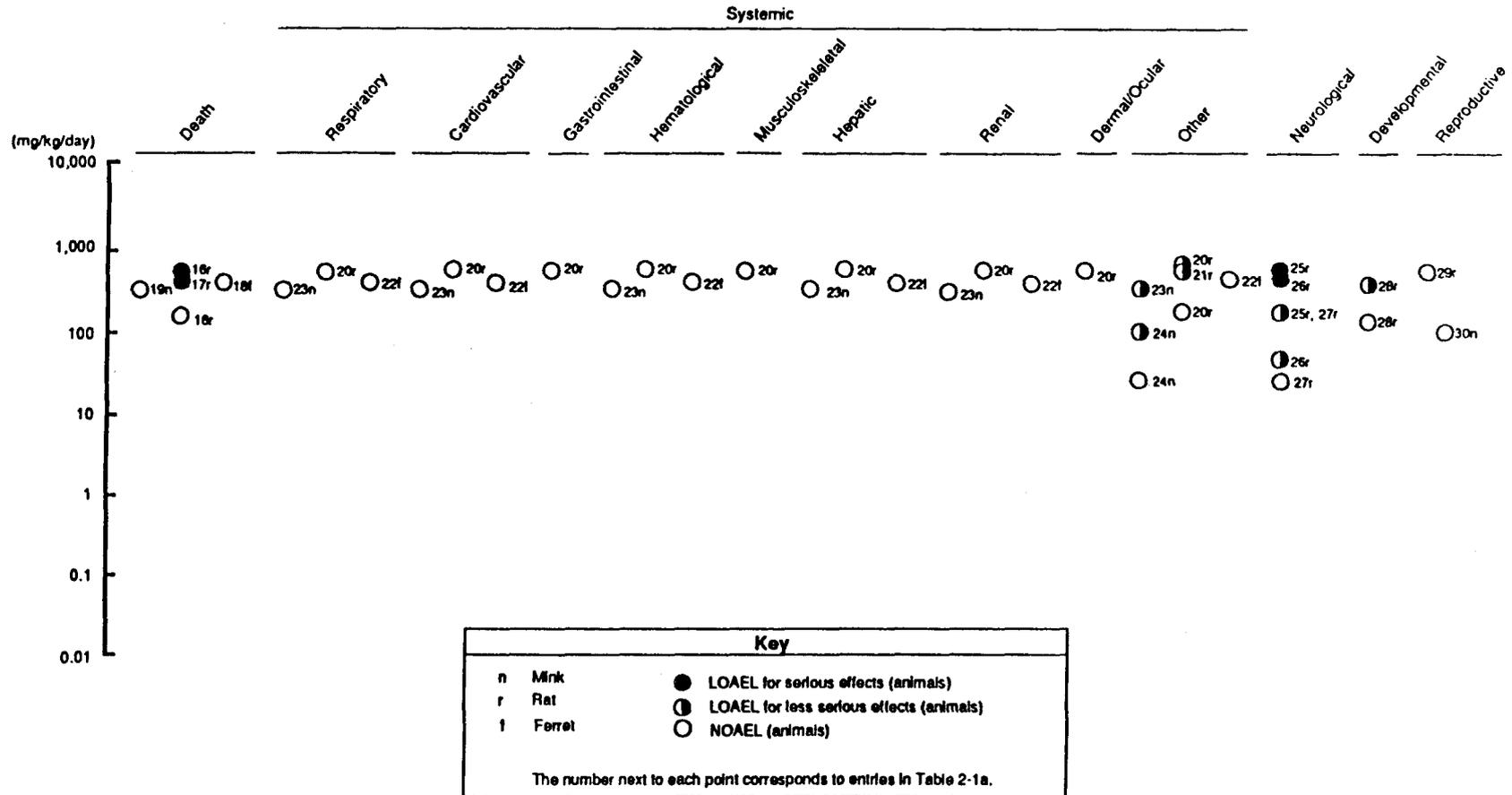


FIGURE 2-1b. Levels of Significant Exposure to p-Cresol - Oral

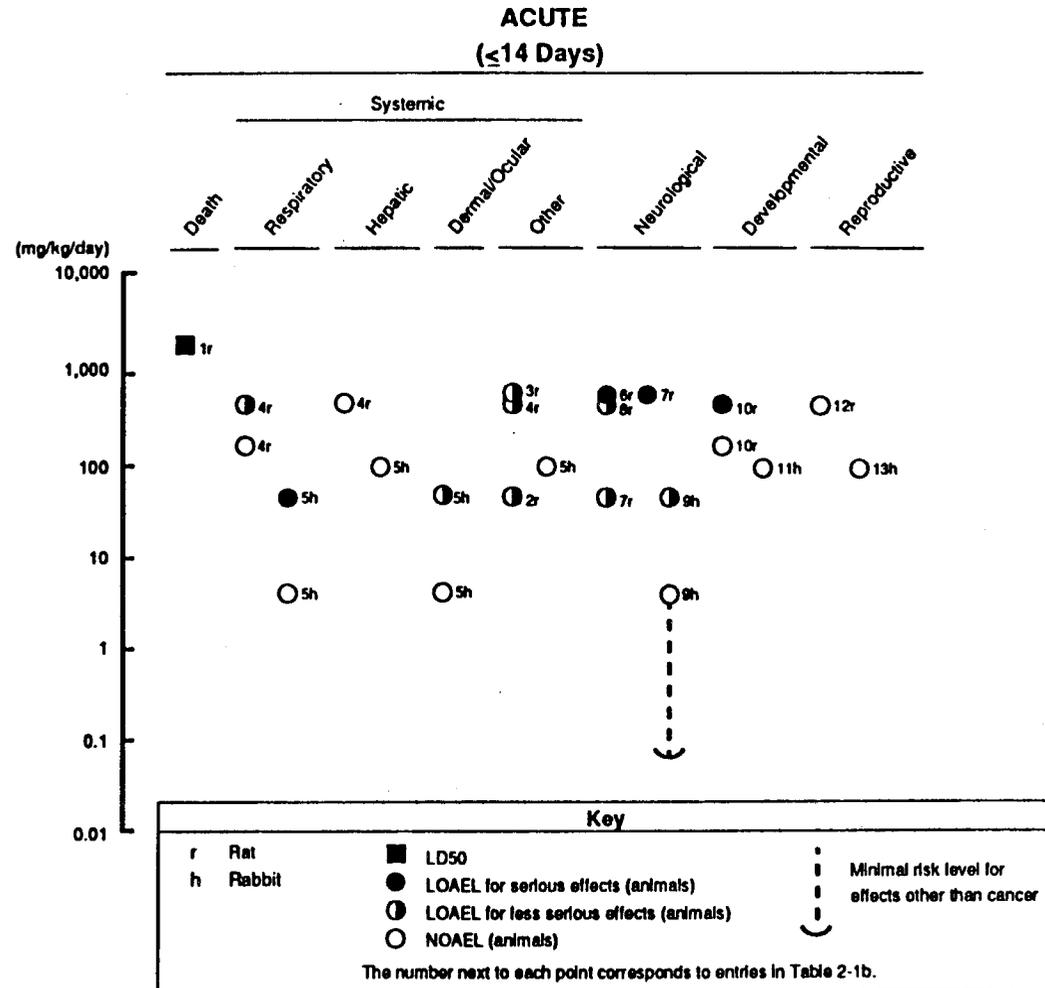
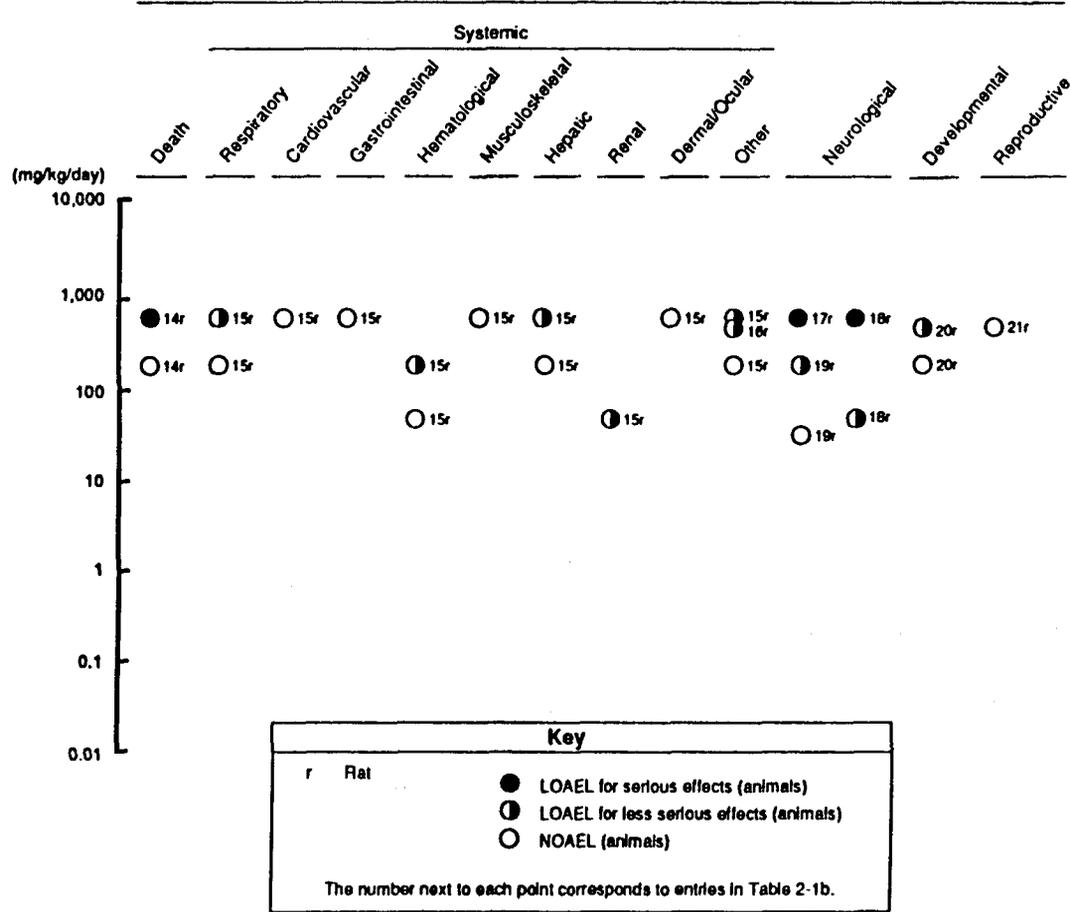
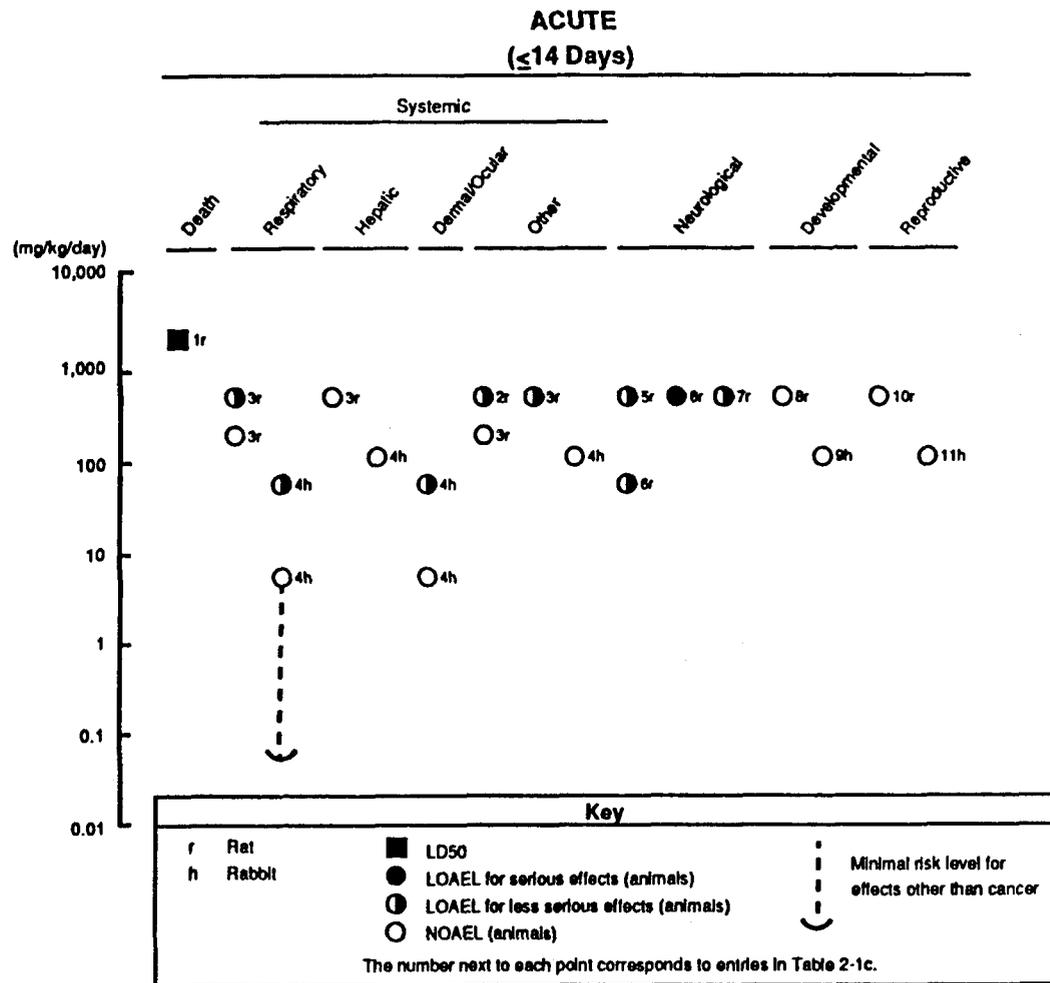


FIGURE 2-1b (Continued)

INTERMEDIATE  
(15-364 Days)

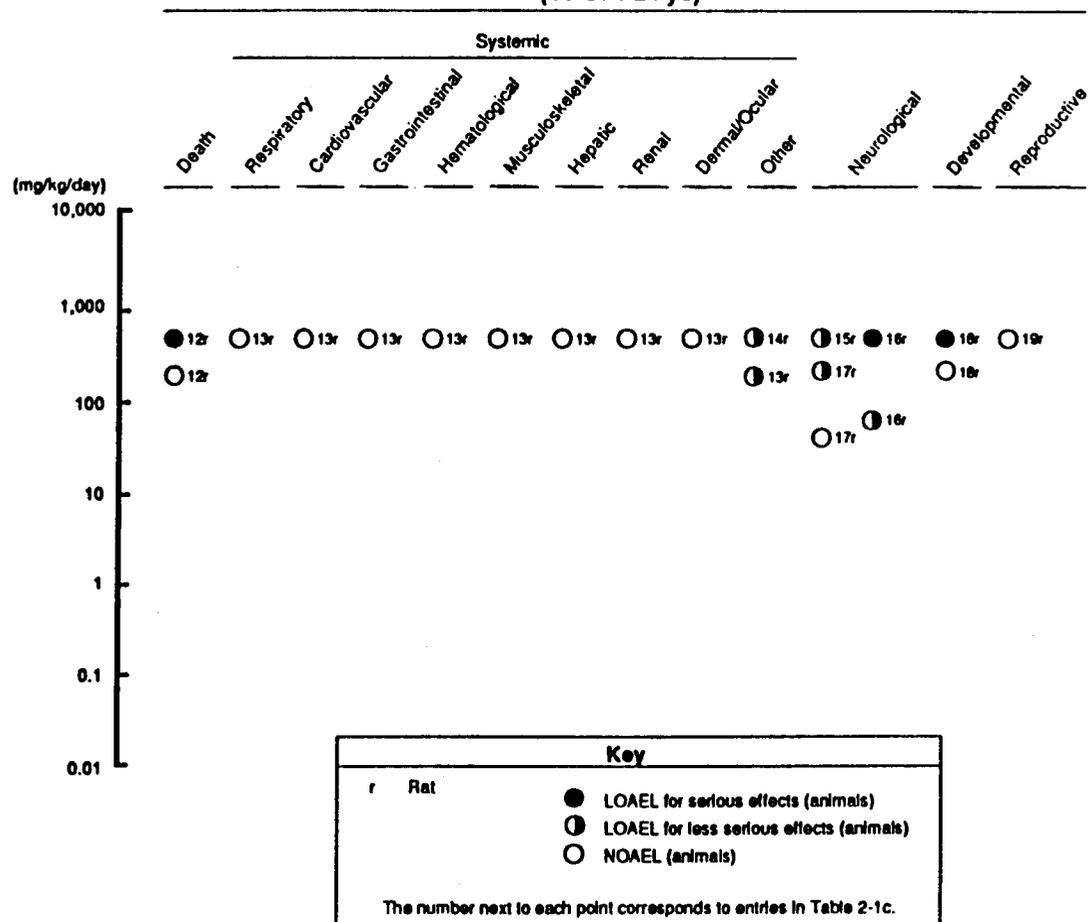


**FIGURE 2-1c. Levels of Significant Exposure to m-Cresol - Oral**



**FIGURE 2-1c (Continued)**

**INTERMEDIATE  
(15-364 Days)**



## 2. HEALTH EFFECTS

have been reported in animals exposed to cresols (Hornshaw et al. 1986; MBA 1988c), but the significance of these changes is doubtful without accompanying histological effects. Thus, the heart has not been shown to be a target organ for cresols.

**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 (Jougard 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).

Rats exposed to cresols for 13 weeks by gavage in corn oil did not have gastrointestinal lesions (MBA 1988a, 1988b, 1988c). However, p-cresol given in the feed produced an increased incidence of mild and moderate hyperplasia of the forestomach of hamsters exposed for 20 weeks (Hirose et al. 1986). This result suggests that p-cresol may have the potential to act as a promoter in forestomach carcinogenesis. Rats exposed to a similar concentration in the feed for a shorter time period did not have this effect, although this species is, in general, less sensitive to inducers of forestomach lesions (Altmann et al. 1986). Insufficient data were provided to derive doses given in the two feeding studies, so these studies were not used to derive NOAEL or LOAEL values.

**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 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). 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 (Jougard et al. 1971). Isaacs (1922) did not find abnormalities in the blood of any of 52

## 2. HEALTH EFFECTS

patients who had ingested cresols, but the specific analyses performed were not reported. 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 exposed to 175 mg/kg of p-cresol for 13 weeks (MBA 1988b), but the effects were not produced by the other isomers (MBA 1988a, 1988c). Mild and contradictory changes in red blood cell count seen in mink were of questionable significance (Hornshaw et al. 1986). Based on the available information, oral exposure to cresols at 175 mg/kg/day or above may be associated with changes in red blood cell and hematocrit in animals.

**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 for 13 weeks (MBA 1988a, 1988b, 1988c).

**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).

Following oral exposure of animals to cresols, increased relative liver weight and increased serum transaminase levels were reported. Relative liver weights in rats increased following exposure to high levels (450 mg/kg/day) of cresols during pregnancy (BRRC 1988a). Longer-term exposure to 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 glutamic oxaloacetic transaminase (SGOT) and serum glutamic pyruvic transaminase (SGPT) were seen in female rats given 600 mg/kg/day of p-cresol for 13 weeks and appeared to be correlated with the presence of hepatic inflammation (MBA 1988b).

**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

## 2. HEALTH EFFECTS

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). 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).

Effects seen in animals orally exposed to cresols included mild increases in kidney weight (Hornshaw et al. 1986; MBA 1988b) and a slight increase, which did not appear to be dose related, in the incidence of histological changes characteristic of chronic nephropathy in male rats exposed to p-cresol for 13 weeks (MBA 1988b). No changes were seen in similar studies of o- and m-cresol (MBA 1988a, 1988c). The evidence is not conclusive as to whether the kidney is a target organ of cresol toxicity in animals.

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

Pregnant rabbits repeatedly given 50 mg/kg/day or more of the cresol isomers during gestation were found to have significant amounts of ocular discharge, some of which may have been due to hemorrhaging (BRRC 1988b), but no gross or microscopic lesions of the eye or skin were found in rats given cresols orally for 13 weeks (MBA 1988a, 1988b, 1988c).

**Other Systemic Effects.** No studies were located regarding other systemic effects in humans following oral exposure to cresols.

In animals, a common response to oral cresols exposure was decreased growth, often associated with decreased food consumption (BRRC 1988a, 1989a, 1989b, 1989c; Hornshaw et al. 1986; MBA 1988a, 1988b, 1988c; TRL 1986). The lowest dose to produce this effect in a systemic toxicity study was 50 mg/kg/day of p-cresol in rats (MBA 1988b). An even lower dose, 30 mg/kg/day of m-cresol, produced low body weight in F<sub>1</sub> adult rats in a two-generation reproduction study (BRRC 1989c). None of these studies involved pair-feeding protocols, so the significance of any reported weight gain reductions is uncertain, even though food consumption was usually monitored as well.

### 2.2.2.3 Immunological Effects

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

No immunotoxicity tests were included in acute animal studies, and the only immunological end points examined in longer-term animal studies were spleen weight and histopathology. Spleen weight was unaffected by 28-day

## 2. HEALTH EFFECTS

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 rats given 600 mg/kg/day of p-cresol for 13 weeks, but relative spleen weight was unaffected and no lesions were found (MBA 1988b); no changes were found in rats given o- or m-cresol (MBA 1988a, 1988c). NOAEL values were not derived from these studies because these end points are not sufficiently sensitive to assess subtle immunological effects.

### 2.2.2.4 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, has been reported in animals acutely exposed to cresols (BRRRC 1988a, 1988b; Deichmann and Witherup 1944; Hornshaw et al. 1986; TRL 1986). The lowest dose at which neurological effects were reported was 50 mg/kg/day, which produced hypoactivity and audible respiration in pregnant female rabbits repeatedly dosed with o- or p-cresol during gestation (BRRRC 1988b). Based on the NOAEL values of 5 mg/kg/day for o- and p-cresol in this study, acute oral MRLs of 0.05 mg/kg/day were calculated, as described in footnote b in Tables 2-1a and 2-1b. In rats, effects such as hypoactivity, rapid labored respiration, and hyperreactivity 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 (TRL 1986). A host of clinical observations indicative of 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 few neurobehavioral tests were significantly altered by treatment, and 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). Other studies of prolonged oral exposure to cresols had similar findings (BRRRC 1989a, 1989b, 1989c; Hornshaw et al. 1986; MBA 1988a,

## 2. HEALTH EFFECTS

1988b, 1988c). The only intermediate-duration studies to determine NOAEL values for neurological effects were the two-generation reproduction studies in rats (BRRC 1989a, 1989b, 1989c). Neurological NOAEL values of 30 mg/kg/day were reported for all three cresol isomers in these studies.

The highest NOAEL values and all reliable LOAEL values for neurological effects in each species and duration category are recorded in Tables 2-1a, 2-1b, and 2-1c and plotted in Figures 2-1a, 2-1b, and 2-1c.

### 2.2.2.5 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 throughout gestation (audible respiration, reduced body weight gain, reduced food consumption, ataxia, tremors, and hypoactivity) occurred at 450 mg/kg/day. 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 (BRRC 1988a). In rabbits dosed throughout gestation, maternal effects, such as audible respiration, ocular discharge, and hypoactivity, were seen following exposure to o- or p-cresol at 50 mg/kg/day. At 100 mg/kg/day, o-cresol produced slight fetotoxicity (increased incidences of subepidermal hematoma on the head and poorly ossified sternbrae), but no other effects at any dose. Neither p- nor m-cresol produced any developmental effects in this study (BRRC 1988b).

Fetotoxicity was also observed at parenterally-toxic doses in two-generation reproduction studies. Rats treated with 450 mg/kg/day of o- and p-cresol produced F<sub>1</sub> offspring that had reduced body weight 4-6 weeks after birth. This dose also produced overt toxicity in the parents (BRRC 1989a, 1989b). 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 produced effects on body weight of offspring at the low dose of 30 mg/kg/day and reduced pup survival during lactation at the high dose of 450 mg/kg/day (BRRC 1989c). Parental toxicity was also reported at the low dose of 30 mg/kg/day, but the possibility remains that developmental effects could occur at doses lower than those producing parental toxicity; therefore, this study is inconclusive regarding the developmental toxicity of this isomer.

NOAEL and LOAEL values derived from these studies are recorded in Tables 2-1a, 2-1b, and 2-1c and plotted in Figures 2-1a, 2-1b, and 2-1c.

## 2. HEALTH EFFECTS

### 2.2.2.6 Reproductive Effects

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

No reproductive effects were seen in animals exposed to cresols by ingestion. Developmental toxicity studies in which pregnant rats (BRRC 1988a) and rabbits (BRRC 1988b) were exposed to cresols 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 and mink also failed to detect adverse effects on reproductive function or lesions in reproductive tissues (BRRC 1989a, 1989b, 1989c; Hornshaw et al. 1986). 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 cresols for prolonged periods in other studies (Hornshaw et al. 1986; MBA 1988a, 1988b, 1988c). NOAEL values derived from these studies are recorded in Tables 2-1a, 2-1b, and 2-1c and plotted in Figures 2-1a, 2-1b, and 2-1c.

### 2.2.2.7 Genotoxic Effects

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

Dominant lethal assays in mice were performed using o- and p-cresols. Male mice were given a single dose of o-cresol (0, 75, 250, or 750 mg/kg) or p-cresol (0, 100, 275, or 550 mg/kg) by gavage in corn oil and mated to untreated females in order to assess dominant lethal effects. The matings were continued for 6 weeks so that all stages of male germ cell development were tested. Exposure to neither cresol isomer had any effect on the occurrence of dominant lethal mutations in mice (Hazleton Labs 1989a, 1989b). m-Cresol was tested for ability to induce chromosomal aberrations in mouse bone marrow *in vivo*. Male and female mice were given a single dose of 0, 96, 320, or 960 mg/kg by gavage in corn oil and sacrificed after 6, 24, and 48 hours for extraction and examination of bone marrow. No effect on chromosomal aberrations was found (Hazleton Labs, 1989c).

Other genotoxicity studies are discussed in Section 2.4.

### 2.2.2.8 Cancer

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

Lifetime cancer bioassays using orally exposed animals were not located. In a shorter-term study, exposure to p-cresol in the feed for 20 weeks produced an increased incidence of forestomach hyperplasia in hamsters,

## 2. HEALTH EFFECTS

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. p-Cresol did not produce forestomach hyperplasia in rats (Altmann et al. 1986), but rats are generally less sensitive than hamsters to inducers of forestomach lesions.

### 2.2.3 Dermal Exposure

#### 2.2.3.1 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. 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 LD<sub>50</sub> 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 2-2. Based on these LD<sub>50</sub> values, p-cresol appears to be more toxic dermally than o-cresol, with m-cresol being the least toxic of the three isomers.

#### 2.2.3.2 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).

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 2-2. Levels of Significant Exposure to Cresols - Dermal

Species	Exposure frequency/duration	System	NOAEL (mg/kg/day)	LOAEL (effect)		Reference	Isomer
				Less serious (mg/kg/day)	Serious (mg/kg/day)		
ACUTE EXPOSURE							
Death							
Rabbit	1 d 24hr/d				890 (LD <sub>50</sub> )	Vernot et al. 1977	o-
Rabbit	1 d 24hr/d				300 (LD <sub>50</sub> )	Vernot et al. 1977	p-
Rabbit	1 d 24hr/d				2,830 (LD <sub>50</sub> )	Vernot et al. 1977	m-
Rabbit	1 d 24hr/d				2,000 (LD <sub>50</sub> )	Vernot et al. 1977	mix
Systemic							
Rabbit	1 d 4hr/d	Derm/oc			147 (skin corrosion)	Vernot et al. 1977	o-
Rabbit	1 d 4hr/d	Derm/oc			147 (skin corrosion)	Vernot et al. 1977	p-
Rabbit	1 d 4hr/d	Derm/oc			147 (skin corrosion)	Vernot et al. 1977	m-
Rabbit	1 d 4hr/d	Derm/oc			147 (skin corrosion)	Vernot et al. 1977	mix

d = day; Derm/oc = dermal/ocular; hr = hour; LD<sub>50</sub> = lethal dose 50% kill; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

## 2. HEALTH EFFECTS

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 2.2.2.2).

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).

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

**Dermal/Ocular 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. 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 2-2.

## 2. HEALTH EFFECTS

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 author suggests that only p-cresol is 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.

**Other Systemic Effects.** No studies were located regarding other systemic effects in humans or animals following dermal exposure to cresols.

### 2.2.3.3 Immunological Effects

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

### 2.2.3.4 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 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.

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

### 2.2.3.5 Developmental Effects

### 2.2.3.6 Reproductive Effects

### 2.2.3.7 Genotoxic Effects

Genotoxicity studies are discussed in Section 2.4.

## 2. HEALTH EFFECTS

### 2.2.3.8 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. The EPA has assigned all three cresol isomers to cancer group C as possible human carcinogens based on the results of this study (IRIS 1991).

## 2.3 TOXICOKINETICS

### 2.3.1 Absorption

#### 2.3.1.1 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 (Campbeil 1941; Kurlyandsky et al. 1975; Uzhdavini et al. 1972).

#### 2.3.1.2 Oral Exposure

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

## 2. HEALTH EFFECTS

Rabbits were orally exposed to all three cresol isomers by Bray et al. (1950). 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.

### 2.3.1.3 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. No studies were located that sought to quantify the rate or extent of absorption in intact humans. 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).

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

### 2.3.2 Distribution

#### 2.3.2.1 Inhalation Exposure

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

#### 2.3.2.2 Oral Exposure

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

#### 2.3.2.3 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.

### 2.3.3 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.

## 2. HEALTH EFFECTS

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.

### 2.3.4 Excretion

#### 2.3.4.1 Inhalation Exposure

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

#### 2.3.4.2 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).

#### 2.3.4.3 Dermal Exposure

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

## 2.4 RELEVANCE TO PUBLIC HEALTH

Effects associated with exposure to cresols in humans include irritation and burning of skin, eyes, mouth, and throat, abdominal pain and vomiting, tachycardia and ventricular fibrillation, hemolytic anemia, liver and kidney damage, facial paralysis, coma, and death. Studies in animals have documented the irritative and neurological effects of cresols, and provided some evidence for target organ effects on the kidney, liver, and the blood. Other effects seen in animals, but not observed in humans, include slightly reduced body weight gain, mild developmental effects, and tumor promotion.

**Inhalation MRLs were not derived for cresols due to the lack of acceptable data. Acute oral MRLs for o-, p-, and m-cresols were based on the occurrence of neurological effects (and secondary respiratory stress) in exposed animals. For all three cresol isomers, the acute MRL was calculated to be 0.05 mg/kg/day by applying an uncertainty factor of 100 (10 for**

## 2. HEALTH EFFECTS

extrapolation from animals to humans and 10 for human variability) to the NOAEL for neurological/respiratory effects of 5 mg/kg/day obtained in pregnant rabbits dosed during gestation (BRRC 1988b). The most prominent neurological/respiratory effects observed at the LOAEL of 50 mg/kg/day were hypoactivity and audible respiration. Similar effects were reported in rats exposed to 50 mg/kg/day in a study specifically designed to investigate neurological effects (TRL 1986).

Intermediate oral MRLs for all three cresol isomers could have been calculated based on NOAEL values of 30 mg/kg/day for neurological effects in two-generation reproductive studies in rats (BRRC 1989a, 1989b, 1989c). However, these intermediate oral MRLs were not derived because they would have been less protective than the acute MRLs. This apparent anomaly reflects the fact that lower doses were employed in the developmental toxicity study used as the basis for the acute MRLs than in longer term studies. Dermal MRLs were not derived for cresols due to the lack of an appropriate methodology.

**Death.** Human deaths have occurred following ingestion or dermal exposure to highly concentrated solutions of cresols and as a result of intentional intravaginal or intrauterine exposure for the purpose of inducing abortion (Finzer 1961; Presley and Brown 1956; Vance 1945). Exposure levels associated with human deaths have not been reliably reported. However, based on crude estimates for cases of accidental or intentional ingestion of cresol-containing formulations, the lethal oral exposure level for humans appeared to be at or above 2 g/kg (Chan et al. 1971). The lethal dose was also approximately 2 g/kg following dermal exposure (Green 1975). Death following cresol exposure is apparently caused by intravascular hemolysis and thrombosis.

Studies in animals have shown that cresols can be lethal when exposure is through the inhalation, oral, or dermal routes. The lethal exposure levels varied from 1,350 to 2,020 mg/kg in orally exposed rats and 300 to 2,830 mg/kg in dermally exposed rabbits, depending on the isomer tested. By either route, m-cresol was the least toxic isomer. Lethal levels were not determined in inhalation studies, but one study (Campbell 1941) reported that brief repeated inhalation exposures produced lethality at concentrations that were not lethal when a single, longer exposure period was used. The estimated lethal dose in humans (2,000 mg/kg) is within the range of values reported in other species. Other observations regarding the lethality of cresols to animals might also apply to acutely-exposed humans.

**Systemic Effects.** Effects reported in humans include mucosal irritation following inhalation; mouth and throat burns, abdominal pain, vomiting, tachycardia and ventricular fibrillation, hemolytic anemia, and impaired kidney function following ingestion of highly concentrated solutions; and hemolytic anemia, anuria, elevated blood urea levels, and severe skin corrosion following spilling of highly concentrated solutions on the skin.

## 2. HEALTH EFFECTS

Autopsies of people who died following cresol exposure revealed gross lesions in the lungs, pancreas, liver, and kidneys, although these data cannot be considered reliable indicators of target organ effects. Data from animal studies generally support the portal of entry effects reported in humans, such as mucosal irritation following inhalation, gastrointestinal irritation following oral administration, and severe skin damage following dermal application. Other effects, such as hemolytic anemia, have not been reported in animals; however, the doses given in the animal studies that examined toxic effects to the blood are probably well below those to which the humans were exposed. Other acute effects reliably reported to occur in animals include labored breathing, ocular discharge, and reduced body weight gain.

No longer-term exposure data are available for humans. In rats, intermediate-duration oral exposure to o- or m-cresol produced reductions in body weight gain and occasional organ weight changes. In addition to these effects, p-cresol produced some more notable changes, such as an increased incidence of epithelial metaplasia in the trachea, mild reductions in hemoglobin, hematocrit and red blood cell counts, increased serum transaminase levels (indicative of liver damage and associated with liver inflammation in this study), and mild nephropathy. It is not known if similar changes would occur in humans if they were exposed to cresols for extended periods.

**Immunological Effects.** Immunological effects of cresols in humans have not been reported. The immunotoxicity potential of cresol has not been evaluated in animals.

**Neurological Effects.** Coma has frequently been noted in case reports of humans exposed to highly concentrated cresols taken in the mouth or spilled on the skin. Facial paralysis was observed in one case of dermal exposure. Coma has also been observed in animals exposed to high doses. Other neurological effects observed in animals include lethargy, incoordination, muscle tremors, and convulsions. Cresols produce neurological effects following oral, dermal, and inhalation exposure, and although severity increases with dose, even low doses produce some of these effects. The acute oral MRL of 0.05 mg/kg/day was based on hypoactivity in pregnant female rabbits.  $CD_{50}$  values (dose that produced convulsions in 1/2 of the animals tested) for the production of myoclonic convulsions in anesthetized mice given cresols by intraperitoneal injection were similar for all three isomers, increasing from 102 mg/kg for m-cresol to 110 mg/kg for p-cresol to 117 mg/kg for o-cresol (Angel and Rogers 1972). No reliable studies have reported structural damage to the nervous system or other irreversible effects. The mechanism by which cresols affect the nervous system is unknown. Studies attempting to investigate cresol neurotoxicity from a mechanistic point of view have reported enzymatic changes in the brains of rats after extended oral exposure to o-cresol (Savolainen 1979), and excitation of somatosensory evoked potential and electroencephalogram at levels producing muscle tremors and hyperactivity in rats that were acutely exposed to intravenous o-cresol (Mattsson et al. 1989).

## 2. HEALTH EFFECTS

Although only severe neurological effects have been reported in humans, the occurrence of less severe effects in animals suggests that these more subtle effects might occur in humans as well, but at doses far lower than those producing gross effects.

**Developmental Effects.** No developmental effects have been reported in humans exposed to cresols. Slightly elevated incidences of minor variations in rats and rabbits exposed to o- and p-cresols at maternally toxic doses indicate that these chemicals are weak developmental toxicants capable of producing mild fetotoxic effects in these species. Fetotoxicity was also indicated by effects on pup body weight and, for m-cresol, survival at parenterally toxic doses in two-generation reproduction studies in rats. Based on these data, it is not likely that cresols pose a serious developmental hazard to humans; however, the fact that they produce some effects on the developing fetus in animals suggests that care, should be taken to limit exposure in pregnant women.

**Reproductive Effects.** No reproductive effects have been reported in humans exposed to cresols. Although several studies in animals, including two-generation studies in rats and mink, examined the reproductive effects of cresols, no such effects were seen even at parenterally toxic doses. These results suggest that cresols do not have reproductive effects in animals or humans.

**Genotoxic Effects.** The genotoxic effects of cresols have been well studied. Genotoxicity assays on o-cresol are shown in Table 2-3a. Positive results were reported only in assays for chromosomal aberrations (Hazleton Labs 1988a) and sister chromatid exchange (Litton Bionetics 1981) in Chinese hamster ovary cells. The positive response in the assay for sister chromatid exchange is in contrast to negative results for sister chromatid exchange in human fibroblasts *in vitro* and mouse bone marrow, alveolar macrophages, and regenerating liver cells *in vivo* (Cheng and Kligerman, 1984). Although there are some discrepancies in the data, these findings suggest that o-cresol may be clastogenic under certain circumstances. The results of genotoxicity assays on p-cresol are shown in Table 2-3b. As was the case for o-cresol, p-cresol produced chromosomal aberrations in Chinese ovary cells (Hazleton Labs 1988a), but did not produce sister chromatid exchange in *in vitro* or *in vivo* assays by Cheng and Kligerman (1984). p-Cresol also produced cell transformation in mouse BALB/C-3T3 cells (Hazleton Labs, 1988d) and a minor increase in DNA synthesis in human peripheral lymphocytes *in vitro* (Daugherty and Franks 1986). These results suggest p-cresol has broader genotoxic activity than was implicated for o-cresol. Table 2-3c shows the results of genotoxicity testing of m-cresol. A weak positive result was reported for SV40 induction in Syrian hamster kidney cells (Moore and Coohill 1983), but all other test results were negative, indicating that m-cresol is probably not genotoxic. The apparent genotoxicity of o- and p-cresols is supported by the finding that a 1:1:1 mixture of the three cresol isomers was positive in tests

TABLE 2-3a. Genotoxicity of o-Cresol

Species (test system)	End point	Results		Reference
		With activation	Without activation	
<u>Prokaryotic organisms (in vitro):</u>				
<u>Salmonella typhimurium</u> on plates	Reverse mutation	-	-	Douglas et al. 1980; Florin et al. 1980; Haworth et al. 1983; Litton Bionetics 1981; Pool and Lin 1982
<u>Eukaryotic organisms (in vitro):</u>				
Mammalian cells:				
L5178Y mouse lymphoma cells	Forward mutation	-	-	Litton Bionetics 1981
Primary rat hepatocytes	Unscheduled DNA synthesis	No data	-	Litton Bionetics 1981
Chinese hamster ovary cells	Chromosomal aberrations	+	+	Hazleton Labs 1988a
Chinese hamster ovary cells	Sister chromatid exchange	+	+	Litton Bionetics 1981
Cultured human fibroblasts	Sister chromatid exchange	No data	-	Cheng and Kligerman 1984
Mouse BALB/C-3T3 cells	Cell transformation	-	-	Hazleton Labs 1988b; Litton Bionetics 1981
<u>Eukaryotic organisms (in vivo):</u>				
<u>Drosophila melanogaster</u>	Sex-linked recessive lethal	No data	-	Hazleton Labs 1989d
Mouse	Dominant lethal	No data	-	Hazleton Labs 1989a
Mouse	Sister chromatid exchange (bone marrow, alveolar macrophages, and regener- ating liver cells)	No data	-	Cheng and Kligerman 1984

- = negative result; + = positive result

TABLE 2-3b. Genotoxicity of p-Cresol

Species (test system)	End point	Results		Reference
		With activation	Without activation	
<b>Prokaryotic organisms (<i>in vitro</i>):</b>				
<u>Salmonella typhimurium</u> on plates	Reverse mutation	-	-	Douglas et al. 1980; Florin et al. 1980; Haworth et al. 1983; Pool and Lin 1982
<b>Eukaryotic organisms (<i>in vitro</i>):</b>				
Mammalian cells:				
L5178Y mouse lymphoma cells	Forward mutation	-	-	Hazleton Labs 1988c
Human peripheral lymphocytes	Semiconservative/repair DNA synthesis	No data	(+)	Daugherty and Franks 1986
Chinese hamster ovary cells	Chromosomal aberrations	+	+	Hazleton Labs 1988a
Cultured human fibroblasts	Sister chromatid exchange	No data	-	Cheng and Kligerman 1984
Mouse BALB/C-3T3 cells	Cell transformation	No data	+	Hazleton Labs 1988d
<b>Eukaryotic organisms (<i>in vivo</i>):</b>				
<u>Drosophila melanogaster</u>	Sex-linked recessive lethal	No data	-	Hazleton Labs 1989e
Mouse	Dominant lethal	No data	-	Hazleton Labs 1989b
Mouse	Sister chromatid exchange (bone marrow, alveolar macrophages, and regenerating liver cells)	No data	-	Cheng and Kligerman 1984

- = negative result; + = positive result; (+) = weakly positive

TABLE 2-3c. Genotoxicity of m-Cresol

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms ( <u>in vitro</u> ): <u>Salmonella typhimurium</u> on plates	Reverse mutation	-	-	Douglas et al. 1980; Florin et al. 1980; Haworth et al 1983; Pool and Lin 1982
Eukaryotic organisms ( <u>in vitro</u> ): Mammalian cells:				
Syrian hamster kidney cells	SV40 induction	No data	(+)	Moore and Coohill 1983
L5178Y mouse lymphoma cells	Forward mutation	-	-	Hazleton Labs 1988c
Freshly cultured rat hepatocytes	Unscheduled DNA synthesis	No data	-	Hazleton Labs 1988e
Chinese hamster ovary cells	Chromosomal aberrations	-	-	Hazleton Labs 1988a
Cultured human fibroblasts	Sister chromatid exchange	No data	-	Cheng and Kligerman 1984
Mouse BALB/C-3T3 cells	Cell transformation	-	-	Hazleton Labs 1986d, 1986f
Eukaryotic organisms ( <u>in vivo</u> ):				
Mouse	Chromosomal aberrations (bone marrow)	No data	-	Hazleton Labs 1989c
Mouse	Sister chromatid exchange (bone marrow, alveolar macrophages, and regener- ating liver cells)	No data	-	Cheng and Kligerman 1984

- = negative result; (+) = weakly positive

## 2. HEALTH EFFECTS

for forward mutation in mouse lymphoma cells, sister chromatid exchange in Chinese hamster ovary cells, and cell transformation in mouse BALB/C-3T3 cells (Table 2-3d) (Litton Bionetics 1980a). Although o- and p-cresols and a 1:1:1 mixture of all three cresol isomers gave some indication of genotoxic activity in in vitro assays, all in vivo assays were negative, and it is uncertain if cresols pose a genotoxic hazard in humans or other mammals following natural exposure.

**Cancer.** Studies found no relationship between endogenous p-cresol levels in the urine and the occurrence of large bowel cancer (Bone et al. 1976) or bladder cancer (Renwick et al. 1988) in humans. There are no data available regarding the carcinogenicity of exogenous cresols in humans. No cancer bioassays have been conducted in animals, but the results of a promotion study in mice suggested that cresols can be cancer promoters. Cresols have some ability to interact with mammalian DNA in vitro, but it is impossible to assess the potential hazard to humans without more information.

### 2.5 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).

A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s) or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time biologic 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 2.5.1.

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

TABLE 2-3d. Genotoxicity of a 1:1:1 Mixture of o-, p-, and m-Cresol

Species (test system)	End point	Results		Reference
		With activation	Without activation	
<b>Prokaryotic organisms (<i>in vitro</i>):</b>				
<u>Salmonella typhimurium</u> on plates	Reverse mutation	-	-	Litton Bionetics 1980a
<b>Eukaryotic organisms (<i>in vitro</i>):</b>				
<b>Mammalian cells:</b>				
L5187Y mouse lymphoma cells	Forward mutation	+	(+)	Litton Bionetics 1980a
Chinese hamster ovary cells	Sister chromatid exchange	+	+	Litton Bionetics 1980a
Mouse BALB/C-3T3 cells	Cell transformation	+	No data	Litton Bionetics 1980a

- = negative result; + = positive result; (+) = weakly positive

## 2. HEALTH EFFECTS

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 often not 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 2.5.2.

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, biologically effective dose, or target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 2.7, "POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE."

### 2.5.1 Biomarkers Used to Identify and/or Quantify Exposure to Cresols

No biomarkers that 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 cresol in the body could be due to exposure to this substance. Therefore, even the cresols themselves cannot be considered to be biomarkers of cresol exposure unless very high levels are found. There is some evidence that methemoglobinemia, reduced glutathione levels in red blood cells, and Heinz body formation are associated with oral exposure to cresols in humans (Chan et al. 1971; Cote et al. 1984), but these effects are too general and occur at too high doses to be useful as biomarkers of exposure to cresols.

### 2.5.2 Biomarkers Used to Characterize Effects Caused by Cresols

No biomarkers of effects caused by cresols have been identified in humans or animals. It may be possible to use methemoglobinemia and Heinz body formation, which precede hemolytic anemia in humans (Chan et al. 1971; Cote et al. 1984), as biomarkers for the hemolytic effects of cresols, although these changes may be too general and occur at too high doses to be useful for this purpose.

## 2.6 INTERACTIONS WITH OTHER CHEMICALS

Cresols promote the development of skin papillomas in mice following initiation with DMBA (Boutwell and Bosch 1959). It is possible that they would also promote the development of tumors initiated by other chemicals. Although no evidence is available, it is likely that cresols would interact with phenol on the central nervous system to produce convulsions and coma (Deichmann and Witherup 1944), and on the red blood cells to produce methemoglobinemia (Chan et al. 1971). Cresols have an oxidizing effect on red blood cells (Chan et al. 1971), and it is likely that these effects would be

## 2. HEALTH EFFECTS

enhanced in the presence of other oxidizing compounds (e.g., hydroquinone). Cresols may also offer protection from the effects of some chemicals; all three isomers acted antagonistically to reduce paralysis produced by a-tubocurarine in rat diaphragm-phrenic nerve preparations (Mogey and Young 1949).

### 2.7 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

Several populations that may have increased vulnerability to the effects of cresols have been identified, although no strong evidence exists for any of them. There is some evidence that individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency may have increased susceptibility to the 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 (Ghan et al. 1971). Infants may represent another population that is unusually sensitive to the effects of cresols. This possibility was suggested by the death of a 1-year-old baby dermally exposed to high levels of cresols. People with immune deficiencies (e.g., human immuno-deficiency virus (HIV) infection) might be unusually susceptible to the apparent cancer promotional effects of cresols. In addition, individuals with seizure disorders might be expected to be more vulnerable to the effects of cresols on the central nervous system, such as coma and convulsions, than other people.

### 2.8 MITIGATION OF 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 mechanisms by which cresols produce toxic effects are unknown, and the toxicokinetics of these compounds are not well understood. 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.

Procedures that have been used to manage people exposed to cresols are available (Bronstein and Currance 1988; Haddad and Winchester 1990; Stutz and Janusz 1988). 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

## 2. HEALTH EFFECTS

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 followed by thorough washing with soap or mild detergent and water.

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 considered. Additional information regarding the treatment of individuals exposed to cresols may be obtained from Bronstein and Currance (1988), Haddad and Winchester (1990), and Stutz and Janusz (1988).

### 2.9 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 or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

#### 2.9.1 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 2-2. 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 imply anything about the quality of the study or studies. Gaps in this figure should not be interpreted as "data needs" information.

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.

2. HEALTH EFFECTS

FIGURE 2-2. Existing Information on Health Effects of Cresols

	Death	SYSTEMIC			Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Cancer
		Acute	Intermed.	Chronic						
Inhalation		●								
Oral	●	●			●					
Dermal	●	●			●					

**HUMAN**

	Death	SYSTEMIC			Immunologic	Neurologic	Developmental	Reproductive	Genotoxic	Cancer
		Acute	Intermed.	Chronic						
Inhalation	●	●	●		●	●				
Oral	●	●	●		●	●	●	●	●	
Dermal	●	●	●		●					●

**ANIMAL**

● Existing Studies

## 2. HEALTH EFFECTS

The existing information on the health effects of cresols in humans comes almost entirely from case reports of people who either swallowed cresol-containing substances or had these substances spilled on them. The single exception was an inhalation study of mucosal irritation in humans.

A small number of studies investigated the effects of cresol inhalation in animals. These were acute- and intermediate-duration studies that either tried to determine lethal levels or looked at systemic and neurologic end points. One study included measurement of an end point relevant to immunotoxicity. Many studies of acute oral exposure were conducted in animals, mostly to determine lethal levels, but they include observations of systemic and neurologic effects. A recently completed series of intermediate-duration studies investigated the systemic and neurologic effects of each isomer in detail and also included immunologic and reproductive end points. Other oral studies included a series of detailed studies of the developmental effects of each isomer and two-generation reproduction studies. 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.

### 2.9.2 Data Needs

**Acute-Duration Exposure.** Case reports of humans exposed to high doses of cresols, either orally or dermally, have provided acute toxicity information (Chan et al. 1971; Cote et al. 1974; Green 1975; Isaacs 1922; Jouglard et al. 1971; Klinger and Norton 1945; Labram and Gervais 1968; Larcen et al. 1974). The primary targets for cresol toxicity in humans appear to be the blood, kidneys, and nervous system. Lethal levels have been crudely estimated for both oral and dermal exposure. Animal studies of the acute toxicity of cresols have determined dose levels that produce skin irritation and death in dermally exposed animals, and reduced body weight, neurotoxicity, fetotoxicity, and death in orally exposed animals (BRRC 1988a, 1988b; MBA 1988a, 1988b, 1988c; TRL 1986, Vernot et al. 1977). Inhalation studies did not reliably identify target organs or hazardous levels, and pharmacokinetic data that might allow extrapolation from oral or dermal data are not available. Although the data were insufficient to derive inhalation MRLs, acute oral MRLs were calculated, based on maternal neurological effects in a developmental toxicity study (BRRC 1988b). Knowledge about the acute toxicity of cresols is important because people living near hazardous waste sites might be exposed to cresols for brief periods. Acute inhalation studies would enable determination of hazardous levels and identification of target organs for this route of exposure. Although case studies of exposed humans reported that the blood and kidneys are targets of cresol toxicity, acute effects on these organs have not been seen in animals. Careful study of these end points in acute animal studies would be appropriate. Acute oral and dermal studies that included gross and microscopic examination of all exposed animals would

## 2. HEALTH EFFECTS

provide better identification of possible target organs than necropsy of only the dead animals, as was done in existing studies. Examination of more subtle end points in these studies would also serve this purpose, and perhaps identify biomarkers of exposure and effects for cresols.

**Intermediate-Duration Exposure.** No information is available regarding humans exposed to cresols for an extended period of time. Oral 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 (Homshaw et al. 1986; MBA 1988a, 1988b, 1988c; TRL 1986). Intermediate-duration studies by other routes of exposure were not located, and pharmacokinetic data that might allow extrapolation from oral data were not located. Additional oral studies might enable determination of intermediate MRLs. Intermediate-duration toxicity information is important because people living near hazardous waste sites might be exposed for corresponding time periods. Inhalation studies of intermediate duration would enable determination of hazardous levels and identification of target organs for this route of exposure, and might find effects that could not be detected in acute inhalation studies.

**Chronic-Duration Exposure and Cancer.** No studies of chronic duration were found in humans or animals. Chronic toxicity information is important because people living near hazardous waste sites might be exposed to cresols for many years. Prolonged exposure to cresols in humans might occur by oral, inhalation, or dermal routes. Chronic studies would enable discovery of effects produced by long-term exposure to relatively low levels of cresols, which might not be detected in shorter-term studies.

No studies were located regarding the carcinogenicity of cresols in humans or animals. Cancer bioassays would be pertinent in light of results suggesting tumor-promoting potential following dermal application in mice (Boutwell and Bosch 1959) and positive results in some genotoxicity assays in mammalian cells *in vitro* (Hazleton Labs 1988a, 1988d; Litton Bionetics 1980a, 1981). Prolonged exposure to cresols in humans might occur by the oral, inhalation, or dermal routes, so cancer bioassays by any of these routes would provide useful information. Using known animal carcinogens to further study the promotional capabilities of cresols might also provide valuable information. For example, the potential of orally administered cresols to act as tumor promoters in the hamster forestomach, suggested by the results of Hirose et al. (1986), could be assessed.

**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

## 2. HEALTH EFFECTS

animals in vivo reported only negative results (Cheng and Kligerman 1984; Hazleton Labs 1989a, 1989b, 1989c, 1989e, 1989f). Results were mixed in in vitro studies using mammalian cells (Hazleton Labs 1988a, 1988b, 1988c, 1988d, 1988e, 1988f; Litton Bionetics 1980a, 1981), and uniformly negative in Salmonella assays (Douglas et al. 1980; Florin et al. 1980; Haworth et al. 1983; Litton Bionetics 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. More in vivo testing of cresols for genotoxic effects would enable better estimation of the actual genotoxic threat to humans posed by environmental exposure to these compounds.

**Reproductive Toxicity.** There are no data available regarding the reproductive effects of cresols in humans. Studies in animals, including two-generation studies in rats and mink (BRRC 1989a, 1989b, 1989c; Hornshaw et al. 1986), developmental toxicity studies in rats and rabbits (BRRC 1988a, 1988b), and intermediate-duration toxicity studies in several species (Hornshaw et al. 1986; MBA 1988a, 1988b, 1988c), found no evidence of reproductive toxicity. However, these studies were all performed using oral exposure. Since it is unknown how route of exposure affects the toxicokinetics of cresols, inhalation or dermal toxicity studies that included investigation of reproductive end points would provide further information about the potential reproductive hazard to humans posed by exposure to cresols. If positive results were obtained in these studies, multigeneration studies by these routes would be appropriate.

**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 orally exposed to each cresol isomer (BRRC 1988a, 1988b, 1989a, 1989b, 1989c). These studies generally reported mild fetotoxicity at maternally toxic doses, which suggests that cresols are not developmental toxins in these species and may not pose a developmental hazard in humans. However, further testing of m-cresol, which produced effects on both parent and pup body weight at the low dose of a two-generation reproduction study (BRRC 1989c), would enable better assessment of the developmental toxicity of this isomer. It is unknown how route of exposure affects the toxicokinetics of cresols; therefore, studies using dermal or inhalation exposure would provide additional information about the potential developmental hazard to humans posed by exposure to cresols.

**Immunotoxicity.** No immunological effects were reported in case studies of human exposure. There was a decrease in spleen weight in rats orally exposed to p-cresol for 90 days (MBA 1988b), which, although unaccompanied by histopathological changes, suggests the possibility that cresols may affect the immune system. A battery of immune function tests would better enable assessment of the immunotoxicity of cresols in humans and animals.

## 2. HEALTH EFFECTS

**Neurotoxicity.** Exposure to cresols can produce facial paralysis and coma in humans (Chan et al. 1971; Green 1975; Isaacs 1922; Labram and Gervais 1968). Effects leading up to coma have been identified in animal studies, and include hypoactivity, ataxia, and convulsions (BRRC 1988a, 1988b; MBA 1988a, 1988b, 1988c; TRL 1986). These effects are seen regardless of test species or route of exposure, and the levels at which these gross effects occur have been roughly identified. Acute MRLs were based on neurological effects in pregnant rabbits (BRRC 1988b). A few studies have included histopathological examination of nervous tissues, and one reported the occurrence of lesions, although exposure levels were not reported reliably (Uzhdavini et al. 1972). A detailed study of neurological effects reported clinical signs of neurotoxicity, but did not identify many significant differences between treated rats and controls in behavioral tests (TRL 1986). Two studies looked for, and found, subtle biochemical and neurophysiological changes in the brain (Mattsson et al. 1989; Savolainen 1979). Neurophysiological and neurochemical studies designed to assess the effects of cresol exposure would provide a much finer level of detail about the neurological effects of cresols than is currently known, and might identify the mechanism by which these effects occur.

**Epidemiological and Human Dosimetry Studies.** Epidemiology studies reported no relationship between urinary levels of endogenous p-cresol and bladder and bowel cancer (Bone et al. 1976; Renwick et al. 1988). No other epidemiological or human dosimetry studies regarding cresols were located. Epidemiological studies of exogenous cresol exposure would be useful to determine the effects of long-term exposure on humans, with particular attention paid to neurological effects. Although many people may be exposed to low cresol levels in the air or water, a study that focused on people exposed to higher levels, such as employees of industries that produce or use large amounts of cresol-containing substances, might provide more information because of the greater ability to detect a dose-response relationship between exposure and manifest disease. If a specific cause/effect relationship were established between cresol exposure and health effects in humans, monitoring of individuals living near hazardous waste sites could be performed in order to determine if exposure levels exceeded recommended limits and if body tissue and fluid levels of cresols and metabolites exceeded potentially hazardous levels.

**Biomarkers of Exposure and Effect.** 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. Distinguishing biomarkers of exposure to cresols would enable early detection of cresol exposure and provide the opportunity for early treatment. One possibility

## 2. HEALTH EFFECTS

that can be further investigated is Heinz body formation in the blood of exposed humans (Chan et al. 1971; Cote et al. 1984).

No biomarkers of effect have been identified for cresols. Studies designed to investigate subtle effects might discern these biomarkers, which would enable finer delineation of the dose-response relationship for an effect and allow better estimation of the levels of cresols to which people could be exposed without risk. Case reports in humans have reported methemoglobinemia and Heinz body formation that may be predictive of hemolytic anemia (Ghan et al. 1971; Cote et al. 1984).

**Absorption, Distribution, Metabolism, and Excretion.** Levels of cresols in blood were obtained from a single case report of a dermally exposed human (Green 1975). Data on the toxicokinetics of cresols in animals were contained in two acute oral studies that provided only limited quantitative information on the absorption, metabolism, and excretion of cresols (Bray et al. 1950; Williams 1938). A more complete oral toxicokinetics study, in addition to studies using dermal and inhalation exposure, would provide data that could be used to develop predictive pharmacokinetic models for cresols. Inclusion of several dose levels and exposure durations in these studies would provide a more complete picture of the toxicokinetics of cresols and allow a more accurate route by route comparison, because it would allow detection of saturation effects. Studies of the tissue distribution of cresols in the body might help identify possible target organs.

**Comparative Toxicokinetics.** The nervous system is a target of cresols in both humans and animals. The blood and kidneys also appear to be targets in humans, although they have not clearly been identified as targets in animal studies using rats, rabbits, mink, or ferrets. The failure to detect these effects in animals could be related to differences in either dose received or toxicokinetics. No information is available regarding the toxicokinetics of cresols in humans; the two available toxicokinetic studies on cresols were both performed using rabbits (Bray et al. 1950; Williams 1938). Toxicokinetic studies in more species and using current techniques would result in either greater confidence on extrapolating the results to humans, if the results were similar in the species studied, or in extra caution about extrapolating to humans, if the results varied widely between species. As noted, variation in interspecies toxicokinetic parameters could also explain possible species differences in susceptibility to cresols.

**Mitigation of Effects.** Few data are available concerning the mechanism of action of cresols or the toxicokinetics of these compounds. Additional studies might identify specific steps that can be taken to alter the mechanism of action or the toxicokinetics of cresols so that the chance to interact with target organs is reduced. For example, knowledge of the influence of urinary pH on clearance and biological half-life might be useful for determining ways of increasing elimination of cresols.

## 2. HEALTH EFFECTS

### **2.9.3 On-going Studies**

The National Toxicology Program (NTP) is performing subchronic tests of cresol toxicity in which either o-cresol or mixed cresol isomers are given to rats and mice in the feed. In addition, studies of the effects of cresols on reproduction and fertility in mice are being performed by the NTP. The results of these studies are not yet available.



### **3. CHEMICAL AND PHYSICAL INFORMATION**

#### **3.1 CHEMICAL IDENTITY**

Data pertaining to the chemical identity of cresols are listed in Table 3-1.

#### **3.2 PHYSICAL AND CHEMICAL PROPERTIES**

The physical and chemical properties of cresols are presented in Tables 3-2.

TABLE 3-1. Chemical Identity of Cresols

Characteristic	o-Cresol	p-Cresol	m-Cresol	o-, m-, and p-Cresol	References
Chemical name	o-Cresol	p-Cresol	m-Cresol	(o,m,p)-Cresol	CAS 1989
Synonyms	2-Methylphenol; 2-hydroxytoluene; o-cresylic acid	4-Methylphenol; 4-hydroxytoluene; p-cresylic acid	3-Methylphenol 3-hydroxytoluene; m-cresylic acid	Methylphenol; hydroxytoluene; cresylic acid	SANSS 1989; Chemline 1989; CAS 1989; HSDB 1989
Trade names	No data				
Chemical formula	C <sub>7</sub> H <sub>8</sub> O	C <sub>7</sub> H <sub>8</sub> O	C <sub>7</sub> H <sub>8</sub> O	C <sub>7</sub> H <sub>8</sub> O	CAS 1989
Chemical structure				Mixture of three previous isomers	
Identification numbers:					
CAS registry	95-48-7	106-44-5	108-39-4	1319-77-3	CAS 1989
NIOSH RTECS	GO6300000	GO6475000	GO61250000	GO5950000	SANSS 1989
EPA hazardous waste	F004; U052	F004; U052	F004; U052	F004; U052	HSDB 1989
OHM/TADS	7216652	7216653	7216651	No data	OHM/TADS 1989
DOT/UN/NA/IMCO shipping	UN 2076; IMO 6.1	UN 2076; IMO 6.1	UN 2076; IMO 6.1	UN 2076; IMO 6.1	HSDB 1989
HSDB	1813	1814	1815	250	HSDB 1989
NCI	No data	No data	No data	No data	

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

TABLE 3-2. Physical and Chemical Properties of Cresols

Property	o-Cresol	m-Cresol	p-Cresol	Mixture of o-, p-, and m-cresol	References
Molecular weight	108.14	108.14	108.14	108.14	Weast et al. 1988
Color	White crystals darken with age	Colorless to yellowish	No data	Colorless, yellowish or pinkish	Sax and Lewis 1987; Windholz et al. 1983
Physical state	Solid	Liquid	Solid	Liquid	Sax and Lewis 1987
Melting point	30.944°C	12.22°C	34.739°C	11-35°C	Riddick et al. 1986; Sax and Lewis 1987
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		Weast et al. 1988; Sax and Lewis 1987
Density (20°C)	1.0273 g/mL	1.0336 g/mL	1.0178 g/mL	1.030-1.047 g/mL	Weast et al. 1988
Odor	Phenol-like	Phenol-like	Phenol-like	Phenol-like	Sax and Lewis 1987
Odor threshold					
Water	No data	0.00023 mg/L	No data	No data	Amoore and Hautula 1983
Air	0.65 ppm	0.00028 ppm	0.0455 ppm	No data	OHM/TADS 1989; Amoore and Hautula 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(aq)	Alcohol, ether, acetone, benzene, chloroform, alkali hydroxides(aq)	Alcohol, ether, acetone, benzene, chloroform, alkali hydroxides(aq)	Alcohol, glycol, base	Weast et al. 1988; Sax and Lewis 1987; Windholz et al. 1983
Partition coefficients					
Log octanol/water	1.95	1.96	1.94	No data	Hansch and Leo 1985
Log K <sub>oc</sub>	1.03	1.54	1.69	No data	Boyd 1982; Artiola- Fortuny and Fuller 1982
Vapor pressure					
25°C	0.299 mmHg	0.138 mmHg	0.11 mmHg	No data	Chao et al. 1983; Daubert and Danner 1985
Henry's law constant					
atm/m <sup>3</sup> -molecule at 25°C	1.2x10 <sup>-6</sup>	8.65x10 <sup>-7</sup> (calculated from vapor pressure and water solubility)	7.92x10 <sup>-7</sup>	No data	Gaffney et al. 1987; Hine and Mookerjee 1975
Flashpoint (closed cup)	81°C	86°C	86°C	82°C	Sax and Lewis 1987
Flammability limits					
Air	1.35 (lower)	1.06-1.35%	1.06-1.4%	No data	OHM/TADS 1989
Conversion factors					
ppm (v/v) to mg/m <sup>3</sup> in air (20°C)	4.50	4.50	4.50	4.50	Verschueren 1983
mg/m <sup>3</sup> 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 <sub>ow</sub> )	1.30	1.24 (calculated from K <sub>ow</sub> )	No data	Lyman et al. 1982; Freitag et al. 1985
Explosive limits	No data	No data	No data	No data	



## 4. PRODUCTION, IMPORT, USE, AND DISPOSAL

### 4.1 PRODUCTION

Since before World War II, multimillion pound quantities of cresols have been produced annually in the United States (O'Brochta 1949), and domestic production and sales of cresols have steadily increased in recent years. Approximately 57.3 (USITC 1986), 73.3 (USITC 1988), and 82.3 (USITC 1989) million pounds of cresols were produced annually in the United States in 1986, 1987, and 1988, respectively. Respective sales were 56.6 (USITC 1986), 66.8 (USITC 1988), and 72.1 (USITC 1989) million pounds. 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 less than 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 (Sax and Lewis 1987). In 1987, the national capacity for producing cresylics was 208 million pounds per year (CMR 1987). Information regarding the production levels of individual isomers and specific mixtures was unavailable.

Cresols are used widely by industry. Information from the EPA's Toxic Release Inventory (TRI) on facilities that either manufactured or processed cresols in 1987 is outlined in Table 4-1. The TRI data should be used with caution since the 1987 data represent first-time reporting by these facilities. Only certain types of facilities were required to report. This is not an exhaustive list. According to the United States International Trade Commission (USITC 1987, 1988, 1989) and the 1989 Directory of Chemical Producers (SRI 1989), cresols are currently produced by five manufacturers in New York, New Jersey, Pennsylvania, Illinois, and Texas. USITC (1987, 1988, 1989) and Stanford Research Institute (SRI 1989) data for individual isomers and the mixture o-, p-, and m-isomers are included in Tables 4-2a through 4-2d. Data from the TRI do not agree with those from the USITC and SRI. For example, the Sloss Industries Coke Plant, which appears to meet SRI and USITC production criteria, was not listed with USITC (1987, 1988, 1989) or SRI (1989).

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.

TABLE 4-1. Facilities that Manufacture or Process Cresols<sup>a</sup>

Facility	Location	Maximum amount on site (lbs)	Use
Sloss Industries Corporation Coke Plant	Birmingham, AL	100,000-999,999	Produce; as an impurity
Chem-Four First, Ltd.	Demopolis, AL	1,000-9,999	Import; as a reactant
Koppers Company, Inc.	Dolomite, AL	10,000-99,999	Import; for sale/distribution; as an article component; in ancillary or other uses
Empire Coke Company	Holt, AL	10,000-99,999	Produce; for on-site use/processing; for sale/distribution; as an impurity
Merichem Company, Inc. (Black Warrior Plant)	Holt, AL	10,000-99,999	As an impurity
Ciba-Geigy Corporation	McIntosh, AL	100,000-999,999	As a reactant
CPS Chemical Company Of Arkansas	West Memphis, AR	100,000-999,999	In re-packaging
Ansell Incorporated	Tucson, AZ	1,000-9,999	As a formulation component
BASF Corporation Coatings and Inks Division	Anaheim, CA	10,000-99,999	As a reactant; as a formulation component
FMC Corporation	Fresno, CA	100,000-999,999	As a formulation component
Blue Coral Inc., McKay Chemical Div.	Los Angeles, CA	1,000-9,999	For on-site use/processing; as a formulation component
Tosco Corporation	Martinez, CA	1,000-9,999	As a processing aid
PMC Specialties Group	Santa Fe Springs, CA	100,000-999,999	For sale/distribution; as a formulation component
Mobil Oil Corporation Refinery	Torrance, CA	1,000,000-9,999,999	Produce; as a formulation component
Uniroyal Chemical Company, Inc.	Naugatuck, CT	100-999	Produce; as an impurity
Texaco	Delaware City, DE	No data	As a reactant
Wilmington Chemical Corporation	New Castle, DE	10,000-99,999	Produce; for on-site use/processing; as a byproduct
Harris Corporation Semiconductor	Palm Bay, FL	10,000-99,999	As a reactant
Westinghouse Electric Corporation	Athens, GA	1,000-9,999	As a manufacturing aid
Zep Manufacturing Company	Atlanta, GA	1,000-9,999	As a processing aid
Amoco Performance Products Inc.	Augusta, GA	1,000-9,999	As an article component
Amrep, Inc.	Cartersville, GA	100,000-999,999	As a processing aid
G.E. Co., Medium Transformer Operation	Rome, GA	1,000-9,999	As an article component
Acme Steel Company	Chicago, IL	10,000-999,999	As a manufacturing aid
PMC Specialties Group	Chicago, IL	100-999	As a byproduct
		100-999	Produce; for on-site use/processing; for sale/distribution; as a formulation component
		100-999	Produce; as a byproduct; as an impurity
		1,000-9,999	Produce; for on-site use/processing; for sale/distribution; as a reactant; as a formulation component
Koppers Company, Inc.	Cicero, IL	100,000-999,999	Import; as an impurity

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

TABLE 4-1 (Continued)

Facility	Location	Maximum amount on site (lbs)	Use
Spaulding Composites Specialty Plastics Div.	Dekalb, IL	10,000-99,999	As a reactant
Chicago Magnet Wire Corp.	Elk Grove Village, IL	10,000-99,999	As a processing aid
Borden, Inc. Chemical Division	Forest Park, IL	10,000-99,999	Import; for on-site use/processing; as a reactant; as a formulation component
Reilly Tar and Chemical Corporation	Granite City, IL	100,000-999,999	In re-packaging
Mobil Joliet Refining Corporation	Joliet, IL	100,000-999,999	Produce; for on-site use/processing; for sale/distribution; as a byproduct; as an impurity; as a reactant; in ancillary or other uses
Essex Group Inc.	Rockford, IL	10,000-99,999	As a formulation component
Shell Oil Company	Roxana, IL	100,000-999,999	Produce; as a byproduct
Essex Group Inc.	Fort Wayne, IN	10,000-99,999	As a formulation component
Essex Inc., Chemical Processing Plant	Fort Wayne, IN	100,000-999,999	As a formulation component
General Electric Company Motor Business	Fort Wayne, IN	10,000-99,999	As a processing aid
Phelps Dodge Magnet Wire Co.	Fort Wayne, IN	100,000-999,999	As a formulation component
Rea Magnet Wire Company, Inc.	Fort Wayne, IN	10,000-99,999	As a formulation component; as a processing aid
Citizens Gas and Coke Utility	Indianapolis, IN	100,000-999,999	Produce; for sale/distribution; as a byproduct
Essex Group Inc.	Kendalville, IN	10,000-99,999	As a reactant; as a formulation component; as an article component; as a processing aid
Rea Magnet Wire Co., Inc.	Lafayette, IN	10,000-99,999	As a processing aid
New Haven Wire and Cable, Inc.	New Haven, IN	10,000-99,999	As a processing aid
Total Petroleum, Inc.	Arkansas City, KS	10,000-99,999	Produce
Texaco Ref. and Mktg., Inc.	El Dorado, KS	100,000-999,999	Produce; for sale/distribution; as a byproduct; as an impurity
Koch Chemical Company	Pittsburg, KS	10,000-99,999	As a reactant
Phelps Dodge Magnet Wire Co.	Hopkinsville, KY	No data	
Borden, Inc. - Chemical Division	Louisville, KY	10,000-99,999	As a reactant
		1,000-9,999	As a reactant
		1,000-9,999	As a reactant
Hi-Tek Polymers, Inc. Plant 2700	Louisville, KY	10,000-99,999	As a reactant
Exxon	Baton Rouge, LA	1,000-9,999	Produce; import; for on-site use/processing; for sale/distribution; as an impurity; as a formulation component
Exxon Chemical Americas	Baton Rouge, LA	100,000-999,999	Produce; as an impurity
Hoehst Celanese Corporation	Baton Rouge, LA	10,000-99,999	As a formulation component
Marathon Petroleum Company	Garyville, LA	1,000-9,999	Produce; as a byproduct
Uniroyal Chemical Co., Inc.	Geismar, LA	100,000-999,999	Import; as a reactant
Citgo Petroleum Corporation	Lake Charles, LA	1,000,000-9,999,999	As a processing aid

TABLE 4-1 (Continued)

Facility	Location	Maximum amount on site (lbs)	Use
Du Pont Pontchartrain Works	Laplace, LA	100,000-999,999	In ancillary or other uses
Murphy Oil USA, Inc.	Meraux, LA	100,000-999,999	As a byproduct
General Electric Company	Shreveport, LA	1,000-9,999	As a manufacturing aid
Conoco Lake Charles Refinery	Westlake, LA	10,000-99,999	As an impurity; as a processing aid
PPG Industries, Inc.	Westlake, LA	10,000-99,999	As a processing aid
Sippican, Inc.	Marion, MA	1,000-9,999	As a manufacturing aid
Anderson Development Company	Adrian, MI	1,000-9,999	As a manufacturing aid
Allied-Signal, Inc.	Detroit, MI	10,000-99,999	As a reactant
Koch Refining Company	St. Paul, MN	10,000-99,999	As a formulation component
Dundee Cement Company	Clarksville, MO	1,000-9,999	As an impurity
Safety Kleen Corporation	Clarksville, MO	10,000-99,999	In ancillary or other uses
Westinghouse Electric Corporation	Jefferson City, MO	10,000-99,999	In ancillary or other uses
P. D. George Company	St. Louis, MO	100,000-999,999	In ancillary or other uses
Borg-Warner Chemicals, Inc. Baymar	Bay St. Louis, MS	100,000-999,999	As a formulation component
Magnetek Universal Manufacturing	Mississippi, MS	10,000-99,999	Produce; for on-site use/processing; as a reactant
Amerada Hess Corporation	Furvis, MS	No Data	As a manufacturing aid; in ancillary or other uses
Sandoz Chemicals Corporation Mt. Holly Plant	Charlotte, NC	10,000-99,999	As a byproduct
General Electric Company Lighting Systems Dept.	Hendersonville, NC	10,000-99,999	As a reactant
General Electric Company Transformer Bus. Dept.	Hickory, NC	10,000-99,999	As a formulation component
Rea Magnet Wire Company, Inc.	Laurinburg, NC	No Data	As a manufacturing aid
Southeastern Adhesives Company	Lenoir, NC	10,000-99,999	As a processing aid
Radiator Specialty Co.	Matthews, NC	0-99	As a manufacturing aid
Thiele-Engdahl, Inc.	Winston-Salem, NC	10,000-99,999	As a formulation component
Elektrisola Inc.	Boscawen, NH	10,000-99,999	As a formulation component; in ancillary or other uses
Concord Chemical Co., Inc.	Camden, NJ	10,000-99,999	As a formulation component
Henkel Corporation	Carlstadt, NJ	100,000-999,999	Import; as a formulation component
Givaudan Corporation	Clifton, NJ	10,000-99,999	As a reactant
Du Pont Chambers Works	Deepwater, NJ	10,000-99,999	As a reactant
FMC Specialties Group	Fords, NJ	10,000-99,999	As a reactant
American Cyanamid Company Warners Plant	Linden, NJ	100,000-999,999	As a reactant
Union Carbide Corporation Bound Book Plant	Piscataway, NJ	10,000-99,999	As a reactant
Ciba-Geigy Corporation	Toms River, NJ	10,000-99,999	As a reactant
Diaz Chemical Corporation	Holley, NY	10,000-99,999	As a reactant
BTL Specialty Resins Corp.	Niagara Falls, NY	10,000-99,999	As a reactant
		100,000-999,999	As a reactant

TABLE 4-1 (Continued)

Facility	Location	Maximum amount on site (lbs)	Use
Occidental Chemical Corp. Durez Division	North Tonawanda, NY	10,000-99,999	As a reactant
General Electric Company Insulating Materials	Rotterdam, NY	10,000-99,999	As a reactant; as a formulation component; as an article component
Schenectady Chemicals, Inc.	Rotterdam Junction, NY	10,000-99,999	As a reactant
		10,000-99,999	As a reactant
		10,000-99,999	As a reactant
Schenectady Chemicals, Inc.	Schenectady, NY	10,000-99,999	As a formulation component
		100,000-999,999	As a reactant; as a formulation component; in ancillary or other uses
General Electric Plastics	Selkirk, NY	No data	Produce; as a byproduct
BASF Corporation Coatings and Inks Division	Cincinnati, OH	10,000-99,999	As a reactant
		10,000-99,999	As a reactant
Hilton Davis Co.	Cincinnati, OH	100,000-999,999	As a reactant
Ashland Chemical Company	Cleveland, OH	10,000-99,999	As a reactant
Reilly Tar and Chemical Corporation	Cleveland, OH	100,000-999,999	In re-packaging
General Electric Company Electromaterials Department	Coshocton, OH	10,000-99,999	As a reactant
Nordson Corporation-RBX Div.	Elyria, OH	1,000-9,999	As a manufacturing aid
Allied-Signal Inc.	Ironton, OH	1,000,000-9,999,999	As a formulation component
New Boston Coke Corporation	New Boston, OH	100,000-999,999	Produce; as a byproduct
Conoco Refinery	Ponca City, OK	100,000-999,999	As an impurity; as a processing aid
Moore Business Forms And Systems Division	Stillwater, OK	10,000-99,999	As a reactant
Aristech Chemical Corporation Tarben Plant	Clairton, PA	10,000-99,999	In re-packaging
		10,000-99,999	In re-packaging
		10,000-99,999	In re-packaging
Westinghouse Electric Corporation	Manor, PA	100,000-999,999	As a reactant; as a formulation component; in re-packaging; in ancillary or other uses
Arco Chemical Company	Monaca, PA	10,000-99,999	As a processing aid
Neville Synthese Organics Inc.	Oil City, PA	10,000-99,999	Produce; for sale/distribution; as a reactant
		10,000-99,999	Produce; for sale/distribution
		10,000-99,999	As a reactant
		10,000-99,999	As a reactant
Rohm and Haas, Inc. Delaware Valley, Philadelphia	Philadelphia, PA	10,000-99,999	As a reactant
Pennzoil Products Company	Rouseville, PA	10,000-99,999	Produce; as an impurity; as a reactant
Olin Hunt Specialty Products Inc.	Lincoln, RI	1,000-9,999	As an article component
Hardwicke Chemical Co.	Elgin, SC	100,000-999,999	As a reactant
Westinghouse Electric Corporation Lower Neches	Hampton, SC	100,000-999,999	As a reactant

4. PRODUCTION, IMPORT, USE, AND DISPOSAL

TABLE 4-1 (Continued)

Facility	Location	Maximum amount on site (lbs)	Use
Essex Group Inc.	Franklin, TN	10,000-99,999	As a processing aid; in ancillary or other uses
Doehler-Jarvis	Greeneville, TN	1,000-9,999	For on-site use/processing; as a reactant
Mapco Petroleum, Inc.	Memphis, TN	10,000-99,999	Produce; as a byproduct
W.m. Barr And Company, Inc.	Memphis, TN	10,000-99,999	As a formulation component
Berryman Products, Inc.	Arlington, TX	100,000-999,999	As a formulation component; in re-packaging
Beaumont Refinery	Beaumont, TX	100,000-999,999	As a reactant
Neches River Treatment Corporation	Beaumont, TX	100-999	In ancillary or other uses
Arco Chemical Company	Channelview, TX	10,000-99,999	As a processing aid
The Goodyear Tire and Rubber Co.	Cheek, TX	10,000-99,999	As a reactant
Koch Refining Company	Corpus Christi, TX	100,000-999,999	For sale/distribution; as a byproduct
Zep Manufacturing Company	De Soto, TX	10,000-99,999	As an article component
W. J. Smith Wood Preserving Company	Denison, TX	10,000-99,999	As an article component
		10,000-99,999	As an article component
The Dow Chemical Company Texas Operations	Freeport, TX	100,000-999,999	As a reactant
Hill Petroleum Company	Houston, TX	1,000-9,999	As an impurity
Koppers Company, Inc.	Houston, TX	1,000-9,999	For on-site use/processing; for sale/distribution; as an article component; in ancillary or other uses
Amrep, Inc.	Lancaster, TX	1,000-9,999	As an article component
Reilly Tar and Chemical Corporation	Lone Star, TX	100,000-999,999	In re-packaging
Crown Central Petroleum Corporation	Pasadena, TX	10,000-99,999	Produce; as a byproduct
Hoechst Celanese Corporation Bayport Works	Pasadena, TX	10,000-99,999	Import; as a processing aid
Sea Lion Chemical	Texas City, TX	10,000-99,999	Produce
		10,000-99,999	As a reactant
Sterling Chemicals, Inc.	Texas City, TX	1,000-9,999	As a processing aid
Du Pont	Victoria, TX	1,000-9,999	Produce; as an impurity
Kennecott Utah Copper	Copperton, UT	100,000-999,999	As a reactant; as a processing aid
Reilly Tar & Chemical Corporation	Provo, UT	100,000-999,999	In re-packaging
Westinghouse Electric Corp. Wire Division	Abingdon, VA	10,000-99,999	As a manufacturing aid
Northwest Petrochemical Corporation	Anacortes, WA	1,000,000-9,999,999	Produce; for sale/distribution
Mobil Oil Corporation	Ferndale, WA	10,000-99,999	Produce; for sale/distribution; as a byproduct
Plastics Engineering Company	Sheboygan, WI	100,000-999,999	As a reactant
Koppers Company, Inc.	Follansbee, WV	1,000,000-9,999,999	Import; for sale/distribution; as a byproduct; as an impurity
Akzo Chemicals Inc.	Gallipolis Ferry, WV	1,000,000-9,999,999	As a reactant
FMC Corporation	Nitro, WV	1,000,000-9,999,999	As a reactant

<sup>a</sup>Derived from TRI 1989

## 4. PRODUCTION, IMPORT, USE, AND DISPOSAL

TABLE 4-2a. Current U.S. Producers of o-Cresol<sup>a</sup>

Company	Location <sup>b</sup>
PMC Inc. PMC Specialties Group Division	Chicago, IL
General Electric Company GE Plastics	Selkirk, NY
Merichem Company	Houston, TX
Northwest Petrochemical Corporation	Anacortes, WA

<sup>a</sup>Derived from SRI 1989; USITC 1989.

<sup>b</sup>May represent headquarters rather than production facilities.

## 4. PRODUCTION, IMPORT, USE, AND DISPOSAL

TABLE 4-2b. Current U.S. Producers of p-Cresol<sup>a</sup>

Company	Location <sup>b</sup>
PMC Inc.	
PMC Specialties Group Division	Chicago, IL
Merichem Company	Houston, TX
Bell Flavors and Fragrances Inc.	Northbrook, IL
Sherman-Williams Company	Oakland, NJ

<sup>a</sup>Derived from SRI 1989; USITC 1989; Fiege and Bayer 1987.

<sup>b</sup>May represent headquarters rather than production facilities.

## 4. PRODUCTION, IMPORT, USE, AND DISPOSAL

TABLE 4-2c. Current U.S. Producers of m-Cresol<sup>a</sup>

Company	Location <sup>b</sup>
Merichem Company Neville-Synthese Organics Inc.	Houston, TX <sup>c</sup> Oil City, PA

<sup>a</sup>Derived from SRI 1989; USITC 1989.

<sup>b</sup>May represent headquarters rather than production facilities.

<sup>c</sup>Also produces a mixture of m- and p-isomers.

## 4. PRODUCTION, IMPORT, USE, AND DISPOSAL

TABLE 4-2d. Current U.S. Producers of the Mixture of o-, p- and m-Cresols<sup>a</sup>

Company	Location <sup>b</sup>
PMC Inc.	
PMC Specialties Group Division	Chicago, IL
General Electric Company	
GE Plastics	Selkirk, NY
Merichem Company	Houston, TX
Northwest Petrochemical Corporation	
Stimson Lumber Company	Anacortes, WA <sup>c</sup>

<sup>a</sup>Derived from SRI 1989; USITC 1989.

<sup>b</sup>May represent headquarters rather than production facilities.

<sup>c</sup>Plant is currently shut down and up for sale.

#### 4. PRODUCTION, IMPORT, 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).

##### 4.2 IMPORT/EXPORT

Just over 13.5 million pounds of cresols were imported into the United States in 1983. Table 4-3 contains import data for 1983. More recent information on U.S. imports was not located.

##### 4.3 USE

A considerable amount of o-cresol is consumed 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 (Sax and Lewis 1987). 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 phenolformaldehyde resins. The manufacture of certain herbicides and pesticides, including 4-chloro-2-methylphenoxyacetic acid (MCPA),  $\gamma$ (4-chloro-2-methylphenoxy)-propionic acid (MCPB), 7(4-chloro-2-methylphenoxy)-butyric acid (MCPB), and 4,6-dinitro-o-cresol (DNCO), 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-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 (Windholz et al. 1983). Synthetic food flavors also contain p-cresol (Sax and Lewis 1987). p-Cresol carboxylic acid esters and anisaldehyde are used in perfumes (Sax and Lewis 1987). The latter is made from p-cresol methyl ether (Fiege et al. 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),

## 4. PRODUCTION, IMPORT, USE, AND DISPOSAL

TABLE 4-3. Recent U.S. Imports of Cresols<sup>a</sup>

Chemical name	Import volume (in thousands of pounds)
o-Cresol	43.0
p-Cresol	1,996.6
m-Cresol	2,892.3
(o,m)-Cresol	381.6
(m,p)-Cresol	8,188.6

<sup>a</sup>Derived from USITC 1984.

#### 4. PRODUCTION, IMPORT, USE, AND DISPOSAL

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 (Windholz et al. 1983). 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).

#### 4.4 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 °C-1600 °C and a residence time of seconds. Cresols may also be disposed of in a fluidized bed incinerator with a temperature range of 450 °C-980 °C and a residence time of seconds (HSDB 1989).



## 5. POTENTIAL FOR HUMAN EXPOSURE

### 5.1 OVERVIEW

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 probably degrade rapidly because of reactions with photochemically produced hydroxyl radicals. Biodegradation is probably 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.

High levels of cresol exposure may result from the ingestion of foods containing it. However, more quantitative data on the occurrence of cresols in food are necessary to accurately assess the exposure via the oral route. Based on the available information, the most common route of exposure for the general population is probably 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 largescale 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 1967)

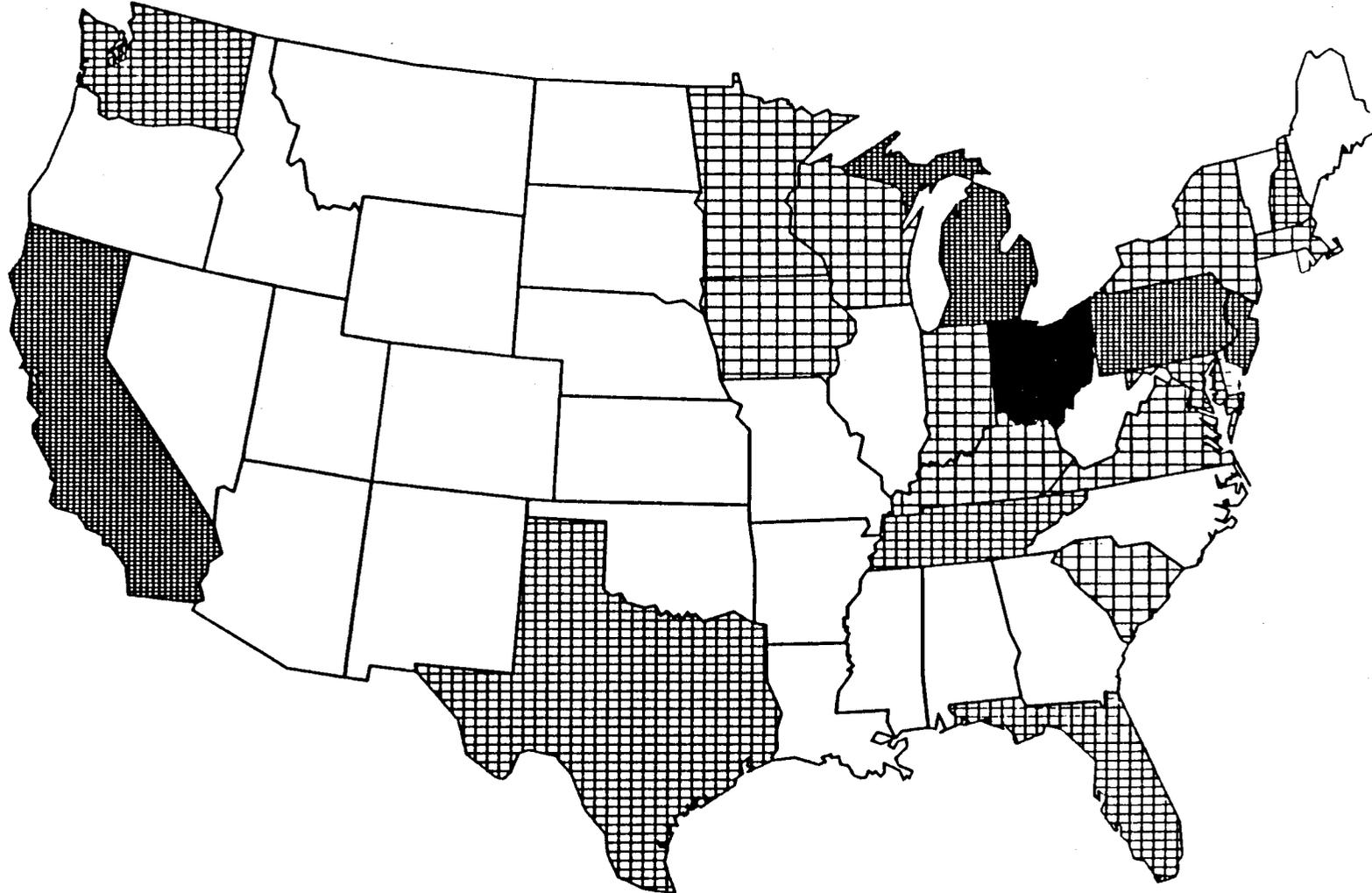
The EPA has identified 1,177 NPL sites. o-Cresol, p-cresol, m-cresol and the mixed isomers have been found at 10, 25, 2, and 12, respectively, of the sites evaluated for these chemicals. However, we do not know how many of the 1,177 NPL sites have been evaluated for these chemicals. As more sites are evaluated by the EPA, these numbers may change (View 1989). The frequency of these sites within the United States can be seen in Figure 5-1.

### 5.2 RELEASES TO THE ENVIRONMENT

#### 5.2. Air

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 and 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

FIGURE 5-1. FREQUENCY OF NPL SITES WITH CRESOLS CONTAMINATION \*



FREQUENCY

	1 SITE		2 SITES
	3 TO 4 SITES		5 SITES

\* Derived from View 1989

## 5. POTENTIAL FOR HUMAN EXPOSURE

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 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. Table 5-1 includes information from the Toxic Chemical Release Inventory (TRI 1989) on atmospheric releases of cresols from facilities that process or manufacture cresols. According to the TRI (1989), 140 of 163 facilities that manufacture or process cresols released an estimated 859,600 pounds of this compound to the atmosphere in 1987. The largest single annual air emission was 71,000 pounds. The TRI data should be used with caution since the 1987 data represent first-time reporting by these facilities. Only certain types of facilities were required to report. This is not an exhaustive list.

Low levels of cresols are constantly emitted to the atmosphere in the exhaust from motor vehicle engines using petroleum based-fuels (Hampton et al. 1982; Johnson et al. 1989; Seizinger and Dimitriades 1972). Cresols have been identified in stack emissions from municipal waste incinerators (James et al. 1984; 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) 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).

### 5.2.2 Water

Cresols are widely distributed natural compounds. As discussed above, they are formed as metabolites of microbial activity and are excreted in the urine of mammals (Fiege and Bayer 1987) and humans (Needham et al. 1984). Cresols from human urine are probably 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.

TABLE 5-1. Releases to the Environment from Facilities that Manufacture or Process Cresols<sup>a</sup>

Facility	Location	Total (lbs)						Off-site transfer
		Air	Underground injection	Water	Land	Environment	POTW <sup>b</sup> transfer	
Sloss Industries Corporation Coke Plant	Birmingham, AL	1,250	0	0	0	1,250	0	0
Chem-Four First, Ltd.	Demopolis, AL	0	0	0	0	0	0	250
Koppers Company, Inc.	Dolomite, AL	500	0	0	0	500	0	0
Empire Coke Company	Holt, AL	108	0	1	0	109	2	0
Merichem Company, Inc. (Black Warrior Plant)	Holt, AL	370	0	14	0	384	18,897	0
Ciba-Geigy Corporation	McIntosh, AL	500	0	250	250	1,000	0	0
CPS Chemical Company Of Arkansas	West Memphis, AR	0	0	1,200	0	1,200	0	23,000
Ansell Incorporated	Tucson, AZ	0	0	0	0	0	0	0
Basf Corporation Coatings and Inks Division	Anaheim, CA	310	0	0	0	310	0	0
FMC Corporation	Fresno, CA	33	0	0	0	33	0	0
Blue Coral Inc., McKay Chemical Div.	Los Angeles, CA	250	0	0	0	250	0	250
Tosco Corporation	Martinez, CA	500	0	250	250	1,000	0	0
FMC Specialties Group	Santa Fe Sprin, CA	3,240	0	0	0	3,240	3,240	0
Mobil Oil Corporation Torrance Refinery	Torrance, CA	47,250	0	0	0	47,250	47,250	0
Uniroyal Chemical Company, Inc.	Torrance, CA	0	0	0	0	0	3,000	0
Texaco	Naugatuck, CT	3,915	0	0	0	3,915	750	0
Wilmington Chemical Corporation	Delaware City, DE	0	0	0	0	0	0	0
Harris Corporation Semiconductor	New Castle, DE	220	0	0	0	220	0	0
Westinghouse Electric Corporation	Palm Bay, FL	3,600	250	0	0	3,850	0	14,172
Zep Manufacturing Company	Athens, GA	500	0	0	0	500	0	750
Amoco Performance Products Inc.	Atlanta, GA	186	0	1	0	187	91	0
Amrep, Inc.	Augusta, GA	500	0	0	0	500	250	4,900
G.E. Co., Medium Transformer Operation	Cartersville, GA	5	0	0	0	5	1	0
Acme Steel Company	Rome, GA	7,950	0	0	0	7,950	0	1,025
FMC Specialties Group	Chicago, IL	500	0	0	0	500	250	0
FMC Specialties Group	Chicago, IL	8,966	0	0	0	8,966	13,752	0
FMC Specialties Group	Chicago, IL	2,975	0	0	0	2,975	2,349	0
Koppers Company, Inc. Spaulding Composites Specialty Plastics Div.	Chicago, IL	26,698	0	0	0	26,698	289,499	0
	Cicero, IL	500	0	0	0	500	0	0
	Dekalb, IL	500	0	0	0	500	0	500

5. POTENTIAL FOR HUMAN EXPOSURE

TABLE 5-1 (Continued)

Facility	Location	Total (lbs)						POTW <sup>b</sup> transfer	Off-site transfer
		Air	Underground injection	Water	Land	Environment			
Chicago Magnet Wire Corp.	Elk Grove Village, IL	16,001	0	0	0	16,001	0	16,000	
Borden, Inc. Chemical Division	Forest Park, IL	998	0	0	0	998	999	0	
Reilly Tar and Chemical Corporation	Granite City, IL	1,000	0	0	0	1,000	250	342,168	
Mobil Refining Corporation	Joliet, IL	250	0	250	0	500	0	0	
Essex Group Inc.	Rockford, IL	0	0	0	0	0	0	8,317	
Shell Oil Company	Roxana, IL	250	0	0	500	750	0	0	
Essex Group Inc.	Fort Wayne, IN	29,000	0	0	0	29,000	250	19,800	
Essex Inc., Chemical Processing Plant	Fort Wayne, IN	500	0	0	0	500	0	28,250	
General Electric Company Motor Business	Fort Wayne, IN	51,901	0	0	0	51,901	0	16,513	
Phelps Dodge Magnet Wire Co.	Fort Wayne, IN	28,250	0	0	0	28,250	0	81,400	
Rea Magnet Wire Company, Inc.	Fort Wayne, IN	27,000	0	0	0	27,000	0	2,330	
Citizens Gas and Coke Utility	Indianapolis, IN	208	0	0	0	208	0	3,154	
Essex Group Inc.	Kendalville, IN	13,500	0	0	0	13,500	0	2,900	
Rea Magnet Wire Co., Inc.	Lafayette, IN	71,000	0	0	0	71,000	0	23,000	
New Haven Wire and Cable, Inc.	New Haven, IN	4,300	0	0	0	4,300	0	1,179	
Essex Group Inc.	Vincennes, IN	16,050	0	0	750	16,800	0	1,202,950	
Total Petroleum, Inc.	Arkansas City, KS	1	0	0	15	16	0	0	
Texaco Ref. and Mktg., Inc.	El Dorado, KS	1,200	0	250	0	1,450	0	0	
Koch Chemical Company	Pittsburg, KS	1,000	0	0	0	1,000	1,053	750	
Phelps Dodge Magnet Wire Co.	Hopkinsville, KY	35,250	0	0	0	35,250	0	45,441	
Borden, Inc. Chemical Division	Louisville, KY	998	0	0	0	998	0	0	
		998	0	0	0	998	0	0	
		998	0	0	0	998	0	0	
Hi-Tek Polymers, Inc. Plant 2700	Louisville, KY	3	0	0	0	3	0	16	
Exxon Refinery	Baton Rouge, LA	680	0	0	74	754	0	0	
Exxon Chemical Americas Chemical Plant	Baton Rouge, LA	810	0	100	0	910	0	130	
Hoechst Celanese Corporation	Baton Rouge, LA	3	0	2	0	5	0	0	
Marathon Petroleum Company	Garyville, LA	0	0	250	250	500	0	0	
Uniroyal Chemical Co., Inc.	Geismar, LA	445	0	0	0	445	0	0	

5. POTENTIAL FOR HUMAN EXPOSURE

TABLE 5-1 (Continued)

Facility	Location	Total (lbs)						Off-site transfer
		Air	Underground injection	Water	Land	Environment	POTW <sup>b</sup> transfer	
Citgo Petroleum Corporation	Lake Charles, LA	24,000	0	20	8	24,028	0	7
Du Pont Pontchartrain Works	Laplace, LA	162	0	0	0	162	0	0
Murphy Oil USA, Inc.	Meraux, LA	0	0	200	20	220	0	0
General Electric Company	Shreveport, LA	1,000	0	0	0	1,000	0	0
Conoco Lake Charles Refinery	Westlake, LA	500	0	250	0	750	0	0
PPG Industries, Inc.	Westlake, LA	0	0	0	0	0	0	0
Sippican, Inc.	Marion, MA	250	0	0	0	250	0	250
		250	0	0	0	250	0	250
Anderson Development Company	Adrian, MI	250	0	0	0	250	0	23,400
Allied-Signal, Inc.	Detroit, MI	1	0	0	0	1	9,960	990
Koch Refining Company	Saint Paul, MN	0	0	0	5	5	0	0
Dundee Cement Company	Clarksville, MO	2	0	0	0	2	0	0
Safety Kleen Corporation	Clarksville, MO	6	0	0	0	6	0	1
Westinghouse Electric Corporation	Jefferson City, MO	8,450	0	0	0	8,450	0	0
P. D. George Company	St. Louis, MO	500	0	0	0	500	250	1,000
Borg-Warner Chemicals, Inc. Baymar	Bay St. Louis, MS	6,945	0	0	0	6,945	0	0
Magnetek Universal Manufacturing	Mississippi, MS	8,180	0	0	0	8,180	0	750
Amerada Hess Corporation	Purvis, MS	0	0	0	0	0	0	240,000
Sandoz Chemicals Corporation Mt. Holly Plant	Charlotte, NC	500	0	250	250	1,000	0	0
General Electric Company Lighting Systems Dept.	Hendersonville, NC	3,450	0	0	0	3,450	0	0
General Electric Company Transformer Bus. Dept.	Hickory, NC	34,586	0	0	0	34,586	0	250
Rea Magnet Wire Company, Inc.	Laurinburg, NC	92,000	0	0	0	92,000	0	500
Southeastern Adhesives Company	Lenoir, NC	250	0	0	0	250	250	0
Radiator Specialty Co.	Matthews, NC	500	0	0	0	500	0	250
Thiele-Engdahl, Inc.	Winston-Salem, NC	64,621	0	0	0	64,621	0	3,000
Elektrisola Inc.	Boscawen, NH	58,840	0	0	0	58,840	0	5,803
Concord Chemical Co., Inc.	Camden, NJ	1,900	0	0	0	1,900	0	0
Henkel Corporation	Carlstadt, NJ	6,635	0	0	0	6,635	0	0
Givaudan Corporation	Clifton, NJ	500	0	0	0	500	250	0
Du Pont Chambers Works	Deepwater, NJ	0	0	0	12	12	0	0
PMC Specialties Group	Fords, NJ	1,000	0	0	0	1,000	250	14,604

5. POTENTIAL FOR HUMAN EXPOSURE

TABLE 5-1 (Continued)

Facility	Location	Total (lbs)						POTW <sup>b</sup> transfer	Off-site transfer
		Air	Underground injection	Water	Land	Environment			
American Cyanamid Company Warners Plant	Linden, NJ	500	0	0	0	500	250	0	
Union Carbide Corporation Bound Book Plant	Piscataway, NJ	448	0	0	0	448	0	0	
Ciba-Geigy Corporation	Toms River, NJ	322	0	0	200	522	0	0	
Diaz Chemical Corporation	Holley, NY	182	0	455	0	637	0	27,838	
BTL Specialty Resins Corp.	Niagara Falls, NY	0	0	0	0	0	250	12,570	
Occidental Chemical Corp. Durez Division	North Tonawanda, NY	500	0	0	0	500	0	0	
General Electric Company Insulating Materials	Rotterdam, NY	500	0	0	0	500	0	0	
Schenectady Chemicals, Inc.	Rotterdam Junction, NY	2,000	0	0	0	2,000	0	25,000	
Schenectady Chemicals, Inc.	Schenectady, NY	500	0	250	0	750	0	0	
		500	0	250	0	750	0	0	
		1,000	0	250	0	1,250	0	18,400	
General Electric Plastics	Selkirk, NY	1,000	0	0	0	1,000	0	0	
BASF Corporation Coatings and Inks Division	Cincinnati, OH	8,350	0	0	0	8,350	0	144,000	
BASF Corporation Coatings and Inks Division	Cincinnati, OH	31,847	0	16	0	31,863	0	0	
Hilton Davis Co.	Cincinnati, OH	60	0	0	0	60	0	11,790	
Ashland Chemical Company	Cleveland, OH	85	0	0	0	85	0	47,000	
Reilly Tar and Chemical Corporation	Cleveland, OH	500	0	0	250	750	750	0	
General Electric Company Electromaterials Department	Cleveland, OH	500	0	0	0	500	0	6,431	
Nordson Corporation-RBX Div.	Coshocton, OH	1,000	0	0	0	1,000	250	42,160	
Allied-Signal Inc.	Elyria, OH	5,450	0	0	0	5,450	0	0	
New Boston Coke Corporation	Ironton, OH	500	0	0	0	500	0	2,000	
Conoco Refinery	New Boston, OH	5,373	0	0	0	5,373	0	0	
Moore Business Forms and Systems Division	Ponca City, OK	1,000	0	250	250	1,500	0	0	
Aristech Chemical Corporation Tarben Plant	Stillwater, OK	0	0	0	0	0	0	250	
	Clairton, PA	118	0	0	0	118	0	18,107	
		131	0	0	0	131	0	13,938	
		170	0	0	0	170	0	15,979	

5. POTENTIAL FOR HUMAN EXPOSURE

TABLE 5-1 (Continued)

Facility	Location	Total (lbs)						
		Air	Underground injection	Water	Land	Environment	POTW <sup>b</sup> transfer	Off-site transfer
Westinghouse Electric Corporation	Manor, PA	3,250	0	0	0	3,250	0	0
Arco Chemical Company	Monaca, PA	0	0	0	0	0	0	0
Neville Synthese Organics Inc.	Oil City, PA	1,000	0	250	0	1,250	0	114,600
		3,350	0	0	0	3,350	0	0
		2,050	0	0	0	2,050	0	0
Rohm And Haas, Inc. Delaware Valley, Philadelphia	Philadelphia, PA	0	0	0	0	0	910	0
Pennzoil Products Company Rouseville Refinery	Rouseville, PA	500	0	250	0	750	0	0
Olin Hunt Specialty Products Inc.	Lincoln, RI	500	0	0	0	500	0	0
Hardwicke Chemical Co.	Elgin, SC	2,882	0	0	0	2,882	0	1,600
Westinghouse Electric Corporation	Hampton, SC	900	0	0	0	900	0	8,800
Essex Group Inc.	Franklin, TN	16,173	0	0	0	16,173	0	1,807
Doehler-Javis	Greeneville, TN	2,000	0	0	3,000	5,000	0	0
Mapco Petroleum, Inc.	Memphis, TN	0	0	0	0	0	20,600	0
W.m. Barr And Company, Inc.	Memphis, TN	0	0	0	0	0	250	0
Berryman Products, Inc.	Arlington, TX	250	0	0	0	250	0	0
Beaumont Refinery	Beaumont, TX	0	0	250	0	250	0	44,000
Neches River Treatment Corporation, Lower Neches	Beaumont, TX	0	0	220	0	220	0	3,500
Arco Chemical Company	Channelview, TX	30	0	0	0	30	0	2,480
The Goodyear Tire and Rubber Co.	Cheek, TX	750	0	250	5,200	6,200	0	0
Koch Refining Company	Corpus Christi, TX	3,900	0	0	830,000	833,900	0	130,000
Zep Manufacturing Company	De Soto, TX	119	0	0	0	119	0	0
W. J. Smith Wood Preserving Company	Denison, TX	1	0	0	0	1	10	0
		1	0	0	0	1	2	0
The Dow Chemical Company Texas Operations	Freeport, TX	158	0	8	0	166	0	0
Hill Petroleum Company	Houston, TX	500	0	250	0	750	0	1,250
Koppers Company, Inc.	Houston, TX	250	0	0	0	250	0	0
Merichem Company, Inc.	Houston, TX	8,772	1,295,095	5	0	1,303,872	0	17,315
Amrep, Inc.	Lancaster, TX	5	0	0	0	5	1	0
Reilly Tar and Chemical Corporation	Lone Star, TX	500	0	0	0	500	750	0
Crown Central Petroleum Corporation	Pasadena, TX	250	0	0	0	250	0	0

5. POTENTIAL FOR HUMAN EXPOSURE

TABLE 5-1 (Continued)

Facility	Location	Total (lbs)						
		Air	Underground injection	Water	Land	Environment	POTW <sup>b</sup> transfer	Off-site transfer
Hoechst Celanese Corporation Bayport Works	Pasadena, TX	0	0	0	0	0	36	0
Sea Lion Chemical	Texas City, TX	250	0	0	0	250	0	44,950
Sterling Chemicals, Inc.	Texas City, TX	250	0	0	0	250	0	1,250
Du Pont	Victoria, TX	750	0	0	0	750	250	0
Kennecott Utah Copper	Copperton, UT	360	96,000	0	11,200	107,560	0	0
Reilly Tar and Chemical Corporation (Ironton Plant)	Copperton, UT	250	0	250	250	750	0	0
Westinghouse Electric Corp. Wire Division	Provo, UT	1,000	0	250	0	1,250	0	250
Northwest Petrochemical Corporation	Abingdon, VA	7,250	0	0	0	7,250	0	17,000
Mobil Oil Corporation	Anacortes, WA	500	0	0	0	500	0	2,000
Plastics Engineering Company	Ferndale, WA	0	0	250	500	750	0	0
Koppers Company, Inc.	Sheboygan, WI	55	0	0	0	55	105	25
Akzo Chemicals Inc.	Follansbee, WV	758	0	0	0	758	0	0
FMC Corporation	Gallipolis Fer, WV	750	0	6,900	2	7,652	0	5,272
	Nitro, WV	1,812	0	250	0	2,062	0	18,569

<sup>a</sup>Derived from TRI 1989.

<sup>b</sup>POTW = publicly-owned treatment works.

## 5. POTENTIAL FOR HUMAN EXPOSURE

Various plant lipid constituents contain cresols (Fiege and Bayer 1987). Runoff from terrestrial sources may contribute cresols to surface waters in addition to endogenous sources such as aquatic plants, animals, and microbes.

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 of cresols to water are fugitive or accidental discharges during the manufacture, use, transport, and storage of cresols or associated products of the coal tar and petroleum industries. Table 5-1 includes information from the TRI (1989) on releases of cresols to water from facilities that process or manufacture cresols. However, the data do not separate groundwater releases from those made to surface waters. According to the TRI, 32 of 163 facilities that manufacture or process cresols released an estimated 14,400 pounds of this compound to water in 1987. The largest single annual discharge was 6,900 pounds. One hundred thirty-one facilities claimed that no cresol was released to water, while 7 sites discharged 20 pounds or less in 1987 (TRI 1989).

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 Dimitriadis 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 5-2a through 5-2e include monitoring data for these sources.

Very little information regarding the release of individual isomers was located in the literature. A coal liquefaction waste water effluent contained o-cresol at a concentration of 586 mg/L (Fedorak and Hrudey 1986). o-Cresol was detected at an average concentration of 1.1 µg/L for three samples of retort water from a shale oil production facility (Hawthorne and Sievers 1984).

Waste water effluents from coal gasification facilities contained p-cresol at concentrations of 880 mg/L (Neufeld et al. 1985) and 5,120 ppb (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 779 µg/L (Pellizzari et al. 1979), respectively. p-Cresol was

## 5. POTENTIAL FOR HUMAN EXPOSURE

TABLE 5-2a. Detection of o-Cresol in the Groundwater of Hazardous Waste Sites and Landfills

Type/location	Sampling dates	Number of samples	Number positive	Concentration	Reference
<u>Waste sites, groundwater</u>					
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

## 5. POTENTIAL FOR HUMAN EXPOSURE

TABLE 5-2b. Detection of p-Cresol in the Groundwater of Hazardous Waste Sites and Landfills

Type/location	Sampling dates	Number of samples	Number Positive	Concentration	Reference
<u>Waste sites, groundwater</u>					
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
<u>Landfill, groundwater</u>					
Municipal/ Southington, Connecticut	1982-1983	No data	No data	1.5 mg/L	Sawhney and Kozloski 1984

## 5. POTENTIAL FOR HUMAN EXPOSURE

TABLE 5-2c. Detection of m-Cresol in the Groundwater of Hazardous Waste Sites and Landfills

Type/location	Sampling dates	Number of samples	Number positive	Concentration	Reference
<u>Waste sites, groundwater</u>					
Wood preserving/ Pensacola, Florida	March 1984	19	4	0.05-13.73 mg/L	Goerlitz et al. 1985
<u>Infiltration of wastewater, groundwater</u>					
Municipal, secondary/ Fort Devens, Massachusetts	No data	2	1	0.02 µg/L	Bedient et al. 1984; Hutchins et al. 1980
<u>Landfill, Groundwater</u>					
Municipal/ Southington, Connecticut	1982-1983	No data	No data	0.6 mg/L	Sawhney and Kozloski 1984

## 5. POTENTIAL FOR HUMAN EXPOSURE

TABLE 5-2d. Combined 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
<u>Waste sites, groundwater</u>					
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

## 5. POTENTIAL FOR HUMAN EXPOSURE

TABLE 5-2a. Detection of Unspecified Isomers of Cresol in the Groundwater of Hazardous Waste Sites and Landfills

Type/location	Sampling dates	Number of samples	Number positive	Concentration	Reference
<u>Waste Sites, Groundwater</u>					
Underground solvent storage tanks/ Santa Clara, California	March 1983	10	1	0.04 mg/L	Oliveira and Sitar 1985
Hazardous waste/ Coventry, Rhode Island	1979-1984	4	1	0.114 mg/L	Ram et al. 1985

## 5. POTENTIAL FOR HUMAN EXPOSURE

emitted with the waste water of a poultry processing plant at concentrations ranging from 2.14 to 22.5  $\mu\text{g/L}$  (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 2,670  $\mu\text{g/L}$  (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 561  $\mu\text{g/L}$  (Pellizzari et al. 1979), respectively.

Waste water effluents from coal gasification plants 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  $\mu\text{g/L}$  for three samples of retort water from a shale oil production facility (Hawthorne and Sievers 1984).

### 5.2.3 Soil

The dominant anthropogenic sources for the release of cresols to land are most likely spills during the manufacture, use, transport, and storage of cresols or associated products of the coal tar and petroleum industries. Table 5-1 includes information from the TRI (1989) on releases of cresols to land from facilities that process or manufacture cresols. According to the TRI (1989), only 23 of 163 facilities that manufacture or process cresols released an estimated 853,256 pounds of this compound to land in 1987. The largest single annual discharge was 830,000 pounds. One-hundred forty facilities claimed that no cresol was released to land, while 5 sites discharged 20 pounds or less in 1987.

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). Various plant lipid constituents contain cresols (Fiege and Bayer 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 5.3.2.3). Also, rural and suburban septic tanks and grazing animals on pasture lands may contribute 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 5-2a through 5-2e 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).

## 5. POTENTIAL FOR HUMAN EXPOSURE

### 5.3 ENVIRONMENTAL FATE

#### 5.3.1 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 (Lyman et al. 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 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,  $0.11 \pm 0.30$  mmHg at 25.5 °C (Chao et al. 1983; Daubert and Danner 1985), suggests that these compounds will exist predominantly in the vapor phase (Eisenreich et al. 1981). 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 Vancauwenbergh 1978). The relatively high water solubility of the cresol isomers, 21,520-25,950 ppm (Yalkowsky et al. 1987), indicates that wet deposition may remove them from the atmosphere. This is confirmed by the detection of cresols in rainwater (Section 5.4.2). The short atmospheric residence time expected for the cresols (Section 5.3.2.1) 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

## 5. POTENTIAL FOR HUMAN EXPOSURE

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 the 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-claycontent soil (Southworth and Keller 1986), but not to two others (Luh and Baker 1970).

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  $1.2 \times 10^{-6}$  to  $8.65 \times 10^{-7}$  atm-m<sup>3</sup>/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 (Lyman et al. 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.

### 5.3.2 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, but half-lives are less certain, although probably on the order of a week or less.

#### 5.3.2.1 Air

Cresols degrade rapidly in air. Removal during the day is dominated by the reaction with hydroxyl radical (HO•), while nighttime removal is probably 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 nitro-cresol (Atkinson et al. 1980; Grosjean 1984,

## 5. POTENTIAL FOR HUMAN EXPOSURE

1985). Products may vary, depending on whether the reaction takes place in the gas or particle phase (Grosjean 1984). Atkinson (1985), after reviewing the kinetic data for hydroxyl radical reactions, determined the following second-order rate constants for o-, p-, and m-cresol:  $4.0 \times 10^{-11}$ ,  $4.4 \times 10^{-11}$ , and  $5.7 \times 10^{-11} \text{ cm}^3 \text{ molecule}^{-1} \text{ sec}^{-1}$ , respectively. He also stated that the estimated overall uncertainty in the rate constant for o-cresol was  $\pm 30\%$ , while the estimated overall uncertainty for p- and m-cresol was  $\pm 35\%$ . Using  $5 \times 10^5 \text{ molecules cm}^{-3}$  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. These values correspond to daylight hours when hydroxyl radicals are present.

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 major reaction of this species is attack by the  $\text{NO}_2$  radical to give products of nitration. Atkinson et al. (1984) and Carter et al. (1981) reported the reaction kinetics of nitrate radicals with cresol isomers. The reaction rate constants reported by these authors are similar and overlap when the uncertainties are considered. Averaged reaction second-order rate constants for the reaction between o-, p-, and m-cresol and the nitrate radical from data of Atkinson et al. (1984) and Carter et al. (1981) for the three isomers are  $1.01 \times 10^{-11}$ ,  $0.70 \times 10^{-11}$ , and  $1.08 \times 10^{-11} \text{ cm}^3 \text{ molecule}^{-1} \text{ sec}^{-1}$ , respectively. The half-lives for these reactions, assuming an average nitrate radical concentration of  $2.4 \times 10^8$ , are 4.8, 4.5, and 6.9 minutes for o-, m-, and p-cresols, respectively (Atkinson et al. 1984; Carter et al. 1981). An order-of-magnitude decrease in the concentration of nitrate radicals yields half-lives of approximately 1 hour for all isomers. Under conditions of high nitrate concentrations, removal rates increase and half-lives decrease.

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 Index 1960a, 1960b, 1966). Therefore, direct photolysis is also possible; however, the photolysis rate is probably slow compared to the reaction with atmospheric radicals.

### 5.3.2.2 Water

Cresols have been tested for biodegradability in numerous screening tests and sewage treatment plant simulation tests, as well as in surface water, groundwater, and estuarine and sea water. Most tests indicate that the cresol isomers rapidly and completely degrade to simpler molecules under aerobic conditions in fresh water and that degradation is slower in salt water and under anaerobic conditions, although this is not always the case. m-Cresol gives more variable results in biodegradation tests than the other isomers. There are no hydrolyzable groups on cresol, so hydrolysis is not a

## 5. POTENTIAL FOR HUMAN EXPOSURE

removal mechanism. Under some conditions, chemical oxidation may occur in water. Photolysis, especially in the presence of humic acid as a catalyst, may also be a significant removal mechanism.

All cresol isomers were found to degrade rapidly in biodegradation screening and sewage treatment plant simulation studies with half-lives between less than 24 hours to less than 7 days (Alexander and Lustigman 1966; Babeu and Vaishnav 1987; Baird et al. 1974; Chambers et al. 1963; 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 1971; Pitter 1976; Singer et al. 1979; 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 greater than 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 more than 99% removal of starting material (4,448 ppm of p-cresol) in 3 days under sewage treatment plant conditions). The available screening tests indicate that the cresols are readily degraded by microorganisms under sewage treatment plant conditions and in the environment, but no information about the degradation times in the environment can be inferred from screening study rate data.

Masunaga et al. (1983, 1986) reported the results of a study to determine the products of o-cresol degradation by activated sludge. o-Cresol was combined with phenol-acclimated activated sludge and samples, taken and analyzed by GC/MS over a 24-hour period. After less than 1.5 hours, o-cresol was not detected and hydroxylation products (dihydroxytoluenes) appeared, of which 3-methylcatechol seemed to be the major product. Catechols were subject to further hydroxylation reactions and ring opening reactions. While it is not known if the pathway used by a pure culture to metabolize a compound will be the same as that used by a mixed culture, similar pathways have been reported for p-cresol and m-cresol degradation with pure cultures isolated from industrial process effluents (Bayly and Wigmore 1973). These data suggest that the pathway of aerobic cresol degradation in sewage is similar to that reported for o-cresol.

In screening studies using digester sludge as the inoculum under anaerobic conditions, degradation is significantly slower than under aerobic conditions. o-Cresol yielded no detectable biodegradation in up to 98 days of incubation (Battersby and Wilson 1988, 1989; Boyd et al. 1983; Fedorak and Hrudey 1984; Horowitz et al. 1982; Shelton and Tiedje 1981; Wang et al. 1988, 1989) while p- and m-cresol showed extensive degradation under the same conditions in 20-98 days (Battersby and Wilson 1988, 1989; Boyd et al. 1983; Fedorak and Hrudey 1984, 1986; Fedorak et al. 1986; Horowitz et al. 1982; Roberts et al. 1987; Shelton and Tiedje 1981, 1984; Wang et al. 1988, 1989); however, p-cresol degrades more rapidly and with shorter acclimation times than m-cresol. o-Cresol also resists degradation in other anaerobic systems such as an anaerobic carbon filter (Suidan et al. 1981) and biofilms (Hu and

## 5. POTENTIAL FOR HUMAN EXPOSURE

Shieh 1987), although some degradation is seen at low concentrations. m-Cresol also has shown resistance to anaerobic degradation under some conditions (Fedorak and Hrudey 1984). The degradation patterns of the cresol isomers appear to be the result of different degradation pathways for each isomer (Fedorak and Hrudey 1984, 1986; Fedorak et al. 1986; Roberts et al. 1987; Young and Rivera 1985). In general, the first reaction is hydroxylation of the methyl group on the aromatic ring, followed by oxidation to the hydroxy benzoic acid. Steric hindrance or electronic effects may make this a slow process for m-cresol and very-slow for o-cresol (Bossert and Young 1986; Suflita et al. 1989). These studies indicate that anaerobic degradation as a waste water treatment process for waste waters containing cresols will not be effective for removal, except for p-cresol. When used in combination with aerobic treatment, however, complete removal probably will occur.

Surface water grab samples are the best surrogates of natural behavior in aerobic environments, and rates determined in these systems are probably the closest to the rates seen in the environment. Research efforts studying the degradation of cresols in surface water grab samples generally have been directed at a better understanding of the kinetics involved in biodegradation. Of particular interest are the effects on biodegradation kinetics of substrate concentration (Hwang et al. 1989; Rogers et al. 1984; Spain and van Veld 1983), nutrient concentrations (Lewis et al. 1986; Shimp and Pfaender 1985a), spatial and temporal variations (including temperature variations) (Bartholomew and Pfaender 1983; Hwang et al. 1989; Palumbo et al. 1988; Visser et al. 1977), concentration of humic substances (Shimp and Pfaender 1985b), water source (and hence, bacterial population) (Paris et al. 1983; Rogers et al. 1984; Smith et al. 1978), and biofilms (Gantzer et al. 1988; Kollig et al. ; Lewis et al. 1984, 1987). All of these factors affect the biodegradation kinetics, and no single equation has been formulated to consider their effects. First-order kinetics do not appear to describe adequately the biodegradation of cresols (Gantzer et al. 1988; Kollig et al. 1987; Lewis et al. 1984; Paris et al. 1983); rather, more complex relationships (e.g., Michaelis-Menten kinetics), and second-order kinetics ( $L \text{ organism}^{-1} \text{ hour}^{-1}$ ) better describe the disappearance of cresols.

In general, second-order rate constants from diverse microbial communities are on the order of  $10^{-9}$  to  $10^{-10} L \text{ organism}^{-1} \text{ hour}^{-1}$  (Paris et al. 1983; Rogers et al. 1984; Smith et al. 1978), indicating that microbial populations capable of degrading cresols are ubiquitous in the environment and can degrade cresols at similar rates. Higher nutrient concentrations result in more rapid cresol degradation (Lewis et al. 1986; Shimp and Pfaender 1985a), while the presence of humic substances may slow degradation (Shimp and Pfaender 1985b). Cresol degradation is markedly slower at lower temperatures (Bartholomew and Pfaender 1983; Hwang et al. 1989) suggesting that, since metabolic rates slow down in winter, dilution may be a more important mechanism than biodegradation. In general, however, cresol isomers appear to degrade in natural waters rapidly with half-lives on the order of less than 1 hour to about 43 hours (Paris et al. 1983; Rogers et al. 1984; Smith et al.

## 5. POTENTIAL FOR HUMAN EXPOSURE

1978; van Veld and Spain 1983). An adaptation period when no degradation occurs is sometimes important in natural microbial communities (Gantzer et al. 1988; Kollig et al. 1987; Lewis et al. 1984), but not always (Spain and van Veld 1983).

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. No confirmation of this order, however, could be found. In addition, 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 (Smith et al. 1978; Spain and van Veld 1983). Nonetheless, degradation probably proceeds along the same pathway described above for activated sludge.

In contrast to aerobic conditions, cresols do not appear to degrade rapidly in anaerobic freshwater 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 degradation pattern (i.e., p-cresol > m-cresol > o-cresol) seen in anaerobic sewage sludge experiments. However, aerobically incubated groundwater samples from anaerobic environments degrade all cresol isomers rapidly (Aelion et al. 1987; Arvin et al. 1988; Jensen et al. 1988; Swindoll et al. 1988). Smolenski and Suflita (1987) and Suflita et al. (1988) found that o-cresol under either sulfate-reducing or methanogenic conditions did not degrade when incubated with anoxic aquifer slurries. By contrast, p-cresol showed a lag time of less than 10 and 46 days under sulfate-reducing and methanogenic conditions, respectively, and m-cresol showed a lag time of 43 and 46-90 days under the same conditions. A more rapid degradation was seen after the lag time. Kuhn et al. (1988) also reported that o-cresol resisted degradation on anoxic columns filled with aquifer material and acclimated to m-xylene, while p- and m-cresol were degraded. Similar results were reported by Godsy et al. (1983) and Delfino and Miles (1985), while Thomas et al. (1989) reported that o-cresol concentrations decreased,

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 1987; Suflita et

## 5. POTENTIAL FOR HUMAN EXPOSURE

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

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 similar to those discussed above have been studied with m- and p-cresol in salt water, including 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 general, degradation decreases with increasing salinity, but probably not to an extent great enough to preclude biodegradation as a significant removal pathway (Palumbo et al. 1988). Under some conditions, acclimation appears to be significant (van Veld and Spain 1983), but this is not always the case (Spain and van Veld 1983). Degradation can be extremely sensitive to the location of the water sample used to conduct degradation tests. Variations were noted in water samples taken a few feet apart (Palumbo et al. 1988). The addition of sediments increases the degradation rate most of the time (van Veld and Spain 1983). Temperature, however, appears to be the most sensitive parameter studied (Bartholomew and Pfaender 1983; Palumbo et al. 1988; Pfaender and Bartholomew 1982a, 1982b). First-order kinetics do not fit biodegradation in saline water (Bartholomew and Pfaender 1983; Palumbo et al. 1988; Pfaender and Bartholomew 1982a, 1982b; van Veld and Spain 1983) and times to 50% disappearance are on the order of  $15 \pm 50$  hours or more.

p-Cresol has been reported to degrade under anaerobic conditions by microbes isolated from a salt marsh (Balba et al. 1982). but no kinetic data were presented.

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 Holgne (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 (Smith et al 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

## 5. POTENTIAL FOR HUMAN EXPOSURE

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. Smith et al. (1978) studied the direct photolysis of p-cresol in water. In pure water and using solar irradiation in April, Smith et al. (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 (Smith et al. 1978). Thus, the amount of light absorbed by cresols will change with pH as will the degradation rates. Smith et al. (1978) estimated a half-life of p-cresol in environmental waters from direct photolysis of 300-400 days under summer light conditions. This and the other estimates presented above suggest 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 ferrous iron [Fe(II)] and manganese [Mn(II/III)] oxides are capable of oxidizing p-cresol. Fe(II) and Mn(II/III) oxides are common species found in surface water particulate and soils, as well as in dust and ash. Rate constants for p-cresol ranged from  $10^{-9}$  to  $10^{-6} \text{ M}^{-1} \text{ min}^{-1}$  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. The exact concentration of Fe(II) and Mn(II/III) oxides in environmental media and their availability for reaction, however, are not clear; therefore, the roles of these species in the degradation of cresols in the environment are difficult to determine.

### 5.3.2.3 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  $\text{CO}_2$  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  $\text{CO}_2$ . In surface soils, first-order rate constants based on  $\text{CO}_2$  evolution were

## 5. POTENTIAL FOR HUMAN EXPOSURE

$7.55 \times 10^{-5}$  -  $6.31 \times 10^{-4}$  hour<sup>-1</sup>, 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-cresol, p-cresol, 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 CO<sub>2</sub> 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 are incorporated.

### 5.4 LEVELS MONITORED OR ESTIMATED IN THE ENVIRONMENT

#### 5.4.1 Air

Monitoring data have not shown cresols to be widely occurring atmospheric pollutants. 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 (Shah and Heyerdahl 1989). 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 0.359 ppb for 32 samples (Shah and Heyerdahl 1989).

Cresol was detected in the ambient air of Upland, California; however, specific isomers were not identified (Kolber et al. 1981).

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 5.3.2.1).

## 5. POTENTIAL FOR HUMAN EXPOSURE

### 5.4.2 Water

Information pertaining to the occurrence of cresols in surface waters was limited. STORET (1989) and the CLPSD (1988) contained no records for o-cresol in ambient surface water. o-Cresol was detected in freshwater 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 was attributed to the Mount St. Helens eruption on May 18, 1980 (McKnight et al. 1982). Whether or not the cresols originated from wood fires or the actual eruption was not clarified.

According to STORET (1989), the minimum, maximum, mean, and median p-cresol concentrations for 8 unremarked ambient surface water data points (those data points that are not noted to be less than a given value, usually the detection limit) are 10.0, 77.0, 39.1, and 29.0  $\mu\text{g/L}$ . p-Cresol was detected in surface water with a frequency of occurrence of 1.5% and with a geometric mean concentration of 11 ppb for positive samples (CLPSD 1988). p-Cresol was identified as a contaminant of mixed water and sediment samples from the Tennessee River (Gordon and Goodley 1971) at a concentration of 200  $\mu\text{g/L}$  (Goodley and Gordon 1976). p-Cresol also was detected in freshwater samples from Spirit Lake, Washington, on August 7, 1980 at unreported concentrations (McKnight et al. 1982).

The minimum, maximum, mean, and median m-cresol concentrations for 2 unremarked ambient surface water data points are 16.0, 23.0, 19.5, and 16.0  $\mu\text{g/L}$  (STORET 1989). 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 freshwater samples from Spirit Lake, Washington, on August 7, 1980 at unreported concentrations (McKnight et al. 1982).

The mean and median concentration of mixed cresols for 1 unremarked ambient surface water data point is 29.0  $\mu\text{g/L}$  (STORET 1989). Information on mixtures of cresols was not included by the CLPSD (CLPSD 1988). Likewise, unspecified isomers of cresol were detected from 1 of 7 sample sites along the Delaware River at a concentration of 20 ppb. 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 ppb, respectively; this suggested that rapid biodegradation prevents cresol detection during the warmer months (Sheldon and Hites 1978).

Again, the absence of monitoring data does not necessarily indicate a lack of cresols in the environment. Cresols are widely occurring natural and

## 5. POTENTIAL FOR HUMAN EXPOSURE

anthropogenic products. However, biodegradation is probably the dominant mechanism responsible for the rapid removal of cresols from surface waters (see Section 5.3.2.2). 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.

Tables 5-2a through 5-2e summarize the literature data on cresols found in groundwater and their respective anthropogenic sources. STORET (1989) did not contain records for o-cresol in groundwater.

The minimum, maximum, mean, and median p-cresol concentrations for 3 unremarked groundwater data points are 10.0, 4,000.0, 1,364.0, and 82.0  $\mu\text{g/L}$  (STORET 1989).

The minimum, maximum, mean, and median m-cresol concentrations for 104 unremarked groundwater data points are 0.0, 100,000.0, 9,713.0, and 7.0  $\mu\text{g/L}$  (STORET 1989).

The minimum, maximum, mean, and median concentrations of mixed cresols for three unremarked groundwater data points are all 5.0  $\mu\text{g/L}$  (STORET 1989).

Only two reports were found in the literature that quantified cresols in precipitation. Rainwater at Portland, Oregon, contained o-cresol at concentrations ranging from 240 to 2,800 ng/L, with an average concentration of 1,020 ng/L for 7 rainfalls between February 12, 1984 and April 12, 1984. Combined p- and m-cresol concentrations ranged from 380 to 2,000 ng/L, with an average concentration of greater than 1,100 ng/L (Leuenberger et al. 1985a). o-Cresol was detected in rainwater from a rural site (Grepden, Switzerland) on April 3, 1986, at concentrations ranging from not detected to 1.3  $\mu\text{g/L}$ . Combined p- and m-cresol concentrations ranged from 0.65 to 9.3  $\mu\text{g/L}$  (Czuczwa et al. 1987).

### 5.4.3 Soil

Monitoring data pertaining to cresols found in soil were not found in the literature. Nonetheless, o-cresol was detected in 3.7% of the soil samples in the CLPSD (CLPSD 1988).

For the CLPSD, p- and m-cresol were detected with frequencies of occurrence of 4.4% and 0.9%, and with geometric mean concentrations of 257 and 1,105 ppb for the positive samples, respectively. Information on mixtures of cresols was not included by the CLPSD (CLPSD 1988).

Cresols are an excretory product of mammals and an intermediate biotransformation product of natural aromatics such as lignin constituents (Fiege and Bayer 1987). Consequently, 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 5.3.2.3).

## 5. POTENTIAL FOR HUMAN EXPOSURE

### 5.4.4 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 mammals. 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.

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 ranging from 0.01 to 0.20 ppm, 0.01 to 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 all three isomers is about 7.5  $\mu\text{g}$  per cigarette (Wynder and Hoffman 1967). An individual who smokes two packs of cigarettes a day may inhale approximately 3.0  $\mu\text{g}/\text{day}$ .

### 5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

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).

The most common route of exposure for the general population is probably inhalation. However, cresols have a short residence time in both day- and night-time air; despite continual releases of cresols to the atmosphere, levels are probably low. Very few atmospheric monitoring data are available

## 5. POTENTIAL FOR HUMAN EXPOSURE

in the literature; therefore, an average daily intake via inhalation was not calculated. Cigarette smoke is also a source of atmospheric exposure. An individual who smokes two packs of cigarettes a day may inhale 3.0 µg/day (Wynder and Hoffman 1967).

Ingestion of certain foods may be as 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, as well as the air for individuals living near hazardous waste sites or cresol production facilities. 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.

An estimated 21,156, 33,257, 11,162, and 1,261,818 workers were potentially exposed to o-, p-, m-, and the mixture of isomers, respectively, in the workplace, according to the National Occupational Hazard Survey (NOHS) conducted between 1972 and 1974 (NIOSH 1984). According to the National Occupational Exposure Survey (NOES) conducted by NIOSH in the workplace between 1980 and 1983, 3,214, 3,269, 5,573, and 121,573 workers were potentially exposed to o-, p-, m-, and the mixture of isomers, respectively (NIOSH 1989). Neither the NOHS nor NOES data bases 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 cresol 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 less than 0.1 mg/m<sup>3</sup> (Heikkila et al. 1987). Workers of a bench scale coal conversion process were exposed to atmospheric levels of cresols less than 0.1 ppm in 1981 and 1982 (Dreibelbis et al. 1985).

## 5. POTENTIAL FOR HUMAN EXPOSURE

### 5.6 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 may be exposed to high amounts of cresols.

### 5.7 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 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 or eliminate the uncertainties of human health assessment. In the future, the above data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed,

#### 5.7.1 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 (Amoore and Hautula 1983; Artiola-Fortuny and Fuller 1982; Boyd 1982; Chao et al. et al. 1985; Gaffney et al. 1983; Daubert and Danner 1985; Freitag 1987; Hansch and Leo 1985; Hine and Mookerjee 1975; OHM/TADS 1989; Riddick et al. 1986; Sax and Lewis 1987; Verschueren 1983; Weast et al. 1988; 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 (Lyman et al. 1982).

**Production, Import/Export, Use, and Disposal.** Current production volumes are available (USITC 1989), as are historical and predictive production volume information (CMR 1987; USITC 1986). 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;

## 5. POTENTIAL FOR HUMAN EXPOSURE

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 Dimitriades 1972; Snider and Manning 1982) from manufacturing, production, and use (TRI 1989) 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. 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.

According to the Emergency Planning and Community Right-to-Know Act of 1986, 42 U.S.C. Section 11023, industries are required to submit chemical release and off-site transfer information to the EPA. The Toxic Release Inventory, which contains this information for 1987, became available in May of 1989. This database will be updated yearly and should provide a list of industrial production facilities and emissions.

**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 data base is available describing the aerobic (rapid) (Alexander and Lustigman 1966; Babeu and Vaishnav 1987; Baird et al. 1974; Chambers et al. 1963; 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 1971; Pitter 1976; Singer et al. 1979; Tabak et al. 1964; Young et al. 1968) and anaerobic (slow) (Battersby and Wilson 1988, 1989; Boyd et al. 1983; Fedorak and Hrudehy 1984; Horowitz et al. 1982; Shelton and Tiedje 1981; Wang et al. 1988, 1989) degradation of cresols in water and appears to be consistent; however, soil biodegradation data are few and conflicting. 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).

**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 located in water, soil, 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 would allow determination of the rate and extent of absorption from each of these media and comparison of the potential hazard posed by cresols contained in each.

## 5. POTENTIAL FOR HUMAN EXPOSURE

**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 (Lyman et al. 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.

**Exposure Levels in Environmental Media.** Information on exposure levels in environmental media is available for groundwater (Bendient et al. 1984; Drinkwater et al. 1986; Goerlitz et al. 1985; Hutchins et al. 1980; Oliveira and Sitar 1985; Ram et al. 1985; Sawhney and Kozlowski 1984; Stuermer et al. 1982; Weber and Matsumota 1987) only (sources of groundwater contamination include hazardous waste sites). Data describing the exposure levels in air and surface water are lacking. It is not clear whether monitoring studies were not performed, or were not found. Quantified levels of cresols in food are also lacking. Estimates of human intake are not available.

**Exposure Levels in Humans.** Cresols are naturally occurring substances that are present in human urine (Fiege and Bayer 1987), and data on this are available. 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 monitoring for cresols in humans does not necessarily mean exposure to them. The ability to rigorously establish cresol exposure levels in humans has yet to be demonstrated.

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

### 5.7.2 On-going Studies

For o-, p-, and m-cresol, as well as the mixed isomers, anaerobic degradation studies, analytical methods development, and transformation studies are all on-going (EPA 1989b). Additionally, for o-cresol, studies on water purification techniques are on-going, while for p-cresol, aerobic degradation and toxicity studies are on-going.

As part of the Third National Health and Nutrition Evaluation Survey (NHANES III), the Environmental Health Laboratory Sciences Division of the

## 5. POTENTIAL FOR HUMAN EXPOSURE

Center for Environmental Health and Injury Control, Centers for Disease Control, will be analyzing human urine samples for cresols and other phenolic compounds. These data will give an indication of the frequency of occurrence and background levels of these compounds in the general population.



## 6. ANALYTICAL METHODS

The purpose of this chapter is to describe the analytical methods that are available for detecting and/or measuring and monitoring cresols in environmental media and in biological samples. The intent is not to provide an exhaustive list of analytical methods that could be used to detect and quantify cresols. Rather, the intention is to identify well-established methods that are used as the standard methods of analysis. Many of the analytical methods used to detect cresols in environmental samples are the methods approved by federal agencies 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 refine previously used methods to obtain lower detection limits, and/or to improve accuracy and precision.

### 6.1 BIOLOGICAL MATERIALS

Numerous methods for the determination of o-, m-, and p-cresol in urine have appeared in the literature, but none have been standardized. Cresol in urine is often measured to determine exposure to toluene or other aromatic compounds, of which cresol is a metabolite. The analytical methods summarized in Table 6-1 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), and o-cresol is an indicator of toluene exposure (DeRosa et al. 1987).

The isomers of cresol are excreted in the urine as their glucuronides and sulfates (Biemiak 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 1985; Needham et al. 1984). Separation of the cresol isomers by gas chromatography is readily accomplished, and the use of an appropriate internal standard allows the determination of their concentrations. Although exact detection limits were not given for the above GC methods, a concentration of 10 ppm appears to be readily determined.

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

Sample matrix	Preparation method	Analytical method	Sample detection limit	Percent recovery	Reference	Isomer
Urine	Hydrolyze with sulfuric acid; extract with ethyl acetate	GC/FID	No data	78-97	Needham et al. 1984	o,m,p
Urine	Hydrolyze with HCl extract with isopropyl ether; remove solvent; dissolve residue in water; add $\beta$ -cyclodextrin	HPLC/UV	1 ppm	97-102	Yoshikawa et al. 1986	o,m,p
Urine	Acidify; steam distill; extract with methylene chloride	GC/MS	No data	No data	Angerer 1985	o
Urine	Hydrolyze with sulfuric acid; extract with $\text{CH}_2\text{Cl}_2$ ; concentrate	HPLC/UV	No data	No data	DeRosa et al. 1987	o
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

m = m-cresol

MS = mass spectrometry

o = o-cresol

p = p-cresol

UV = ultraviolet spectroscopy

## 6. ANALYTICAL METHODS

The three isomers of cresol are not as readily separated by HPLC, although recent techniques have been developed to accomplish this task. Reversed-phase chromatography columns have been used for the analysis of cresols with limited success. Recently, a new 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  $\beta$ -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.

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.

### 6.2 ENVIRONMENTAL SAMPLES

Methods for determining cresols in environmental media are summarized in Table 6-2. Procedures for the determination of *o*- and *p*-cresol in water, soil, and sediment samples at hazardous waste sites are outlined by EPA (1988a). 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, CLP guidelines state that the aqueous sample be brought to pH 11 by the addition of sodium hydroxide (NaOH). The basic mixture is then 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 1988b). However, numerous methods for their

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

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	o,m,p
Air	Aerodispersive enrichment into water	HPLC/ED	No data	No data	Vecera and Janak 1987	o
Water	Adjust pH to 11, extract with CH <sub>2</sub> Cl <sub>2</sub> , concentrate	GC/MS	10 ppb	No data	EPA 1988a	o,p
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	Hoffman and Tanner 1986	o,m,p
Rain water	Acidify, extract with CH <sub>2</sub> Cl <sub>2</sub> , concentrate, methylate	GC/MS	No data	>50	Kawamura and Kaplan 1986	o,m,p
Soil, sediment	Extract sample with CH <sub>2</sub> Cl <sub>2</sub> using ultra sonic probe	GC/MS	330 ppb	No data	EPA, 1988a	o,p
Sediment	Extract rapidly stirred sediment slurry with CH <sub>2</sub> Cl <sub>2</sub> 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 <sup>3</sup>	No data	Neiminen and Heikkila 1986	o,m,p

CD = conductivity detector  
 ED = electrochemical detector  
 GC = gas chromatography  
 HPLC = high performance liquid chromatography  
 m = meta-cresol  
 MS = mass spectrometry  
 o = ortho-cresol  
 p = para-cresol  
 UV = ultraviolet detector

## 6. ANALYTICAL METHODS

determination have appeared in the open literature. Methods for the determination of cresols in ambient air (Kolber et al. 1981; Kuwata and Tanaka 1988; Tembbreull and Lubman 1984; Vecera and Janak 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) rainwater (Hoffman and Tanner 1986; 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 5.3.2). 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.

### 6.3 ADEQUACY OF THE DATABASE

Section 104(i)(5) of CERCLA as amended directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cresols is available. Where adequate information is not available, ATSDR, in conjunction with the NTP, is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of 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 or eliminate the uncertainties of human health assessment. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

#### 6.3.1 Data Needs

**Methods for Determining Biomarkers of Exposure and Effect.** There are no known biomarkers of exposure that are unique to cresol. 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

## 6. ANALYTICAL METHODS

population could be established using existing techniques (Angerer 1985; DeRosa et al. 1987; Krotoszynski and O'Neill 1982; Needham et al. 1984; Yoshikawa et al. 1986). 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 exposure and 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 (EPA 1988a; Goodley and Gordon 1976; Hites 1979; Hoffman and Tanner 1986; Kawamura and Kaplan 1986; Kuwata and Tanaka 1988; Neiminen and Heikkila 1986; Vecera and Janak 1987). These procedures are capable of both identifying areas that have been contaminated with cresol and determining 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.

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 5.3.2). As a result, the determination of these intermediates cannot be accurately extrapolated back to levels of cresol contamination in the environment.

### 6.3.2 On-going Studies

On-going studies developing new analytical methods for detecting the three isomers of cresol have been identified (EPA 1989b).

The Environmental Health Laboratory Sciences Division of the Center for Environmental Health and Injury Control, Centers for Disease Control, is developing methods for the analysis of cresols and other phenolic compounds in urine. These methods use purge and trap methodology and magnetic mass spectrometry which gives detection limits in the low ppt range.

## **7. REGULATIONS AND ADVISORIES**

National and state regulations and guidelines pertinent to human exposure to cresols are summarized in Table 7-1.

## 7. REGULATIONS AND ADVISORIES

TABLE 7-1. Regulations and Guidelines Applicable to Cresols

Agency	Description	Information	References
<b><u>NATIONAL</u></b>			
Regulations:			
a. Air:			
OSHA	PEL	22 mg/m <sup>3</sup>	OSHA 1989 (29 CFR 1910)
	TWA	22 mg/m <sup>3</sup>	54 FR 2922 (01/19/89)
b. Other:			
EPA OERR	Reportable quantity	1000 pounds	40 CFR 117,302 51 FR 34541 (09/29/86)
Guidelines:			
a. Air:			
ACGIH	TWA	22 mg/m <sup>3</sup>	ACGIH 1989
b. Non-specific:			
EPA	RfD for chronic oral exposure	0.05 mg/kg/d	IRIS 1981
<b><u>STATE</u></b>			
Regulations and Guidelines:			
a. Air:	Acceptable ambient limits of toxic air pollutants		NATICH 1987
<b><u>Cresols</u></b>			
Connecticut		200 µg/m <sup>3</sup> 8 hr	
North Carolina		2220 µg/m <sup>3</sup> 1 hr	
North Dakota		220 µg/m <sup>3</sup> 8 hr	
Nevada		524 µg/m <sup>3</sup> 8 hr	
New York		73 µg/m <sup>3</sup> 1 yr	
South Carolina		220 µg/m <sup>3</sup> 24 hr	
<b><u>ortho-Cresol</u></b>			
Florida (Tampa)		220 µg/m <sup>3</sup> 8 hr	
Indiana		110 µg/m <sup>3</sup> 8 hr	
New York		73 µg/m <sup>3</sup> 1 yr	
Virginia		370 µg/m <sup>3</sup> 4 hr	
<b><u>para-Cresol</u></b>			
Florida (Tampa)		220 µg/m <sup>3</sup> 8 hr	
Massachusetts		12 µg/m <sup>3</sup> 24 hr	
New York		73 µg/m <sup>3</sup> 1 yr	
Virginia		370 µg/m <sup>3</sup> 24 hr	
<b><u>meta-Cresol</u></b>			
Florida (Tampa)		220 µg/m <sup>3</sup> 8 hr	
New York		73 µg/m <sup>3</sup> 1 yr	
Virginia		370 µg/m <sup>3</sup> 24 hr	

ACGIH = American Conference of Governmental Industrial Hygienists  
EPA = Environmental Protection Agency  
hr = hour  
OERR = Office of Emergency and Remedial Response  
OSHA = Occupational Safety and Health Administration  
PEL = Permissible Exposure Limit  
RfD = Reference Dose  
TWA = Time-Weighted Average  
yr = year

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## 9. GLOSSARY

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

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

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

**Anthropogenic** -- Of or relating to, or resulting from the influence of human beings on nature.

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

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

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

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

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

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

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

## 9. GLOSSARY

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

**Immediately Dangerous to Life or Health (IDLH)** -- The maximum environmental concentration of a contaminant from which one could escape within 30 min without any escape-impairing symptoms or irreversible health effects. **Intermediate Exposure** -- Exposure to a chemical for a duration of 15-364 days as specified in the Toxicological Profiles.

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

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

**In Vivo** -- Occurring within the living organism.

**Lethal Concentration<sub>(L0)</sub> (LC<sub>L0</sub>)** -- The lowest concentration of a chemical in air which has been reported to have caused death in humans or animals.

**Lethal Concentration<sub>(50)</sub> (LC<sub>50</sub>)** -- A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

**Lethal Dose<sub>(L0)</sub> (LD<sub>L0</sub>)**-- The lowest dose of a chemical introduced by a route other than inhalation that is expected to have caused death in humans or animals.

**Lethal Dose<sub>(50)</sub> (LD<sub>50</sub>)** -- The dose of a chemical which has been calculated to cause death in 50% of a defined experimental animal population.

**Lethal Time<sub>(50)</sub>, (LT<sub>50</sub>)** -- A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

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

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

## 9. GLOSSARY

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

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

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

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

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

**Oligotrophic** -- Deficient in plant nutrients and having plentiful dissolved oxygen.

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

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

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

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

## 9. GLOSSARY

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

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

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

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

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

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

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

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

## APPENDIX A

### USER'S GUIDE

#### Chapter 1

##### Public Health Statement

This chapter of the profile is a health effects summary written in nontechnical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or substance 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 substance.

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

#### Chapter 2

##### Tables and Figures for Levels of Significant Exposure (LSE)

Tables (2-1, 2-2, and 2-3) and figures (2-1 and 2-2) are used to summarize health effects by duration of exposure and endpoint and to illustrate graphically levels of exposure associated with those effects. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed- Adverse-Effect Levels (LOAELs) for Less Serious and Serious health effects, or Cancer Effect Levels (CELs). In addition, these tables and figures illustrate differences in response by species, Minimal Risk Levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. The LSE tables and figures can be used 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.

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

#### LEGEND

##### See LSE Table 2-1

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

## APPENDIX A

three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 2-1, 2-2, and 2-3, respectively). LSE figures are limited to the inhalation (LSE Figure 2-1) and oral (LSE Figure 2-2) routes.

- (2). Exposure Duration Three exposure periods: acute (14 days or less); intermediate (15 to 364 days); and chronic (365 days or more) are presented within each route of exposure. In this example, an inhalation study of intermediate duration exposure is reported.
- (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.
- (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 define a NOAEL and a Less Serious LOAEL (also see the two "18r" data points in Figure 2-1).
- (5). Species The test species, whether animal or human, are identified in this column.
- (6). Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to [substance x] via inhalation for 13 weeks, 5 days per week, for 6 hours per day.
- (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 in this study.
- (8). NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote sc").
- (9). LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest exposure level 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

## APPENDIX A

quantify the adverse effect accompanies the LOAEL. The "Less Serious" respiratory effect reported in key number 18 (hyperplasia) occurred at a LOAEL of 10 ppm.

- (10). Reference The complete reference citation is given in Chapter 8 of the profile.
- (11). CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiological studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses which did not cause a measurable increase in cancer.
- (12). Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "c" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

**LEGEND****See LSE Figure 2-1**

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

- (13). Exposure Duration The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.
- (14). Health Effect These are the categories of health effects for which reliable quantitative data exist. The same health effects appear in the LSE table.
- (15). Levels of Exposure Exposure levels for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure levels are reported on the log scale "y" axis. Inhalation exposure is reported in mg/m<sup>3</sup> or ppm and oral exposure is reported in mg/kg/day.
- (16). NOAEL In this example, 18r NOAEL is the critical end point for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates a NOAEL for the test species (rat). The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).
- (17). CEL Key number 38r is one of three studies for which Cancer Effect Levels (CELs) were derived. The diamond symbol refers to a CEL for the test species (rat). The number 38 corresponds to the entry in the LSE table.

APPENDIX A

- (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 EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels ( $q_1^*$ ).
- (19). Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

# SAMPLE

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

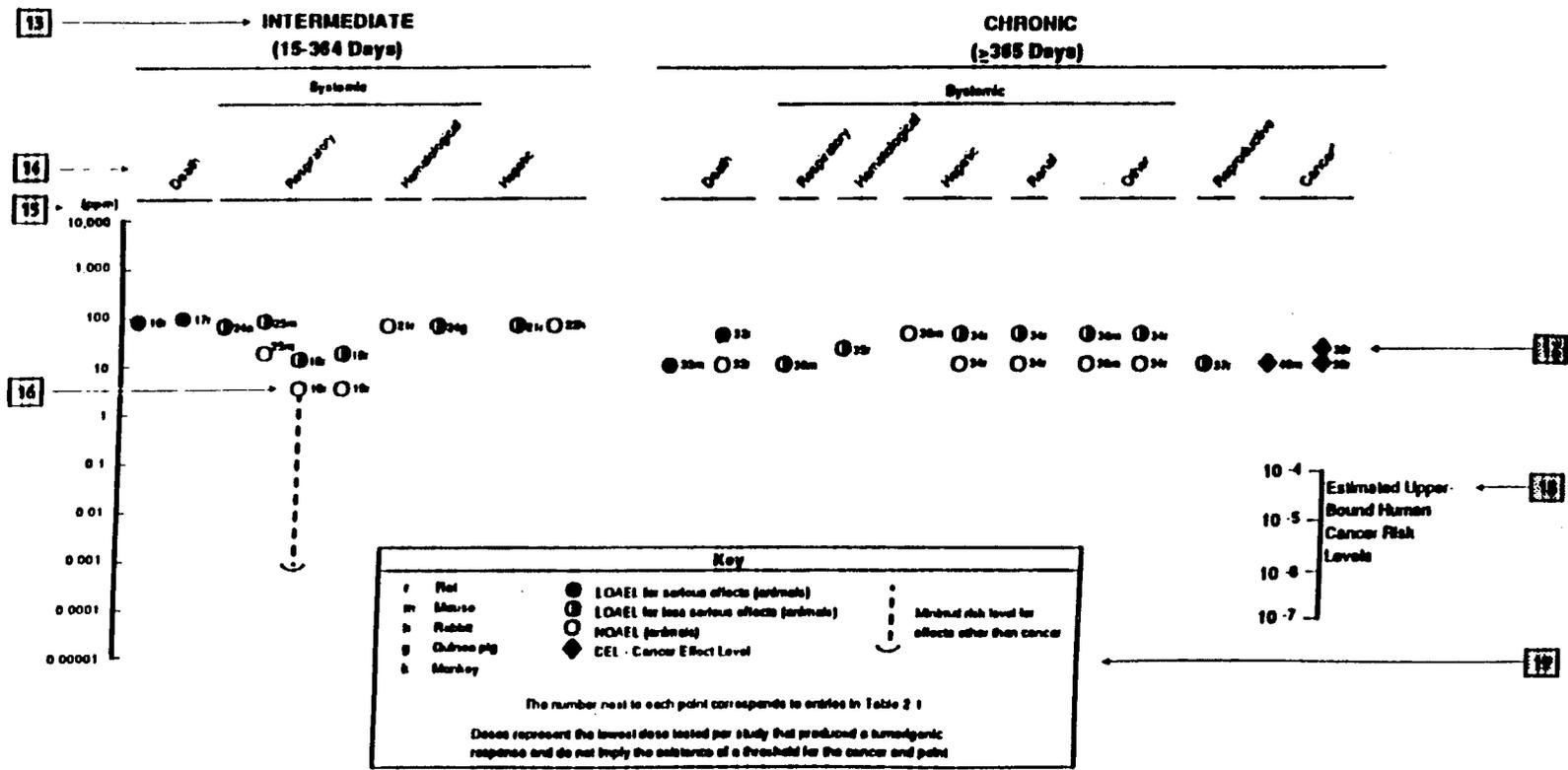
Key to figure <sup>a</sup>	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
<b>2</b> → INTERMEDIATE EXPOSURE							
<b>3</b> → Systemic	<b>5</b> ↓	<b>6</b> ↓	<b>7</b> ↓	<b>8</b> ↓	<b>9</b> ↓		<b>10</b> ↓
<b>4</b> → 18	Rat	13 wk 5d/wk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

<sup>a</sup> The number corresponds to entries in Figure 2-1.

**12** → <sup>b</sup> Used to derive an intermediate inhalation Minimal Risk Level (MRL) of  $5 \times 10^{-3}$  ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

CEL = cancer effect level; d = day(s); hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

# SAMPLE



**FIGURE 2-1. Levels of Significant Exposure to [Chemical X]-Inhalation**

## APPENDIX A

**Chapter 2 (Section 2.4)****Relevance to Public Health**

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

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

The section discusses health effects by end point. Human data are presented first, then animal data. Both are organized by route of exposure (inhalation, oral, and dermal) and by duration (acute, intermediate, and chronic). In vitro data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

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

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

**Interpretation of Minimal Risk Levels**

Where sufficient toxicologic information was available, MRLs were derived. MRLs are specific for route (inhalation or oral) and duration (acute, intermediate, or chronic) of exposure. Ideally, MRLs can be derived from all six exposure scenarios (e.g., Inhalation - acute, -intermediate, -chronic; Oral - acute, -intermediate, - chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a substance emission, given the concentration of a contaminant in air or the estimated daily dose received via food or water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

## APPENDIX A

MRL users should be familiar with the toxicological information on which the number is based. Section 2.4, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 2.6, "Interactions with Other Chemicals" and 2.7, "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 used by the Environmental Protection Agency (EPA) (Barnes and Dourson, 1988; EPA 1989a) to derive reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the end point which, in its best judgement, represents the most sensitive humanhealth 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 effects (e.g., systemic, neurological, and developmental). In order to compare NOAELs and LOAELs for specific end points, all inhalation exposure levels are adjusted for 24hr exposures and all intermittent exposures for inhalation and oral routes of intermediate and chronic duration are adjusted for continuous exposure (i.e., 7 days/week). If the information and reliable quantitative data on the chosen end point are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. The NOAEL is the most suitable end point for deriving an MRL. When a NOAEL is not available, a Less Serious LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 is employed.

MRLs are not derived from Serious LOAELs. Additional uncertainty factors of 10 each are used 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 adjusted inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

## APPENDIX B

## ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADME	Absorption, Distribution, Metabolism, and Excretion
ATSDR	Agency for Toxic Substances and Disease Registry
BCF	bioconcentration factor
BSC	Board of Scientific Counselors
CDC	Centers for Disease Control
CEL	Cancer Effect Level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
CLP	Contract Laboratory Program
cm	centimeter
CNS	central nervous system
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DOL	Department of Labor
ECG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
EKG	see ECG
FAO	Food and Agricultural Organization of the United Nations
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
f <sub>1</sub>	first generation
fpm	feet per minute
ft	foot
FR	Federal Register
g	gram
GC	gas chromatography
HPLC	high performance liquid chromatography
hr	hour
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
K <sub>d</sub>	adsorption ratio
kg	kilogram
K <sub>oc</sub>	octanol-soil partition coefficient
K <sub>ow</sub>	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC <sub>Lo</sub>	lethal concentration low
LC <sub>50</sub>	lethal concentration 50 percent kill
LD <sub>Lo</sub>	lethal dose low
LD <sub>50</sub>	lethal dose 50 percent kill

## APPENDIX B

LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
mg	milligram
min	minute
mL	milliliter
mm	millimeters
mmol	millimole
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectroscopy
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSH TIC	NIOSH's Computerized Information Retrieval System
nm	nanometer
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPL	National Priorities List
NRC	National Research Council
NTIS	National Technical Information Service
NTP	National Toxicology Program
OSHA	Occupational Safety and Health Administration
PEL	permissible exposure limit
pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportional mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure limit
RfD	Reference Dose
RTECS	Registry of Toxic Effects of Chemical Substances
sec	second
SCE	sister chromatid exchange
SIC	Standard Industrial Classification
SMR	standard mortality ratio
STEL	short-term exposure limit
STORET	<u>STORAGE</u> and <u>RETRIEVAL</u>
TLV	threshold limit value
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States

## APPENDIX B

UF	uncertainty factor
WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
δ	delta
γ	gamma
μm	micron
μg	microgram



APPENDIX C

PEER REVIEW

A peer review panel was assembled for cresols. The panel consisted of the following members: Dr. David Brown, Director of Toxicology Programs, Northeastern University, Boston, Massachusetts; Dr. Norman Trieff, Professor of Environmental Toxicology, University of Texas Medical Branch, Galveston, Texas; Dr. Edmond LaVoie, Professor of Medicinal Chemistry, Rutgers University, Piscataway, New Jersey. These experts collectively have knowledge of cresols' 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 the Comprehensive Environmental Response, Compensation, and Liability Act of 1986, Section 104.

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

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

