PRIORITY DATA NEEDS FOR CRESOLS

Prepared by:

Syracuse Research Corporation
Under Contract No. 200-2004-09793

Prepared for:

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

NOTE TO THE READER

The Priority Data Needs documents are intended to characterize substance-specific priority data needs determined via the ATSDR Decision guide for identifying substance-specific data needs related to toxicological profiles (54 Federal Register 37618, September 11, 1989). The identified priority data needs reflect the opinion of the Agency, in consultation with other federal programs, of the research necessary for fulfilling its statutory mandate under the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (Superfund) or CERCLA. They are not intended to represent the priority data needs for any other program.

CONTRIBUTORS

DOCUMENT MANAGER(S)/AUTHOR(S):

Nickolette Roney MPH
Yee-Wan Stevens, M.S.
ATSDR, Division of Toxicology and Environmental Medicine, Atlanta, GA

Fernando Llados, Ph.D.
Sari Paikoff, Ph.D.
Syracuse Research Corporation, North Syracuse, NY

The document has been reviewed by John Risher, Ph.D., team member for ATSDR's Toxicological Profile for Cresols. In addition, it was reviewed by the National Institute of Environmental Health Sciences and the National Center for Toxicological Research of the United States Food and Drug Administration.

TABLE OF CONTENTS

I. Executive Summary 1
II. Introduction: ATSDR's Substance-Specific Applied Research Program 3
A. Legislative 3
B. Impact on Public Health 4
C. Procedures 5
D. Selection Criteria 7
1. Frequency of Occurrence 7
2. Potential for Human Exposure 7
3. Toxicity 10
III. Identification of Data Needs 14
A. Exposure Data Needs (Table 1) 14
1. Levels I & II Data Needs 14
a. Analytical Methods 14
b. Physical/Chemical Properties 15
c. Exposure Levels 16
(1) Environmental Media 16
(2) Humans 17
d. Exposures of Children 18
e. Environmental Fate 19
f. Bioavailability and Bioaccumulation Potential 20
2. Level III Data Needs 21
a. Registries of Exposed Persons 21
B. Toxicity Data Needs (Table 2) 22
1. Levels I & II Data Needs 22
a. Acute-Duration Exposure 23
b. Intermediate-Duration Exposure 25
c. Chronic-Duration Exposure 26
(1) Toxicity Assessment 26
(2) Cancer Assessment 27
d. Genotoxicity 28
e. Endocrine Disruption 29
f. Reproductive Toxicity 31
g. Developmental Toxicity 33
h. Immunotoxicity 34
i. Neurotoxicity 35
j. Toxicokinetics 37
2. Level III Data Needs 39
a. Epidemiologic Studies 39
b. Mechanism of Toxic Action 40
c. Biomarkers 41
d. Clinical Methods for Mitigating Toxicity 42
e. Children's Susceptibility 43
IV. Summary: Prioritization of Data Needs for Cresols 44
A. Exposure 44
B. Toxicity 44
V. References 47

Table 1. Exposure Data Needs 58

Table 2. Toxicity Data Needs 59

Table 3. ATSDR Substance-Specific Applied Research Program for Cresols 60

Substance-Specific Applied Research Program

Priority Data Needs for:

Cresols

Prepared by: Agency for Toxic Substances and Disease Registry/
Division of Toxicology and Environmental Medicine (ATSDR/DTEM)

Date prepared: May 2009

I. Executive Summary

Cresols are included in the priority list of hazardous substances identified by ATSDR (ATSDR 2007a). This list contains substances that have been identified at National Priorities List (NPL) sites and determined to pose a human health risk based on (1) known or suspected human toxicity, (2) frequency of occurrence at NPL sites or other facilities, and (3) the potential for human exposure to the substance. An updated Toxicological Profile for Cresols was published by ATSDR in September 2008.

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; generally, pure cresols are solid, while mixtures tend to be liquid. Cresols have a medicinal odor and when dissolved in water, they give it a medicinal smell and taste. All cresol isomers and mixtures are very soluble in alcohol, chloroform, ether, benzene, acetone, and water. Cresols evaporate more slowly than water with a vapor pressure ranging from 0.11 to 0.30 mm Hg. Aqueous solutions of cresols do not readily volatilize from water with a Henry's law constants ranging from $1.2x10^{-6}$ to $7.92x10^{-7}$ m^3/mol.

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, crude oil, and coal tar. In addition, cresols can also be manufactured and used as disinfectants and deodorizers, to dissolve substances, and as starting chemicals for making other chemicals. According to the 2005 Directory of Chemical Producers,

cresols are currently produced by five manufacturers in New York, Pennsylvania, Illinois, and Texas.

The mobility of cresols in soil is considered high based on K_{oc} levels of approximately 17.5–117, indicating that leaching into groundwater is possible. However, the rate of cresol biodegradation in the soil may be so rapid that the probability of groundwater contamination may be low.

Cresols are not highly persistent in the environment. Cresols are degraded in the air by both hydroxy and nitrate radicals. Cresols have been shown to biodegrade in both water and soil.

Inhalation exposure is likely to be the most common route of exposure for the general population, including children, to cresols. However, since cresols have a short residence time in both day- and night-time air; atmospheric levels are probably low despite their ubiquitous nature. Proximity to cigarette smoke and automobile exhaust may increase the risk of inhalation exposure to cresols as these vapors contain cresols. Cresols can be formed in the body by degradation of toluene and exposure to toluene could lead to increased levels of cresols. Occupational exposure may occur through inhalation or dermal contact at places where cresols are produced or used. Similar to the general public, populations residing near hazardous waste sites will be exposed to low levels of cresols through the inhalation of ambient air. Additional exposures above background concentrations can arise from ingestion of contaminated media, especially drinking water obtained from groundwater wells due to the possibility of cresols leaching into groundwater, particularly near landfills.

Cresols, particularly in high concentrations, are irritating and corrosive substances, making the skin and mucosal membranes targets of toxicity in humans and animals. Individuals exposed acutely to high amounts of cresols also have experienced other systemic effects that may not have been caused directly by cresols, but may represent secondary reactions to shock caused by external and internal burns. Acute exposure to relatively high amounts of cresols has also caused adverse neurological effects characterized by coma. No populations have been identified that have been exposed to cresols for prolonged periods of time; therefore, potential health effects following such exposures are unknown. Intermediate-duration dietary studies in animals indicated nasal epithelial lesion to be a sensitive target for cresols' toxicity. Aside from these lesions, cresols exhibited little toxicity. A chronic-duration (2-year) toxicity and carcinogenicity bioassay in animals confirmed the presence of nasal lesions reported in the intermediate studies

and also observed increased incidences of bronchiolar hyperplasia and follicular degeneration of the thyroid gland in treated mice. No acute-duration dietary studies were located; therefore, it is unknown whether nasal lesion can be induced following short-term exposure to cresols. Cresols affected reproductive end points in animals at relatively high dose levels. Cresols also induced adverse developmental effects in animals in oral studies at dose levels that also affected the mother. The available data do not suggest that cresols have properties of endocrine disruptors. It is not known if children are more susceptible to the toxicity of cresols than adults.

On the basis of the available data, ATSDR has identified the following priority data needs:

Exposure

- Exposure levels in humans living near hazardous waste sites and other populations
- Exposure levels in children

Toxicity

- Dose-response data for acute-duration via oral exposure

II. Introduction: ATSDR's Substance-Specific Applied Research Program

A. Legislative

Section 104(i)(5) of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of cresols is available. Where adequate information is not available, ATSDR, in cooperation with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine these health effects. Such program shall include, to the extent necessary to supplement existing information, but shall not be limited to--

- laboratory and other studies to determine short, intermediate, and long-term health effects;

- laboratory and other studies to determine organ-specific, site-specific, and system-specific acute and chronic toxicity;
- laboratory and other studies to determine the manner in which such substances are metabolized or to otherwise develop an understanding of the biokinetics of such substances; and
- where there is a possibility of obtaining human data, the collection of such information.

Section 104(i)(5)(C): In the development and implementation of the research program ATSDR is required to coordinate with EPA and NTP to avoid duplication of research being conducted in other programs and under other authorities.

Section 104(i)(5)(D): It is the sense of Congress that the costs for conducting this research program be borne by private industry, either under the Toxic Substances Control Act (TSCA), the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), or cost recovery under CERCLA.

B. Impact on Public Health

The major purpose of this research program is to supplement the substance-specific informational needs of the public and the scientific community. More specifically for ATSDR, this program will supply necessary information to improve the database to conduct public health assessments. This is more fully described in the ATSDR Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles (54 Federal Register 37618) [henceforth referred to as the ATSDR Decision Guide].

Experience from ATSDR health assessments shows the need for more information for select substances, on both exposure and toxicity, so the Agency can more completely assess human health effects. Exposure data collected from this substance-specific research will complement data being collected on a site-specific basis by ATSDR's Division of Health Studies and the Division of Health Assessment and Consultation. More specifically, the Agency will use the exposure data to help identify populations that need follow-up exposure or health-outcome studies.

Regarding substance toxicity, the collected data will be used to characterize the toxicity of the substance for the public and scientific community. For ATSDR, the data are necessary and essential to improve the design and conduct of follow-up health studies.

C. Procedures

Section 104(i)(2) of CERCLA, as amended, requires that ATSDR (1) with EPA develop a list of hazardous substances found at NPL sites (in order of priority), (2) prepare toxicological profiles of those substances, and (3) assure the initiation of a research program to fill identified data needs associated with the substances.

The first step in implementing the ATSDR substance-specific research program for cresols occurred when the data needs for cresols were determined in the ATSDR Toxicological Profile for Cresols. Considered a subset of all information gaps on cresols, these data needs were reviewed by scientists from ATSDR and other federal agencies. They were peer reviewed by an external review panel and made available for public comment. All comments received by ATSDR on the identification of data needs for cresols were addressed before the toxicological profile was finalized.

The purpose of this paper is to take the data needs identified in the Toxicological Profile for Cresols and subject them to further scientific evaluation. This will lead to priorities and ultimately to ATSDR's substance-specific research agenda. To affect this step, ATSDR developed and presented a logical scientific approach to priority setting in its Decision Guide.

Briefly, data needs are categorized as exposure or toxicity and are then subcategorized across three levels (Tables 1 and 2). Level I research is a base set of exposure and toxicity information to identify basic characteristics of each substance. Level II research is conducted to confirm the toxicity and exposure indicated by Level I data. Level III research will improve the application of the results of Level II research to people.

The Decision Guide recognized three general principles for setting priorities:

- Not all information gaps identified in toxicological profiles are data needs.
- All data needs are not the same priority.
- Substances should be considered individually, but may be grouped, because of structural similarity or other relevant factors.

Other considerations spelled out in the Decision Guide include:

- All levels of data should be considered in selecting priority data needs.
- Level I gaps are not automatically in the priority grouping. In general, Level I data have priority when there are no higher level data for the same category, and when data are insufficient to make higher level priority testing decisions. For example, priority would generally not be assigned to multigenerational animal studies (Level II) if an adequate subchronic study (Level I) had not been conducted that evaluated reproductive organ histopathology.
- Priority for either exposure or toxicity data requires thorough evaluation of research needs in other areas to help achieve a balanced research program for each substance.

The Decision Guide listed the following eight tenets to determine research priorities:

- Development and/or confirmation of appropriate analytical methods.
- Determination of environmental and human exposure levels when analytical methods are available.
- Bioavailability studies for substances of known significant toxicity and exposure.
- Studies available to characterize target organs and dose response.
- Disposition studies and comparative physiologically-based pharmacokinetics when a toxic end point has been determined and differences in species response have been noted.
- Mechanistic studies on substances with significant toxicity and substantial human exposure.
- Investigation of methods to mitigate toxicity for substances when enough is known about mode of action to guide research.
- Epidemiologic studies designed to link human disease with a substance of known significant toxicity.

These last three "prioritizing" tenets address Level III research. When Level III research is identified as priority, ATSDR will not develop detailed methods to successfully fulfill the data needs. Because there are no standard "testing guidelines" for Level III research, we expect considerable discussion between ATSDR and parties interested in conducting this research. Thus, ATSDR will only announce that its scientists believe that the accumulation of Level III research is appropriate, and it is a priority at this time. ATSDR will state the reasons why this is so.

D. Selection Criteria

ATSDR prepares toxicological profiles on substances that are most commonly found at facilities on the NPL sites and which, in its sole discretion, pose the most significant threat to human health because of their known or suspected toxicity and potential for human exposure.

Briefly, the rationale is as follows:

1. Frequency of Occurrence

***Finding*:** Cresols are included in the priority list of hazardous substances identified by ATSDR (ATSDR 2007a).

o-Cresol, *m*-cresol, *p*-cresol, and mixed cresols have been identified in at least 210, 22, 310, and 70, respectively, of the 1,678 National Priorities List (NPL) hazardous waste sites in the United States (HazDat 2006). Exposure to cresols at these sites may occur by contacting contaminated air, water, soil, or sediment. ATSDR is presently evaluating the extent of media-specific contamination at these and other sites.

2. Potential for Human Exposure

***Finding*:** ATSDR scientists have determined that there has been significant past human exposure and that the potential exists for current human exposure to cresols via inhalation, ingestion, and skin contact.

The following is a brief summary of the potential for human exposure to cresols. For a more detailed discussion of available information, refer to the ATSDR Toxicological Profile for cresols, Chapter 6, on Potential for Human Exposure (ATSDR 2008).

Pure cresols are colorless chemicals, but they may be found in brown mixtures such as creosote and cresylic acids (e.g., wood preservatives). Cresols can be either solid or liquid, depending on how pure they are; generally, pure cresols are solid, while mixtures tend to be liquid. Cresols have a medicinal odor and when dissolved in water, they give it a medicinal smell and taste. All cresol isomers and mixtures are very soluble in alcohol, chloroform, ether, benzene, acetone, and

water. Cresols evaporate more slowly than water with a vapor pressures ranging from 0.11 to 0.30 mm Hg. Aqueous solutions of cresols do not readily volatilize from water with a Henry's law constants ranging from $1.2x10^{-6}$ to $7.92x10^{-7}$ m^3/mol.

Cresol is an important substance for research because of its widespread environmental contamination. According to the Toxics Release Inventory (TRI), estimated releases of 3,313 pounds (~1.5 metric tons) of *o*-cresol, 41.496 pounds (~19 metric tons) of *m*-cresol, 31,393 pounds (~14 metric tons) of *p*-cresol, and 932,106 pounds (~423 metric tons) of mixed isomers of cresol, to the atmosphere from 23, 28, 27, and 157 domestic manufacturing and processing facilities in 2005, accounted for about <1, 21, 21 and 72% of the estimated total environmental releases of *o*-cresol, *m*-cresol, *p*-cresol, and cresol mixed isomer from facilities required to report to the TRI (TRI05 2007), respectively. Estimated releases of 123 pounds (~0.6 metric tons) of *o*-cresol, 544 pounds (~0.2 metric tons) of *m*-cresol, 254 pounds (~0.1 metric tons) of *p*-cresol, and 60,721 pounds (~28 metric tons) of mixed isomers of cresols to surface water from 23, 28, 27,and 157 domestic manufacturing and processing facilities in 2005, accounted for about 0.06, 0.2, 0.1, and 4.7% of the estimated total environmental releases of *o*-cresol, *m*-cresol, *p*-cresol, and cresol mixed isomer from facilities required to report to the TRI (TRI05 2007), respectively. Estimated releases of 270 pounds (~0.1 metric tons) of *o*-cresol, 780 pounds (~0.4 metric tons) of *m*-cresol, 666 pounds (~0.3 metric tons) of *p*-cresol, and 10,971 pounds (~5 metric tons) of mixed isomers of cresol to soils from 23, 28, 27, and 157 domestic manufacturing and processing facilities in 2005, accounted for about 0.1, 0.4, 0.4, and 0.9% of the estimated total environmental releases of *o*-cresol, *m*-cresol, *p*-cresol, and mixed isomers respectively, from facilities required to report to the TRI (TRI05 2007). An additional 182,006 pounds (~83 metric tons) of *o*-cresol, 153,332 pounds (~70 metric tons) of *m*-cresol, 117,221 pounds (~53 metric tons) of *p*-cresol, and 244066 pounds (~111 metric tons) of mixed isomers of cresols constituting about 98, 78, 78, and 19% of the total environmental emissions for *o*-cresol, *m*-cresol, *p*-cresol, and mixed isomers respectively, were released via underground injection (TRI05 2007).

Cresols degrade rapidly in air. Removal during the day is dominated by the reaction with hydroxyl radical (HO•), while night-time removal is dominated by the nitrate radical. Reaction with other oxidants in air (e.g., ozone) will be much slower than reactions with hydroxyl or nitrate radical (Atkinson and Carter 1984). The half-lives for these reactions, assuming an average night-time nitrate radical concentration of $2.4x10^8$ molecules per cm^3, are 4.8, 4.5, and 6.9 minutes for *o*-, *m*-, and *p*-cresol, respectively (Atkinson et al. 1984; Carter et al. 1981). The

half-lives for the reaction with photochemically generated hydroxyl radicals are 9.63, 8.75, and 6.76 hours for *o*-, *p*-, and *m*-cresol, respectively, using an atmospheric hydroxyl radical concentration of $5x10^5$ radicals per cm^3.

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

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) concluded that the data for cresol degradation fit first-order kinetics, but with very different rates. Dobbins and Pfaender (1988) found that 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 CO_2. In surface soils, first-order rate constants based on CO_2 evolution were $7.55x10^{-5}$–$6.31x10^{-4}$ $hour^{-1}$, which yields half-lives from 46 days to about 1 year for the ultimate biodegradation of cresols. Namkoong et al. (1988) reported a more rapid rate of degradation of the cresol isomers in surface soils from an uncultivated grassland site. *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 complete disappearance in the soil were reportedly 16, 9, and 27 days for *o*-, *p*-, and *m*-cresol, respectively.

o-Cresol, *m*-cresol, *p*-cresol, and mixed cresols have been identified in at least 210, 22, 310, and 70 of the 1,678 hazardous waste sites that have been proposed for inclusion on the EPA National Priorities List (NPL), respectively (HazDat 2006).

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

cigarette smoke and areas high in vehicular traffic may increase the likelihood of exposure. The total concentration of *o*-cresol and combined *m*-cresol and *p*-cresol in cigarette smoke ranged from approximately 14 to 26 µg/cigarette and from 41 to 82 µg/cigarette, respectively (Wynder and Hoffman 1967). 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 elevated cresol levels in air. Cresols are also frequently detected in groundwater at high levels near hazardous waste sites; therefore, persons residing near hazardous waste sites may also be exposed through the ingestion of contaminated drinking water from wells.

3. Toxicity

***Finding*:** ATSDR considers that short-, intermediate-, and long-term health effects can result from inhalation, ingestion, and dermal contact of cresols. Target organs or systems known to be affected include the skin and mucosal membranes. The nervous system has been shown to be a target in animals treated by gavage, but not in feeding studies.

The following is a brief summary of the toxicology of cresols. Refer to the ATSDR Toxicological Profile for cresols chapter on "Health Effects" for a more detailed discussion of available information (ATSDR 2008).

Cresols are irritating and corrosive substances, making the skin and mucosal membranes targets of toxicity, but other effects have also been reported. Fatalities due to ingestion and dermal exposure have been described (Bruce et al. 1976; Cason 1959; Chan et al. 1971; Green 1975; Isaacs 1922; Labram and Gervais 1968; Monma-Ohtaki et al. 2002). Other effects reported in these high oral and/or dermal exposure scenarios include respiratory failure, tachycardia and ventricular fibrillation, abdominal pain, vomiting, and corrosive lesions of the gastrointestinal tract, methemoglobinemia, leukocytosis and hemolysis, hepatocellular injury, renal alterations, metabolic acidosis, and unconsciousness. Many of these effects may not have been caused directly by cresols, but may represent secondary reactions to shock caused by external and

internal burns. No information is available regarding humans exposed to cresols for intermediate- or chronic-duration periods.

Two animal studies in which a variety of species were exposed to mixtures of cresol vapors and aerosols provided data on lethality, as well as information on effects on the respiratory system (irritation, inflammation, edema, hemorrhage) and nervous system (excitation, fatigue, convulsions) (Campbell 1941; Uzhdavini et al. 1972). Animals that died had fatty degeneration and necrosis of the liver, degeneration of the tubular epithelium in the kidneys, bronchitis, pulmonary hemorrhage, and dystrophic changes in the heart and in nerve cells and glia in the brain. Because of limitations in study design (mainly in the methodology for generating and monitoring the vapor concentrations) and reporting, these studies were not useful for risk assessment. All three cresol isomers, either alone or in combination, severely irritated the skin of rabbits, producing visible and irreversible tissue destruction (Vernot et al. 1977).

Results from oral studies in animals indicate that cresols administered by gavage are much more toxic than when administered in the diet, a phenomenon that is probably related to the toxicokinetics of cresols. Acute exposure of animals to cresols by gavage significantly reduced weight gain (Tyl 1988a) and caused death (Deichmann and Witherup 1944; EI Dupont Denemours 1969; NTP 1992b). No acute-duration studies were available of cresols given to animals via a relevant oral mode of administration. Gavage studies of intermediate duration in animals have been performed for all three cresol isomers, and have helped to identify the levels at which cresols produce neurological, respiratory, hepatic, renal, hematological, and body weight changes in orally exposed animals (EPA 1988a, 1988b, 1988c; TRL 1986). In the only intermediate-duration dietary study in animals, nasal epithelial lesions appeared to be a particularly sensitive effect of exposure to cresols. Dietary exposure of rats and mice to *p*-cresol or to a mixture of *m/p*-cresol (58.5% *m*-cresol, 40.9% *p*-cresol) for 28 days or 13 weeks induced dose-related alterations in the nasal respiratory epithelium at doses of 95 mg/kg/day and higher (NTP 1992b). The incidence of nasal lesions in male rats was used to derive an intermediate-duration oral MRL for *m/p*-cresol. Other systemic effects observed in this study were limited to increased liver and kidney weights and decreased weight gain at higher doses (NTP 1992b). A mixture of *m/p*-cresol was tested in male Fischer-344 rats and female B6C3F1 mice in a 2-year toxicity and carcinogenicity bioassay sponsored by NTP (NTP 2008). Although the study is yet to be finalized, preliminary results confirmed the presence of nasal lesions reported in the 28-day and 13-week studies (NTP 1992b) and also observed increased incidences of bronchiolar

hyperplasia and follicular degeneration of the thyroid gland in treated mice (0, 100, 300, and 1,040 mg/kg/day). The data for bronchiole hyperplasia and follicular degeneration of the thyroid gland in female mice exposed for 2 years were used to derive a chronic-duration oral MRL for cresols.

No studies were located regarding immunological effects of cresols in humans. No significant alterations in weight or histology of lymphoreticular organs have been observed in animals following cresol exposure, but immunocompetence has not been evaluated (EPA 1988a, 1988b, 1988c; Hornshaw et al. 1986; NTP 1992b). A common feature of oral poisoning with cresols in humans is coma (Chan et al. 1971; Isaacs 1922; Labram and Gervais 1968). Gavage studies in rodents often observed adverse clinical signs indicative of neurological impairment such as hypoactivity, excessive salivation, labored respiration, and tremors (Neeper-Bradley and Tyl 1989a, 1989b; TRL 1986; Tyl and Neeper-Bradley 1989). In no cases have gross or microscopic alterations of the brain, spinal cord, or sciatic nerve been observed. None of the clinical signs seen in gavage studies have been seen in dietary studies, or if seen, they have occurred at much higher dose levels than in gavage studies (NTP 1992b). This difference is probably related to the different disposition of cresols and metabolites between the two modes of oral dosing.

There are no data to judge whether cresols cause adverse reproductive or developmental effects in humans. Studies in animals do not suggest that reproductive end points are sensitive targets for cresols toxicity (EPA 1988a, 1988b, 1988c; Hornshaw et al. 1986; Neeper-Bradley and Tyl 1989a, 1989b; NTP 1992a, 1992b, 1992c; Tyl and Neeper-Bradley 1989). Continuous breeding protocol studies in mice with *o*-cresol and *m/p*-cresol found no evidence of reproductive toxicity for *o*-cresol (NTP 1992a); *m/p*-cresol, at a dose that caused minor maternal toxicity, produced a decrease in the number of pups/litter and increased the cumulative days to litter, but did not affect other reproductive function end points (NTP 1992c). In intermediate-duration dietary studies in rats and mice, effects were limited to mild to moderate uterine atrophy and lengthening of the estrous cycle, generally at the highest dose levels tested (NTP 1992b). Cresol isomers caused mild fetotoxicity in rodents exposed to each isomer by gavage (Neeper-Bradley and Tyl 1989a, 1989b; Tyl 1988a, 1988b; Tyl and Neeper-Bradley 1989) and in pregnant mice exposed to *o*-cresol or *m/p*-cresol in the diet in continuous breeding protocol studies (NTP 1992a, 1992c). In general, adverse effects were observed at dose levels that caused frank neurological effects in the mother. There are no data regarding reproductive and developmental effects in animals following

inhalation or dermal exposure to cresols. Based on the available information, there is no clear evidence that cresols are endocrine disruptors in humans or in animals.

No studies were located regarding the carcinogenicity of cresols in humans. A 2 year bioassay found equivocal evidence of carcinogenetic activity of *m/p*-cresol (60%/40%) in male Fischer-344 rats based on a nonsignificant increase in the incidence of renal tubule adenoma (NTP 2008). The same study found some evidence of carcinogenetic activity in female B6C3F1 mice based on an increased incidence of forestomach squamous cell papilloma. Cresols gave indications of promotion potential in a dermal skin promotion assay; *p*-cresol was the least potent isomer, *o*-cresol was approximately 3 times more potent than *p*-cresol, and *m*-cresol was in between (Boutwell and Bosch 1959). The International Agency for Research on Cancer (IARC) and the Department of Health and Human Services (DHHS) have not classified cresols as to carcinogenicity. Based on inadequate evidence in humans and limited data in animals, EPA (IRIS 2006) assigned cresols to Group C, possible human carcinogens. Under updated guidelines (EPA 2005b), cresols fall in the category of chemicals for which there is: "inadequate information to assess carcinogenic potential" (IRIS 2006).

No studies were located regarding the genotoxicity of cresols in humans following inhalation, oral, or dermal exposure. Cresols have been tested in a variety of *in vivo* (Cheng and Kligerman 1984; Ivett 1989a, 1989b, 1989c; Sernav 1989a, 1989b) and *in vitro* (Brusick 1988a, 1988b, 1988c; Cheng and Kligerman 1984; Cifone 1988a, 1988b; Daugherty and Franks 1986; Douglas et al. 1980; Florin et al. 1980; Haworth et al. 1983; Kubo et al. 2002; Murli 1988; Pepper, Hamilton & Scheetz 1981; Pool and Lin 1982) tests. The results of these tests have been mostly negative.

p-Cresol is normally found in the body where it is generated from protein breakdown. Patients with chronic renal failure constitute a group with increased susceptibility to *p*-cresol. In these patients, the concentration of *p*-cresol in the blood is 10 times higher than in healthy subjects due to both overgrowth of intestinal bacteria responsible for *p*-cresol production and reduced renal clearance (Bammens et al. 2006; De Smet et al. 1998, 2003). It is not known whether children are more sensitive to cresols than adults. To the extent that the enzymes involved in the metabolism of cresols are developmentally regulated, the metabolism, and consequently the toxicity of cresols, in immature humans may be different than in adults. Since point-of-contact

irritation is the main toxic action of high doses of cresols, children are not likely to be more susceptible to the effects of cresols at the tissue level.

III. Identification of Data Needs

In evaluating the exposure and toxicity testing needs for cresols, ATSDR considered all available published and unpublished information that has been peer-reviewed. From its evaluation of these data, ATSDR is recommending the conduct of specific research or testing.

A. Exposure Data Needs (Table 1)

Three of the eight "prioritizing" tenets presented in the Decision Guide directly address exposure data needs:

- Development and/or confirmation of appropriate analytical method;
- Determination of environmental and human exposure levels when analytical methods are available; and
- Bioavailability studies for substances of known significant toxicity and exposure.

The progressive accumulation of exposure information begins with developing suitable analytical methods to analyze the compound in all relevant biological and environmental media, followed by confirmation of exposure information, before the conduct of any Level III research. However, in order to know what analytes are available to monitor, some basic environmental fate information is generally required and becomes a priority if it is lacking.

Bioavailability and food chain bioaccumulation studies are appropriately placed in Level II, and should be undertaken after analytical methods are developed and the substance has been confirmed at many hazardous waste sites and in environmental media.

1. Levels I & II Data Needs

a. Analytical Methods

***Purpose*:** To determine if available methods are adequate to detect and quantify levels of cresols in environmental and biological matrices. The methods should be sufficiently specific and sensitive to measure (1) background levels in the environment and the population; and (2) levels at which biological effects might occur.

***Finding*:** A data need has not been identified. Analytical methods are available that are capable of determining low levels of the cresol isomers in biological media, and background levels in the population could be established using existing techniques (Angerer and Wulf 1985; DeRosa et al. 1987; Krotoszynski and O'Neill 1982; Needham et al. 1984; Yoshikawa et al. 1986). Gas chromatography/mass spectrometry (GC/MS) has been employed to determine cresol levels in blood at the ppb level (Boatto et al. 2004; De Smet et al. 1998). High performance liquid chromatography (HPLC) has been used to analyze for cresol isomers in urine at the ppm level (Yoshikawa et al. 1986), while a gas chromatography/flame ionization detector (GC/FID) method is available for analysis at the ppb level (NIOSH 1994b). These methods are sensitive, accurate, reliable, and precise, and are sensitive enough to measure background levels in the general population and levels at which health effects might occur following acute or chronic exposures.

Numerous methods for the determination of cresol in environmental matrices have been located in the literature (DOE 1985; EPA 2005a; Goodley and Gordon 1976; Hites 1979; Kawamura and Kaplan 1986; Kuwata and Tanaka 1988; Neiminen and Heikkila 1986; Vecera and Janak 1987). GC (including GC/MS) and HPLC methods are available for the determination of cresol isomers in air (Kuwata and Tanaka 1988; NIOSH 1994a, 1994b; Vecera and Janak 1987), water (EPA 2000a, 2001, 2005a; Hites 1979), and soil (EPA 1998, 2005a). These methods are both reproducible and sensitive and can determine levels that are unlikely to be associated with adverse human health effects.

***Priority Recommendation*:** A data need has not been identified.

b. Physical/Chemical Properties

***Purpose*:** To determine whether adequate data on the chemical and physical properties of cresols are available to permit estimation of its environmental fate under various conditions of release, and evaluation of its pharmacokinetics under different exposure durations and routes.

***Finding*:** A data need has not been identified.

The physical and chemical properties of phenol are sufficiently well defined to allow assessments of the environmental fate of this compound to be made. The most important properties such as Henry's law constant (Gaffney et al. 1987; Hine and Mookerjee 1975), vapor pressure (Chao et al. 1983; AIChE 1989, 2000), solubility (Lewis 2001; Lide 2005; Windholz et al. 1983; Yalkowsky et al. 1987), log K_{ow} (Hansch and Leo 1985), melting point (Riddick et al. 1986; Lewis 2001), and boiling point (Riddick et al. 1986; Lewis 2001, Lide 2005) have been measured.

***Priority Recommendation*:** A data need has not been identified.

c. Exposure Levels

(1) Environmental Media

***Purpose*:** To determine whether adequate data are available on the levels of cresols in the ambient and contaminated environments for purposes of conducting meaningful follow-up exposure and health studies.

Finding: A need to obtain reliable and current data on concentrations of cresols in contaminated environmental media at hazardous waste sites has been identified.

Monitoring data indicate that cresols are present in ambient air at relatively low levels. A national emissions study conducted from 1990 to 1998 reported an estimated ambient concentration average of 31.7 ng/m^3 (EPA 2000b). Elevated levels may be found near point sources or areas high in vehicular traffic. The median air concentration of *o*-cresol at source-dominated sites was reported as 1.62 µg/m^3 for 32 samples (EPA 1988d). High levels of cresols have been reported in groundwater at hazardous waste sites. For example, the concentrations of *o*-cresol in groundwater samples at an abandoned pine tar manufacturing facility in Gainesville, Florida ranged from 0.3 to 5,200 mg/L (McCreary et al. 1983) and its concentration at a hazardous waste site in Buffalo, New York was reported as 2.3 mg/L (Weber and Matsumoto 1987). Cresols are only occasionally detected in soil samples because these compounds degrade rapidly, possess high mobility, and tend to leach readily. However, areas where contamination is

high may have elevated levels in surface and subsurface soils. *o*-Cresol was detected at maximum concentrations of 12,000, 21,000, 34,000, and 55,000 µg/kg in the soil of an abandoned pine tar manufacturing plant in Gainesville, Florida at four separate sites (McCreary et al. 1983).

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

***Priority Recommendation*:** The identified need is not considered priority at this time. Reliable and current monitoring data for the levels of cresols in contaminated media at hazardous waste sites are needed so that the information obtained on levels of cresols in the environment and the resulting body burden of cresols can be used to assess the potential risk of adverse health effects in populations living in the vicinity of hazardous waste sites. However, ATSDR has developed a hazardous substance release/health effects database (HazDat) that includes the extant data for the 210, 22, 310, and 70 NPL sites at which *o*-cresol, *m*-cresol, *p*-cresol, and mixed cresols, respectively, have been found. This database includes maximum concentrations of cresols in on- and off-site media, and an indication of relevant routes of exposure. Further evaluation of this database is needed first to assess if collection of additional media-specific data is assigned priority.

(2) Humans

***Purpose*:** To determine whether adequate data are available on the levels of cresols in human tissues for the general population and exposed populations for purposes of conducting meaningful follow-up exposure and health studies.

***Finding*:** A need has been identified. No data are available on the levels of cresols in body tissues or fluids for people living near hazardous waste sites. *p*-Cresol occurs naturally in human

urine as a breakdown product of tyrosine and toluene, and humans normally excrete 16–39 mg per day (Needham et al. 1984). Cresols have been detected in the urine of persons occupationally exposed to cresols at levels of 0.54 and 18.14 mg/L for *o*-cresol and *m/p*-cresol, respectively, while the levels in nonoccupationally exposed persons were 0.041 and 14.38 mg/L for *o*-cresol and *m/p*-cresol, respectively (Bieniek 1997). No reports or studies of cresol in baby food or breast milk were located. Current biological monitoring data for cresols are not available in the National Report on Human Exposure to Environmental Chemicals or in the Third National Health and Nutrition Examination Survey (NHANES III). The general population is exposed to low levels of cresols through inhalation of ambient air. Populations residing near hazardous waste sites may also be exposed to levels above background concentrations from ingestion of drinking water obtained from groundwater wells.

Priority Recommendation: The identified data need to collect additional information is considered priority. For a sound database to serve as a solid foundation for higher level environmental or toxicological research, it should contain exposure information on the levels of cresols in body tissues or fluids, particularly in populations living near hazardous waste sites. This information is necessary to better define exposure estimates in the general population and the workforce, and to examine the relationship between levels of cresols in the environment, human tissues levels, and the subsequent development of health effects.

d. Exposures of Children

Purpose: To determine if adequate data on exposures of children to cresols are available for the purpose of conducting meaningful follow-up exposure and health studies.

Finding: A data need to conduct additional studies to assess exposures of children to cresols has been identified.

No data regarding cresol levels in children were found. No reports or studies of cresol in baby food or breast milk were located. The most likely route of exposure to cresols for children is through inhalation of ambient air. Some of the factors that would increase the risk of children exposure include living with a smoker, and living near gas stations, heavy traffic areas, and

companies that use and/or produce cresol. It is unknown whether children are different in their weight-adjusted intake of cresol. A data need exists to establish cresol exposure in children.

Priority Recommendation: The identified data need to conduct additional studies to assess exposures of children to cresols is considered priority. Collecting information on the levels of cresol in children is important in order to determine the extent of a child's exposure to cresols through oral, dermal and inhalation routes as well as to identify ways to reduce the potential sources for exposure risks.

e. Environmental Fate

***Purpose*:** To determine whether the available data are adequate to estimate exposure to cresols under various conditions of environmental release for purposes of planning and conducting meaningful follow-up exposure and health studies.

***Finding*:** A data need has not been identified. Information concerning the partitioning of cresols in the environment is available; cresols occur in all environmental media and the environmental fate properties in these media are understood. Information on the transport of cresols in environmental media is also available.

In the atmosphere, cresols are degraded through reaction with photochemically produced hydroxyl radicals and night-time nitrate radicals. The half-life for the reaction with nitrate radicals is on the order of a few minutes, and the half-life for the reaction with hydroxyl radicals is a few hours, depending upon the isomer (Atkinson et al. 1984; Carter et al. 1981).

Generally, cresols possess high mobility in soil and have the potential to leach into groundwater; however, the hydroxyl function of cresol is capable of forming relatively strong hydrogen bonds with active sites in soil containing low amounts of organic carbon, 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).

An extensive database is available describing the aerobic (Alexander and Lustigman 1966; Babeu and Vaishnav 1987; Baird et al. 1974; Chambers et al. 1963; EPA 1979; Heukelekian and Rand 1955; Ludzack and Ettinger 1960; Lund and Rodriguez 1984; Malaney 1960; Malaney and

McKinney 1966; McKinney et al. 1956; Pauli and Franke 1972; Pitter 1976; Tabak et al. 1964; Young et al. 1968) and anaerobic (Battersby and Wilson 1988, 1989; Boyd et al. 1983; EPA 1981; Fedorak and Hrudey 1984; Horowitz et al. 1982; Wang et al. 1988, 1989) degradation of cresols in water. In contrast to aerobic conditions, cresols do not appear to degrade rapidly in anaerobic freshwater sediments. 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 for anaerobic sludges, the *m*- and *p*-cresol isomers showed the most degradation, while *o*-cresol resisted degradation.

Data exist regarding the biodegradation of cresols in soils (Dobbins and Pfaender 1988; Medvedev and Davidov 1981a, 1981b; Namkoong et al. 1988). Biodegradation experiments using surface soils from an uncultivated grassland site maintained under aerobic conditions, resulted in half-lives from <1 to about 1.6 days for the three cresol isomers (Namkoong et al. 1988).

***Priority Recommendation*:** A data need has not been identified.

f. Bioavailability and Bioaccumulation Potential

***Purpose*:** To determine whether adequate data are available to predict the potential of cresols to be taken up by people exposed via contaminated air, soil, water, and the food chain, in order to plan and conduct meaningful follow-up exposure and health studies.

***Finding*:** A data need has not been identified. 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 cresols do not bioconcentrate to any significant extent (Thomas 1982). Information concerning the potential for biomagnification has not been described, however, based on the small K_{ow} values (Hansch and Leo 1985), biomagnification is expected to be insignificant.

While cresols are expected to be readily absorbed via inhalation, ingestion, and dermal contact, rapid degradation in air, water, and soil is expected to attenuate human exposure. No information is available regarding oral or dermal absorption of cresols in water and soil matrices, or plant materials; however, cresols are not expected to accumulate in environmental media due to their

rapid rate of degradation. The most likely routes of exposure to cresols at hazardous waste sites are from ingestion with contaminated media. No data needs exist at this time.

Priority Recommendation: A data need has not been identified.

2. Level III Data Needs

a. Registries of Exposed Persons

***Purpose*:** To help assess long-term health consequences of exposure to cresols in the environment. The ATSDR Division of Health Studies will be asked to consider this substance for selection as a primary contaminant to establish a cresols subregistry of the National Exposure Registry.

***Finding*:** A data need has been identified. *o*-Cresol, *m*-cresol, *p*-cresol, and mixed cresols have been found in at least 210, 22, 310, and 70 NPL hazardous waste sites, respectively. At this time, no formal registries exist that identify people known to have been exposed to cresols. The development of an exposure registry should provide an important reference tool to help assess long-term health consequences of exposure to cresols. It should also facilitate the conduct of epidemiologic or health studies to assess any increased incidence of chronic disease or late-developing effects such as cancer. An effort is currently under way at ATSDR to identify those sites where humans have been exposed to site contaminants. From those identified sites, ATSDR can determine which sites list cresols as a contaminant and the size of the potentially exposed population.

***Priority Recommendation*:** The identified data need is not considered priority. The development of a cresols subregistry at this time would not contribute significantly to the current database. The development of an exposure subregistry should await information on levels in populations living near hazardous waste sites.

B. Toxicity Data Needs (Table 2)

The five remaining "prioritizing" tenets presented in the Decision Guide address toxicity data needs.

- Studies available for all toxicological profile substances to characterize target organs and dose response.
- Disposition studies and comparative physiologically-based pharmacokinetics when a toxic end point has been determined and differences in species response have been noted.
- Mechanistic studies on substances with significant toxicity and substantial human exposure.
- Investigation of methods for mitigation of toxicity for substances where enough is known about mode of action to guide research.
- Epidemiologic studies that will provide a direct answer on human disease for a substance of known significant toxicity.

The following is a brief summary of the toxicity data needs for cresols. Please refer to the ATSDR Toxicological Profile for Cresols, chapter on "Health Effects" for a more detailed discussion of available information (ATSDR 2008). Generally, ATSDR believes that the most relevant route(s) of human exposure to cresols at waste sites is ingestion of contaminated environmental media, thus ATSDR scientists believe that the proposed toxicity studies should be conducted via the oral route. Additionally, animal testing should be conducted on the species with metabolism most similar to humans or the most sensitive species.

1. Levels I & II Data Needs

ATSDR determines Minimal Risk Levels (MRLs) which are defined as estimates of daily human exposure to a chemical that are likely to be without appreciable risk of deleterious effects over a specified duration. In order to derive MRLs for acute, intermediate, and chronic exposure durations, ATSDR evaluates the substance-specific database to identify studies of the appropriate route and duration of exposure. Thus, in order to derive acute MRLs, ATSDR evaluates studies of 14 days or less duration that identify the target organs and levels of exposure associated with these effects. Similar studies are identified for intermediate and chronic duration exposures.

Currently, ATSDR is using tools such as physiologically-based pharmacokinetic modeling and pharmacodynamic modeling to extrapolate data across routes or durations of exposure. ATSDR acknowledges that such extrapolations may be done on a substance-by-substance basis after adequate toxicokinetics information has been collected.

As reflected in the Decision Guide, ATSDR assigns priorities to identified data needs for acute/intermediate (Level I) studies by the most relevant route of exposure at Superfund sites. Regarding the need to conduct studies by other routes of exposure, ATSDR usually first requires toxicokinetic studies for the three routes of exposure to determine the need for the additional route-specific information.

Regarding chronic studies, ATSDR acknowledges that appropriately conducted 90-day studies can generally predict the target organs for chronic exposure. However, they might fall short in accurately predicting the levels of exposure associated with these effects. Although ATSDR acknowledges this fact, it will generally await the results of prechronic and toxicokinetic studies before assigning priority to chronic toxicity studies. Note: Chronic toxicity studies may be separated from cancer bioassays; they require a one-year exposure.

a. Acute-Duration Exposure

***Purpose*:** To determine whether adequate data exist to identify target organs and levels of exposure that present a significant risk to cause acute human health effects.

***Finding*:** A data need to conduct additional studies via inhalation, oral, and dermal exposure has been identified. Cresols produce corrosive damage at sites of contact; therefore, the skin and mucosal membranes are targets for cresols toxicity. The only acute inhalation information in humans is that volunteers exposed briefly to 6 mg/m^3 of *o*-cresol in the air complained of respiratory tract irritation (Uzhdavini et al. 1972). More information is available from case reports of humans exposed to high doses of cresols either orally or by dermal contact. Fatalities due to ingestion and dermal exposure have been described (Bruce et al. 1976; Cason 1959; Chan et al. 1971; Green 1975; Isaacs 1922; Labram and Gervais 1968; Monma-Ohtaki et al. 2002). Other effects reported in these acute high exposure scenarios include respiratory failure (Liu et al. 1999), tachycardia and ventricular fibrillation (Labram and Gervais 1968), abdominal pain, vomiting, and corrosive lesions of the gastrointestinal tract (Hayakawa 2002; Isaacs 1922;

Jouglard et al. 1971; Kamijo et al. 2003; Wu et al. 1998; Yashiki et al. 1999), methemoglobinemia (Chan et al. 1971; Minami et al. 1990), leukocytosis and hemolysis (Cote et al. 1984; Wu et al. 1998), hepatocellular injury (Chan et al. 1971; Hashimoto et al. 1998; Hayakawa 2002; Kamijo et al. 2003), renal alterations (Chan et al. 1971; Isaacs 1922; Labram and Gervais 1968; Wu et al. 1998), skin damage (Cason 1959; Green 1975; Herwick and Treweek 1933; Klinger and Norton 1945; Pegg and Campbell 1985), metabolic acidosis (Hayakawa 2002; Kamijo et al. 2003), and unconsciousness (Chan et al. 1971; Isaacs 1922; Labram and Gervais 1968). Many of these effects may not have been caused directly by cresols, but may represent secondary reactions to shock caused by external and internal burns. The acute database in humans is inadequate for constructing dose-response relationships for cresols.

There is information regarding effects in animals exposed acutely to cresols by inhalation, but the available studies involved mixtures of vapors and aerosols that provided insufficient information to estimate exposure levels reliably; therefore, an acute-duration inhalation MRL for cresols has not been derived. Still, these studies (Campbell 1941; Uzhdavini et al. 1972) provided some data on lethality of airborne cresols as well as information on the respiratory system (irritation), liver (fatty degeneration and necrosis), renal (tubular degeneration), and nervous system (excitation, fatigue, convulsions). Inhalation studies that use reliable methodology to generate and control exposure atmospheres and that evaluate a wide range of end points are needed to construct dose-response curves for acute inhalation exposure.

There are studies that examined the acute oral effects of cresols in animals, and all of these studies administered cresols by gavage, a dosing mode that, as mentioned earlier in Section II.D.3, induces different effects than those observed in dietary studies and is not considered relevant for risk assessment. Gavage studies showed reduced body weight, neurotoxicity, fetotoxicity, and death in exposed animals (EPA 1988a, 1988b, 1988c; TRL 1986; Tyl 1988a, 1988b). No acute dietary or drinking water studies were located for cresols; thus, no acute-duration oral MRL was derived. Therefore, acute-duration dietary studies are needed for defining targets and generating dose-response relationships for this exposure duration.

The only available acute dermal exposure study in animals provided information on levels that produce skin irritation and death (Vernot et al. 1977). Additional acute-duration dermal studies are needed to determine no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs) for local and systemic effects of skin exposure.

***Priority Recommendation*:** The identified data need to conduct additional studies via the oral route of exposure is considered priority. Additional 14-day oral studies in animals by the oral route (other than gavage) are a priority to determine dose-response relationships for the effects of acute oral exposure to cresols on a wide range of potential target tissues. These data are needed to provide a basis for the derivation of an acute-duration MRL via oral exposure, the most relevant exposure route at waste sites. The data needs for additional inhalation and dermal exposure studies are not considered priority because these are not primary routes of exposure for individuals living near hazardous waste sites.

b. Intermediate-Duration Exposure

***Purpose*:** To determine whether adequate data exist to identify target organs and levels of exposure that present a significant risk to cause subchronic human health effects.

Finding: A data need to conduct additional studies via inhalation and dermal exposure has been identified. No information is available regarding humans exposed to cresols for intermediate-duration periods. The inhalation database in animals is limited to one study that provided information on adverse respiratory, cardiovascular, hepatic, renal, and neurological effects in rodents, but the methods used at the time to generate and monitor the exposure atmospheres were inadequate to estimate exposure concentrations with any precision (Uzhdavini et al. 1972). Studies that use reliable methods to generate and control exposure concentrations are needed to define targets of toxicity and to establish dose-response relationships for cresols by the inhalation route.

Gavage studies of intermediate duration in animals have been performed for all three cresol isomers. These studies have provided information on levels at which cresols produce neurological, respiratory, hepatic, renal, hematological, and body weight changes (EPA 1988a, 1988b, 1988c; TRL 1986). However, as mentioned previously, gavage administration of cresols induces effects different from those observed in dietary studies, and do not resemble human environmental exposure scenarios to cresols. A comprehensive intermediate-duration dietary study is available in which rats and mice were administered the individual cresol isomers and a mixture of *m*- and *p*-cresol (*m/p*-cresol) for 28 or 90 days (NTP 1992b). The most sensitive effect was nasal lesions in both species exposed to *p*-cresol and *m/p*-cresol. Other effects were limited

to the most part to changes in organ weights at high-doses. The data from the 13-week study in rats exposed to *m/p*-cresol were used to derive an intermediate-duration oral MRL of 0.1 mg/kg/day for cresols based on a $BMDL_{10}$ of 13.9 mg/kg/day for nasal lesions. There are also two intermediate-duration multigeneration reproductive toxicity studies in mice dosed with *o*-cresol (NTP 1992a) and a mixture of *m*- and *p*-cresol (NTP 1992c). Additional intermediate oral studies do not seem necessary at this time since the NTP (1992b) study evaluated a comprehensive number of end points and cresols exhibited relatively little toxicity.

Only one intermediate-duration dermal study in animals was located. In that study, dermal application of 0.5% *p*-cresol for 6 weeks produced permanent depigmentation of the skin and hair of mice (Shelley 1974). Additional dermal studies are needed to define thresholds for skin effects as well as for possible systemic effects of cresols.

***Priority Recommendation*:** The identified data need to conduct additional studies via inhalation and dermal exposure is not considered priority. Although there is a need to conduct additional inhalation and dermal exposure studies that could help identify thresholds and dose-response relationships, these data needs are not assigned priority because inhalation and dermal exposures are not considered the primary exposure routes for populations living near waste sites.

c. Chronic-Duration Exposure

(1) Toxicity Assessment

***Purpose*:** To determine whether adequate data exist to identify target organs and levels of exposure that present a significant risk to cause chronic human health effects.

***Finding*:** A data need to conduct additional studies via inhalation and dermal exposure has been identified. No studies of chronic duration were found in humans. A mixture of *m/p*-cresol was tested in male Fischer-344 rats and female B6C3F1 mice in a 2-year toxicity and carcinogenicity bioassay sponsored by NTP (NTP 2008). In rats, the response with the lowest threshold appeared to be hyperplasia of the respiratory epithelium of the nose, which occurred with an incidence of 3/50, 17/50, 31/50, and 47/50 in rats dosed with mean time-weighted average (TWA) doses of 0, 70, 320, and 720 mg/kg/day, respectively; severity was minimal to mild. The incidence in the low-dose group (17/50, 34%) was very similar to that reported in the 13-week study (NTP

1992b). Other nasal lesions observed in rat included squamous metaplasia of the nasal epithelium, hyperplasia of the goblet cell, and inflammation of the nose. In mice, the most sensitive response was hyperplasia of the bronchiole of the lung, occurring with incidences of 0/50, 42/50, 44/49, and 47/50 in mice dosed with mean TWA doses of 0, 100, 300, and 1,040 mg/kg/day, respectively. Dose-related elevated incidences of respiratory epithelium hyperplasia were also reported at 300 and 1,040 mg/kg/day in mice (NTP 2008). The LOAEL of 100 mg/kg/day for bronchiole hyperplasia in female mice exposed for 2 years was used to derive a chronic-duration oral MRL of 0.1 mg/kg/day for *m/p* cresol. Additional oral long-term studies do not seem necessary at this time.

***Priority Recommendation*:** The identified data need to conduct additional studies via inhalation and dermal exposure is not considered priority. Additional inhalation and dermal exposure studies could help identify thresholds and dose-response relationships, however, these data needs are not assigned priority because inhalation and dermal exposures are not considered the primary exposure routes for populations living near waste sites.

(2) Cancer Assessment

***Purpose*:** To determine whether populations potentially exposed to cresols are at an increased risk for developing cancer for purposes of conducting meaningful follow-up exposure and health studies. Similar to toxicity end point assessment, when bioassays are indicated because of the potential for substantial exposure and the lack of information on carcinogenicity, ATSDR will generally only assign priority to a bioassay conducted via the most relevant route of human exposure at Superfund sites.

Comparative toxicokinetic information across routes as previously discussed will be assigned priority and conducted before assigning priority to any additional routes of exposure. In cases where the assessment of chronic toxicity and carcinogenicity can be combined, they will.

***Finding*:** A data need to conduct additional studies for the carcinogenicity of cresols via inhalation and dermal exposure has been identified. There are no studies of carcinogenicity of cresols in humans. In a 2-year NTP-sponsored bioassay, an *m/p*-cresol mixture administered in the diet to male Fischer-344 rats and female B6C3F1 mice induced a nonsignificant increase in the incidence of renal tubule adenoma in rats at 720 mg/kg/day, which was considered an

equivocal finding of carcinogenicity by NTP (2008); no other neoplastic effects were reported in rats. In mice, treatment with 1,040 mg/kg/day *m/p*-cresol induced a significant increase in the incidence of squamous cell papilloma in the forestomach. Results of one study suggested tumor-promoting potential following dermal application in mice (Boutwell and Bosch 1959) and there were positive results in a few genotoxicity assays in mammalian cells *in vitro* (Brusick 1988b; Murli 1988; Pepper, Hamilton and Scheetz 1980, 1981). IARC and the DHHS have not classified cresols as to its carcinogenicity. Based on inadequate evidence in humans and limited data in animals, EPA (IRIS 2006) assigned cresols to Group C, possible human carcinogens. Under updated guidelines (EPA 2005b), cresols fall in the category of chemicals for which there is "inadequate information to assess carcinogenic potential" (IRIS 2006). EPA did not derive quantitative estimates of carcinogenic risk for cresols. EPA's assessment of cresols' carcinogenicity was conducted before the results of the NTP (2008) study became available. Additional oral carcinogenicity bioassays do not seem necessary at this time.

***Priority Recommendation*:** The identified data need to conduct additional studies via inhalation and dermal exposure is not considered priority because these routes are not considered primary routes of exposure for populations near hazardous waste sites.

d. Genotoxicity

***Purpose*:** To evaluate the mechanism of cresol-induced toxicity for purposes of future mitigation activities. Generally, priority is assigned genotoxicity studies if information is lacking to assess the genotoxic potential of this substance both *in vivo* (mouse micronucleus) and *in vitro* (Ames *Salmonella*). This is particularly true if there are human data to suggest that the substance may act by a genotoxic mechanism to cause cancer, reproductive toxicity, etc., or there exists "structural alerts" that suggest that the substance may be genotoxic. Additional studies will not be assigned priority simply to confirm or refute an equivocal database without justification.

***Finding*:** A data need to conduct additional genotoxicity studies has been identified. No studies were located on the genotoxicity of cresols in humans or in laboratory animals exposed by the inhalation, oral (feed or drinking water), or dermal routes. Studies of the genotoxicity of cresols in animals treated *in vivo* by gavage or intraperitoneal injection reported negative results for dominant lethal, chromosomal aberrations and mouse bone marrow, alveolar macrophages, and regenerating liver cells *in vivo* (Cheng and Kligerman 1984; Ivett 1989a, 1989b, 1989c; Sernav

1989a, 1989b). Micronucleus frequency was increased in mice exposed to *o*-cresol by intraperitoneal injection (Li et al. 2005). An oral feeding study of *o*- and *p*-cresol in *Drosophila* was negative for sex-linked recessive lethality (Sernav et al. 1989a, 1989b). There is also information available from *in vitro* studies. All three cresols isomers were negative for sister chromatid exchange in cultured human cells (Cheng and Kligerman 1984) and positive for unscheduled DNA synthesis for *p*-cresol (Daugherty and Franks 1986). Results were mixed in *in vitro* studies using mammalian cells (Brusick 1988a, 1988b, 1988c; Cifone 1988a, 1988b; Murli 1988; Pepper, Hamilton & Scheetz 1980, 1981), and uniformly negative in *Salmonella* assays (Douglas et al. 1980; Florin et al. 1980; Haworth et al. 1983; Kubo et al. 2002; Pepper, Hamilton & Scheetz 1981; Pool and Lin 1982).

***Priority Recommendation*:** The identified data need to conduct additional genotoxicity tests is not considered priority. Although additional *in vivo* genotoxicity studies, particularly by an environmentally relevant mode of oral administration (dietary or drinking water as opposed to gavage or intraperitoneal injection), are needed to evaluate the genotoxic potential of cresols, these studies are not given priority because there is little evidence of genotoxicity in *in vitro* tests and evaluation of an ongoing oral cancer bioassay is pending. In addition, the results of the structure-activity relationship (SAR) analyses, conducted by the ATSDR Computational Toxicology Methods Development Unit, do not provide supporting evidence to suggest that cresols would be mutagenic (ATSDR 2007b).

e. Endocrine Disruption

***Purpose*:** To determine whether populations potentially exposed to cresols are at an increased risk to develop toxicity of the endocrine system for purposes of conducting meaningful follow-up exposure and health studies. Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones, or otherwise interfere with the normal function of the endocrine system. Chemicals with this type of activity are most commonly referred to as endocrine disruptors. While there is some controversy over the public health significance of endocrine disrupting chemicals, it is agreed that the potential exists for these compounds to affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior.

Generally, when considering the need to assign priority, in the absence of all information on this end point, ATSDR will assign priority to screening studies that examine effects on a) male and female reproductive organs, and b) other endocrine organs including hypothalamus, pituitary, thyroid, parathyroid, adrenal, pancreas, paraganglia, and pineal body. Such screening level studies include, but are not limited to, *in vitro* studies [e.g., 1) Estrogen Receptor Binding/Transcriptional Activation Assay, 2) Androgen Receptor Binding/Transcriptional Activation Assay, and 3) Steroidogenesis Assay with Minced Testis], and *in vivo* studies [e.g., 1) Rodent 3-day Uterotropic Assay, 2) Rodent 20-day Pubertal Female Assay with Thyroid, 3) Rodent 5–7-day Herschberger Assay].

If any of the following is true, then ATSDR will consider assigning Level II priority to 2-generation reproductive studies: if (1) there are suggestions that cresols may have endocrine disrupting potential from Level I studies; or (2) if there have been human anecdotal reports of endocrine disrupting effects following cresol exposure; or (3) if there are structurally similar compounds that affect the endocrine system.

As before, priority will be assigned to studies conducted by the most relevant route of human exposure at Superfund sites; comparative toxicokinetic studies will be performed and evaluated before assigning priority to studies conducted via additional routes of exposure.

***Findings*:** A data need to conduct additional studies on the endocrine system via inhalation and dermal exposure has been identified. There are no human data on the potential of cresols to disrupt the endocrine system. No studies were located that examined potential endocrine disruption in animals exposed to cresols by inhalation or dermal exposure. Such studies are needed to establish thresholds and dose-response relationships for effects on the endocrine system by these routes of exposure. There are intermediate-duration oral studies in rats and mice that provide information on weight and gross and microscopic appearance of endocrine glands and reproductive organs and on additional reproductive parameters in male and female animals (NTP 1992b). In general, the few alterations reported occurred at relatively high doses of cresols. Treatment of rats with *m/p*-cresol in the diet for 13 weeks did not affect reproductive organs' morphology, but significantly lengthened the estrous cycle of rats (NTP 1992b). In mice, exposure to *o*-cresol for 28 days also induced mild atrophy of the uterus, and *m*-cresol induced mild to moderate atrophy of the mammary gland, uterus, and ovaries (NTP 1992b). In addition, administration of *o*-cresol for 13 weeks lengthened the estrous cycle in female mice. In these

studies, there was no biologically significant effect on males' reproductive organs or on sperm parameters. Multiple-generation reproductive studies that administered cresols by gavage (Neeper-Bradley and Tyl 1989a 1989b; Tyl and Neeper-Bradley 1989) or through the diet (NTP 1992a, 1992c) have provided no evidence of endocrine-mediated alterations on reproduction or development. In standard developmental toxicity studies in rats and rabbits, cresols have induced slight fetotoxicity (dilated lateral ventricles in the brain and minor skeletal variations in rats treated with both *o*- and *p*-cresol; subepidermal hematoma on the head and poorly ossified sternebrae in rabbits treated with *o*-cresol) at maternally toxic doses (Tyl 1988a, 1988b). A study in which embryos of rats were incubated *in vitro* with *p*-cresol reported increased incidence of structural abnormalities such as hind limb bud absence and tail defects, but there is no evidence that this was endocrine-mediated (Oglesby et al. 1992). Additional information from a study *in vitro* is limited to a report that *p*-cresol tested positive and *o*-cresol negative for estrogenic activity in a reporter gene expression assay using yeast cells (Nishihara et al. 2000). Collectively, the available evidence does not suggest that cresols represent a hazard due to properties of endocrine disrupters at environmentally-relevant levels. Additional oral studies do not seem necessary at this time.

***Priority Recommendation*:** The identified data need to conduct additional studies on the endocrine system via inhalation and dermal exposure is not considered priority. Ingestion of contaminated media is the primary exposure route for cresols at hazardous waste sites. Sufficient studies by the oral route of exposure do not suggest that cresols are endocrine disruptors, although some alterations to reproductive parameters have been observed at relatively high doses. Inhalation and dermal data are lacking, but there is no evidence that the effects of cresols (other than those at the point of contact) are route-dependent, and also the inhalation and dermal routes are not primary routes for populations living near waste sites.

f. Reproductive Toxicity

***Purpose*:** To determine whether populations potentially exposed to cresols are at an increased risk to develop reproductive effects for purposes of conducting meaningful follow-up exposure and health studies. ATSDR scientists believe it is important to acquire reproductive toxicity data in order to consider the needs of susceptible populations. It is desirable to have information on reproductive toxicity before developing MRLs to ensure that target organs have been adequately evaluated.

Generally, when considering the need to assign priority, in the absence of all information on this end point, ATSDR will assign priority to the conduct of 90-day studies with special emphasis on reproductive organ pathology. If any of the following is true, then ATSDR will consider assigning priority to multigeneration animal studies: (1) If any indication is found in these studies that the reproductive system of either male or female animals is a target organ of substance exposure; or (2) if there have been human anecdotal reports of reproductive effects following substance exposure; or (3) if there are structurally similar compounds that affect reproduction.

As before, priority will be assigned to studies conducted by the most relevant route of human exposure at Superfund sites; comparative toxicokinetic studies will be performed and evaluated before assigning priority to studies conducted via additional routes of exposure.

***Finding*:** A data need to conduct additional reproductive studies via inhalation and dermal exposure has been identified. There are no data available regarding reproductive effects of cresols in humans. There are no studies of reproductive end points in animals following inhalation or dermal exposure to cresols. Studies by these routes of exposure are needed to develop dose-response relationships and establish threshold levels for indices of reproductive toxicity. There are several oral studies in animals that do not suggest that reproductive end points are sensitive targets for cresols toxicity (EPA 1988a, 1988b, 1988c; Hornshaw et al. 1986; Neeper-Bradley and Tyl 1989a, 1989b; NTP 1992a, 1992b, 1992c; Tyl and Neeper-Bradley 1989). Well-conducted dietary continuous breeding protocol studies in mice dosed with *o*-cresol and *m/p*-cresol found no evidence of reproductive toxicity for *o*-cresol (NTP 1992a); *m/p*-cresol, at a dose that caused minor maternal toxicity (reduced body weight gain), produced a decrease in the number of pups/litter and increased the cumulative days to litter, but did not affect other reproductive function end points (NTP 1992c). In the intermediate-duration dietary studies in rats and mice conducted by NTP (1992b), effects were limited to mild to moderate uterine atrophy and lengthening of the estrous cycle, generally at the highest dose levels tested, but there was no biologically significant effect on males' reproductive organs or on sperm parameters. Additional studies by the oral route do not seem warranted at this time.

***Priority Recommendation*:** The identified data need to conduct additional reproductive toxicity studies via inhalation and dermal exposure is not considered priority because the available oral

studies provide a sufficient indication that cresols do not impair reproductive performance. Additionally, the inhalation and dermal routes are not primary routes of exposure for populations living near hazardous waste sites.

g. Developmental Toxicity

***Purpose*:** To determine whether populations potentially exposed to cresols are at an increased risk for developmental effects for purposes of conducting meaningful follow-up exposure and health studies. Similar to reproductive toxicity assessment, Agency scientists believe it is important to assess the developmental toxicity data.

In the absence of any reproductive or teratologic information, ATSDR will consider proposals to simultaneously acquire reproductive and teratological information. ATSDR acknowledges that, in some circumstances, developmental studies may be assigned priority if the following statements are true: (1) if a two-generation reproductive study provides preliminary information on possible developmental toxicity of cresols, (2) if there are human anecdotal reports of developmental effects following cresol exposure, *or* (3) if structurally similar compounds have caused developmental effects.

As for reproductive toxicity, priority will be assigned to studies conducted by the most relevant route of human exposure at Superfund sites; comparative toxicokinetic studies will be performed and evaluated before assigning priority to the conduct of studies via additional routes of exposure.

***Finding*:** A data need to conduct additional developmental studies via inhalation and dermal exposure has been identified. There are no data available regarding developmental effects of cresols in humans. There are no studies of reproductive end points in animals following inhalation or dermal exposure to cresols. Studies by these routes of exposure are needed to develop dose-response relationships and establish threshold levels for developmental end points. Information is available on developmental effects of cresols from a series of studies in which pregnant rats and rabbits were exposed by gavage to each cresol isomer (Neeper-Bradley and Tyl 1989a, 1989b; Tyl 1988a, 1988b; Tyl and Neeper-Bradley 1989) and in pregnant mice exposed to *o*-cresol or *m/p*-cresol in the diet in continuous breeding protocol studies (NTP 1992a, 1992c). These studies generally reported fetotoxicity (reduced pup weight and viability) at doses that caused frank maternal toxicity. Additional relevant information is available from a comparative

study that observed tremors in newborn mice exposed by gavage to 100 mg/kg/day *m*-cresol on postnatal days 4–21, but no such effects occurred in adults exposed to up to 300 mg/kg/day for 28 days (Koizumi et al. 2003). Since the data from gestation exposure studies in animals indicate that developmental effects generally occur at relatively high-dose levels that induce serious effects in the mother, such as tremors and significant reduction food consumption, further oral studies examining the potential developmental toxicity of cresols do not seem necessary at this time. In addition, the results of the SAR analyses, conducted by the ATSDR Computational Toxicology Methods Development Unit, do not provide supporting evidence to suggest developmental health would be a health effect of concern (ATSDR 2007b).

***Priority Recommendation*:** The identified data need to conduct additional developmental toxicity studies via inhalation and dermal exposure is not considered priority because the available oral data suggest that developmental end points are not particularly sensitive end points for cresols and inhalation and dermal exposure are not primary routes of exposure for populations living near hazardous waste sites.

h. Immunotoxicity

***Purpose*:** To evaluate the mechanism of cresol-induced toxicity for purposes of defining target organs and future mitigation activities. There is evidence to suggest that the immune system might be a susceptible target organ for many environmental contaminants. In the absence of any information on the immune system as a target organ, priority will be assigned to the evaluation of the immune system (lymphoid tissue, blood components) as an end point in 90-day studies (Level I) before assigning priority to an immunotoxicology battery as recently defined by the NTP.

For those substances that either (1) show evidence of immune system effects in 90-day studies, (2) have human anecdotal data to suggest that the immune system may be affected, or (3) are structurally similar to known immunotoxicants, an immunotoxicology battery of tests will be assigned priority.

***Finding*:** A data need to conduct additional immunotoxicity studies via inhalation, oral, and dermal exposure has been identified. There are no data available regarding immunological effects of cresols in humans. There are no studies of immunological end points in animals following inhalation or dermal exposure to cresols. Studies by these routes of exposure are

needed to develop dose-response relationships and establish threshold levels for immunological end points. There are gavage studies and dietary studies in rodents that have shown no significant alterations in weight or histology of lymphoreticular organs following exposure to cresols, but immunocompetence has not been evaluated (EPA 1988a, 1988b, 1988c; Hornshaw et al. 1986; NTP 1992b, 2008).

***Priority Recommendation*:** The identified data need to conduct additional immunotoxicity studies via inhalation, oral, and dermal exposure is not considered priority. Although the oral route of exposure is considered a primary route of exposure for populations near waste sites, priority is not assigned to oral studies because the information available does not suggest that the immune system is a target for cresol toxicity, although specialized tests have not been conducted. Additionally, the inhalation and dermal routes are not primary routes of exposure for populations living near hazardous waste sites.

i. Neurotoxicity

***Purpose*:** To evaluate the mechanism of cresol-induced toxicity to define target organs and future mitigation activities. Similar to immunotoxicity, there is a growing body of data to suggest that the nervous system is a very sensitive target organ for many environmental chemicals. In the absence of any information on the nervous system as a target organ, priority will be assigned evaluation of the nervous system as an end point in 90-day studies (Level I) before assigning priority to a neurotoxicology battery.

It may be possible to assign priority to evaluation of demeanor in 90-day studies along with neuropathology. For those substances that either (1) show evidence of nervous system effects in 90-day studies, (2) have human anecdotal data to suggest that the nervous system may be affected, or (3) are structurally similar to known neurotoxicants, a neurotoxicology battery of tests will be assigned priority.

***Finding*:** A data need to conduct additional neurotoxicity studies via inhalation and dermal exposure has been identified. There are limited data regarding neurological effects of cresols in humans and all are derived from reports of acute oral or dermal exposure to high amounts of cresols. A feature commonly observed in these cases was coma (Cason 1959; Chan et al. 1971; Green 1975; Isaacs 1922; Labram and Gervais 1968). The information provided by these studies

is inadequate for dose-response assessment because, at best, only near lethal or lethal doses could be estimated. There is very limited information regarding neurological effects in animals following inhalation and dermal exposure to cresols. Animals exposed to cresol aerosols showed mild nervous excitation, muscle twitching accompanied by general fatigue, and clonic convulsions (Uzhdavini et al. 1972). The exposure concentrations associated with these effects were not reliably documented. Rats showed shallow breathing and convulsions 5–30 minutes after 1.0–3.5 mL/kg of certain cresylic acid (a mixture of cresol isomers and other phenolic solvents that boils above 204 °C) formulations were applied to the skin (Campbell 1941). Inhalation and dermal studies are needed to identify thresholds and establish dose-response relationships for neurological effects following exposure by these routes. Considerable more information is available regarding neurological effects of cresols in animals following oral exposure. Gavage studies in rodents often induced adverse clinical signs indicative of neurological impairment such as hypoactivity, excessive salivation, labored respiration, and tremors (Deichmann and Witherup 1944; Hornshaw et al. 1986; Neeper-Bradley and Tyl 1989a, 1989b; Tyl and Neeper-Bradley 1989). In no cases have gross or microscopic alterations of the brain, spinal cord, or sciatic nerve been observed. None of the clinical signs seen in gavage studies have been seen in dietary studies, or if seen, they have occurred at much higher dose levels than in gavage studies (NTP 1992b). This difference is probably related to the different disposition of cresols and metabolites between the two modes of oral dosing. Neurobehavioral tests conducted with the three cresol isomers in an gavage study in rats showed only sporadic differences with controls and/or alterations were not dose-related (TRL 1986). In gavage studies, LOAELs for adverse neurological signs were around 50–60 mg/kg/day. Collectively, the information available indicates that the nervous system is not a sensitive target for cresols administered by an environmentally-relevant oral route; additional oral studies do not seem necessary at this time.

***Priority Recommendation*:** The identified data need to conduct additional neurotoxicity studies via inhalation and dermal exposure is not considered priority. The available data show that the same general type of neurotoxic effects manifest after inhalation, oral, and dermal exposure to cresols. Also, the need for additional inhalation and dermal data is not given priority because these routes are not considered primary routes of exposure for populations living near hazardous waste sites.

j. Toxicokinetics

***Purpose*:** To evaluate the disposition of cresols across species and routes of exposure to elucidate target organs and mechanisms of toxicity, and to assess the need to conduct studies by routes other than the primary route of exposure.

***Finding*:** A data need to assess the toxicokinetics of cresols following inhalation, oral, and dermal exposure has been identified. There are no studies regarding the rate and extent of absorption of inhaled cresols in humans or in animals. However, since some studies have reported adverse health effects and death in animals following inhalation exposure (Campbell 1941; Kurlyandskiy et al. 1975; Uzhdavini et al. 1972), it is reasonable to assume that pulmonary absorption occurred. A significant number of reports of accidental or intentional ingestion of cresols indicate that cresols can be absorbed through the gastrointestinal tract, as judged by the adverse health effects that occurred, including death (Bruce 1976; Chan et al. 1971; Hashimoto et al. 1998; Kamijo et al. 2003; Labram and Gervais 1968). Studies in animals indicate that all three cresol isomers are well absorbed in the gastrointestinal tract (at least 65–84% of the administered dose) and that fasting accelerates absorption (Bray et al. 1950). A more recent study showed that after a single gavage dose of a cresol soap solution (*p*- and *m*-cresol) to rats, 50% of the administered dose disappeared from the gastric contents in 15 minutes and almost all of the administered cresol disappeared within 8 hours (Morinaga et al. 2004). There are two case reports of humans who went into a coma and eventually died following dermal exposure to cresols, providing indirect evidence of dermal absorption (Carson 1959; Green 1975). There are no studies regarding the rate and extent of absorption of cresols in animals following dermal exposure. Since humans near hazardous waste sites may be exposed by dermal contact to cresols in soil or in water, there is a need for studies that can provide quantitative information regarding bioavailability from these media. The only information regarding distribution of cresols in humans is that cresols (unspecified isomers) were identified in the liver and brain from an infant who died hours after a cresol solution was spilled on his head (Green 1975). There is only one study that examined the distribution of cresols in rats (Morinaga et al. 2004). Cresols were found in the brain, lung, muscle, spleen, liver, and kidneys. Very limited information is available regarding the metabolism of cresols in humans and animals. In humans and in the small number of rodent species studied, cresols form sulfate and glucuronic acid conjugates, which are excreted in the urine (Bray et al. 1950; Fuke et al. 1998; Morinaga et al. 2004; Williams 1938). The proportions of the conjugates are known to vary with the dose, differ to some extent among cresol

isomers, and differ from one species to another. However, these differences have not been studied systematically and research in this area is needed. More detailed information is available regarding the metabolism of *p*-cresol in *in vitro* preparations of rat and human liver microsomes (Thompson et al. 1994, 1995, 1996; Yan et al. 2005). In human liver microsomes, Yan et al. (2005) showed that the activation of *p*-cresol by oxidation forms a reactive quinone methide, which formed a conjugate, glutationyl-4-methyphenol. In addition, a new pathway was identified consisting of aromatic oxidation leading to the formation of 4-methyl-o-hydroquinone, which is further oxidized to 4-methyl[1,2]benzoquinone. The latter formed three adducts with glutathione, but the predominant adduct was found to be 3-(glutathione-S-yl)-5-methyl-o-hydroquinone. It was also found that 4-hydroxybenzylalcohol, a major metabolite formed by oxidation of the methyl group in liver microsomes, was further converted to 4-hydroxybenzaldehyde. Experiments with recombinant P-450s demonstrated that the formation of the quinone methide intermediate was mediated by several P-450s including CYP2D6, 2C19, 1A2, 1A1, and 2E1. The ring oxidation pathway was found to be mediated primarily by the CYP2E1 and to a lesser extent by CYP1A1, 1A2, and 2D6. Formation of 4-hydroxybenzaldehyde was catalyzed by 1A2 and also 1A1 and 2D6. Human liver microsomes formed the same adducts as rat liver microsomes suggesting that the metabolism of *p*-cresol may be similar in humans and rats. However, this does not necessarily mean that the rat is an appropriate animal model; further research is needed to identify an appropriate animal model. Additional studies are needed to obtain comparable information regarding the *o*- and *m*-cresol isomers. There is limited information from studies in rat liver slices *in vitro* that indicate that the hepatotoxicity of cresol isomers at the cellular level may be mediated by a reactive intermediate, but there are some differences between the isomers (Thompson et al. 1994, 1995, 1996). Additional studies are needed to determine the role of metabolism in the toxic effects of cresols *in vivo*. Aside from the corrosive effects on the skin and mucosal surfaces of humans and animals produced by direct contact with high concentrations of cresols, there is not enough information to determine whether humans and animals share additional target organ for cresols.

***Priority Recommendation*:** The identified data need to assess the toxicokinetics of cresols following oral exposure is not considered priority. While additional oral studies would be useful because there is minimal information on the absorption kinetics of cresols, which if comparable to phenol, is likely to play an important role in the manifestation of the neurological effects (tremors and convulsions) induced by cresols, these effects occur only following acute exposure to high amounts of cresols (such as with gavage). Such exposure scenario is unlikely near

hazardous waste sites, where sustained exposure to low amounts through ingestion of contaminated media is more likely to occur. Data are also insufficient to compare toxicokinetics of cresols across routes of exposure, but these studies are not given priority because inhalation and dermal contact are not considered the primary exposure routes for populations living near waste sites.

2. Level III Data Needs

a. Epidemiologic Studies

***Purpose*:** To evaluate the extant epidemiologic database and to propose the conduct of additional studies that may lead to cause- and effect- findings. The ATSDR Division of Health Studies will be informed of all candidate substances.

***Finding*:** A data need has been identified. There is no information on possible health effects in humans exposed to cresols for prolonged periods of time by any route of exposure. Information about the health effects of cresols in humans is derived mainly from case reports of accidental or intentional ingestion of cresol solutions or from accidental contact of cresols with the skin. These cases and a single study in volunteers exposed briefly to *o*-cresol in the air (Uzhdavini et al. 1972) indicate that cresols produce corrosive damage at the site of contact, making the skin and mucosal membranes targets for cresol toxicity. Effects reported in these acute high oral and/or dermal exposure scenarios include respiratory failure, tachycardia and ventricular fibrillation, abdominal pain, vomiting, and corrosive lesions of the gastrointestinal tract, methemoglobinemia, leukocytosis and hemolysis, hepatocellular injury, renal alterations, skin damage, metabolic acidosis, unconsciousness, and death (specific references can be found under *Acute-Duration Exposure*). Doses were generally not available so that no dose-response relationships could be established. Moreover, many of these effects may not have been caused directly by cresols, but may represent secondary reactions to shock caused by external and internal burns. As mentioned above, no group of the general population has been identified as having being exposed exclusively or predominantly to low levels of cresols for a long time. Based on data from long-term dietary studies in animals, it would be difficult to determine what specific end points to monitor in humans exposed to cresols because, with the exception of nasal epithelial lesions, cresols caused relatively little systemic toxicity in the animal studies.

Priority Recommendation: The identified data need to conduct epidemiologic studies on cresols is not considered priority. Although many people are potentially exposed to cresols because these substances have been detected in hazardous waste sites (HazDat 2006), studies of these people are likely to be confounded by exposure to other chemicals from the hazardous waste sites. If either worker or general populations with appropriate exposures can be identified, epidemiological studies should be undertaken. However, the specific end points that should be monitored under such exposure scenario (prolonged low-level exposure) are not immediately apparent.

b. Mechanism of Toxic Action

***Purpose*:** To evaluate the mechanism of cresol-induced toxicity to define target organs and future mitigation activities.

***Finding*:** A data need has been identified. Cresols are irritating and corrosive at high concentrations as supported by numerous cases of accidental dermal exposure or intentional or accidental ingestion of cresols. Cresols damage the stratum corneum and produce coagulation necrosis by denaturing and precipitating proteins. This makes the respiratory tract, eyes, and mucosal membranes in general targets for cresols toxicity. Cresols exhibited little toxicity in intermediate-duration dietary studies in rats and mice (NTP 1992b). Hyperplastic or metaplastic lesions in the nasal respiratory epithelium were the most sensitive effects, but the mechanism by which this occurs is not known and needs to be investigated. Many studies in which the animals were dosed with cresols by gavage reported adverse neurological signs ranging from lethargy to tremors and convulsions (EPA 1988b, 1988c; TRL 1986; Tyl 1988a, 1988b). Dietary studies reported occasional tremors only at the highest doses administered. The mechanism by which cresols induce these effects is unknown; cresols could be acting at multiple sites including sites at the periphery. Studies aimed at investigating the mechanism of neurological effects may need to be tied to kinetics studies since it is likely that pharmacokinetics plays a role in the manifestation of neurological signs, as occurs in the case of the structurally-related chemical, phenol (Hiser et al. 1994). Studies with precision-cut rat liver slices have suggested that the cell toxicity of cresol isomers may be related to the formation of reactive intermediates (Thompson et al. 1994, 1995, 1996; Yan et al. 2005). Further studies on the role of metabolism on the toxicity of cresols are needed; yet, the practical application of the findings is unknown since cresols exhibited little or no liver toxicity in dietary studies in rats and mice (NTP 1992b).

***Priority Recommendation*:** The identified data need is not considered priority. Additional research focused on elucidating mechanisms of cresol-induced toxicity, while still a data need, is not given priority at this time because of the need to further define target organs in humans, in particular, following long-term, low-level exposure, and to identify threshold levels that cause adverse health effects via oral exposure, a primary exposure route at hazardous waste sites.

c. Biomarkers

***Purpose*:** To evaluate the need to develop additional biomarkers of exposure and effect for purposes of future medical surveillance that can lead to early detection and treatment.

***Finding*:** A data need has been identified. There are no specific biomarkers of exposure or effect for cresols. There are analytical methods available to measure cresols in the blood and the urine (Bieniek 1994, 1997; Boatto et al. 2004; De Smet et al. 1998); however, cresols are also formed as breakdown products of toluene. Also, *p*-cresol is one of the metabolites of the amino acid tyrosine. Measurement of total cresols in the urine is a useful biomarker following inhalation exposure to cresols. As mentioned above, the test is nonspecific and should not be used when workers are exposed to toluene or to household products containing cresols. Dermal exposure may also result in overestimation of inhalation exposure. In persons not exposed to cresols or toluene, De Smet et al. (1998) reported a mean concentration of 8.6 µmol/L (0.93 mg/L) of *p*-cresol in serum. Dose-response relationships between ambient concentrations of cresols and cresols in the urine have not been established. However, for the general population, the use of cresols as a biomarker of exposure to cresols would require a considerable elevation to exceed biological background levels and potential confounding from conversion of other environmental agents.

***Priority Recommendation*:** The identified data need is not considered priority. The lack of a specific biomarker of exposure or effect for cresols is not considered essential to conduct human studies. This is because there is no unique disease state associated with cresols and the identification of cresols in body fluids can be fairly diagnostic when combined with observations of irritation or burns at sites of contact following ingestion or dermal exposure to relative high amounts of cresols. However, development of more specific and sensitive tests might be necessary to adequately evaluate the health status of individuals exposed continuously to low

levels of cresols at waste sites. These considerations will be more appropriately addressed in the future once populations have been identified with known exposure to cresols and further information is gathered regarding the mechanism(s) of cresol action.

d. Clinical Methods for Mitigating Toxicity

***Purpose*:** To determine whether any efforts are currently under way to mitigate the effects of exposure to cresols.

***Finding*:** A data need has been identified. Target organs after acute exposure to high amounts of cresols include any site of direct contact such as the skin, eyes, and mucosal membranes, and the nervous system. No group of the general population has been identified as having being exposed exclusively or predominately to low levels of cresols for a long time; therefore, no target organ(s) has been identified in humans following long-term, low-level exposure to cresols. The irritant properties of cresols are due to the fact that these substances damage the stratum corneum and induce of coagulation necrosis by denaturing and precipitating proteins (Ellenhorn et al. 1997). The mechanism(s) by which cresols induce other effects, i.e., neurological effects following acute exposure to high doses, is not known and studies aimed at elucidating these mechanisms would help design appropriate counteractions. There is adequate information available regarding procedures for reducing absorption of cresols following exposure (HSDB 2006). 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 cresols are corrosive and may cause seizures, emesis should not be induced. If the eyes have been exposed, they should be thoroughly irrigated as soon as possible with running water or saline. If the skin has been exposed, it should be flushed promptly with copious amounts of water or undiluted polyethylene glycol followed by thorough washing with soap or mild detergent and water. There is no antidote for cresol poisoning; treatment consists of measures to support respiratory and cardiovascular functions.

***Priority Recommendation*:** The identified data need is not considered priority. More information is needed regarding effects of long-term, low-level exposure to cresols to determine the type of studies that might help elucidate the mechanisms involved in such effects. So far, no unique disease has been associated with exposure to cresols, and populations with specific substance-induced adverse health effects have not been identified.

e. Children's Susceptibility

***Purpose*:** To determine whether adequate data exist to identify potential health effects from exposures to cresols during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation.

***Finding*:** A data need to conduct additional studies relevant to children's susceptibility via inhalation, oral, and dermal exposure has been identified. There are no studies that specifically addressed exposure to cresols in children. Data on the effects of cresols in adults are derived almost exclusively from cases of accidental or intentional ingestion of cresol solutions (see *Acute-Duration Exposure* for specific references). Exposure to these high amounts of cresols produced corrosion at the points of contact including the skin and gastrointestinal tract. Similar effects would be expected in children exposed to high amounts of cresols. There is no information on whether the developmental process is altered in humans exposed to cresols. Studies in animals suggest that fetotoxicity occurs with doses of cresols that are also toxic to the mother (Neeper-Bradley and Tyl 1989a, 1989b; Tyl 1988a; 1988b; Tyl and Neeper-Bradley 1989) and further standard developmental toxicity studies do not appear necessary at this time. A study showed that newborn rats (exposed daily on postnatal days 4–21) were more sensitive to the neurological effects of bolus doses of cresols than young rats (exposed daily for 28 days) (Koizumi et al. 2003). This may be due to age-related differences in toxicokinetics. This work has not been duplicated and there is no additional information evaluating the toxicity of cresols at various ages. Such studies need to be conducted in order to follow-up this observation. Results from a study in mice administered *o*-cresol by intraperitoneal injection suggest that *o*-cresol potentially could affect the germ cells, opening the possibility that parental exposure would result in adverse childhood development or cancer (Li et al. 2005). However, the results of two-generation reproduction studies utilizing much higher doses do not support that possibility (Hornshaw et al. 1986; Neeper-Bradley and Tyl 1989a, 1989b; Tyl and Neeper-Bradley 1989).

There are no data to evaluate whether toxicokinetics of cresols in children are different from adults. Studies *in vitro* have shown that cresols are metabolized by various cytochrome isozymes and also form sulfate and glucuronide conjugates (Thompson et al. 1994; Yan et al. 2005). To the

extent that the enzymes involved in the metabolism of cresols are developmentally regulated, the metabolism, and consequently the toxicity of cresols, in immature humans may be different than in adults. However, since there is not enough information to determine which is the toxic entity, cresols or a metabolite, it is not known how metabolism will influence the susceptibility of children to cresols exposure. Additional studies investigating the role of metabolism on cresols toxicity are needed to determine whether children are more or less susceptible than adults to cresols toxicity. There is no information on whether cresols can cross the placenta and there are no studies on whether cresols can be transferred from mother to offspring through maternal milk. Research into the development of biomarkers of exposure for cresols would be valuable for both adults and children. There are no data on the interactions of cresols with other chemicals in children. There are no pediatric-specific methods to mitigate the effects of exposure to high amounts of cresols. Based on the information available, it is reasonable to assume that the supportive methods recommended for maintaining vital functions in adults exposed to excessive amounts of cresols will also be applicable to children.

Priority Recommendation: The identified data need to conduct additional studies on children's susceptibility via inhalation, oral, and dermal exposure is not considered priority because more basic information is needed, particularly regarding mechanism of action and thresholds after oral exposure (the primary route of exposure at hazardous waste sites) and placental and breast milk transfer. Studies by the inhalation and dermal routes are not considered priority because these are not priority routes of exposure for populations near hazardous waste sites.

IV. Summary: Prioritization of Data Needs for Cresols

A. Exposure

Application of the hierarchy of research priorities presented in the Decision Guide begins with the evaluation of available analytical methods for cresols and proceeds through assessing the need for epidemiologic studies. As stated previously, much information is available on cresols, though some of the studies are very old. This does not mean that data derived from older studies are not adequate. ATSDR agrees with the National Research Council in that it is not appropriate to judge the quality of past and future studies solely by the standards of today.

Building a sound basic data foundation for higher level environmental research via the Decision Guide requires the determination of human exposure levels and media-specific data on cresols. Although a lot of information is available, a need to evaluate existing data on concentrations of cresols in contaminated environmental media at hazardous waste sites has been identified.

Furthermore, a need to collect data on levels of cresols in body tissues and fluids for populations living near hazardous waste sites has been identified. This information is necessary to establish a database that can be used to assess the need to conduct follow-up human health studies of adult and children populations exposed to cresols.

One effort is now under way at ATSDR that will examine the extant data at the 210, 22, 310, and 70 NPL sites at which *o*-cresol, *m*-cresol, *p*-cresol, and mixed cresols, respectively, have been found. This database will include maximum concentrations of cresols in on-site and off-site media, and an indication of relevant routes of exposure. This database will be evaluated before the need to collect additional media-specific data is assigned priority. This database will not, however, supply information on the levels of cresols (or its metabolites) in the tissues of adults and children living near hazardous waste sites or other exposed populations such as workers.

Thus, on the basis of the findings given in Section II and above, ATSDR is recommending the initiation of research or studies to fill the following exposure priority data needs (Table 3):

- Exposure levels in humans living near hazardous waste sites and other populations
- Exposure levels in children

B. Toxicity

The toxicity of cresols has been studied in animals by inhalation, oral, and dermal exposure. For all exposure routes, the site of contact is a target for cresols' toxicity, as shown primarily by irritation of the respiratory tract, eyes, and skin. Exposure to doses of cresols that result in high amounts of parent compound in the bloodstream in a short time, as may occur following inhalation, gavage, or dermal exposure, caused adverse neurological effects in animals characterized by tremors, convulsions, and possible death. In a study in which rats and mice were exposed to cresols in the diet for intermediate-duration periods, nasal epithelial lesions were the most sensitive target for cresols' toxicity; these lesions were observed in animals treated with

p-cresol and with a mixture of *p*- and *m*-cresol. Aside from the nasal lesions, cresols exhibited little toxicity in intermediate-duration dietary studies. A chronic-duration (2-year) toxicity and carcinogenicity bioassay in animals confirmed the presence of nasal lesions reported in the intermediate studies and also observed increased incidences of bronchiolar hyperplasia and follicular degeneration of the thyroid gland in treated mice. Cresols induced reproductive and developmental effects at dose levels that caused maternal toxicity. There is not enough information to determine with certainty whether children are more susceptible to cresols than adults. An acute-duration oral MRL was not derived for cresol because all available studies administered cresol by gavage, a mode of administration that is not considered environmentally-relevant. Therefore, oral studies with cresols in the diet or in drinking water are needed to identify sensitive targets and establish dose-relationships for acute-duration exposure.

These nonhuman research needs are justified because of the widespread domestic and environmental contamination of cresols, and the possibility that significant past exposures have affected many people.

Thus, on the basis of the findings given in Section II and above, ATSDR recommends the initiation of research or studies to fill the following toxicity priority data need (Table 3):

- Dose-response data for acute-duration via oral exposure

V. References

AIChE. 1989. *o-, p*-Cresols. C7H8O. In: Physical and thermodynamic properties of pure chemicals. American Institute of Chemical Engineers, Design Institute for Physical Property Data. Philadelphia, PA: Taylor and Francis.

AIChE. 2000. *m*-Cresols. C7H8O. In: Physical and thermodynamic properties of pure chemicals. American Institute of Chemical Engineers, Design Institute for Physical Property Data. Philadelphia, PA: Taylor and Francis.

Alexander M, Lustigman BK. 1966. Effect of chemical structure on microbial degradation of substituted benzenes. J Agric Food Chem 14:410-413.

Angerer J, Wulf H. 1985. Occupational chronic exposure to organic solvents. XI. Alkylbenzene exposure of varnish workers: Effects on hematopoietic system. Int Arch Occup Environ Health 56:307-321.

Arrendale RF, Severson RF, Chortyk OT, et al. 1982. Analyses of mono- and dihydroxybenzenes in tobacco smoke and pyrolzates by glass capillary gas chromatography. J Chromatogr Sci 20(3):136-143.

Artiola-Fortuny J, Fuller WH. 1982. Adsorption of some monohydroxybenzene derivatives by soils. Soil Sci 133:18-26.

Atkinson R, Carter WPL. 1984. Kinetics and mechanisms of the gas-phase reactions of ozone with organic compounds under atmospheric conditions. Chem Rev 84:437-470.

Atkinson R, Carter WPL, Plum CN, et al. 1984. Kinetics of the gas-phase reactions of NO_3 radicals with a series of aromatics at 296$\pm$2 K. Int J Chem Kinet 16:887-898.

ATSDR. 2007a. Notice of the revised priority list of hazardous substances that will be the subject of toxicological profiles. Agency for Toxic Substances and Disease Registry. Fed Regist 73: 12178-12179.

ATSDR. 2007b. Toxicity assessment report prepared by the ATSDR Computational Toxicology Methods Development Unit using TOPKAT 6.2. Atlanta, GA: Agency for Toxic Substances and Disease Registry.

ATSDR. 2008. ATSDR toxicological profile for cresols. Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/toxprofiles/tp34.html.

Babeu L, Vaishnav DD. 1987. Prediction of biodegradability for selected organic chemicals. J Ind Microb 2:107-115.

Baird RB, Kuo CL, Shapiro JS, et al. 1974. The fate of phenolics in wastewater -- determination by direct-injection GLC and Warburg respirometry. Arch Environ Contam Toxicol 2:165-178.

Bammens B, Evenepoel P, Keuleers H, et al. 2006. Free serum concentrations of the protein-bound retention solute p-cresol predict mortality in hemodialysis patients. Kidney Int 69(6):1081-1087.

Battersby NS, Wilson V. 1988. Evaluation of a serum bottle technique for assessing the anaerobic biodegradability of organic chemicals under methanogenic conditions. Chemosphere 17:2441-2460.

Battersby NS, Wilson V. 1989. Survey of the anaerobic biodegradation potential of organic chemicals in digesting sludge. Appl Environ Microbiol 55:433-439.

Bieniek G. 1994. Concentrations of phenol, *o*-cresol, and 2,5-xylenol in the urine of workers employed in the distillation of the phenolic fraction of tar. Occup Environ Med 51(5):354-356.

Bieniek G. 1997. Urinary excretion of phenols as an indicator of occupational exposure in the coke-plant industry. Int Arch Occup Environ Health 70(5):334-340.

Boatto G, Nieddu M, Carta A, et al. 2004. Determination of phenol and *o*-cresol by GC/MS in a fatal poisoning case. Forensic Sci Int 139(2-3):191-194.

Boutwell RK, Bosch DK. 1959. The tumor-promoting action of phenol and related compounds for mouse skin. Cancer Res 19:413-424.

Boyd SA. 1982. Adsorption of substituted phenols by soil. Soil Science 134:337-343.

Boyd SA, Shelton DR, Berry D, et al. 1983. Anaerobic biodegradation of phenolic compounds in digested sludge. Appl Environ Microbiol 46:50-54.

Bray HG, Thrope WV, White K. 1950. Metabolism of derivatives of toluene. Biochem J 46:275-278.

Bruce AM, Smith H, Watson AA. 1976. Cresol poisoning. Med Sci Law 16:171-176.

Brusick DJ. 1988a. Mutagenicity tests on *o*-cresol in the *in vitro* transformation of BALB/C-3T3 cells assay in the presence of rat liver cell activation system. Chemical Manufacturers Association. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0517697.

Brusick DJ. 1988b. Mutagenicity tests on meta-cresol and para-cresol in the *in vitro* transformation of BALB/C-3T3 cells assay. Chemical Manufacturers Association. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0517694.

Brusick DJ. 1988c. Mutagenicity tests on *m*-cresol in the *in vitro* transformation of BALB/C-3T3 cells assay. Chemical Manufacturers Association. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0517698.

Campbell I. 1941. Petroleum cresylic acids. A study of their toxicity and the toxicity of cresylic disinfectants. Soap Sanit Chem 17(4):103.

Carter WPL, Winer AM, Pitts JN Jr. 1981. Major atmospheric sink for phenol and the cresols: Reaction with the nitrate radical. Environ Sci Technol 15(7):829-831.

Cason JS. 1959. Report on three extensive industrial chemical burns. Br Med J 1:827-829.

Cha YJ, Cadwallader KR. 1995. Volatile components in salt-fermented fish and shrimp pastes. J Food Sci 60:19-24.

Chambers CW, Tabak HH, Kabler PW. 1963. Degradation of aromatic compounds by phenol-adapted bacteria. J Water Pollut Contr Fed 35:1517-1528.

Chan TK, Mak LW, Ng RP. 1971. Methemoglobinemia, Heinz bodies and acute massive intravascular hemolysis in Lysol poisoning. Blood 38:739-744.

Chao J, Lin CT, Chung TH. 1983. Vapor pressure of coal chemicals. J Phys Chem Ref Data 12(4):1033-1063.

Cheng M, Kligerman AD. 1984. Evaluation of the genotoxicity of cresols using sister-chromatid exchange (SCE). Mutat Res 137(1):51-55.

Chung HY. 1999. Volatile components in fermented soybean (glycine max) curds. J Agric Food Chem 47:2690-2696.

Cifone MA. 1988a. Mutagenicity tests of *p*-cresol and *m*-cresol in a mouse lymphoma mutation assay. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0517693.

Cifone MA. 1988b. Mutagenicity tests on meta-cresol in a rat primary hepatocyte unscheduled DNA synthesis assay. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0517692.

Cote MA, Lyonnais J, Leblond PF. 1984. Acute Heinz-body anemia due to severe cresol poisoning: Successful treatment with erythrocytapheresis. Can Med Assoc J 130(10):1319-1322.

Daugherty JP, Franks H. 1986. Effect of monocyclic derivatives on DNA repair in human lymphocytes. Res Commun Chem Pathol Pharmacol 54(1):133-136.

Deichmann WB, Witherup S. 1944. Phenolic studies VI: The acute and comparative toxicity of phenol and *o*-, *m*-, and *p*-cresols for experimental animals. J Pharmacol Exp Ther 80:233-240.

DeRosa E, Bartolucci GB, Sigon M, et al. 1987. Hippuric acid and ortho-cresol as biological indicators of occupational exposure to toluene. Am J Ind Med 11(5):529-537.

De Smet R, David F, Sandra P, et al. 1998. A sensitive HPLC method for the quantification of free and total *p*-cresol in patients with chronic renal failure. Clin Chim Acta 278(1):1-21.

De Smet R, Van Kaer J, Van Vlem B, et al. 2003. Toxicity of free *p*-cresol: A prospective and cross-sectional analysis. Clin Chem 49(3):470-478.

Dobbins DC, Pfaender FK. 1988. Methodology for assessing respiration and cellular incorporation of radiolabeled substrates by soil microbial communities. Microb Ecol 15:257-273.

DOE. 1985. Detection of organic acids in atmosphere precipitation. Granville, OH: U.S. Department of Energy. DE8005294.

Douglas GR, Nestmann ER, Betts JL, et al. 1980. Mutagenic activity in pulp mill effluents. Water Chlorin Environ Impact Health Eff 3:865-880.

EI Dupont Denemours. 1969. Toxicity data sheets for *o*-, *p*-, and *m*-cresol. EI Dupont Denemours & Co., Inc. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS205862.

Ellenhorn MJ, Schonwald S, Ordog G, et al. 1997. Cresols. Ellenhorn's medical toxicology: Diagnosis and treatment of human poisoning. 2nd ed. Baltimore, MD: Williams and Wilkins, 1210-1211.

EPA. 1979. Treatability and assessment of coal conversion wastewaters: Phase I. Research Triangle Park, NC: U.S. Environmental Protection Agency. EPA600779248.

EPA. 1981. Development of test for determining anaerobic biodegradation potential. Washington, DC: U.S. Environmental Protection Agency. EPA560581013.

EPA. 1988a. Subchronic toxicity of meta-cresol in Sprague Dawley rats. Washington, DC: U.S. Environmental Protection Agency. PB88195292.

EPA. 1988b. Subchronic toxicity of ortho-cresol in Sprague Dawley rats. Washington, DC: U.S. Environmental Protection Agency. PB88197496.

EPA. 1988c. Subchronic toxicity of para-cresol in Sprague Dawley rats. Washington, DC: U.S. Environmental Protection Agency. PB88195292.

EPA. 1988d. National ambient volatile organic compound (VOCs) data base update. Washington, DC: U.S. Environmental Protection Agency. EPA600388010a.

EPA. 1998. Method 8270D: Semivolatile organic compounds by GC/MS. In: Draft update IVA of SW-846 on-line. U.S. Environmental Protection Agency. http://www.epa.gov/epaoswer/hazwaste/test/pdfs/8270d.pdf. December 7, 2006.

EPA. 2000a. Method 528: Determination of phenols in drinking water by solid phase extraction and capillary column gas chromatography/mass spectrometry (GC/MS). In: Methods for the determination of organic and inorganic compounds in drinking water, volume 1. Washington, DC: U.S. Environmental Protection Agency. EPA815R00014.

EPA. 2000b. National air pollutant emission trends, 1900-1998. Research Triangle Park, NC: U.S. Environmental Protection Agency, Office of Air Quality Planning and Standards. EPA454R00002.

EPA. 2001. Method 1625: Semivolatile organic compounds by isotope dilution GCMS. U.S. Environmental Protection Agency. Code of Federal Regulations. 40 CFR Part 136, Appendix A. http://web1.er.usgs.gov/nemi/method_pdf/4686.pdf. May 23, 2006.

EPA. 2005a. Analytical method for the analysis of semivolatile organic compounds. Multi-media, multi-concentration organics analysis, SOM01.1. U.S. Environmental Protection Agency, Superfund Analytical Services, Contract Laboratory Program. http://www.epa.gov/superfund/programs/clp/download/som/som11d-svoa.pdf. April 12, 2006.

EPA. 2005b. Guidelines for carcinogen risk assessment. Washington, DC: U.S. Environmental Protection Agency. EPA630P03001F.

Fedorak PM, Hrudey SE. 1984. The effects of phenol and some alkyl phenolics on batch anaerobic methanogenesis. Water Res 18:361-367.

Fiege H, Bayer AG. 1987. Cresols and xylenols. In: Ullman's encyclopedia of industrial chemistry. Leverkusen: Federal Republic of Germany, 25-29.

Freitag D, Ballhorn L, Geyer H, et al. 1985. Environmental hazard profile of organic chemicals: An experimental method for the assessment of the behaviour of organic chemicals in the ecosphere by means of simple laboratory tests with 14C labelled chemicals. Chemosphere 14(10):1589-1616.

Florin I, Rutberg L, Curvall M, et al. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicol 15(3):219-232.

Fuke C, Sakai Y, Yagita K, et al. 1998. The quantitative analysis of cresols in a case of cresol poisoning following percutaneous absorption. Chudoku Kenkyu 11(1):55-60.

Gaffney JS, Streit GE, Spall WD, et al. 1987. Beyond acid rain: Do soluble oxidants toxins interact with SO_2 and NO_x to increase ecosystem effects? Environ Sci Technol 21(6):519-523.

Goodley PC, Gordon M. 1976. Characterization of industrial organic compounds in water. Trans Ky Acad Sci 37:11-15.

Green MA. 1975. A household remedy misused - fatal cresol poisoning following cutaneous absorption (a case report). Med Sci Law 15:65-66.

Hansch C, Leo AJ. 1985. Medchem Project. Claremont, CA: Pomona College, Issue 26.

Hashimoto T, Iida H, Dohi S. 1998. Marked increases of aminotransferase levels after cresol ingestion. Am J Emerg Med 16(7):667-668.

Haworth S, Lawlor T, Mortelmans K, et al. 1983. *Salmonella* mutagenicity test results for 250 chemicals. Environ Mutagen Suppl 1:3-142.

Hawthorne SB, Krieger MS, Miller DJ, et al. 1989. Collection and quantitation of methoxylated phenol tracers for atmospheric pollution from residential wood stoves. Environ Sci Technol 23(4):470-475.

Hawthorne SB, Miller DJ, Barkley RM, et al. 1988. Identification of methoxylated phenols as candidate tracers for atmospheric wood smoke pollution. Environ Sci Technol 22(10):1191-1196.

Hayakawa M. 2002. Severe hepatic dysfunction following cresol poisoning. Intensive Care Med 28(8):1190-1191.

HazDat. 2006. Cresols. HazDat Database: ATSDR's Hazardous Substance Release and Health Effects Database. Atlanta, GA: Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/hazdat.html. July 5, 2006.

Herwick RP, Treweek DN. 1933. Burns from anesthesia mask sterilized in compound solution of cresol. J Am Med Assoc 100:407-408.

Heukelekian H, Rand MC. 1955. Biochemical oxygen demand of pure organic compounds. J Water Pollut Contr Assoc 29:1040-1053.

Hine J, Mookerjee PK. 1975. The intrinsic hydrophilic character of organic compounds. Correlations in terms of structural contributions. J Org Chem 40:292-298.

Hiser MF, Kropscott BE, McGuirk RJ, et al. 1994. Pharmacokinetics metabolism and distribution of 14C-Phenol in Fischer 344 rats after gavage, drinking water and inhalation exposure. Dow Chemical Company. Submitted to U.S. Environmental Protection Agency under TSCA Section 8D. Study ID: K-002727-022. OTS0557473.

Hites RA. 1979. Sources and fates of industrial organic chemicals; a case study. Proceedings of the 8th National Conference on Municipal Sludge Management 8:107-119.

Hornshaw TC, Aulerich RJ, Ringer RK. 1986. Toxicity of *o*-cresol to mink and European ferrets. Environ Toxicol Chem 5(8):713-720.

Horowitz A, Shelton DR, Cornell CP, et al. 1982. Anaerobic degradation of aromatic compounds in sediments and digested sludge. Dev Ind Microbiol 23:435-444.

HSDB. 2006. Cresols. Hazardous Substances Data Bank. National Library of Medicine. http://toxnet.nlm.nih.gov. March 5, 2006.

IRIS. 2006. Cresol. Washington, DC: Integrated Risk Information System. U.S. Environmental Protection Agency. http://www.epa.gov/iris/subst/. March 8, 2006.

Isaacs R. 1922. Phenol and cresol poisoning. Ohio State Med J 18:558-561.

Ivett JL. 1989a. Dominant lethal assay in mice: Ortho cresol CRE-9.1-DL-HLA. Final report. Chemical Manufacturers Association. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0529223.

Ivett JL. 1989b. Dominant lethal assay in mice: Para cresol CRE945. Final report. Chemical Manufacturers Association. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0529223.

Ivett JL. 1989c. Mutagencity test on meta-cresol in the mouse bone marrow cytogenetic assay (final report) with attachments and cover letter dated 020289. Chemical Manufacturers Association. Submitted to U.S. Environmental Protection Agency under TSCA Section 4. OTS529219.

James RH, Adams RE, Finkel JM, et al. 1984. Evaluation of analytical methods for the determination of POHC in combustion products. In: Johnson LD, eds. Proceedings: 77th APCA annual meeting; June 24-29, 1984, San Francisco, CA. Pittsburgh, PA: Air Pollution Control Association. Paper 84-18.5, 1-25.

Jouglard J, Aquaron R, Gatua-Pelanchon J, et al. 1971. [Acute poisoning with a household antiseptic: "Cresyl".] Mars Med 108:425-431. (French)

Junk GA, Ford CS. 1980. A review of organic emissions from selected combustion processes. Chemosphere 9:187-230.

Kamijo Y, Soma K, Kokuto M, et al. 2003. Hepatocellular injury with hyperaminotransferasemia after cresol ingestion. Arch Pathol Lab Med 127(3):364-366.

Kawamura K, Kaplan IR. 1986. Compositional change of organic matter in rainwater during precipitation events. Atmos Environ 20(3):527-536. (Retrieval in Progress)

Klinger ME, Norton JF. 1945. Toxicity of cresylic acid-containing solvent. US Nav Med Bull 44(2):438-439.

Koizumi M, Noda A, Furukawa M, et al. 2003. Higher susceptibility of newborn than young rats to 3-methylphenol. J Toxicol Sci 28(2):59-70.

Krotoszynski BK, O'Neill HJ. 1982. Involuntary bioaccumulation of environmental pollutants in nonsmoking heterogeneous human population. J Environ Sci Health Part A Environ Sci Eng 17(6):855-883.

Kubo T, Urano K, Utsumi H. 2002. Mutagenicity characteristics of 255 environmental chemicals. J. Health Sci 48(6):545-554.

Kurlyandskiy BA, Partsef DP, Chernomorskiy AR. 1975. [A procedure for determining the mean daily maximum permissible concentration of tricresol in atmospheric air.] Gig Sanit 5:85-87. (Russian)

Kuwata K, Tanaka S. 1988. Liquid chromatographic determination of traces of phenols in air. J Chromatogr 442:407-411.

Labram C, Gervais P. 1968. [A case of massive cresol poisoning.] Sem Hop Paris 44:3029-3031. (French)

Lewis RJ, ed. 2001. Cresols. Hawley's condensed chemical dictionary, 14th ed. New York: John Wiley & Sons, 306-307.

Li Y, Qu M, Sun L, et al. 2005. Genotoxicity study of phenol and *o*-cresol using the micronucleus test and the comet assay. Toxicol Environ Chem 87(3):365-372.

Lide DR. 2005. Cresols. CRC handbook of chemistry and physics. 86th ed. Boca, FL: CRC Press. Taylor and Francis Group, 3-122.

Liu YY, Lu CC, Perng RP. 1999. Acute respiratory distress syndrome following cutaneous exposure to Lysol: A case report. Zhonghua Yi Xue Za Zhi 62(12):901-906.

Ludzack FJ, Ettinger MB. 1960. Chemical structures resistant to aerobic biochemical stabilization. J Water Pollut Control Fed 32:1173-2000.

Lund FA, Rodriguez DS. 1984. Acclimation of activated sludge to mono-substituted derivatives of phenol and benzoic acids. J Gen Appl Microbiol 30:53-61.

Malaney GW. 1960. Oxidative abilities of aniline-acclimated activated sludge. J Water Pollut Control Fed 32:1300-1311.

Malaney GW, McKinney RE. 1966. Oxidative abilities of benzene-acclimated activated sludge. Water Sewage Works 113:302-309.

McCreary JJ, Jackson JG, Zoltek J. 1983. Toxic chemicals in an abandoned phenolic waste site. Chemosphere 12:1619-1632.

McKinney RE, Tomlinson HD, Wilcox RL. 1956. Metabolism of aromatic compounds by activated sludge. Sew Indust Wastes 28:547-557.

Medvedev VA, Davidov VD. 1981a. The influence of isomers on the transformation rate of phenols in Chernozem soil. In: Overcash MR, ed. Decomposition of toxic and nontoxic organic compounds in soil. Ann Arbor, MI: Ann Arbor Sci Publ., 175-181.

Medvedev VA, Davidov VD. 1981b. The transformation of various coke industry products in Chernozem soil. In: Overcash MR, ed. Decomposition of toxic and nontoxic organic compounds in soil. Ann Arbor, MI: Ann Arbor Sci Publ., 245-254.

Minami M, Katsumata M, Tomoda A. 1990. Methemoglobinemia with oxidized hemoglobins and modified hemoglobins found in blood of workers handling aromatic compounds and those in a man who drank creosol solution. Biomed Biochim Acta 49(2-3):S327-S333.

Monma-Ohtaki J, Maeno Y, Nagao M, et al. 2002. An autopsy case of poisoning by massive absorption of cresol a short time before death. Forensic Sci Int 126(1):77-81.

Morinaga Y, Fuke C, Arao T, et al. 2004. Quantitative analysis of cresol and its metabolites in biological materials and distribution in rats after oral administration. Leg Med 6(1):32-40.

Murli H. 1988. Mutagenicity tests on *o*-, *m*-, and *p*-cresol in an *in vitro* cytogenetic assay measuring chromosomal aberration frequencies in CHO cells. Chemical Manufacturers Association. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0517691.

Namkoong W, Loehr RC, Malina JF Jr. 1988. Kinetics of phenolic compounds removal in soil. Hazard Waste Hazard Mater 5(4):321-328.

Needham LL, Head SL, Cline RE. 1984. Determination of phenols and cresols in urine by gas chromatography. Anal Lett 17(B14):1555-1565.

Neeper-Bradley TL, Tyl RW. 1989a. Two-generation reproduction study of *p*-cresol (CAS No. 106-44-5) administered by gavage to Sprague-Dawley (CD®) rats. Project report 52-512. Union Carbide Corporation. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0529224.

Neeper-Bradley TL, Tyl RW. 1989b. Two-generation reproduction study of *m*-cresol (CAS No. 108-39-4) administered by gavage to Sprague-Dawley (CD®) rats. Project report 51-634. Union Carbide Corporation. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0529224.

Nieminen E, Heikkila P. 1986. Simultaneous determination of phenol, cresols and xylenols in workplace air, using a polystyrene-divinylbenzene column and electrochemical detection. J Chromatogr 360(1):271-278.

NIOSH. 1994a. Method 2546. Cresol (all isomers) and phenol. In: NIOSH manual of analytical methods. 4th ed. National Institute for Occupational Safety and Health. http://www.cdc.gov/niosh/nmam/. March 8, 2006.

NIOSH. 1994b. Method 8305: Phenol and p-cresol in urine. NIOSH manual of analytical methods (NMAM) 4th ed. National Institute of Occupational Safety and Health. http://www.cdc.gov/niosh/nmam/pdfs/8305.pdf. May 25, 2006.

Nishihara T, Nishikawa J, Kanayama T, et al. 2000. Estrogenic activities of 517 chemicals by yeast two-hybrid assay. J Health Sci 46(4):282-298.

Novotny M, Merli F, Wiesler D, et al. 1982. Fractionation and capillary gas chromatographic-mass spectrometric characterization of the neutral components in marijuana and tobacco smoke condensates. J Chromatogr 238(1):141-150.

NTP. 1992a. Final report on the reproductive toxicity of ortho-cresol (OCRE) in CD-1 Swiss mice II. Research Triangle Park, NC: National Toxicology Program. PB92176890.

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

NTP. 1992c. Final report on the reproductive toxicity of meta-/para-cresol (MPCREE) (CAS No. 1319-77-3) in Swiss mice. Research Triangle Park, NC: National Toxicology Program. PB92191741.

NTP. 2008. Toxicology and carcinogenesis studies of cresols (CAS No. 1319-77-3) in male F344/N rats and female B6C3F1 mice (feed studies). Research Triangle Park, NC: National Toxicology Program. TR-550. Draft technical report.

Oglesby LA, Ebron-McCoy MT, Logsdon TR, et al. 1992. In vitro embryotoxicity of a series of para-substituted phenols: Structure, activity, and correlation with in vivo data. Teratology 45:11-33.

Pauli O, Franke G. 1972. Behaviour and degradation of technical preservatives in the biological purification of sewage. In: Walters AH, Hueck-Van Der Plas EH, eds. Biodeterioration of materials. New York, NY: Halsted Press Division, Wiley, 52-60.

Pegg SP, Campbell DC. 1985. Children's burns due to cresol. Burns Incl Therm Inj 11(4):294-296.

Pepper, Hamilton, & Scheetz. 1980. Sister chromatid exchange assay, Ames assay, mouse lymphoma foward mutation assay, and transformation assay for *o*-, *m*-, and *p*-cresol with cover letter dated 071180. Pepper, Hamilton, & Scheetz, Attorneys at Law. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0517528.

Pepper, Hamilton, & Scheetz. 1981. Sister chromatid exchange assay, Ames assay, mouse lymphoma foward mutation assay, cell transformation on *o*-cresol. Pepper, Hamilton, & Scheetz, Attorneys at Law. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0517531.

Pitter P. 1976. Determination of biological degradability of organic substances. Water Res 10:231-235.

Pool BL, Lin PZ. 1982. Mutagenicity testing in the *Salmonella typhimurium* assay of phenolic compounds and phenolic fractions obtained from smokehouse smoke condensates. Food Chem Toxicol 20(4):383-391.

Riddick JA, Bunger WB, Sakano TK. 1986. Organic solvents. New York, NY: John Wiley and Sons, Inc., 224-229.

Sernav RC. 1989a. Mutagenicity test on ortho-cresol (lot number RC645A) *Drosophila melanogaster* sex-linked recessive lethal test. Chemical Manufacturers Association. Submitted to U.S. Environmental Protection Agency under TSCA Section 4. OTS0529221.

Sernav RC. 1989b. Mutagenicity test on para-cresol lot number 1206 *Drosophila melanogaster* sex-linked recessive lethal test. Chemical Manufacturers Association. Submitted to U.S. Environmental Protection Agency under TSCA Section 4. OTS0529221.

Shelley WB. 1974. *p*-Cresol: Cause of ink-induced hair depigmentation in mice. Br J Dermatol 90:169-174.

Southworth GR, Keller JL. 1986. Hydrophobic sorption of polar organics by low organic carbon soils. Water Air Soil Pollut 28(3-4):239-248.

Tabak HH, Chambers CW, Kabler PW. 1964. Microbial metabolism of aromatic compounds. I. Decomposition of phenolic compounds and aromatic hydrocarbons by phenol-adapted bacteria. J Bacteriol 87:910-919.

Thomas RG. 1982. Volatilization from water. In: Lyman WJ, Reehl WF, Rosenblatt DH, eds. Handbook of chemical property estimation methods. New York, NY: McGraw-Hill, Inc., 15-1 to 15-15-34.

Thompson DC, Perera K, Fisher R, et al. 1994. Cresol isomers: Comparison of toxic potency in rat liver slices. Toxicol Appl Pharmacol 125(1):51-58.

Thompson DC, Perera K, London R. 1995. Quinone methide formation from *para* isomers of methylphenol (cresol), ethylphenol, and isopropylphenol: Relationship to toxicity. Chem Res Toxicol 8(1):55-60.

Thompson DC, Perera K, London R. 1996. Studies on the mechanism of hepatotoxicity of 4-methylphenol (p-cresol): Effects of deuterium labeling and ring substitution. Chem Biol Interact 101(1):1-11.

TRI05. 2007. TRI explorer: Providing access to EPA's toxics release inventory data. Washington, DC: Office of Information Analysis and Access. Office of Environmental Information. U.S. Environmental Protection Agency. Toxics Release Inventory. http://www.epa.gov/triexplorer/. December 26, 2007.

TRL. 1986. Subchronic neurotoxicity study in rats of ortho-, meta-, and para-cresol. Unpublished data submitted by Toxicity Research Laboratories to EPA.

Tyl RW. 1988a. Developmental toxicity evaluation of *o*-, *m*-, or *p*-cresol administered by gavage to Sprague Dawley (CD) rats. Chemical Manufacturers Association. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0517695.

Tyl RW. 1988b. Developmental toxicity evaluation of *o*-, *m*-, or *p*-cresol administered by gavage to New Zealand white rabbits. Chemical Manufacturers Association. Submitted to the U.S. Environmental Protection Agency under TSCA Section 4. OTS0517695.

Tyl RW, Neeper-Bradley TL. 1989. Two-generation reproduction study of *o*-cresol (CAS No. 95-48-7) administered by gavage to Sprague-Dawley (CD®) rats. Project report 51-614. Chemical Manufacturers Association. Submitted to The U.S. Environmental Protection Agency under TSCA Section 4. OTS0529224.

Uzhdavini ER, Astaf'yeva IK, Mamayeva AA, et al. 1972. [Inhalation toxicity of *o*-cresol.] Tr Uzb Nauchno Issled Inst Sanit Gig Profzabol 7:115-119. (Russian)

Vecera Z, Janak J. 1987. Continuous aerodispersive enrichment unit for trace determination of pollutants in air. Anal Chem 59 (11):1494-1498.

Vernot EH, MacEwen JD, Haun CC, et al. 1977. Acute toxicity and skin corrosion data from some organic and inorganic compounds and aqueous solutions. Toxicol Appl Pharm 42:417-423.

Wang YT, Suidan MT, Pfeffer JT, et al. 1988. Effects of some alkyl phenols on methanogenic degradation of phenol. Appl Environ Microbiol 54(5):1277-1279.

Wang YT, Suidan MT, Pfeffer JT, et al. 1989. The effect of concentration of phenols on their batch methanogenesis. Biotechnol Bioeng 33(10):1353-1357.

Weber AS, Matsumoto MR. 1987. Feasibility of intermittent biological treatment for hazardous wastes. Environmental Progress 6(3):166-171.

Williams RT. 1938. CXVIII. Studies in detoxication. I. The influence of (a) dose and (b) *o*-, *m*- and *p*-substitution on the sulfate detoxication of phenol in the rabbit. Biochem J 32:878-887.

Windholz M, Budavari S, Blumetti RF, et al., eds. 1983. The Merck index. Rahway, NJ: Merck and Co., Inc., 2568.

Wu ML, Tsai WJ, Yang CC, et al. 1998. Concentrated cresol intoxication. Vet Hum Toxicol 40(6):341-343.

Wynder EL, Hoffman D. 1967. Tobacco and tobacco smoke studies in experimental carcinogenesis. New York, NY: Academic Press, 387.

Yalkowsky SH, Valvani SC, Kuu W. 1987. Arizona database of aqueous solutions. http://www.pharmacy.arizona.edu/outreach/aquasol/index.html. August 15, 2006.

Yan Z, Zhong HM, Maher N, et al. 2005. Bioactivation of 4-methylphenol (*p*-cresol) via cytochrome P450-mediated aromatic oxidation in human liver microsomes. Drug Metab Dispos 33(12):1867-1876.

Yashiki M, Kojima T, Miyazaki T, et al. 1990. Gas chromatographic determination of cresols in the biological fluids of a non-fatal case of cresol intoxication. Forensic Sci Int 47:21-29.

Yoshikawa M, Taguchi Y, Arashidani K, et al., 1986. Determination of cresols in urine by high-performance liquid chromatography. J Chromatogr 362(3):425-429.

Young RHF, Ryckman DW, Buzzell JC Jr. 1968. An improved tool for measuring biodegradability. J Water Pollut Contr Fed 8:354-368.

Table 1. Exposure Data Needs

Exposure	Level I	Level II	Level III
Analytical	Methods for parent compound in REM*	Methods for degradation products in REM*	
	Methods for parent compound in blood or urine	Methods for parent compound/ metabolites/ biomarkers	
	Structure-activity relationships (SAR)		
Physical chemical properties	Water solubility		
	Volatility/vapor pressure		
	K_{ow}		
	Henry's law		Registries of exposed persons
Exposure levels	Production volume, Use, Release/ disposal (may be used in lieu of monitoring data)	Monitoring in REM*	Human dosimetry studies
		Monitoring for human exposure (personal sampling, biomarkers of exposure, tissue levels)	Epidemiology
			Disease registries
		Exposures of children	
Environmental fate	Aerobic/anaerobic Biodegradation in H_2O Oxidation Hydrolysis Aerosolization Photoreactivity Volatilization Soil adsorption/desorption	Small field plot studies	
		Monitoring for products in REM*	
Bioavailability		Food chain bioaccumulation	
		Availability from REM* (analytical or toxicity) emphasize *in vivo*	

*REM = Relevant Environmental Media

Table 2. Toxicity Data Needs

Toxicity	Level I	Level II	Level III
Single dose exposure	Single dose disposition Skin/eye irritation Acute toxicity		
Repeated dose exposure	14-day by relevant route 90-day subchronic	Comparative toxicokinetics*	
Chronic exposure	Structure-activity relationships (SAR)	1-Year chronic 2-Year bioassay	Epidemiology*
Genotoxicity*	Ames Micronucleus	Additional genotoxicity studies*	Mechanism of toxic action*
Endocrine disruption	*In vivo* & *in vitro* screen	2-Generation reproductive study	
Reproductive toxicity	Extended repro workup in subchronic	2-Generation or continuous breeding	Biomarkers* Clinical methods for mitigating toxicity*
Developmental toxicity*	Short term *in vivo* screen*	2-Species developmental*	Children's susceptibility**
Immunotoxicity	Use subchronic results	Immunotox battery	
Neurotoxicity	Neuropath in subchronic	Neurotox battery	
Sensitization	Dermal sensitization		
Carcinogenicity	Use muta & subchronic results	2-Year bioassay	

*Useful data for examining children's susceptibility issues

**Data needed for addressing children's susceptibility issues include genotoxicity (Level II), developmental toxicity (Levels I and II), epidemiology, mechanism of toxic action, biomarkers, and clinical methods for mitigating toxicity (Level III)

Table 3. ATSDR Substance-Specific Applied Research Program for Cresols

	EXPOSURE		
	Level I	Level II	Level III
Analytical			
Physical chemical properties			
Exposure levels		exp levels in env media *EXP LEVELS IN HUMANS* *EXP LEVELS IN CHILDREN*	potential candidate for exposure registry
Environmental fate			
Bioavailability			
	TOXICITY		
	Level I	Level II	Level III
Acute	inhalation, *ORAL*, dermal		
Repeated	inhalation, dermal	toxicokinetics	
Chronic		inhal, oral, dermal	epidem
Genotoxicity		*in vivo* genotoxicity studies	biomarkers mechanisms
Endocrine disruption	endocrine histopath inhalation, dermal		
Reproductive toxicity		inhalation, dermal	mitigation
Developmental toxicity		inhalation, dermal	
Children's susceptibility			inhalation, oral, dermal
Immunotoxicity	inhalation, oral, dermal		
Neurotoxicity	inhalation, dermal		
Carcinogenicity		inhalation, oral, dermal	

UPPER CASE: Priority Data Needs identified for cresols