DRAFT OF
PRIORITY DATA NEEDS FOR PHENOL

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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.

We plan to revise these documents in response to public comments and as additional data becomes available. Therefore, we encourage comments that will make these documents of the greatest use.

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Substance-Specific Applied Research Program

Priority Data Needs for:

Phenol

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

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I. Executive Summary

Phenol is included in the priority list of hazardous substances identified by ATSDR and the Environmental Protection Agency (EPA) (ATSDR 2005). 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 Phenol (Draft for Public Comment) was published by ATSDR in September 2006. Currently, the updated toxicological profile is being finalized.

Phenol is a colorless-to-white solid when pure; however, the commercial product, which contains some water, is a semi-volatile liquid. Phenol has a distinct odor that is sickeningly sweet and tarry. Phenol is very soluble in alcohol, chloroform, ether benzene, acetone, and water. Phenol evaporates more slowly than water with a vapor pressure of 0.35 mm Hg. Commercial phenol does not volatilize rapidly from aqueous solutions with a Henry's law constant of 4.0×10^{-7} atm m^3/mol. Currently, there are 10 manufacturers of phenol in the United States, with a production capacity of approximately 6.9×10^9 pounds. The two major uses of phenol in 2004 were the production of bisphenol-A (48%) and of phenolic resins.

Phenol is released to the air and water as a result of its manufacture, its use in phenolic resins, and organic synthesis. Phenol is found in petroleum products such as coal tar and creosote and, can be released by combustion of wood and auto exhaust. Phenol is also produced by the natural degradation of organic wastes including benzene. Phenol is a major metabolite of benzene, which is found extensively in the environment; therefore, phenol may be formed in the environment as a result of the natural degradation of benzene. Phenol is degraded rapidly in air by gas-phase

hydroxyl radical reaction (estimated half-life 14.6 hours), but may persist in water for a somewhat longer period. Half-lives for biodegradation range from <1 day in samples of lake water to 9 days in estuarine water. In soil, phenol will generally biodegrade rapidly. If biodegradation is sufficiently slow, phenol in sunlit water will undergo photooxidation with photochemically produced peroxyl radicals, and phenol in soil will leach to groundwater.

The mobility of phenol in soil is considered high based on K_{oc} levels of approximately 16–100, indicating that leaching into groundwater is possible. However, the rate of phenol biodegradation in the soil may be so rapid, except in cases of large releases such as spills or continuous releases such as leaching from landfill sites, that the probability of groundwater contamination may be low.

Monitoring data indicate that the most likely route of exposure to the general population is via ingestion or dermal contact with consumer or medicinal products containing phenol. Other routes of exposure include inhalation of ambient air and ingestion of food and drinking water. For populations residing near hazardous waste sites, the most likely route of exposure is expected to be through ingestion of contaminated drinking water.

Phenol, particularly in high concentrations, is an irritating and corrosive substance, making the skin and mucosal membranes targets of toxicity in humans and animals. Acute exposure to relatively high amounts of phenol has also caused electrocardiographic alterations and adverse neurological effects characterized by tremors. No clear target for toxicity has been identified in studies of populations exposed to phenol for prolonged periods of time; however, the number of studies available is small and they all suffer from limitations. Long-term oral studies in animals administered phenol in the drinking water found essentially no toxicity. A 2-year oral bioassay found no evidence of carcinogenicity of phenol in mice and female rats, but the results in male rats were inconclusive. Phenol induced adverse developmental effects in animals in oral gavage studies, generally at dose levels that also affected the mother. The available data do not suggest that phenol has endocrine disruptor properties. It is not known if children are more susceptible to the toxicity of phenol 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
- Exposure levels of children

Toxicity

- Two-year oral carcinogenicity bioassay

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 phenol 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 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 phenol occurred when the data needs for phenol were determined in the ATSDR Toxicological Profile for Phenol. Considered a subset of all information gaps on phenol, 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 phenol were addressed before the toxicological profile was finalized. In preparing the priority data needs document, a literature search was conducted to provide updated information on phenol.

The purpose of this paper is to take the data needs identified in the Toxicological Profile for Phenol and subject them to further scientific evaluation. This will lead to priorities and ultimately to ATSDR's substance-specific research agenda. To effect 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 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*:** Phenol is included in the priority list of hazardous substances identified by ATSDR and EPA (ATSDR 2005).

Phenol has been detected in at least 595 of 1,678 National Priorities List (NPL) hazardous waste sites in the United States (HazDat 2006). Exposure to phenol 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 phenol via inhalation, ingestion, and skin contact.

The following is a brief summary of the potential for human exposure to phenol. For a more detailed discussion of available information, refer to the ATSDR Toxicological Profile for phenol, Chapter 6, on Potential for Human Exposure (ATSDR 2006).

Phenol is a colorless-to-white solid when pure; however, the commercial product, which contains some water, is a semi-volatile liquid. Phenol has a distinct odor that is sickeningly sweet and tarry. It is very soluble in most organic solvents and in water. Phenol is largely used in the production of phenolic resins and in the organic synthesis of other chemicals. Phenol is found in petroleum products such as coal tar and creosote, and can be released by combustion of wood and auto exhaust. Phenol is also produced by the natural degradation of organic wastes including benzene. Phenol is a major metabolite of benzene, which is found extensively in the environment; therefore, phenol may be formed in the environment as a result of the natural degradation of benzene. Phenol is also used in several consumer products, including mouthwashes, gargles, and throat sprays with concentrations ranging from 0.5 to 1.4%.

Phenol is an important substance for research because of its widespread environmental contamination. Phenol has been found in at least 595 of the 1,678 current or former NPL sites (HazDat 2006). According to the Toxics Release Inventory (TRI), 689 facilities manufactured or processed phenol in 2004 (TRI04 2006). It was estimated that 4.9 million pounds of phenol, amounting to 62% of the total environmental release, was discharged to air from manufacturing and processing facilities in the United States in 2004 (TRI04 2006). Estimated releases of 85,700 pounds of phenol to surface water from 689 domestic manufacturing and processing facilities in 2004 accounted for about 0.1% of the estimated total environmental releases from facilities required to report to the TRI (TRI04 2006). Estimated releases of 1.2 million pounds of phenol to soils from 689 domestic manufacturing and processing facilities in 2004 accounted for about 16% of the estimated total environmental releases from facilities required to report to the TRI (TRI04 2006). An additional 1.3 million pounds, constituting about 17% of the total environmental emissions, were released via underground injection (TRI04 2006).

Phenol has been found in at least 595 of the 1,678 current or former NPL sites (HazDat 2006). Maximum concentrations in soil, sludge, and sediment were 276,000, 26,000, and 1,700 µg/kg, respectively (HazDat 2006). In air, a maximum concentration of 11 µg/m3 was reported (HazDat 2006). Fish, groundwater, and leachate had maximum concentrations of 15.9 ppm, 28,800 µg/L, and 38,400µg/L, respectively (HazDat 2006).

Phenol may partition to air, water, and soil depending upon its release medium. In air, phenol degrades rapidly via reaction with photochemically produced hydroxyl radicals. The half-life for this reaction in the atmosphere is estimated as approximately 14 hours (EPA 1979a). The reaction of phenol with nitrate radicals during the night may constitute a significant removal process. This is based on a rate constant of 3.8×10^{-12} cm^3/molecule second for this reaction, corresponding to a half-life of 15 minutes at an atmospheric concentration of 2×10^8 nitrate radicals per cm^3 (Atkinson et al. 1987). The reaction of phenol with nitrate radicals present in the atmosphere during smog episodes may decrease the half-life of phenol in polluted atmospheres. The above data indicate that phenol has a short half-life in the atmosphere, probably <1 day.

Using the Henry's law constant of 4×10^{-7} atm m^3/mol (Lide 1993), a volatilization half-life of 88 days was calculated for phenol evaporation from a model river 1 m deep with a current of 1 m/second and a wind velocity of 3 m/second (Lyman et al. 1982). Although phenol does not absorb light at wavelengths >290, phenols react rapidly to sunlit natural water via an indirect

reaction with photochemically produced hydroxyl radicals and peroxyl radicals; typical half-lives for hydroxyl and peroxyl radical reactions are on the order of 100 and 19.2 hours of sunlight, respectively (Canonica et al. 1995; Mill and Mabey 1985). These reactions require dissolved natural organic materials that function as photosensitizers (Canonica et al. 1995). Phenol is readily biodegradable in natural water, provided the concentration is not high enough to cause significant inhibition through microbial toxicity. Complete degradation in <1 day has been reported in water from three lakes; the rates of degradation were affected by the concentration of organic and inorganic nutrients in the water (Rubin and Alexander 1983). Complete removal of phenol in river water has been reported after 2 days at 20 °C and after 4 days at 4 °C (Ludzack and Ettinger 1960). The degradation of phenol is somewhat slower in salt water, and a half-life of 9 days has been reported in an estuarine river (EPA 1979b). Available data indicate that phenol biodegrades in soil under both aerobic and anaerobic soil conditions. The half-life of phenol in soil is generally <5 days (Baker and Mayfield 1980), but acidic soils and some surface soils may have half-lives of up to 23 days (Shiu et al. 1994).

The general population is exposed to phenol through the use of consumer products containing this compound. Phenol is readily adsorbed though the skin; therefore, dermal contact is likely to be a source of exposure. Phenol is present in a number of consumer products that are swallowed, rubbed on, or applied to various parts of the body. These include throat lozenges, mouthwashes, gargles, and antiseptic lotions. Commercial antiseptic lotions may contain up to 1.4% phenol (Darisimall 2006). Package labeling information indicates that commercial throat lozenges contain up to 29 mg of phenol per lozenge (Darisimall 2006). Other consumer products such as disinfectants and cleaners may contain concentrations of phenol ranging from 0.45 to 26% (CA EPA 1998; Forum for Scientific Excellence, Inc. 1990). It has been found that the smoke of one nonfiltered cigarette contains 60–140 µg of phenol; 19–35 µg was found in a filter-tipped cigarette and 24–107 µg phenol was found in cigars (IARC 1986; NCI 1998).

Work place exposure is likely to occur via inhalation and dermal contact with phenol. People living near factories producing or using phenol as well as those living near areas of heavy traffic are likely to be exposed to increased levels of phenol. People who are exposed to large amounts of benzene are also likely to be exposed to large amounts of phenol, a metabolite of benzene. Elevated levels of phenol have been detected in workers occupationally exposed to benzene.

Populations residing near hazardous waste sites may also be exposed to phenol through the ingestion of contaminated drinking water using contaminated surface water or groundwater as a source. Its presence in groundwater is probably the result of release to soil, often industrial releases or leachate from waste dumps, and the subsequent leaching of phenol through the soil to the groundwater. Phenol was detected at a maximum concentration of 1.9 ppm in leachates from landfill sites in Illinois (Clark and Piskin 1977). Near a landfill in central Florida, phenol was found in groundwater and surface water at about 17 and 15 ppb, respectively (Chen and Zoltek 1995). Phenol was detected, but not quantified, in the groundwater at 13.6% of 178 CERCLA hazardous waste sites (Plumb 1987).

3. Toxicity

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

The following is a brief summary of the toxicology of phenol. Refer to the ATSDR Toxicological Profile for phenol chapter on "Health Effects" for a more detailed discussion of available information (ATSDR 2006).

Phenol is an irritating and corrosive substance, making the skin and mucosal membranes targets of toxicity, but other effects have also been reported. Fatalities due to ingestion or contact with a significant area of the skin have been reported (Boatto et al. 2004; Cronin and Brauer 1949; Griffiths 1973; Lewin and Cleary 1982; Soares and Tift 1982; Stajduhar-Caric 1968; Tanaka et al. 1998). Postmortem examination typically showed serious mucosal alterations in the gastrointestinal tract. The cardiovascular and nervous systems also might be considered targets for phenol toxicity. A study of workers found that exposure to phenol was associated with an increased incidence of cardiovascular disease (Wilcosky and Tyroler 1983). Following acute oral and dermal exposure to phenol, electrocardiographic alterations in humans (Gross 1984; Horch et al. 1994; Langford et al. 1998; Truppman and Ellenby 1979; Warner and Harper 1985), as well as vomiting and lethargy (Spiller et al. 1993), have been reported. Studies of populations whose drinking water was contaminated with phenol found increased incidences of nausea and diarrhea,

but exposure to chlorophenols may have also occurred (Baker et al. 1978; Jarvis et al. 1985; Kim et al. 1994). Liver effects were reported in a case of prolonged inhalation exposure to phenol (Merliss 1972) and in workers in an oil-refining plant (Shamy et al. 1994), but exposure to other solvents could not be ruled out in the latter case.

There is only one recent study of inhalation exposure of animals to phenol (Hoffman et al. 2001). In that study, rats that were exposed nose-only intermittently to concentrations up to 25 ppm for 2 weeks showed no gross or microscopic alterations in major tissues and organs, including the nasal cavity, but some rats showed an increased incidence in a red nasal discharge possibly due to the irritating properties of phenol. Other earlier studies in animals showed that exposure to phenol in the air can cause pneumonia and morphological alterations of the myocardium and liver and kidneys (Dalin and Kristoffersson 1974; Deichmann et al. 1944; Flickinger 1976). Although these studies showed that inhaled phenol can affect several organs and tissues, few generalizations can be made due to the different exposure protocols used (i.e., nose-only vs. whole-body; intermittent vs. continuous) and incomplete reporting.

Results from oral studies in animals indicate that phenol administered by oral gavage is much more toxic than when it is administered in the drinking water, a phenomenon that is related to the toxicokinetics of phenol. In general, phenol in oral drinking water studies has exhibited little toxicity. Systemic effects observed in animals following oral exposure include renal tubular necrosis in rats treated with a single gavage dose of 224 mg/kg or with 40 mg/kg/day for 14 days (Berman et al. 1995). However, long-term drinking water studies in rats and mice that received much higher doses of phenol do not suggest that the kidney is a particularly sensitive target for phenol (NCI 1980; Ryan et al. 2001). Phenol also induced decreases in body weight in rats and mice in 13-week and 2-year drinking water studies that were associated with significant reductions in water consumption due probably to poor palability (NCI 1980). Reductions in body weight gain were also observed in pregnant mice (NTP 1983b) and rats (York 1997).

Application of phenol to the skin of animals has caused edema, erythema, necrosis, and death; the cause of death was not provided in the available studies (Conning and Hayes 1970; Deichmann and Witherup 1944). Lethality is influenced by the surface area exposed as well as the concentration of the applied solution. Systemic effects also have been described in animals following dermal exposure to phenol. Rabbits that received a dose of phenol of 24 mg/cm^2/kg suffered cardiac arrhythmia (Wexler et al. 1984).

There is not enough information to determine whether phenol induces immunological effects in humans. A study of office workers exposed for 6 months to a mixture of phenol, formaldehyde, and chlorinated hydrocarbons found alterations in lymphocyte surface markers and natural killer cell activity relative to non-exposed subjects (Baj et al. 1994). However, the specific role of phenol is difficult to ascertain. There are data in animals, but the findings are not conclusive enough to draw definite conclusions. Rats administered phenol by gavage showed necrosis or atrophy of the spleen or thymus (Berman et al. 1995) and mice treated with relative low doses of phenol in water for 28 days showed alterations in some parameters of immunocompetence (Hsieh et al. 1992). However, the findings of Hsieh et al. (1992) were not replicated in a 10-week drinking water study in rats that used much higher doses (Ryan et al. 2001). Rats and mice dosed chronically with relatively high doses of phenol in water showed no alterations in gross or microscopic morphology of lymphoreticular tissues (NCI 1980). Acute oral or dermal exposure to relatively high doses of phenol has induced a wide range of neurological alterations in humans, including death following seizures (Bentur et al. 1998; Kamijo et al. 1999; Lewin and Cleary 1982; Soares and Tift 1982; Spiller et al. 1993). Similar effects have been observed in animals exposed to phenol by inhalation (Dalin and Kristofferson 1974; Flickinger 1976), oral gavage (Moser et al. 1995; NTP 1983b), and dermal contact (Conning and Hayes 1970). However, rats and mice exposed chronically to phenol in the drinking water showed no obvious neurological effects or alterations in gross and microscopic brain morphology (NCI 1980).

There are not enough data to judge whether phenol causes adverse reproductive or developmental effects in humans. Phenol decreased the absolute weight of the seminal vesicles and ovaries of the parental generation in a two-generation reproductive drinking water study, but it did not induce significant alterations in gross or microscopic appearance of the reproductive organs of males and females from the parental and F_1 generations and there were no significant effects on mating performance and fertility, estrus frequency, testicular sperm count, or sperm motility or morphology (Ryan et al. 2001). Chronic exposure of rats and mice to phenol in the drinking water did not significantly alter the gross or microscopic appearance of the reproductive organs (NCI 1980). Phenol has induced developmental effects in rodents; with one exception, this occurred at dose levels that also affect the mothers (NTP 1983a, 1983b; York 1997). There are no data regarding reproductive and developmental effects in animals following inhalation or dermal exposure to phenol. Based on the available information, there is no clear evidence that phenol is an endocrine disruptor in humans or in animals.

A study of phenol-exposed workers reported a small, nonsignificant excess of respiratory cancers (Kauppinen et al. 1986) and a study of phenol production workers reported a small, nonsignificant excess of Hodgkin's disease and of lung, esophageal, rectal, and kidney cancers (Dosemeci et al. 1991). However, the interpretation of these findings is complicated due to lack of dose-response and potential for confounding by simultaneous exposure to other chemicals. Phenol has been tested for carcinogenicity in long-term drinking water bioassays in rats and mice (NCI 1980). Statistically significant increased incidences of pheochromocytomas of the adrenal gland and leukemia or lymphomas were observed in male rats exposed to the low dose of phenol, but not to the high dose of phenol. No significant effects were seen in female rats or in mice. Phenol has consistently been found to be a promoter in initiation-promotion studies in mouse skin (Boutwell and Bosch 1959; Salaman and Glendenning 1957; Wynder and Hoffmann 1961). The International Agency for Research on Cancer (IARC) considers phenol not classifiable as to its carcinogenicity in humans. The Department of Health and Human Services (DHHS) has not classified phenol as to its carcinogenicity. Based on inadequate evidence in humans and animals, EPA (IRIS 2006) assigned phenol to Group D, not classifiable as to human carcinogenicity. Under updated guidelines (EPA 2005), the data regarding carcinogenicity of phenol are: "inadequate for an assessment of human carcinogenic potential" (IRIS 2006).

No studies were located regarding the genotoxicity of phenol in humans following inhalation, oral, or dermal exposure. However, phenol has been tested in a variety of *in vivo* (Chen and Eastmond 1995a; Ciranni et al. 1988; Gocke et al. 1981; Li et al. 2005; Miyagawa et al. 1995; Shelby and Witt 1995; Skare and Schrotel 1984) and *in vitro* (Crebelli et al. 1987; Erexson et al. 1985; Florin et al. 1980; Gocke et al. 1981; Haworth et al. 1983; Jansson et al. 1986; Kubo et al. 2002; Li et al. 2005; Miller et al. 1995; Morimoto et al. 1983; Nagel et al. 1982; Painter and Howard 1982; Pellack-Walker and Blumer 1986; Poirier et al. 1975; Schwartz et al. 1985; Sze et al. 1996; Tsutsui et al. 1997) tests. The results of these tests have been equivocal.

Potentially, individuals with low activities of the enzymes phenol sulfotransferase and glucuronyltransferase may be more susceptible to phenol toxicity. Persons with ulcerative colitis may have an impaired capacity to form a sulfate conjugate (Ramakrishna et al. 1991), which may increase the amount of unchanged phenol that is absorbed following oral exposure. Because phenol is a vesicant, individuals with sensitive skin or pulmonary incapacity may be more sensitive to phenol. Individuals with kidney or liver diseases that impair metabolism or excretion

of phenol and phenol metabolites may be more susceptible to phenol. It is not known whether children are more sensitive to phenol than adults. To the extent that the enzymes involved in the metabolism of phenol are developmentally regulated, the metabolism, and consequently the toxicity of phenol, in immature humans may be different than in adults. Since point-of-contact irritation is the main toxic action of high doses of phenol, children are not likely to be more susceptible to phenol's effects at the tissue level.

III. Identification of Data Needs

In evaluating the exposure and toxicity testing needs for phenol, 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 phenol 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. The analytical methods available (Amlathe et al. 1987; Baldwin et al. 1981; Bieniek and Wilczok 1986; Handson and Hanrahan 1983; Needham et al. 1984; O'Grodnick et al. 1983; Rick et al. 1982; Schaltenbrand and Coburn 1985; Van Roosmalen et al. 1981) are adequate for the quantification of phenol and its conjugates in biological samples. The analytical methods available (Eichelberger et al. 1983; EPA 1982, 1986, 1987; Kuwata et al. 1980; Nieminen and Heikkila 1986; NIOSH 1994; Sithole et al. 1986; Tomkins et al. 1984; Van Rossum and Webb 1978; Yrjanheikki 1978) are adequate for the quantification of phenol in various environmental materials.

***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 phenol 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 phenol to be made. The most important properties such as Henry's law constant (Lide 1993), vapor pressure (HSDB 2006), solubility (Lide 1993), log K_{ow} (HSDB 2006), melting point (Lide 1993), and boiling point (Lide 1993) 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 phenol 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 phenol in contaminated environmental media at hazardous waste sites has been identified.

There are very few monitoring data concerning the presence of phenol in ambient air. Phenol was found at a median concentration of 30 parts per trillion (ppt) in 7 samples from 1 U.S. urban/suburban site in 1974 and at an overall median concentration of 5,000 ppt in 83 samples from 7 source-dominated sites between 1974 and 1978 (EPA 1982). The individual medians of the seven source sites ranged from 520 to 44,000 ppt (EPA 1982). Phenol was detected, but not quantified, in air above the Niagara River in September of 1982 (Hoff and Chan 1987). Phenol concentrations in two urban areas ranged from 13 to 91 ppt and from <5 to 75 ppb with 50% of all measurements <8 ppb (EPA 1981a). Higher phenol concentrations may occur when there is smog or in highly contaminated air. During a smog episode in West Covina, California, in July of 1973, phenol concentrations ranged from 16 to 91 ppt, with a mean concentration of 60 ppt (Cronn et al. 1977).

Phenol has been detected in surface waters, rainwater, sediments, drinking water, groundwater, industrial effluents, and urban runoff, as well as at hazardous waste sites. Background levels of phenol from relatively pristine sites can be as high as 1 ppb for unpolluted groundwater and have been reported to range from 0.01 to 1 ppb in unpolluted rivers (Thurman 1985). Phenol has been detected in Lake Huron water at 3–24 ppb (Konasewich et al. 1978) and industrial rivers in the United States at 0–5 ppb (Sheldon and Hites 1978, 1979). The annual mean concentration of phenol in water from the lower Mississippi River was 1.5 ppb (EPA 1980). River water in an unspecified location in the United States was reported to contain 10–100 ppb of phenol (Jungclaus et al. 1978). Phenol was detected, but not quantified, in a Niagara River watershed (Elder et al. 1981) and in 2 of 110 raw water samples analyzed during the National Organic

Monitoring Survey (EPA 1980). In the STORET database, about 90% of the data points in Illinois waterways in Cook County from 2002 to 2004 were positive for the presence of phenol; the range of the reported concentrations was 2–56 µg/L, with the majority of samples below 10 µg/L (EPA 2006). This is likely a localized exposure to phenol as about 35% of the remaining water samples were positive for the presence of phenol from January 2004 to April 6, 2006 (EPA 2006). Phenol has been detected, but not quantified, in drinking water from 5 of 14 drinking water treatment plants between July 1977 and June 1979 in 1 of 3 sites (groundwater source), in 3 of 10 (surface water source), and in a water source used after distribution (Fielding et al. 1981). Phenol levels in tap water, spring water, and mineral water in Italy were 0.58, 0.051, and 0.161 µg/L, respectively (Achilli et al. 1995). Phenol was detected at a maximum concentration of 1,130 ppm in nine wells in Wisconsin after a spill, and was detected for at least 1.5 years after the spill (Delfino and Dube 1976). Phenol was detected at a maximum concentration of 1.9 ppm in leachates from landfill sites in Illinois (Clark and Piskin 1977). Near a landfill in central Florida, phenol was found in groundwater and surface water at about 17 and 15 ppb, respectively (Chen and Zoltek 1995). Phenol was detected, but not quantified, in the groundwater at 13.6% of 178 CERCLA hazardous waste sites (Plumb 1987).

Very few data concerning the presence of phenol in soils were found. Phenol generally does not adsorb very strongly to soils and tends to leach rapidly through soil, which may account for the lack of monitoring data, since any phenol released to soils is likely to leach to groundwater. Moreover, phenol is readily degraded in the environment, which is expected to attenuate its levels in soil. Sediment collected 6 km northwest of the Los Angeles County wastewater treatment plant discharge zone at Palos Verdes, California, contained 10 ppb (dry weight) phenol (Gossett et al. 1983). In the STORET database, 24% of 407 data points for U.S. sediment samples collected from 2002 and 2006 had detectable levels of phenol; however, each sample was below the quantitative limit. Another 10% of the samples were positive for the presence of phenol with concentrations ranging from 74 to 680 µg/kg (dry weight) (EPA 2006). In a study of contaminants in stream bed sediments across the United States, phenol was detected at 536 sites at a maximum concentration of 210 µg/kg (Lopes and Furlong 2001).

***Priority Recommendation*:** The identified need is not considered priority. Reliable and current monitoring data for the levels of phenol in contaminated media at hazardous waste sites are needed so that the information obtained on levels of phenol in the environment and the resulting body burden of phenol 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 595 NPL sites at which phenol has been found. This database includes maximum concentrations of phenol 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 phenol 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 phenol in body tissues or fluids for people living near hazardous waste sites. While methods exist to detect phenol in urine and blood, the current data concerning human exposure to phenol is neither complete nor recent. Phenol has not been detected in breast milk or fat.

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 phenol 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 phenol in the environment, human tissues levels, and the subsequent development of health effects.

ATSDR has developed a hazardous substance release/health effects database (HazDat) that includes the extant data for the 595 NPL sites at which phenol has been found. This database includes maximum concentrations of phenol in on and off site media, and an indication of relevant routes of exposure. This database will not, however, supply information on the levels of phenol (or its metabolites) in the tissues of individuals living near hazardous waste sites or other exposed populations such as workers.

d. Exposures of Children

Purpose: To determine if adequate data on exposures of children to phenol 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 phenol has been identified. There are no exposure studies or body burden measurements of phenol in children. Oral, dermal, and combined oral-dermal exposures are the most likely routes by which children will be exposed to phenol. Oral exposure to low levels of phenol among children is likely because many consumer products contain phenol, particularly in medicines such as gargles, throat lozenges, and others (Darisimall 2006).

Exposure to phenol through inhalation is a less probable route than oral and dermal. It is known that both cigarettes and cigars contain small amounts (19–140 μg) of phenol (IARC 1986; NCI 1998), and smoking these products indoors produces a measurable amount of phenol (Guerin et al. 1992). If children are present in indoor environments polluted with tobacco smoke, they may be exposed to low levels of phenol. Limiting exposure to cigarette smoke and gasoline vapors should decrease children's exposure to inhalation of phenol. Keep consumer products containing phenol away from children and supervise dosage of pharmaceuticals containing phenol.

Priority Recommendation: The identified data need to conduct additional studies to assess exposures of children to phenol is considered priority. Collecting information on the levels of phenol in children is important in order to determine the extent of a child's exposure to phenol 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 phenol 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. Sufficient data are available to characterize the environmental fate of phenol. When released to air, phenol reacts rapidly with atmospheric

oxidants and the atmospheric half-life <1 day (Atkinson et al. 1987; EPA 1979a). The half-life of phenol in soil is generally <5 days (Baker and Mayfield 1980), but acidic soils and some surface soils may have half-lives of ≤23 days (Shiu et al. 1994). Phenol biodegrades rapidly in water. Complete degradation in <1 day has been reported in water from three lakes; the rates of degradation were affected by the concentration of organic and inorganic nutrients in the water (Rubin and Alexander 1983). Complete removal of phenol in river water has been reported after 2 days at 20 °C and after 4 days at 4 °C (Ludzack and Ettinger 1960). The degradation of phenol is somewhat slower in salt water, and a half-life of 9 days has been reported in an estuarine river (EPA 1979b).

Phenol possesses high mobility in soil based on log K_{oc} values of 1.21–1.96 (Artiola-Fortuny and Fuller 1982; Boyd 1982; Briggs 1981; Sacan and Balcioglu 1996; Scott et al. 1983). These data suggest that phenol may leach to groundwater; however, the rapid rate of degradation may attenuate this process.

***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 phenol 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 been identified. Studies of bioavailability of phenol from ingested soil and foods and dermal contact with contaminated water are needed for evaluating the hazards posed by ingesting materials that have been contaminated with phenol. Phenol is readily adsorbed through inhalation, dermal contact, and ingestion of contaminated water and food. The primary sources of exposure at hazardous waste sites are believed to be through dermal contact with contaminated soil and ingestion of contaminated water. However, the quick degradation of phenol in all of these mediums makes high exposure from these routes unlikely. Because of its quick biodegradation, phenol is not expected to bioaccumulate in plants or animals. Phenol is briefly formed in many organisms as a result of benzene degradation.

Priority Recommendation: The identified data need is not considered priority. Bioavailability from ingestion of soil and foods and from dermal contact with contaminated water are not available. However, these routes of exposure are considered to be less likely than ingestion of phenol from throat lozenges and mouthwash, dermal contact from antiseptic lotions and ointments, or inhalation from wood and gasoline combustion and cigarette smoke.

2. Level III Data Needs

a. Registries of Exposed Persons

***Purpose*:** To help assess long-term health consequences of exposure to phenol 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 phenol subregistry of the National Exposure Registry.

***Finding*:** A data need has been identified. Phenol has been found in at least 595 NPL hazardous waste sites. At this time, no formal registries exist that identify people known to have been exposed to phenol. The development of an exposure registry should provide an important reference tool to help assess long-term health consequences of exposure to phenol. 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 phenol 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 phenol subregistry at this time would not contribute significantly to the current database. The development of an exposure subregistry should await the results of needed studies on exposure levels in humans living near hazardous waste sites and exposure levels of children as well as 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 phenol. Please refer to the ATSDR Toxicological Profile for Phenol, chapter on "Health Effects" for a more detailed discussion of available information (ATSDR 2006). Generally, ATSDR believes that the most relevant routes of human exposure to phenol 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. No relevant acute-duration inhalation human studies were located and the animal database is very limited. It includes a few animal studies of limited scope (Aranyi et al. 1986; De Ceaurriz et al. 1981; Flickinger 1976) and a well-conducted study that used modern methodology to evaluate a number of relevant end points (Hoffman et al. 2001). In the animal studies, a target for phenol toxicity was not clearly defined. Hoffman et al. (2001) exposed rats to various exposure levels up to 25 ppm for 2 weeks and evaluated a number of end points including histopathology, hematology, and clinical chemistry and reported no adverse effects. De Ceaurriz et al. (1981) exposed mice to various concentrations of phenol in air for 5 minutes and determined an RD_{50} (concentration that reduced the respiratory rate by 50%, a protective reflex response in rodents) of 166 ppm. Aranyi et al. (1986) also exposed mice to 5 ppm phenol 3 hours/day for 5 days and reported no significant changes in susceptibility to airborne bacterial agents relative to mice exposed to filtered air. Flickinger (1976) observed loss of coordination

and tremors in rats exposed to 234 ppm phenol for 8 hours; a 1-hour exposure was without effect. No other exposure concentration was tested and no control group was used. Fourteen days later, the rats were sacrificed and subjected to gross necropsy. Flickinger (1976) indicated that no gross lesions were observed, but the scope of the examination was not specified. The no-observed-adverse-effect level (NOAEL) or 25 ppm from the Hoffman et al. (2001) study was used as the basis for the derivation of an acute-duration inhalation MRL of 0.02 ppm for phenol (ATSDR 2006). However, since the MRL is based on a free-standing NOAEL, it may be overly conservative (the adverse effect level may be much higher), additional studies are needed to construct dose-response relationships and establish threshold levels.

The acute-duration oral data in humans are restricted to reports of accidental or intentional ingestion of relatively high doses of phenol, which in many cases were fatal (Boatto et al. 2004; Langford et al. 1998; Lo Dico et al. 1989; Soares and Tift 1982; Stajduhar-Caric 1968; Tanaka et al. 1998). Postmortem examination typically showed serious mucosal alterations in the gastrointestinal tract. Signs and symptoms of neurological stimulation and depression were also reported (Kamijo et al. 1999; Spiller et al. 1993). All of the acute-duration oral studies in animals available administered phenol to the animals by gavage. As discussed in greater detail in Section II.D.3, the effects of phenol administered to animals by oral gavage are different than those observed in drinking water studies, a phenomenon that is related to the toxicokinetics of phenol. Acute-duration oral gavage studies in animals provided information on lethal doses (Berman et al. 1995; Deichmann and Witherup 1944; Flickinger 1976; von Oettingen and Sharpless 1946) and other effects, including renal (Berman et al. 1995), hematological (Ciranni et al. 1988), neurological (Moser et al. 1995), and developmental effects (Narotsky and Kavlock 1995; NTP 1983a, 1983b). A study in which pregnant rats were administered phenol by oral gavage, but divided in three daily doses and in a relatively high volume to minimize the effects of a bolus dose of phenol, reported a significant reduction in body weight gain in the dams at ≥120 mg/kg/day, but no significant developmental effects were reported at this dose level (York 1997). The maternal NOAEL was 60 mg/kg/day. Decreased fetal weight and decreased ossification sites were only seen at the highest dose level, 360 mg/kg/day. The reduction in maternal weight gain during pregnancy was used as the basis for the derivation of an acute-duration oral MRL of 0.6 mg/kg/day for phenol. However, additional studies are needed to develop dose-response relationships for phenol administered by an environmentally-relevant oral route.

Accidental or intentional application of high doses of phenol to the skin has resulted in serious burns and, in some cases, death (Cronin and Brauer 1949; Griffiths 1973; Lewin and Cleary 1982; Soares and Tift 1982). Other effects such cardiovascular, hepatic, renal, and neurological also have been reported (Foxall et al. 1989; Gross 1984; Horch et al. 1994; Soares and Tift 1982; Truppman and Ellenby 1979; Warner and Harper 1985). Application of phenol to the skin of animals has caused edema, erythema, necrosis, and death; the cause of death was not provided in the studies available (Conning and Hayes 1970; Deichmann and Witherup 1944; Pullin et al. 1978). Cardiovascular and neurological effects also have been described in animals following dermal exposure to phenol (Conning and Hayes 1970; Wexler et al. 1984). Additional studies are needed to identify NOAELs and lowest-observed-adverse-effect levels (LOAEL) for local and systemic effects of skin exposure.

***Priority Recommendation*:** The identified data need to conduct additional studies via inhalation, oral, and dermal exposure is not considered priority. Ingestion of contaminated media is the primary exposure route for phenol at hazardous waste sites. Additional studies are needed to define thresholds for effects induced by administration of phenol by an environmentally-relevant mode rather than by oral gavage; however, these studies are not considered priority because the available data were a sufficient basis for MRL derivation. The needs for additional inhalation and dermal data are not priority because inhalation and dermal exposure are not considered primary routes for populations 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, oral, and dermal exposure has been identified. Limited information exists regarding effects of phenol in humans exposed for intermediate durations. A study of office workers exposed to vapors of a liquid wood preservative containing phenol, among a number of other chlorinated compounds, reported adverse respiratory, hematological, hepatic, and ocular effects, but the specific role of phenol, if any, could not be ascertained (Baj et al. 1994). The intermediate-duration database in animals consists of only three studies (Dalin and Kristoffersson 1974; Deichmann et al. 1944; U.S. Air Force 1961), which suffer from numerous limitations including poor control of exposure levels,

lack of a control group, unclear scope of the evaluations, and limited reporting. Dalin and Kristofferson (1974) exposed a small number of rats to 0 or 26 ppm phenol continuously for 15 days and reported mild motor disorders (impaired balance, abnormal gait, muscle twitching) during the first few days of exposure. At termination, the activities of serum transaminases were significantly increased indicating liver damage, but no histopathology examination was conducted. Deichmann et al. (1944) exposed guinea pigs, rats, and rabbits intermittently for 6–12 weeks to a concentration of phenol in air that apparently could not be controlled with any precision, but could have ranged from 26 to 52 ppm. Exposure to phenol caused serious histological alterations in the lungs, heart, liver, and kidneys in rabbits and guinea pigs, but no significant changes were reported in rats. U.S. Air Force (1961) exposed monkeys, rats, and mice continuously to 0 or 5 ppm phenol for 90 days. Although the report indicates that there were no significant histological alterations in organs and tissues, incomplete reporting of the results suggests that there may have been some lung, liver, and kidney pathology. In addition, no data were presented to support the assertion that there were no effects on hematology (three species), blood chemistry (monkeys only), urinalysis (three species), or kidney function tests (monkeys and rats). An intermediate-duration inhalation study that examines a comprehensive number of end points is needed to provide information for dose-response analysis and possible MRL derivation.

There are very limited data regarding health effects in humans following intermediate-duration oral exposure to phenol. Studies of populations whose drinking water was contaminated with phenol found increased incidences of nausea and diarrhea, but exposure to chlorophenols may have also occurred (Baker et al. 1978; Jarvis et al. 1985; Kim et al. 1994). Several studies are available that provide information on the effects of phenol following intermediate-duration exposure in animals and all of them used drinking water to administer phenol. With the exception of one study (Hsieh et al. 1992, see below), doses tested in intermediate-duration oral studies were higher than doses tested in acute-duration oral studies. A 13-week drinking water study in rats and mice evaluated clinical signs and gross and microscopic appearance of a number of organs and tissues and found little evidence of toxicity (NCI 1980). Reduction in body weight gain was observed in both rats and mice at the highest dose levels tested (1,556 mg/kg/day in rats, 2,468 mg/kg/day in mice), which was most likely due to significant decreases in water consumption. Also available is a two-generation reproduction study that found no evidence of reproductive effects in male and female rats (301 and 321 mg/kg/day, respectively), but reported decreased pup weight and reduced viability at 301 and 321 mg/kg/day (Ryan et al. 2001). Significantly reduced water consumption was also reported in the Ryan et al. (2001) study,

particularly in the 301 and 321 mg/kg/day males and females. A specialized 13-week neurotoxicity study in rats reported decreased motor activity in females dosed with 360 mg/kg/day, but not with 107 mg/kg/day (Beyrouty 1998). However, the most significant findings among the intermediate-duration database were reported in a 28-day study in mice (Hsieh et al. 1992). These investigators found hematological (decreased red cell counts) and neurochemical effects in mice at 1.8 mg/kg/day and immunological effects at ≥6.2 mg/kg/day. Although in the Ryan et al. (2001) study, rats exposed to up to 321 mg/kg/day phenol in drinking water showed no significant alterations in a comprehensive number of hematological parameters evaluated, there may be a need to conduct a study to confirm or reject Hsieh's findings. No intermediate-duration oral MRL was derived for phenol, the main reason being the unconfirmed nature of findings observed at relatively very low doses by Hsieh et al. (1992) and because only five mice comprised each dose group in that study. NTP is currently conducting a comprehensive series of tests to evaluate the potential immunotoxicity of phenol in mice.

No relevant intermediate-duration dermal data in humans were located. Skin ulcerations were reported in mice treated dermally with 20% phenol in acetone once per week for 24–32 weeks (Salaman and Glendenning 1957). Because phenol is readily absorbed through the skin, additional intermediate-duration studies examining the systemic effects of dermal exposure to different concentrations of phenol in water are needed.

***Priority Recommendation*:** The identified data need to conduct additional studies via inhalation, oral, and dermal exposure is not considered priority. The needs for additional inhalation and dermal data are not priority because oral and dermal exposure are not considered primary routes for populations living near hazardous waste sites. Although ingestion of contaminated media is the primary exposure route for phenol at hazardous waste sites, the need to conduct an oral study is not considered priority pending evaluation of the ongoing NTP immunotoxicity study. The NTP study may provide a basis for MRL derivation or may support the results of Hsieh et al. (1992), which may be used for MRL derivation.

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, oral, and dermal exposure has been identified. There is limited information on health effects in humans exposed chronically to phenol. Neither morbidity nor mortality was significantly increased in workers in five companies that used formaldehyde and phenol (Dosemeci et al. 1991). In another study of workers in the rubber industry, exposure to phenol was associated with an increased incidence of cardiovascular disease, independently of being associated with exposure to other solvents such as carbon disulfide (Wilcosky and Tyroler 1983). Liver effects, as judged by increased serum activities of alanine aminotransferase (ALT) and aspartate amino transferase (AST), were reported in a single case of prolonged inhalation exposure to phenol (Merliss 1972) and in workers in an oil-refining plant (Shamy et al. 1994), but exposure to other solvents could not be ruled out in the latter case. The lack of exposure data and simultaneous exposure to other chemicals precluded using the human data for derivation of a chronic-duration inhalation MRL for phenol. No chronic-duration inhalation studies in animals were identified. Additional studies are necessary to characterize the effects and dose-response relationships for chronic inhalation exposure.

No information was located regarding health effects in humans following chronic-duration oral exposure to phenol. The only chronic-duration animal studies are the National Cancer Institute (NCI 1980) 103-week drinking water studies in rats and mice. NCI (1980) evaluated clinical signs, organ weights, and gross and microscopic appearance of organs and tissues. The lowest doses tested were 322 mg/kg/day in rats and 590 mg/kg/day in mice. Under the conditions of the study, phenol showed essentially no systemic toxicity. The only reported effect was a significant decrease in body weight in male (≥322 mg/kg/day) and female (≥721 mg/kg/day) rats associated with significant decreases in water intake; food consumption was comparable among all groups. The LOAEL of 322 mg/kg/day was not used as the basis for an MRL because the effect (reduced final body weight) was likely due to decreased water intake. An additional reason for not deriving a chronic-duration oral MRL for phenol is the intermediate-duration data from Hsieh et

al. (1992) suggesting that immunosuppression may be the most sensitive effect, which leaves open the possibility that it could do the same in longer-term studies.

No relevant chronic-duration dermal studies in humans or animals were located. Since phenol is readily absorbed through the skin and the possibility exists of dermal exposure via contaminated media at or near waste sites, a chronic-duration dermal study of phenol may be considered if the results of an intermediate-duration study suggest that adverse systemic effects might happen.

***Priority Recommendation*:** The identified data need to conduct additional studies via inhalation, oral, and dermal exposure is not considered priority. Ingestion of contaminated media is the primary exposure route for phenol at hazardous waste sites. Should the ongoing intermediate-duration oral study on immunotoxicity being conducted by NTP identify the immune system as a sensitive target for phenol, a chronic-duration oral study may be designed to test for possible chronic immunotoxic effects. The needs for additional inhalation and dermal data are not priority because inhalation and dermal exposure are not considered primary routes for populations living near hazardous waste sites.

(2) Cancer Assessment

***Purpose*:** To determine whether populations potentially exposed to phenol 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 phenol via inhalation, oral, and dermal routes has been identified. A study of phenol-exposed wood industry workers reported a small, nonsignificant excess of respiratory cancers (Kauppinen et al. 1986) and a study of phenol production workers reported a small, nonsignificant excess of Hodgkin's

disease and of lung, esophageal, rectal, and kidney cancers (Dosemeci et al. 1991). However, the interpretation of these findings is complicated due to lack of dose-response and potential for confounding due to simultaneous exposure to other chemicals.

No studies were located regarding cancer in animals following inhalation exposure to phenol. No studies were located regarding the carcinogenicity of phenol in humans following oral exposure. The carcinogenicity of orally administered phenol has been examined in F344 rats and $B6C3F_1$ mice administered phenol in the drinking water for 103 weeks (NCI 1980). Pair-wise comparison of the treated groups with controls showed a statistically significant increased incidences of pheochromocytomas of the adrenal gland (13/50, 31/50, 25/50) and leukemia or lymphomas (42/48, 49/50, 47/50) were observed in male rats exposed to the low dose of phenol, 322 mg/kg/day (2,500 ppm), but not in male rats exposed to the high dose of phenol, 645 mg/kg/day (5,000 ppm). No significant effects were seen in female rats or mice of either sex exposed to either exposure level. Although NCI concluded that phenol was "not carcinogenic in male and female F344 rats," the NCI reviewers recommended that phenol be considered for a retest.

No studies were located regarding cancer in humans following dermal exposure to phenol. The possibility that phenol is a cancer promoter has been examined in several dermal initiation-promotion studies in mice (Boutwell and Bosch 1959; Salaman and Glendenning 1957; Wynder and Hoffman 1961). In general, the results have been positive, but since phenol also produces skin ulceration, the question is whether some of the promotion activity may be related to the rapid cell division in the reparation of the skin damage (Salaman and Glendenning 1957). In another study, phenol was dissolved in 1,4-dioxane or benzene, both of which are de-fattening agents, which obscures the interpretation of the results (Boutwell and Bosch 1959). Standard dermal bioassays have not been conducted for phenol. Based on the results of the oral study, it can be predicted that inhalation or dermal exposure to phenol would not likely result in remote site carcinogenicity. However, it is not known if long-term exposure would result in respiratory tract cancer following inhalation exposure or skin cancer following dermal exposure. Inhalation and dermal exposure cancer studies are needed to address these questions. IARC considers phenol not classifiable as to its carcinogenicity in humans (Group 3). DHHS has not classified phenol as to its carcinogenicity (NTP 2005). Based on inadequate evidence in humans and animals, EPA (IRIS 2006) assigned phenol to Group D, not classifiable as to human carcinogenicity. Under

updated guidelines (EPA 2005), the data regarding carcinogenicity of phenol are: "inadequate for an assessment of human carcinogenic potential" (IRIS 2006).

***Priority Recommendation*:** The identified data need to conduct additional studies via oral exposure is considered priority in light of the fact that the NCI (1980) study provided inconclusive, although suggestive, evidence of carcinogenicity in male rats. Tumor incidence was increased in low-dose male rats, but not in high-dose male rats. Of particular concern is the increase in leukemias or lymphomas. EPA (IRIS 2006) noted that benzene, a chemical for which phenol is a metabolite, is leukemogenic in humans, although it has not been shown to induce leukemia in animals. Priority is not assigned to inhalation and dermal bioassays because these two exposure routes are not the primary exposure routes for populations living near hazardous waste sites.

d. Genotoxicity

***Purpose*:** To evaluate the mechanism of phenol-induced toxicity for purposes of future mitigation activities. Generally, priority is assigned to 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 phenol in humans exposed by the inhalation, oral, or dermal routes or in animals exposed by the inhalation or dermal routes. *In vivo* tests in animals treated by oral gavage or intraperitoneal injection have provided mixed results. For example, chromosomal aberrations were reported in spermatogonia and spermatocytes of mice treated by gavage (Bulsiewicz 1977) and in bone marrow from mice treated by intraperitoneal injection (Shelby and Witt 1995), but not in bone marrow from mice treated by injection in other studies (Barale et al. 1990; Chen and Eastmond 1995a; Pashin et al. 1987). Similar mixed results were reported in *in vivo* assays for micronuclei (Barale et al. 1990; Ciranni et al. 1988; Gocke et al. 1981; Li et al. 2005; Shelby and Witt 1995) and sister chromatid exchanges, including human lymphocytes (Erexson et al. 1985; Jansson et al. 1986; Morimoto and Wolff 1980; Tsutsui et al.

1997). *In vitro* tests with phenol for gene mutations in microorganisms have yielded both negative (Florin et al. 1980; Haworth et al. 1983; Kubo et al. 2002; Nagel et al. 1982; Pool and Lin 1982) and positive (Demerec et al. 1951; Gocke et al. 1981) results. Negative results have been reported in *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, and TA1538 with and without S9 activation (Haworth et al. 1983; Kubo et al. 2002; Pool and Lin 1982). However, increased mutagenicity was observed in *S. typhimurium* TA98 with S9 activation (Gocke et al. 1981). Paschin and Bahitova (1982) also reported positive results at the HGPRT locus of V79 for mutagenicity studies involving exposures of Chinese hamster ovary (CHO) cells with S9 activation. Studies of Syrian hamster embryos (SHE) were also positive for mutagenicity (Tsutsui et al. 1997). The mixed nature of the results suggests that phenol may be potentially genotoxic. Additional *in vivo* studies are needed to provide a more sufficient basis for predicting whether phenol poses a genotoxic threat to humans.

***Priority Recommendation*:** The identified data need to conduct additional genotoxicity studies is not considered priority. Although additional *in vivo* genotoxicity studies, particularly by an environmentally relevant mode of administration (as opposed to oral gavage or intraperitoneal injection), are needed to evaluate the genotoxic potential of phenol, these studies are not given priority because phenol was not carcinogenic in an oral bioassay in rats and mice.

e. Endocrine Disruption

***Purpose*:** To determine whether populations potentially exposed to phenol 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 phenol may have endocrine disrupting potential from Level I studies; or (2) if there have been human anecdotal reports of endocrine disrupting effects following phenol 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 phenol to disrupt the endocrine system. No studies were located that examined potential endocrine disruption in animals exposed to phenol by inhalation or dermal exposure. Long-term studies in rats and mice treated with phenol in the drinking water did not report alterations in the gross or microscopic appearance of the reproductive organs or endocrine glands (NCI 1980). In the 13-week experiment, rats and mice received approximately up to 1,700 and 2,700 mg phenol/kg/day, respectively. In the 2-year study, rats received estimated doses of phenol of up to 600–700 mg/kg/day and mice received 1,100–1,200 mg/kg/day. Similar observations were made in a more recent two-generation reproductive study in rats (Ryan et al. 2001). In the latter study, the highest doses of phenol, 301–321 mg/kg/day, had no significant effect on fertility, estrus frequency, testicular sperm count, or sperm motility or morphology. In standard developmental toxicity studies in rats and mice, with one exception, fetotoxicity has only been reported at doses that were also toxic to the mothers (Narotsky and Kavlock 1995; NTP 1983b; Ryan et al. 2001; York 1997). In the study by NTP (1983a) in rats, a 7% decrease in fetal body weight was reported at the high-dose level, 120 mg/kg/day, without any evidence of maternal toxicity. The

only relevant information located from assays *in vitro* is that phenol tested negative for estrogenic activity in a reporter gene expression assay using yeast cells (Nishihara et al. 2000).

***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 phenol at hazardous waste sites. Sufficient studies by the oral route of exposure have provided no evidence of phenol being a potential endocrine disruptor at the doses tested. Inhalation and dermal data are lacking, but there is no evidence that the effects of phenol (other than those at the point of contact) are route-dependent and also the inhalation and dermal routes are not primary routes for populations near waste sites.

f. Reproductive Toxicity

***Purpose*:** To determine whether populations potentially exposed to phenol 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. The only information regarding reproductive effects of phenol in humans is that there was no significant increase in the rate of miscarriage in a group of 576 women laboratory workers in Sweden exposed to organic solvents relative to 576 unexposed pregnancies (Axelsson et al. 1984). Specific mention of phenol was reported in only five cases, all of which were normal deliveries. This information is insufficient to draw conclusions regarding potential reproductive effects of phenol in humans. There are no studies of reproductive end points in animals following inhalation or dermal exposure to phenol. Histopathological changes in reproductive organs were not observed in rats or mice treated with phenol in the drinking water for 13 or 103 weeks (NCI 1980). In a two-generation study in which rats were administered phenol in the drinking water, there were no significant alterations in gross or microscopic appearance of the reproductive organs of males and females from the parental and F_1 generations (Ryan et al. 2001). In addition, there were no significant effects on mating performance and fertility, estrus frequency, testicular sperm count, or sperm motility or morphology. Additional reproductive toxicity studies by the oral route do not seem necessary 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 phenol does not impair reproductive performance. Additionally, the inhalation and dermal routes are not primary routes of exposure near hazardous waste sites.

g. Developmental Toxicity

***Purpose*:** To determine whether populations potentially exposed to phenol 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 phenol, (2) if there are human anecdotal reports of developmental effects following phenol 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. The only information regarding humans is that neither perinatal death rates nor prevalence of malformations were significantly increased in a group of 576 women laboratory worker in Sweden exposed to organic solvents relative to 576 unexposed pregnancies (Axelsson et al. 1984). An abstract by Hernberg et al. (1983) on data from personal interviews of 1,047 Finnish mothers exposed to disinfectants (including phenol) during early pregnancy did not indicate significant associations between exposure to disinfectants and the occurrence of congenital defects. This information is insufficient to draw conclusions regarding potential developmental effects of phenol in humans. There are no studies of developmental effects in animals following inhalation or dermal exposure to phenol. Phenol has been evaluated for developmental effects in rats and mice exposed by oral gavage (Ciranni et al. 1988; Kavlock 1990; Narotsky and Kavlock 1995; NTP 1983a, 1983b; York 1997) and in rats dosed through the drinking water in a two-generation reproduction study (Ryan et al. 2001). These studies indicated that fetotoxicity (decreased fetal weight and decreased ossification sites) occurs at dose levels that are also toxic to the mother. The developmental NOAEL was 120 mg/kg/day and the LOAEL was 360 mg/kg/day for decreased fetal body weight and delayed ossification. Additional developmental studies by the oral route of exposure do not seem necessary at this time.

***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 do not suggest that phenol is a developmental toxicant, phenol toxicity is not route-dependent (other than local irritation effects), and inhalation and dermal exposure are not primary routes at hazardous waste sites.

h. Immunotoxicity

***Purpose*:** To evaluate the mechanism of phenol-induced toxicity for purposes of defining target organs and future mitigation activities. There is increasing 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. The only information regarding immunotoxicity of phenol in humans is that office workers exposed for 6 months to airborne formaldehyde, phenol, and isomers of organic chlorohydrocarbons from Ksylamit™, a widely used liquid wood preservative, showed significant decreases in some lymphocyte surface markers, in lymphocyte responsiveness to the mitogen phytohemagglutinin (PHA), in natural killer (NK) cell cytotoxicity, and in the mixed lymphocyte response assay. However, the role of phenol, if any, is difficult to ascertain. Inhalation data in animals are very limited. Gross and microscopic examination of the spleen of rats exposed intermittently nose-only to up to 25 ppm phenol for 2 weeks did not reveal any significant exposure-related alterations (Hoffman et al. 2001). Increased susceptibility to bacteria was not observed in mice exposed by inhalation to phenol (Aranyi et al. 1986). Necrosis or atrophy of the spleen or thymus was observed in rats given a single dose of 224 mg/kg of phenol by oral gavage, but no effects were observed on the spleen or thymus in rats given 14 daily doses of 40 mg/kg of phenol (Berman et al. 1995). Decreased antibody production in response to immunization with sheep red blood cells (SRBC) was observed in mice treated with ≥6.2 mg/kg of phenol in the drinking water for 28 days (Hsieh et al. 1992). However, similar tests conducted in rats receiving much higher doses of phenol in a different study were negative (Ryan et al. 2001). NTP is currently conducting immunotoxicity studies in mice administered phenol in the drinking water in order to confirm or refute the findings of Hsieh et al. (1992). There are longer-

term studies that did not find significant histopathologic changes in the spleen or thymus of rats or mice exposed to phenol in the drinking water for 13 or 103 weeks, but immunocompetence was not assessed in these studies (NCI 1980). No studies were located regarding immunotoxicity in animals exposed by the dermal route.

***Priority Recommendation*:** The identified data need to conduct additional immunotoxicity studies via inhalation, oral, and dermal exposure is not considered priority. Although ingestion of contaminated media is the primary exposure route for phenol at hazardous waste sites, the need to conduct an oral study is not considered priority pending evaluation of the ongoing NTP immunotoxicity study. The needs for additional inhalation and dermal data are not priority because inhalation and dermal exposure are not considered primary routes for populations living near hazardous waste sites.

i. Neurotoxicity

***Purpose*:** To evaluate the mechanism of phenol-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. Information is available on cases of acute oral and dermal exposure to high doses of phenol that produced serious neurological effects ranging from central nervous system depression to muscle tremors and seizures and, in some cases, death (Bentur et al. 1998; Kamijo et al. 1999; Lewin and Cleary 1982; Soares and Tift 1982; Spiller et al. 1993). There is no information regarding neurological effects in humans acutely exposed to high concentrations

of phenol in air, although it is reasonable to assume that such an exposure scenario would induce effects similar to those seen in cases of acute oral or dermal exposure. Very little is known regarding neurological effects in humans following longer-term exposure to phenol. Merliss (1972) described a case of 'carbol marasmus' characterized by anorexia, headache, and vertigo in a subject exposed chronically to phenol in the air and possibly through contact with the skin. An additional study reported that office workers exposed for 6 months to a liquid wood preservative containing phenol, among other substances, complained of headache and fatigue (Baj et al. 1994). An increase in the number of headaches was reported by persons exposed to phenol in drinking water following an accident, but chlorophenols may have contributed to the observe effects (Kim et al. 1994). Neurological effects (muscle tremor, loss of coordination) have been reported in laboratory animals exposed to phenol in the air (Dalin and Kristoffersson 1974; Deichmann et al. 1944; Flickinger 1976), by oral gavage dosing (Deichmann and Witherup 1944; Liao and Oehme 1981; Moser et al. 1995; NTP 1983b), and by dermal application (Conning and Hayes 1970; Pullin et al. 1978). The inhalation and dermal studies were not of sufficient quality to construct dose-response relationships. In contrast to oral gavage studies, no neurological effects (including neurobehavioral evaluations and histology of nervous tissue) assessment of were observed in rats and mice in drinking water studies of longer durations and with higher doses of phenol than in oral gavage studies (Beyrouty 1998; NCI 1980). These neurological effects correlate with peak blood concentrations of phenol achieved during gavage dosing. Drinking water studies suggest that the nervous system is not a sensitive target for phenol toxicity by this route of exposure. A need to conduct additional oral studies is not apparent since the oral studies available have evaluated neurobehavioral and histopathological end points in multiple species.

***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 phenol. Also, the needs for additional inhalation and dermal data are not priority because inhalation and dermal exposure are not considered primary routes for populations living near hazardous waste sites.

j. Toxicokinetics

***Purpose*:** To evaluate the disposition of phenol 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 phenol following inhalation, oral, and dermal exposure has not been identified. There are studies both in humans and animals that show that phenol is well absorbed by the inhalation, oral, and dermal routes of exposure. In volunteers exposed for 8 hours to concentrations of phenol in air ranging from 1.6 to 5.2 ppm, 60–88% of the inhaled phenol was retained (Piotrowski 1971). Whole-body skin exposures studies conducted in volunteers lightly clothed and unclothed to assess skin absorption of phenol in the air showed that considerable absorption occurs (Piotrowski 1971). The authors estimated a mean absorption coefficient of 0.35 m^3/hour, indicating that an amount of phenol equivalent to that contained in 0.35 m^3 of air was absorbed through the skin each hour. In rats exposed nose-only to 25 ppm ^{14}C-phenol vapors for 6 hours, >90% of the phenol-derived radioactivity was recovered in the urine 30 minutes after initiation of exposure (Hiser et al. 1994). A study in volunteers found that 85–98% of a dose of ^{14}C-phenol given in food or drink was excreted in the urine in 14 hours primarily as phenylsulfate and phenylglucuronide (Capel et al. 1972). Various studies in animals, including one that examined 18 animal species, have demonstrated rapid and efficient gastrointestinal absorption of phenol ranging from 35% of the dose in monkeys to 95% in rats (Capel et al. 1972; French et al. 1974; Hiser et al. 1994; Hughes and Hall 1995; Kao et al. 1979; Kenyon et al. 1995). Application of liquid phenol (2.5, 5.0, or 10.0 g/L) to the forearm of volunteers resulted in constant absorption rate for 60 minutes (0.08 mg/cm^2/hour) and increased proportionately with applied concentration (Baranowska-Dutkiewicz 1981). Approximately 13% of the applied dose was absorbed in 30 minutes, of which 80% (range 58–98%) was recovered in the urine within 24 hours. There is information indicating that absorbed phenol is widely distributed in the body regardless of the route of exposure. Phenol was detected in the brain, lungs, liver, muscle, and kidney from subjects that ingested lethal amounts of phenol (Lo Dico et al. 1989; Tanaka et al. 1998). In studies in laboratory animals, the liver and kidneys generally had the greatest amount of phenol-derived radioactivity regardless of the mode of administration of phenol (oral gavage, drinking water, nose-only inhalation, intratracheal instillation) except following intratracheal administration, in which case the lungs had higher concentrations of

radiolabel (Hiser et al. 1994; Hughes and Hall 1995; Liao and Oehme 1981). No information is available regarding placental transfer and distribution of phenol in the fetus. The metabolism of phenol has been fairly well studied. In mammals, phenol undergoes direct sulfation and glucuronidation, and phenol that is not directly conjugated can be the substrate of oxidative metabolism, principally by cytochrome P4502E1, but other cytochromes also seem to be involved. Cytochrome P4502E1 catalyzes the hydroxylation of phenol to form hydroquinone (and to a much lesser extent, catechol), which is then acted upon by the phase II enzymes (Campbell et al. 1987; Gut et al. 1996; Koop et al. 1989; McFadden et al. 1996; Powley and Carlson 2001; Snyder et al. 1993). Hydroquinone can, in turn, form conjugates, undergo peroxidation to form benzoquinone, or undergo further oxidation to form trihydroxybenzene. All three enzyme systems that metabolize phenol are found in multiple tissues and there is competition among them not only for phenol, but also for subsequent oxidative products, like hydroquinone. As a consequence, the relative amount of the products formed can vary based on species, dose, and route of administration. In most species tested, including humans, sulfation predominates at lower doses. As doses increase, glucuronidation increases, as does the formation of oxidative metabolites. The shift from sulfation to glucuronidation may be caused by a reduction in the availability of co-substrates in conjugation reaction and/or reduction in the sulfate pool (Kim et al. 1995) or due to a difference in K_m of the two pathways in relation to their respective V_{max} (Weitering et al. 1979). Alternatively, the shifts from sulfation to glucuronidation to oxidation have been attributed to the location of the enzymes in the liver in relation to the point of entry and direction of the blood flow in the liver (Ballinger et al. 1995; Hoffmann et al. 1999; Medinsky et al. 1995). The available data in humans and laboratory animals indicate that phenol is rapidly eliminated, primarily in the urine; phenol does not accumulate. In comparative toxicokinetic studies, the rat was the most similar species to humans with respect to the fraction of administered dose excreted in urine in 24 hours (95%) and the number and relative abundance of the four principal metabolites excreted in urine (sulfate and glucuronide conjugates of phenol and 1,4-dihydroxybenzene) and appears to be an appropriate animal model. The available data suggest that the toxicity of phenol, at least of acute high doses, is similar across species, including humans. It is not known whether the parent compound or a metabolite(s) is responsible for phenol's systemic toxicity. A study by Chapman et al. (1994) provides some insight on a possible toxic entity. These investigators found that incubation of whole rat conceptus *in vitro* with phenol resulted in minor dysmorphogenic and embryotoxic effect and that addition of exogenous hepatic bioactivation system greatly increased the toxicity of phenol. The major metabolites formed were hydroquinone, catechol, and benzoquinone and these three metabolites

exhibited similar potency. While this suggests that a metabolite of phenol may be responsible for the effects observed in this particular *in vitro* assay, extrapolation to other toxicities observed in oral gavage studies would be inappropriate.

***Priority Recommendation*:** A data need to assess the toxicokinetics of phenol following inhalation, oral, and dermal exposure has not been identified. The absorption, distribution, metabolism, and excretion of phenol have been addressed in both humans and animals. Although no data were available that addressed portal-of-entry metabolism for the skin, comparative studies are not considered priority because dermal contact is not the primary exposure route for populations living near hazardous 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 a small number of epidemiological studies on the health effects of phenol, but these studies are of limited use because quantitative estimates of exposure were lacking or have other limitations (e.g., multiple exposure routes, simultaneous exposure to other hazardous chemicals). A study of office workers exposed to vapors of a liquid wood preservative containing phenol, among a number of other chlorinated compounds, reported adverse respiratory, hematological, hepatic, and ocular effects, but the specific role of phenol, if any, could not be ascertained (Baj et al. 1994). Studies of populations whose drinking water was contaminated with phenol found increased incidences of nausea and diarrhea, but exposure to chlorophenols may have also occurred (Baker et al. 1978; Jarvis et al. 1985; Kim et al. 1994). Neither morbidity nor mortality was significantly increased in workers in five companies that used formaldehyde and phenol (Dosemeci et al. 1991). In another study of workers in the rubber industry, exposure to phenol was associated with an increased incidence of cardiovascular disease, independently of being associated with exposure to other solvents such as carbon disulfide (Wilcosky and Tyroler 1983). Liver effects, as judged by increased serum activities of ALT and AST, were reported in a case of prolonged inhalation exposure to phenol (Merliss 1972)

and in workers in an oil-refining plant (Shamy et al. 1994), but exposure to other solvents could not be ruled out in the latter case. A study of phenol-exposed wood industry workers reported a small, nonsignificant excess of respiratory cancers (Kauppinen et al. 1986) and a study of phenol production workers reported a small, nonsignificant excess of Hodgkin's disease and of lung, esophageal, rectal, and kidney cancers (Dosemeci et al. 1991). However, the interpretation of these findings is complicated due to lack of dose-response and potential for confounding. Overall, no clear target for phenol toxicity can be identified from the long-term studies available and this is consistent with results from long-term studies in animals, in which phenol exhibited little toxicity. Both ingestion of phenol (Boatto et al. 2004; Soares and Tift 1982; Stajduhar-Caric 1968; Tanaka et al. 1998) and contact of phenol with a significant area of the skin (Cronin and Brauer 1949; Griffiths 1973; Soares and Tift 1982) have caused deaths in humans. The cardiovascular system also might be considered a target for acute phenol toxicity. Supraventricular and ventricular dysrhythmias were reported in a case of acute ingestion of a high dose of phenol (Langford et al. 1998) and cardiac arrhythmia and bradycardia were reported following acute dermal exposure to relatively high amounts of phenol (Gross 1984; Horch et al. 1994; Truppman and Ellenby 1979; Warner and Harper 1985). In general, the effects observed in humans following acute exposure to high amounts of phenol also are consistent with those seen in animals following similar exposures.

Priority Recommendation: The identified data need to conduct epidemiologic studies on phenol is not considered priority. Although many people are potentially exposed to phenol because it has been detected in at least 595 of 1,678 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) are not immediately apparent, although individuals may be monitored for electrocardiographic alterations, as such effects have been observed in acutely exposed subjects.

b. Mechanism of Toxic Action

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

***Finding*:** A data need has been identified. Phenol is irritating and corrosive at high concentrations as supported by numerous cases of accidental dermal exposure or intentional or accidental ingestion of phenol. Phenol damages the stratum corneum and produces coagulation necrosis by denaturing and precipitating proteins. This makes the respiratory tract, eyes, and mucosal membranes in general targets for phenol toxicity. The mechanism of phenol systemic toxicity, as observed specifically following oral gavage administration in animals, is not known. Phenol is a hydroxylated metabolite of benzene and it further undergoes oxidative metabolism to produce other compounds. The major tissues in which metabolism appears to occur are the liver, gut, lung, and kidney (Cassidy and Houston 1984; Powell et al. 1974; Quebbemann and Anders 1973; Tremaine et al. 1984). Studies in which high doses of phenol are rapidly absorbed, as may occur in oral gavage studies in animals or in cases of accidental or intentional ingestion or dermal exposure in humans, have shown that the nervous system is principally affected. While it is clear that the parent compound is responsible for the irritation and possibly burns following contact with phenol, the entity responsible for the hyperactivity (i.e., tremors, seizures) observed in humans and animals after high-dose exposures is not known and additional studies on this topic are needed. Hiser et al. (1994) observed that the development of tremors and sudden jerks in rats given a high gavage dose of phenol coincided with peak blood levels of phenol and disappeared when blood phenol decreased below 3 μg/mL. However, because the levels of phenol metabolites paralleled those of phenol, it cannot be ascertained whether phenol or its metabolites were the toxic agent. There is little indication from studies in animals or from fatal poisoning cases in humans that phenol distributes preferentially to the brain, although tremors also may be caused by actions at the periphery. Injections of phenol (2–3%) have been used to block nerve conduction in a number of neurological disorders (i.e., spasticity in cerebral palsy, cervical dystonia) or to relieve pain in certain cancers. This occurs by phenol physically interrupting the continuity of axons and inducing axonal degeneration. How this may be related to tremors caused by gavage dosing of phenol, if at all, is unknown.

***Priority Recommendation*:** The identified data need is not considered priority. Additional research for elucidating mechanisms of phenol-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 phenol. There are analytical methods available to measure phenol in the blood and the urine; however, phenol and metabolites of phenol may also come from other sources. For example, phenol is a metabolite of benzene and of protein metabolism. Measurement of total phenol in the urine is the most useful biomarker following inhalation exposure to phenol (ACGIH 2005). As mentioned above, the test is nonspecific and should not be used when workers are exposed to benzene or to household products or medications containing phenol. Dermal exposure may also result in overestimation of inhalation exposure. In persons not exposed to phenol or benzene, the total phenol concentration in the urine does not exceed 20 mg/L and the mean is usually <10 mg/L (ACGIH 2005). Phenol can also be measured in the urine after oral exposure, although a dose-response relationship between oral exposure to phenol and phenol in the urine has not been established. Benzene metabolism yields not only phenol, 1,4-dihydroxybenzene, and their sulfates and glucuronides, but also the benzene-specific *t,t*-muconic acid (Popp et al. 1994; Stommel et al. 1989). Thus, determination of urinary concentrations of these metabolites allows delineation of the portion of metabolites stemming from phenol and the portion derived from benzene exposure.

***Priority Recommendation*:** The identified data need is not considered priority. The lack of a specific biomarker of effect for phenol is not considered essential to conduct human studies. This is because there is no unique disease state associated with phenol and the identification of phenol 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 phenol. However, development of more specific and sensitive tests might be necessary to adequately evaluate the health status of individuals exposed to low levels of phenol at waste sites. These considerations will be more appropriately addressed in the future once populations have been identified with known exposure to phenol.

d. Clinical Methods for Mitigating Toxicity

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

***Finding*:** A data need has been identified. Target organs after acute exposure to high amounts of phenol include any site of direct contact such as the skin, eyes, mucosal membranes, nervous system, liver, kidney, and cardiovascular system. No target organ(s) has been identified in humans following long-term, low-level exposure to phenol. The irritant properties of phenol are due to the fact that it damages the stratum corneum and induces coagulation necrosis by denaturing and precipitating proteins. The mechanism(s) by which phenol induces 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 phenol following exposure (HSDB 2006). Following dermal exposure, it is recommended that the skin be washed with undiluted polyethylene glycol. If polyethylene glycol is not available, copious amounts of water should be used and the skin should be washed thoroughly with soap and water for 15 minutes or until there is no longer an odor of phenol. Other substances that have been recommended include glycerin solution and isopropyl alcohol. In case of oral ingestion of phenol, emesis is not recommended because of phenol's corrosive effects and potential for seizures and rapid central nervous system depression. Instead, in the absence of esophageal injury, repeated gastric lavage is recommended followed by administration of olive oil or vegetable oil to remove surface phenol and prevent deeper penetration. This can be followed by administration of a cathartic such as castor oil, sorbitol, or saline. There is no antidote for phenol 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 phenol 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 phenol exposure, 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 phenol 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 adequate studies on health effects of children following exposure to phenol, but there are anecdotal reports of toxic effects of phenol in children (see below). There is one study in animals that found that 10-day-old rats were more sensitive to lethality following oral and subcutaneous exposure to phenol than 5-week-old rats (Deichmann and Witherup 1944), but this work has never been repeated and there is no additional information evaluating the toxicity of phenol at various ages. Such studies need to be conducted in order to follow-up this early observation. There are reports that provide information on adverse health effects, including death, in children applied phenol on the skin to treat skin conditions (Cronin and Brauer 1949; Hinkel and Kintzel 1968; Warner and Harper 1985), exposed orally by drinking a phenol-containing disinfectant (Spiller et al. 1993), exposed by subcutaneous injection to treat neurological disorders (Morrison et al. 1991; Wood 1978), and presumably by inhalation (Doan et al. 1979). The data provided by these studies are insufficient to determine if children are more susceptible to phenol toxicity than adults. There are several standard developmental toxicity studies in rats and mice that, with one exception (NTP 1983a), suggest that fetotoxicity can occur at doses that are also toxic to the mothers (Narotsky and Kavlock 1995; NTP 1983b; Ryan et al. 2001; York 1997). Results from some studies *in vivo* and *in vitro* suggest that phenol potentially could affect the germ cells, opening the possibility that parental exposure would result in adverse childhood development or cancer (Bulsiewicz 1977; Li et al. 2005). However, the results of a well-conducted two-generation reproduction study do not support that possibility (Ryan et al. 2001). There is no information regarding toxicokinetics of phenol in children. Phenol is metabolized by CYP2E1 isozymes and also forms sulfate and glucuronide conjugates. To the extent that the enzymes involved in the metabolism of phenol are developmentally regulated, the metabolism, and consequently the toxicity of phenol, in immature humans may be different than in adults. However, since there is not enough information to determine which is the toxic entity, phenol or a metabolite, it is not known how metabolism will

influence the susceptibility of children to phenol exposure. Additional studies investigating the role of metabolism on phenol toxicity are needed to determine whether children are more or less susceptible than adults to phenol toxicity. It is not known whether phenol can cross the placenta and there are no reports on levels of phenol in maternal milk. There is no physiologically based pharmacokinetic (PBPK) model for children, embryo/fetuses/pregnant women, infants/lactating women, or adolescents. There are no biomarkers of exposure or effects for phenol that have been validated in children or in adults exposed as children. There is no reason to suspect that methods for mitigating the toxicity of phenol in adults could not be applied 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. There are reports of adverse health effects in children acutely exposed orally and dermally to relatively high doses of phenol, but these reports do not indicate that children are more susceptible to phenol than adults, although it must be noted that they were not designed to test that hypothesis. 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 Phenol

A. Exposure

Application of the hierarchy of research priorities presented in the Decision Guide begins with the evaluation of available analytical methods for phenol and proceeds through assessing the need for epidemiologic studies. As stated previously, much information is available on phenol, 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 phenol. Although a lot of information is available, a need to evaluate existing data on concentrations of phenol in contaminated environmental media at hazardous waste sites has been identified.

Furthermore, a need to collect data on levels of phenol 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 phenol.

One effort is now under way at ATSDR that will examine the extant data at the 595 NPL sites at which phenol has been found. When complete, this database will include maximum concentrations of phenol in on-site and off-site media, and an indication of relevant routes of exposure. This database will be developed and evaluated before the need to collect additional media-specific data is assigned priority. This database will not, however, supply information on the levels of phenol (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

- Exposure levels of children

B. Toxicity

The toxicity of phenol has been studied in animals by inhalation, oral, and dermal exposure. For all exposure routes, the site of contact is a target for phenol toxicity, as shown primarily by irritation of the respiratory tract, eyes, and skin. Exposure to doses of phenol that result in high amounts of parent compound in the bloodstream in a short time, as may occur following inhalation, oral gavage, or dermal exposure, caused adverse neurological effects in animals characterized by tremors, convulsions, lethargy, and possibly death. Exposure of animals to low doses of phenol, even for long periods of time, resulted in almost no toxicity, making it difficult to identify target organs or systems for phenol exposure. There is not enough information to determine with certainty whether children are more susceptible to phenol than adults. Phenol was not carcinogenic in mice or in female rats in a 2-year oral bioassay; however, the results in male rats were inconclusive and suggested that there could have been a chemical-related increased

incidence pheochromocytomas and leukemia or lymphoma. Based also on inconclusive results from genotoxicity tests and initiation/promotion studies, an additional 2-year bioassay by the oral route is needed to resolve the question of the carcinogenity of phenol.

These nonhuman research needs are justified because of the widespread domestic and environmental contamination of phenol, 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 needs (Table 3):

- Two-year oral carcinogenicity bioassay

V. References

ACGIH. 2005. Phenol. Threshold limit values for chemical substances and physical agents and biological indices. Cincinnati, OH: American Conference of Government Industrial Hygienists.

Achilli G, Cellerino GP, d'Eril GM, et al. 1995. Simultaneous determination of 27 phenols and herbicides in water by high-performance liquid chromatography with multi-electrode electrochemical detection. J Chromatogr 697:357-362.

Amlathe S, Upadhyay S, Gupta VK. 1987. Spectrophotometric determination of trace amounts of phenol in wastewater and biological fluids. Analyst 112:1463-1465.

Artiola-Fortuny J, Fuller WH. 1982. Adsorption of some monohydroxybenzene derivatives by soils. Soil Sci 133(1):18-26.

Atkinson R, Aschmann SM, Winer AM. 1987. Kinetics of the reactions of NO_3 radicals with a series of aromatic compounds. Environ Sci Technol 21:1123-1126.

ATSDR. 2005. 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 70:72840-72842.

ATSDR. 2006. ATSDR toxicological profile for phenol. Draft for public comment. Agency for Toxic Substances and Disease Registry. http://www.atsdr.cdc.gov/toxprofiles/tp115.html. October 30, 2006.

Aranyi C, O'Shea WJ, Graham JA, et al. 1986. The effects of inhalation of organic chemical air contaminants on murine lung host defenses. Fundam Appl Toxicol 6:713-720.

Axelsson G, Lutz C, Rylander R. 1984. Exposure to solvents and outcome of pregnancy in university laboratory employees. Br J Ind Med 41:305-312.

Baj Z, Majewska E, Zeman K, et al. 1994. The effect of chronic exposure to formaldehyde, phenol and organic chlorohydrocarbons on peripheral blood cells and the immune system in humans. J Invest Allergol Clin Immunol 4:186-191.

Baker EL, Landrigan PJ, Bertozzi PE, et al. 1978. Phenol poisoning due to contaminated drinking water. Arch Environ Health 33:89-94.

Baker MD, Mayfield CI. 1980. Microbial and nonbiological decomposition of chlorophenols and phenol in soil. Water Air Soil Pollut 13:411-424.

Baldwin MK, Selby MA, Bloomberg H. 1981. Measurement of phenol in urine by the method of Van Haaften and Sie: A critical appraisal. Analyst 106:763-767.

Ballinger LN, Cross SE, Roberts MS. 1995. Availability and mean transit times of phenol and its metabolites in the isolated perfused rat liver: Normal and retrograde studies using tracer concentrations of phenol. J Pharm Pharmacol 47:949-956.

Barale R, Marrazzini A, Betti C, et al. 1990. Genotoxicity of two metabolites of benzene: Phenol and hydroquinone show strong synergistic effects *in vivo*. Mutat Res 244:15-20.

Baranowska-Dutkiewicz B. 1981. Skin absorption of phenol from aqueous solutions in men. Int Arch Occup Environ Health 49:99-104.

Bentur Y, Shoshani O, Tabak A, et al. 1998. Prolonged elimination of half-life of phenol after dermal exposure. Clin Toxicol 36(7):707-711.

Berman E, Schlicht M, Moser VC, et al. 1995. A multidisciplinary approach to toxicological screening: I. Systemic toxicity. J Toxicol Environ Health 45:127-143.

Beyrouty P. 1998. Final report: A 13-week neurotoxicity study of phenol administered in the drinking water to the rat, with TSCA notice of receipt of test data. Chemical Manufacturers Association. Submitted to U.S. Environmental Protection Agency under TSCA Section 4. OTS0559602.

Bieniek G, Wilczok T. 1986. Separation and determination of phenol, α-naphthol, *m*- and *p*-, *o*-cresols and 2,5-xylenol and catechol in the urine after mixed exposure to phenol, naphthalene, cresols and xylenols. Br J Ind Med 43:570-571.

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.

Briggs GG. 1981. Theoretical and experimental relationships between soil adsorption, octanol-water partition coefficients, water solubilities, bioconcentration factors and the parachor. J Agric Food Chem 29:1050-1059.

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 Sci 134:337-343.

Bulsiewicz H. 1977. The influence of phenol on chromosomes of mice (*Mus musculus*) in the process of spermatogenesis. Folia Morphol (Warsaw) 36:13-22.

CA EPA 1998. USEPA/OPP Pesticide related database queries: OPP's registered and cancelled pesticide product database. California Environmental Protection Agency. http://www.cdpr.ca.gov/docs/epa/epamenu.htm. November 6, 1998.

Campbell N, Van Loon JA, Weinshilboum RM. 1987. Human liver phenol sulfotransferase: Assay conditions, biochemical properties and partial purification of isozymes of the thermostable form. Biochem Pharmacol 36:1435-1446.

Canonica S, Jans U, Stemmler K, et al. 1995. Transformation kinetics of phenols in water: Photosensitization by dissolved natural organic material and aromatic ketones. Environ Sci Technol 29:1822-1831.

Capel ID, French MR, Millburn P, et al. 1972. Fate of [^{14}C]-phenol in various species. Xenobiotica 2:25-34.

Cassidy MK, Houston JB. 1984. *In vivo* capacity of hepatic and extra hepatic enzymes to conjugate phenol. Drug Metab Dispos 12:619-624.

Chapman DE, Namkung MJ, Juchau MR. 1994. Benzene and benzene metabolites as embryotoxic agents: Effects on cultured rat embryos. Toxicol Appl Pharmacol 128(1):129-137.

Chen CS, Zoltek J Jr. 1995. Organic priority pollutants in wetland-treated leachates at a landfill in central Florida. Chemosphere 31:3455-3464.

Chen H, Eastmond DA. 1995a. Synergistic increase in chromosomal breakage within the euchromatin induced by an interaction of the benzene metabolites phenol and hydroquinone in mice. Carcinogenesis 16:1963-1969.

Ciranni R, Barale R, Marrazzini A, et al. 1988. Benzene and the genotoxicity of its metabolites. I. Transplacental activity in mouse fetuses and in their dams. Mutat Res 208:61-67.

Clark TP, Piskin R. 1977. Chemical quality and indicator parameters for monitoring landfill leachate in Illinois. Environ Geol 1:329-340.

Conning DM, Hayes MJ. 1970. The dermal toxicity of phenol: An investigation of the most effective first-aid measures. Br J Ind Med 27:155-159.

Crebelli R, Conti G, Carere A. 1987. On the mechanism of mitotic segregation induction in *Aspergillus nidulans* by benzene hydroxy metabolites. Mutagenesis 2:235-238.

Cronin TD, Brauer RO. 1949. Death due to phenol contained in foille. JAMA 139:777-778.

Cronn DR, Charlson RJ, Knights RL, et al. 1977. A survey of the molecular nature of primary and secondary components of particles in urban air by high-resolution mass spectrometry. Atmos Environ 11:929-937.

Dalin NM, Kristoffersson R. 1974. Physiological effects of a sublethal concentration of inhaled phenol on the rat. Ann Zool Fenn 11:193-199.

Darisimall. 2006. Sore throat lozenges and sprays. http://store.darisimall.com/sothlosp.html. July 27, 2006.

De Ceaurriz JC, Micillino JC, Bonnet P, et al. 1981. Sensory irritation caused by various industrial airborne chemicals. Toxicol Lett (Amst) 9:137-144.

Deichmann WB. 1944. Phenol studies. V. The distribution, detoxification, and excretion of phenol in the mammalian body. Arch Biochem 3:345-355.

Deichmann WB, Witherup S. 1944. Phenol 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.

Deichmann WB, Kitzmiller KV, Witherup BS. 1944. Phenol studies. VII. Chronic phenol poisoning, with special reference to the effects upon experimental animals of the inhalation of phenol vapor. Am J Clin Pathol 14:273-277.

Delfino JJ, Dube DJ. 1976. Persistent contamination of ground water by phenol. J Environ Sci Health A11:345-355.

Demerec M, Bertran G, Flint J. 1951. A survey of chemicals for mutagenic action on E. coli. American Naturalist 85:119-136.

Doan HM, Keith L, Shennan AT. 1979. Phenol and neonatal jaundice. Pediatrics 64:324-325.

Dosemeci M, Blair A, Stewart PA, et al. 1991. Mortality among industrial workers exposed to phenol. Epidemiology 2:188-193.

Eichelberger JW, Kerns EH, Olynyk P, et al. 1983. Precision and accuracy in the determination of organics in water by fused silica capillary column gas chromatography/mass spectrometry and packed column gas chromatography/mass spectrometry. Anal Chem 55:1471-1479.

Elder VA, Proctor BL, Hites RA. 1981. Organic compounds found near dump sites in Niagara Falls, NY. Environ Sci Technol 15:1237-1243.

EPA. 1979a. Atmospheric reaction products of organic compounds. Washington, DC: U.S. Environmental Protection Agency, Office of Chemical Control, Office of Toxic Substances, 20, 46.

EPA. 1979b. Microbial degradation of organochlorine compounds in estuarine waters and sediments. In: Proceedings Workshop: Microbial Degradation Pollution Marine Environment, 1978. Washington, DC: U.S. Environmental Protection Agency, Office of Research and Development. EPA600979012.

EPA. 1980. Ambient water quality criteria document for phenol. Washington, DC: U.S. Environmental Protection Agency. EPA440580001A. PB81117772.

EPA. 1981a. Exposure and risk assessment for phenol (revised). Washington, DC: U.S. Environmental Protection Agency, Office of Water Regulations and Standards. PB85221695, 114-116.

EPA. 1982. Test methods. Methods for organic chemical analysis of municipal and industrial wastewater. Method No. 604 and 625. Cincinnati, OH: U.S. Environmental Protection Agency.

EPA. 1986. Method Nos. 8250 and 8270: Test methods for evaluating solid waste. SW-846, Vol. IB: Laboratory manual: Physical/chemical methods. 3rd ed. U.S. Washington, DC: Environmental Protection Agency, Office of Solid Waste and Emergency Response.

EPA. 1987. Health and environmental effects profile for phenol. Cincinnati, OH: U.S. Environmental Protection Agency, Office of Solid Waste and Emergency Response.

EPA. 1998. Method 8070D: Semivolatile organic compounds by GC/MS. Draft update IVA of SW-846 on-line. U.S. Environmental Protection Agency, Office of Solid Waste. http://www.epa.gov/epaoswer/hazwaste/test/pdfs/8270d.pdf. April 18, 2006.

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

EPA. 2006. Phenol. Modernized STORET system. Regular results by geographic location (stormodb). Characteristic search by CAS number. U.S. Environmental Protection Agency. http://www.epa.gov/storet/dbtop.html. April 04, 2006.

Erexson GL, Wilmer JL, Kligerman AD. 1985. Sister chromatid exchange induction in human lymphocytes exposed to benzene and its metabolites *in vitro*. Cancer Res 45:2471-2477.

Flickinger CW. 1976. The benzenediols: Catechol, resorcinol and hydroquinone. A review of the industrial toxicology and current industrial exposure limits. Am Ind Hyg Assoc J 37:596-606.

Florin I, Rutberg L, Curvall M, et al. 1980. Screening of tobacco smoke constituents for mutagenicity using the Ames' test. Toxicology 18:219-232.

Forum for Scientific Excellence, Inc. 1990. Index of hazardous contents of commercial products in schools and colleges. Philadelphia, PA: JB Lippincott Co., 97, 109, 110, 145, 179.

Foxall PJD, Bending MR, Gartland KI, et al. 1989. Acute renal failure following accidental cutaneous absorption of phenol: Application of NMR urinalysis to monitor the disease process. Human Toxicol 9:491-496.

French MR, Bababunmi EA, Golding RR et al. 1974. The conjugation of phenol, benzoic acid, 1-naphthylacetic acid and sulfadimethoxine in the lion, civet, and genet. FEBS Lett 46:134-137.

Gocke E, King MT, Eckhardt K, et al. 1981. Mutagenicity of cosmetics ingredients licensed by the European communities. Mutat Res 90:91-109.

Gossett RW, Brown DA, Young DR. 1983. Predicting the bioaccumulation of organic compounds in marine organisms using octanol/water partition coefficients. Marine Pollut Bull 14:387-392.

Griffiths GJ. 1973. Fatal acute poisoning by intradermal absorption of phenol. Med Sci Law 13:46-48.

Gross BG. 1984. Cardiac arrhythmias during phenol face peeling. Plastic Reconst Surg 73:590-594.

Guerin MR, Jenkins RA, Tomkins BA. 1992. The chemical nature of environmental tobacco smoke: Composition and measurement. Chelsea, MD: Lewis Publishers.

Gut I, Nedelcheva V, Soucek P, et al. 1996. Cytochromes P450 in benzene metabolism and involvement of their metabolites and reactive oxygen species in toxicity. Environ Health Perspect 104:1211-1218.

Handson PD, Hanrahan PD. 1983. A rapid gas chromatographic method for the determination of free phenol in blood. J Agric Food Chem 31:447-448.

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

HazDat. 2006. Phenol. 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. April 06, 2006.

Hernberg S, Kurppa K, Ojajarvi J, et al. 1983. Congenital malformations and occupational exposure to disinfectants: A case-referrent study [Abstract]. Scand J Work Environ Health 9:55.

Hinkel Von GK, Kintzel HW. 1968. Phenolvergiftungen bei neugeborenen durch kutane resorption. Dtsch Gesundheitsw 23:2420-2422.

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

Hoff RM, Chan K. 1987. Measurement of polycyclic aromatic hydrocarbons in the air along the Niagara River. Environ Sci Technol 21:556-561.

Hoffman GM, Dunn BJ, Morris CR, et al. 2001. Two-week (ten-day) inhalation toxicity and two-week recovery study of phenol vapor in the rat. Int J Toxicol 20:45-52.

Hoffmann MJ, Ji S, Hedli CC, et al. 1999. Metabolism of [^{14}C]phenol in isolated perfused mouse liver. Toxicol Sci 49:40-47.

Horch R, Spilker G, Stark GB. 1994. Phenol burns and intoxications. Burns 20:45-50.

HSDB. 2006. Phenol. Hazardous Substances Data Bank. National Library of Medicine. http://toxnet.nlm.nih.gov. April 06, 2006.

Hsieh G-C, Sharma RP, Parker RDR, et al. 1992. Immunological and neurobiochemical alterations induced by repeated oral exposure of phenol in mice. Eur J Pharmacol 228:107-114.

Hughes MF, Hall LL. 1995. Disposition of phenol in rat after oral, dermal, intravenous, and intratracheal administration. Xenobiotica 25:873-883.

IARC. 1986. IARC Monographs on the evaluation of the carcinogenic risk of chemicals to humans. Vol. 38. Tobacco smoking. Lyon, France: World Health Organization, International Agency for Research on Cancer, 104-105.

IRIS. 2006. Phenol. Washington, DC: Integrated Risk Information System. U.S. Environmental Protection Agency. http://www.epa.gov/iris/subst/index.html. March 08, 2006.

Jansson T, Curvall M, Hedin A, et al. 1986. *In vitro* studies of biological effects of cigarette smoke condensate. II. Induction of sister chromatid exchanges in human lymphocytes by weakly acidic, semivolatile constituents. Mutat Res 169:129-139.

Jarvis SN, Straube RC, Williams ALJ, et al. 1985. Illness associated with contamination of drinking water supplies with phenol. Br Med J 290:1800-1802.

Kamijo Y, Soma K, Fukuda M, et al. 1999. Rabbit syndrome following phenol ingestion. Clin Toxicol 37:509-511.

Kao J, Bridges JW, Faulkner JK. 1979. Metabolism of [^{14}C]phenol by sheep, pig, rat. Xenobiotica 9:141-147.

Kauppinen TP, Partanen TJ, Nurminen MM. 1986. Respiratory cancers and chemical exposures in the wood industry: A nested case-control study. Br J Ind Med 43:84-90.

Kavlock RJ. 1990. Structure-activity relationships in the developmental toxicity of substituted phenols: *In vivo* effects. Teratology 41:43-59.

Kenyon EM, Seeley ME, Janszen D, et al. 1995. Dose-, route-, and sex-dependent urinary excretion of phenol metabolites in B6C3F$_1$ mice. J Toxicol Environ Health 44:219-233.

Kim D-H, Lee S-K, Chun B-Y, et al. 1994. Illness associated with contamination of drinking water supplies with phenol. J Korean Med Sci 9:218-223.

Kim HJ, Cho JH, Klaassen CD. 1995. Depletion of hepatic 3'-phosphoadenosine 5'-phosphosulfate (PAPS) and sulfate in rats by xenobiotics that are sulfated. J Pharmacol Exp Ther 275:654-658.

Konasewich D, Traversy W, Zar H. 1978. Status report on organic and heavy metal contaminants in the Lake Erie, Michigan, Huron and Superior Basins. Windsor, Ontario: International Joint Commission Great Lakes Water Quality Board, 161.

Koop DR, Laethem CL, Schnier GG. 1989. Identification of ethanol-inducible P450 isozyme 3a (P450IIE1) as a benzene and phenol hydroxylase. Toxicol Appl Pharmacol 98:278-288.

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

Kuwata K, Uebori M, Yamazaki Y. 1980. Determination of phenol in polluted air as p-nitrobenzeneazophenol derivative by reversed phase high performance liquid chromatography. Anal Chem 52:857-860.

Langford CP, Bartlett R, Haddad LM. 1998. Phenol and related agents. In: Haddad LM, Shannon MW, Winchester JF, eds. Clinical management of poisoning and drug overdose. Philadelphia, PA: Saunders, 956-960.

Lewin JF, Cleary WT. 1982. An accidental death caused by the absorption of phenol through skin. A case report. Forensic Sci Int 19:177-179.

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(1-4):365-372.

Liao TF, Oehme FW. 1981. Tissue distribution and plasma protein binding of [^{14}C] phenol in rats. Toxicol Appl Pharmacol 57:220-225.

Lide DR. 1993. CRC handbook of chemistry and physics. Boca Raton, FL: CRC Press, 3-376, 6-60, 16-25.

Lide DR, Milne GWA. 1994. Phenol. In: Handbook of data on organic compounds. Boca Raton, FL: CRC Press, 3990.

Lo Dico C, Caplan YH, Levine B, et al. 1989. Phenol: Tissue distribution in a fatality. J Forensic Sci 34:1013-1015.

Lopes TJ, Furlong ET. 2001. Occurrence and potential adverse effects of semivolatile organic compounds in streambed sediment, United States, 1992–1995. Environ Sci Technol 20:727-737.

Ludzack FJ, Ettinger MB. 1960. Chemical structures resistant to aerobic biochemical stabilization. J Water Pollut Control Fed 32:1173-1200.

Lyman WJ, Reehl WF, Rosenblatt DH. 1982. Handbook of chemical property estimation methods. Environmental behavior of organic compounds. New York, NY: McGraw-Hill Book Co., 15-9 to 15-31.

McFadden SA. 1996. Phenotypicvariation in xenobiotic metabolism and adverse environmental response: Focus on sulfur-dependent detoxification pathways. Toxicology 111:43-65.

Medinsky MA, Kenyon EM, Schlosser PM. 1995. Benzene: A case study in parent chemical and metabolite interactions. Toxicology 105:225-233.

Merliss RR. 1972. Phenol marasmus. Occup Med 14:55-56.

Mill T, Mabey W. 1985. Photodegradation in water. In: Neely WR, Blau GE, eds. Environmental exposure from chemicals. Vol. 1. Boca Raton, FL: CRC Press, 208-211.

Miller BM, Pujadas E, Gocke E. 1995. Evaluation of the micronucleus test *in vitro* using Chinese hamster cells: Results of four chemicals weakly positive in the *in vivo* micronucleus test. Environ Mol Mutagen 26:240-247.

Miyagawa M, Takasawa H, Sugiyama A, et al. 1995. The *in vivo-in vitro* replicative DNA synthesis (RDS) test with hepatocytes prepared from male B6C3F$_1$ mice as an early prediction assay for putative nongenotoxic (Ames-negative) mouse hepatocarcinogens. Mutat Res 343:157-183.

Morimoto K, Wolff S. 1980. Increase of sister chromatid exchanges and perturbations of cell division kinetics in human lymphocytes by benzene metabolites. Cancer Res 40:118-1193.

Morimoto K, Wolff S, Koizumi A. 1983. Induction of sister-chromatid exchanges in human lymphocytes by microsomal activation of benzene metabolites. Mutat Res 119:355-360.

Morrison JE, Matthews D, Washington R, et al. 1991. Phenol motor point blocks in children: Plasma concentrations and cardiac dysrhythmias. Anesthesiology 75:359-362.

Moser VC, Cheek BM, MacPhail RC. 1995. A multidisciplinary approach to toxicological screening: III. Neurobehavioral toxicity. J Toxicol Environ Health 45:173-210.

Nagel R, Adler HI, Rao TK. 1982. Induction of filamentation by mutagens and carcinogens in a ion-mutant of *Escherichia coli*. Mutat Res 105:309-312.

Narotsky MG, Kavlock RJ. 1995. A multidisciplinary approach to toxicological screening: II. Developmental toxicity. J Toxicol Environ Health 45:145-171.

NCI. 1980. Bioassay of phenol for possible carcinogenicity. Bethesda, MD: U.S. Department of Health and Human Services. National Cancer Institute. NCI-CG-TR-203.

NCI. 1998. Cigars. Health effects and trends. Smoking and tobacco control monograph 9. Bethesda, MD: U.S. Department of Health and Human Services. National Cancer Institute. NIH Pub. No. 98-4302.

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

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 360:271-278.

NIOSH. 1994. NIOSH manual of analytical methods. 4th ed. Cincinnati, OH: U.S. Department of Health and Human Services, Centers for Disease Control, National Institute for Occupational Safety and Health.

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.

NTP. 1983a. Teratologic evaluation of phenol (CAS No. 108-95-2) in CD-1 rats. Research Triangle Park, NC: National Toxicology Program. Research Triangle Institute.

NTP. 1983b. Teratologic evaluation of phenol (CAS No. 108-95-2) in CD mice. Laboratory study: September 18, 1980 to January 12, 1981. Research Triangle Park, NC: National Toxicology Program. Research Triangle Institute.

NTP. 2005. Report on carcinogens. 11th ed. Research Triangle Park, NC: National Toxicology Program, Department of Health and Human Services. http://ntp-server.niehs.nih.gov/ntp/roc/toc11.html. March 08, 2006.

O'Grodnick JS, Dupre GD, Gulizia BJ, et al. 1983. Determination of benzene, phenol, catechol and hydroquinone in whole blood of rats and mice. J Chromatog Sci 21:289-292.

Painter RB, Howard R. 1982. The HeLa DNA-synthesis inhibition test as a rapid screen for mutagenic carcinogens. Mutat Res 92:427-437.

Paschin YV, Bahitova LM. 1982. Mutagenicity of benzo[a]pyrene and the antioxidant phenol at the HGPRT locus of V79 Chinese hamster cells. Mutat Res 104:389-393.

Pashin YV, Bakhitova LM, Bentkhen TI. 1987. Dependence of antimutagenic activity of simple phenols on the number of hydroxyl groups. Bull Exp Biol Med 102(2):1121-1123.

Pellack-Walker P, Blumer JL. 1986. DNA damage in L5178YS cells following exposure to benzene metabolites. Mol Pharmacol 39:42-47.

Piotrowski JK. 1971. Evaluation of exposure to phenol: Absorption of phenol vapor in the lungs through the skin and excretion of phenol in urine. Br J Ind Med 28:172-178.

Plumb RH Jr. 1987. A comparison of ground water monitoring data from CERCLA and RCRA sites. Ground Water Monit Rev 7:94-100.

Poirier MC, DeCicco BT, Lieberman MW. 1975. Nonspecific inhibition of DNA repair synthesis by tumor promotors in human diploid fibroblasts damage with N-acetoxy-2-acetylaminofluorene. Cancer Res 35:1392-1397.

Pool PL, Lin PZ. 1982. Mutagenicity testing in the *Salmonella typhimurium* assay of phenolic compounds and phenolic fractions obtained from smokehouse smoke condensates. Food Chem Toxicol 29:383-391.

Popp W, Rauscher D, Muller G et al. 1994. Concentrations of benzene in blood and *S*-phenyl-mercapturic acid and *t,t*-muconic acid in urine in car mechanics. Int Arch Occup Environ Health 66:1-6.

Powley MW, Carlson GP. 2001. Cytochrome P450 isozymes involved in the metabolism of phenol, a benzene metabolite. Toxicol Lett 125:117-123.

Powell GM, Miller JJ, Olavesen AH, et al. 1974. Liver as major organ of phenol detoxification. Nature (London) 252:234-235.

Pullin TG, Pinkerton MN, Johnson RV, et al. 1978. Decontamination of the skin of swine following phenol exposure: A comparison of the relative efficacy of water versus polyethylene glycol/industrial methylated spirits. Toxicol Appl Pharmacol 43:199-206.

Quebbemann AJ, Anders MW. 1973. Renal tubular conjugation and excretion of phenol and p-nitrophenol in the chicken: Differing mechanisms of renal transfer. J Pharmacol Exp Ther 184:695-708.

Ramakrishna BS, Roberts-Thomson IC, Pannall PR, et al. 1991. Impaired sulphation of phenol by the colonic mucosa in quiescent and active ulcerative colitis. Gut 32:46-49.

Rick DL, Licht CF, McCarty LP. 1982. Determination of phenol and pentachlorophenol in plasma and urine samples by gas liquid chromatography. J Anal Toxicol 6:297-300.

Rubin HE, Alexander M. 1983. Effect of nutrients on the rates of mineralization of trace concentrations of phenol and p-nitrophenol. Environ Sci Technol 17:104-107.

Ryan BM, Selby R, Gingell R, et al. 2001. Two-generation reproduction study and immunotoxicity screen in rats dosed with phenol via the drinking water. Int J Toxicol 20:121-142.

Sacan MT, Balcioglu IA. 1996. Prediction of the soil sorption coefficient of organic pollutants by the characteristic root index model. Chemosphere 32(10):1993-2001.

Salaman MH, Glendenning OM. 1957. Tumor promotion in mouse skin by sclerosing agents. Br J Cancer 11:434-444.

Schaltenbrand WE, Coburn SP. 1985. Determination of phenol and p-cresol in urine. Clin Chem 31:2042-2043.

Schwartz CS, Snyder R, Kalf GF. 1985. The inhibition of mitochondrial DNA replication *in vitro* by the metabolites of benzene, hydroquinone and p-benzoquinone. Chem-Biol Interact 53:327-350.

Scott HD, Wolf DC, Lavy TL. 1983. Adsorption and degradation of phenol at low concentrations in soil. J Environ Qual 12:91-95.

Shamy MY, El Gazzar RM El Sayed MA, et al. 1994. Study of some biochemical changes among workers occupationally exposed to phenol, alone or in combination with other organic solvents. Ind Health 32:207-214.

Shelby MD, Witt KL. 1995. Comparison of results from mouse bone marrow chromosomes aberration and microbucleous tests. Environ Mol Mutagen 25(4):302-313.

Shiu WY, Ma KC, Varhanickova AD, et al. 1994. Chlorophenols and alkylphenols: A review and correlation of environmentally relevant properties and fate in an evaluative environment. Chemosphere 29:1155-1224.

Sithole BB, Williams DT, Lastoria C, et al. 1986. Determination of halogenated phenols in raw and potable water by selected ion gas chromatography-mass spectrometry. J Assoc Off Anal Chem 69:466-473.

Skare JA, Schrotel KR. 1984. Alkaline elution of rat testicular DNA: Detection of DNA strand breaks after *in vivo* treatment with chemical mutagens. Mutat Res 130:283-294.

Snyder R, Chepiga T, Yang CS, et al. 1993. Benzene metabolism by reconstituted cytochromes P450 2B1 and 2E1 and its modulation by cytochrome b(5), microsomal epoxide hydrolase, and glutathione transferases: Evidence for an important role of microsomal epoxide hydrolase in the formation of hydroquinone. Toxicol Appl Pharmacol 122(2):172-181.

Soares ER, Tift JP. 1982. Phenol poisoning: Three fatal cases. J Forensic Sci 27(3):729-731.

Spiller HA, Quandrani-Kushner DA, Cleveland P. 1993. A five year evaluation of acute exposures to phenol disinfectant (26%). J Toxicol Clin Toxicol 31:307-313.

Stajduhar-Caric Z. 1968. Acute phenol poisoning. Singular findings in a lethal case. J Forensic Med 15:41-42.

Stommel P, Muller G, Stucker W et al. 1989. Determination of S-phenylmercapturic acid in the urine- An improvement in the biological monitoring of benzene exposure. Carcinogenesis 10:279-282.

Sze C-C, Shi C-Y, Ong C-N. 1996. Cytotoxicity and DNA strand breaks induced by benzene and its metabolites in Chinese hamster ovary cells. J Appl Toxicol 16:259-264.

Tanaka S, Choe N, Kita T, et al. 1998. Distribution of phenol in a fatal poisoning case determined by gas chromatography/mass spectrometry. J Forensic Sci 43(5):1086-1088.

Thurman EM. 1985. Organic geochemistry of natural waters. Boston, MA: Martinus Nijhoff/Dr. W. Junk Publishers, 143-146.

Tomkins BA, Jenkins RA, Griest WH, et al. 1984. Liquid chromatographic determination of phenol and cresols in total particulate matter of cigarette smoke. J Assoc Off Anal Chem 67:919-923.

Tremaine LM, Diamond GL, Quebbemann AJ. 1984. *In vivo* quantification of renal glucuronide and sulfate conjugation of 1-naphthol and *p*-nitrophenol in the rat. Biochem Pharmacol 33:419-427.

TRI04. 2006. 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/. March 16, 2006.

Truppman ES, Ellenby JD. 1979. Major electrocardiographic changes during chemical face peeling. Plast Reconstr Surg 63:44-48.

Tsutsui T, Hayashi N, Maizumi H, et al. 1997. Benzene-, catechol-, hydroquinone- and phenol-induced cell transformation, gene mutations, chromosome aberrations, aneuploidy, sister chromatid exchanges and unscheduled DNA synthesis in Syrian hamster embryo cells. Mutat Res 373(1):113-123.

U.S. Air Force. 1961. Tolerance criteria for continuous inhalation exposure to toxic material. I. Effects on animals of 90-day exposure to phenol, CCl_4 and a mixture of indole, skatole, H_2S and methyl mercaptan. Wright-Patterson Air Force Base, OH: U.S. Air Force systems command, Aeronautical Systems Division. ASD technical report 61-519(I).

Van Roosmalen PB, Purdham J, Drummond I. 1981. An improved method for the determination of phenol in the urine of workers exposed to benzene or phenol. Int Arch Occup Environ Health 48:159-163.

Van Rossum P, Webb RG. 1978. Isolation of organic water pollutants by XAD resins and carbon. J Chromatogr 150:381-392.

Von Oettingen WF, Sharpless NE. 1946. The toxicity and toxic manifestations of 2,2-bis(p-chlorophenyl)-1,1,1-trichloroethane (DDT) as influenced by chemical changes in the molecule. J Pharmacol Exp Ther 88:400-413.

Warner MA, Harper JV. 1985. Cardiac dysrhythmias associated with chemical peeling with phenol. Anesthesiology 62:366-367.

Weitering JG, Kriggsheld KR, Mulder GJ. 1979. The availability of inorganic sulfate as a rate limiting factor in the sulfate conjugation of xenobiotics in the rat. Biochem Pharmacol 28:757-762.

Wexler MR, Halon DA, Teitelbaum A, et al. 1984. The prevention of cardiac arrhythmias produced in an animal model by the topical application of a phenol preparation in common use for face peeling. Plast Reconstr Surg 73:595-598.

Wilcosky TC, Tyroler HA. 1983. Mortality from heart disease among workers exposed to solvents. J Occup Med 25:879-885.

Wood K. 1978. The use of phenol as a neurolytic agent: A review. Pain 5:205-229.

Wynder E, Hoffmann D. 1961. A study of tobacco carcinogenesis. VIII. The role of acidic fractions as promotors. Cancer 14:1306-1315.

York RG. 1997. Oral (gavage) developmental toxicity study of phenol in rats. Proctor & Gamble Company. Submitted to the U.S. Environmental Protection Agency under TSCA Section 8D. OTS0573686.

Yrjanheikki E. 1978. A new method of personnel sampling and analyzing of phenol. Am Ind Hyg Assoc J 39:326-330.

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 Phenol

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

UPPER CASE: Priority Data Needs identified for phenol