3. HEALTH EFFECTS

3.1 INTRODUCTION

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

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

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

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

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

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

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

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

3.2.1.1 Death

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

1991). Workers (exposed and non-exposed) had a mortality rate, from all causes, similar to that of the general U.S. population. Compared to either the general population or unexposed workers, exposed workers had small statistically non-significant excesses in mortality due to Hodgkin's disease (standardized mortality ratio [SMR], 1.7; 95% confidence interval [CI], 0.8–3.1) and esophageal (SMR, 1.6; 95% CI, 0.9–2.6), renal (SMR, 1.3; 95% CI, 0.7–2.1), and rectal (SMR, 1.4; 95% CI, 0.8–2.2) cancers. They also had small reductions in mortality due to: cancer of the stomach, testes, pancreas, buccal cavity/pharynx and brain; lymphosarcoma; liver cirrhosis; emphysema; diseases of the cardiovascular, circulatory, and digestive systems; motor vehicle accidents; and all accidents. The ambiguity of these data, as well as the fact that dose-related trends occurred only for those diseases showing reductions in mortality, makes it difficult to assess the impact on mortality of long-term occupational exposure to phenol.

Deichmann et al. (1944) exposed guinea pigs, rabbits, and rats to phenol vapor at levels ranging from 26 to 52 ppm for 28–88 days. After 28 days of exposure, 5 of 12 guinea pigs died, but no deaths occurred in rabbits or rats. Since only a range was given for the exposure level, the exact level of phenol in air that resulted in death of guinea pigs was not established and may be as low as 26 ppm or as high as 52 ppm. Interpretation of this study is further complicated by an apparent lack of controls. However, since the effects observed in guinea pigs and rabbits (described in subsequent sections in Chapter 3) were so severe, it is difficult to ascribe the mortality to any source other than the phenol exposure. The lower limit of the exposure range, 26 ppm, is recorded as a serious LOAEL in Table 3-1 and plotted in Figure 3-1. No deaths were reported in Rhesus monkeys, rats, or mice exposed to 5 ppm phenol continuously for 90 days (U.S. Air Force 1961).

3.2.1.2 Systemic Effects

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

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

Table 3-1 Levels of Significant Exposure to Phenol - Inhalation

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Systemic								
1	Rat (Fischer- 344)	2 wk 5 d/wk 6 hr/d	Resp	25[b]			Hoffman et al. 2001	NOAELs are for organs weight and histopathology.
			Hemato	25				
			Hepatic	25				
			Renal	25				
			Bd Wt	25				
2	Mouse (Swiss OF1)	5 min	Resp		166 M (50% decrease in respiration rate)		De Ceaurriz et al. 1981	
Immuno/ Lymphoret								
3	Rat (Fischer- 344)	2 wk 5 d/wk 6 hr/d		25			Hoffman et al. 2001	NOAEL is for histopathology of the spleen.
4	Mouse (CD-1)	5 d 3 hr/d		5 F			Aranyi et al. 1986	NOAEL is for no change in susceptibility to infectious agents.
Neurological								
5	Rat Harlan-Wistar	1 hr		234 F			Flickinger 1976	NOAEL is for no adverse neurological signs.

Table 3-1 Levels of Significant Exposure to Phenol - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)		Reference Chemical Form	Comments
6	Rat (Harlan-Wistar)	8 hr				234 F	(loss of coordination and tremors)	Flickinger 1976	
INTERMEDIATE EXPOSURE									
Death									
7	Gn Pig (NS)	6 wk 5 d/wk 7 hr/d				26	(5/12 deaths)	Deichmann et al. 1944	
Systemic									
8	Monkey (Rhesus)	90 d 24 hr/d	Resp	5 M				U.S. Air Force 1961	NOAELs are for organs histopathology.
			Hemato	5 M					
			Hepatic	5 M					
			Renal	5 M					
			Bd Wt	5 M					
9	Rat (White)	15 d 24 hr/d	Hemato	26				Dalin and Kristoffersson 1974	
			Hepatic			26	(serum activities of ALT, AST, LDH, and GLDH increased 2-6-fold; increased serum magnesium)		
			Bd Wt	26					

Table 3-1 Levels of Significant Exposure to Phenol - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
10	Rat (NS)	10 wk 5 d/wk 7 hr/d	Resp	26			Deichmann et al. 1944	NOAELs are for histopathology of tissues.
			Cardio	26				
			Hepatic	26				
			Renal	26				
11	Rat (Sprague-Dawley)	90 d 24 hr/d	Resp	5 M			U.S. Air Force 1961	NOAELs are for histopathology of tissues.
			Hemato	5 M				
			Hepatic	5 M				
			Renal	5 M				
			Bd Wt	5 M				
12	Mouse (NS)	90 d 24 hr/d	Resp	5 M			U.S. Air Force 1961	NOAELs are for histopathology of tissues.
			Hemato	5 M				
			Hepatic	5 M				
			Renal	5 M				
			Bd Wt	5 M				

Table 3-1 Levels of Significant Exposure to Phenol - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)		Reference Chemical Form	Comments
13	Gn Pig (NS)	6 wk 5 d/wk 7 hr/d	Resp			26	(acute lobular pneumonia with occasional abscesses and vascular damage)	Deichmann et al. 1944	
			Cardio			26	(necrosis of the myocardium, extensive reactive inflammation)		
			Hepatic			26	(fatty changes, centrolobular degeneration and necrosis)		
			Renal			26	(edema of the convoluted tubules, slightly advanced focal cortical lesions, glomerular degeneration)		

Table 3-1 Levels of Significant Exposure to Phenol - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
14	Rabbit (NS)	12 wk 5 d/wk 7 hr/d	Resp			26 (confluent lobular pneumonia, chronic purulent bronchitis, hyperplastic peribronchial tissue, degenerative changes in pulmonary vessels)	Deichmann et al. 1944	
			Cardio			26 (myocardial degeneration, necrosis of muscle bundles, interstitial fibrosis, lymphocytic infiltration)		
			Hepatic			26 (centrilobular degeneration and necrosis)		
			Renal			26 (edema of the convoluted tubules, focal cortical lesions, glomerular degeneration)		
Neurological								
15	Monkey (Rhesus)	90 d 24 hr/d		5 M			U.S. Air Force 1961	
16	Rat (White)	15 d 24 hr/d			26 (mild motor disorders during the first 4 days of exposure, 4.4 degrees decrease in sliding angle)		Dalin and Kristoffersson 1974	

Table 3-1 Levels of Significant Exposure to Phenol - Inhalation (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form	Comments
17	Rat (Sprague-Dawley)	90 d 24 hr/d		5 M			U.S. Air Force 1961	NOAEL is for brain histopathology and results of a swimming test.
18	Mouse (NS)	90 d 24 hr/d		5 M			U.S. Air Force 1961	NOAEL is for brain histopathology and results of a swimming test.
19	Gn Pig (NS)	6 wk 5 d/wk 7 hr/d				26 (hindlimb paralysis)	Deichmann et al. 1944	

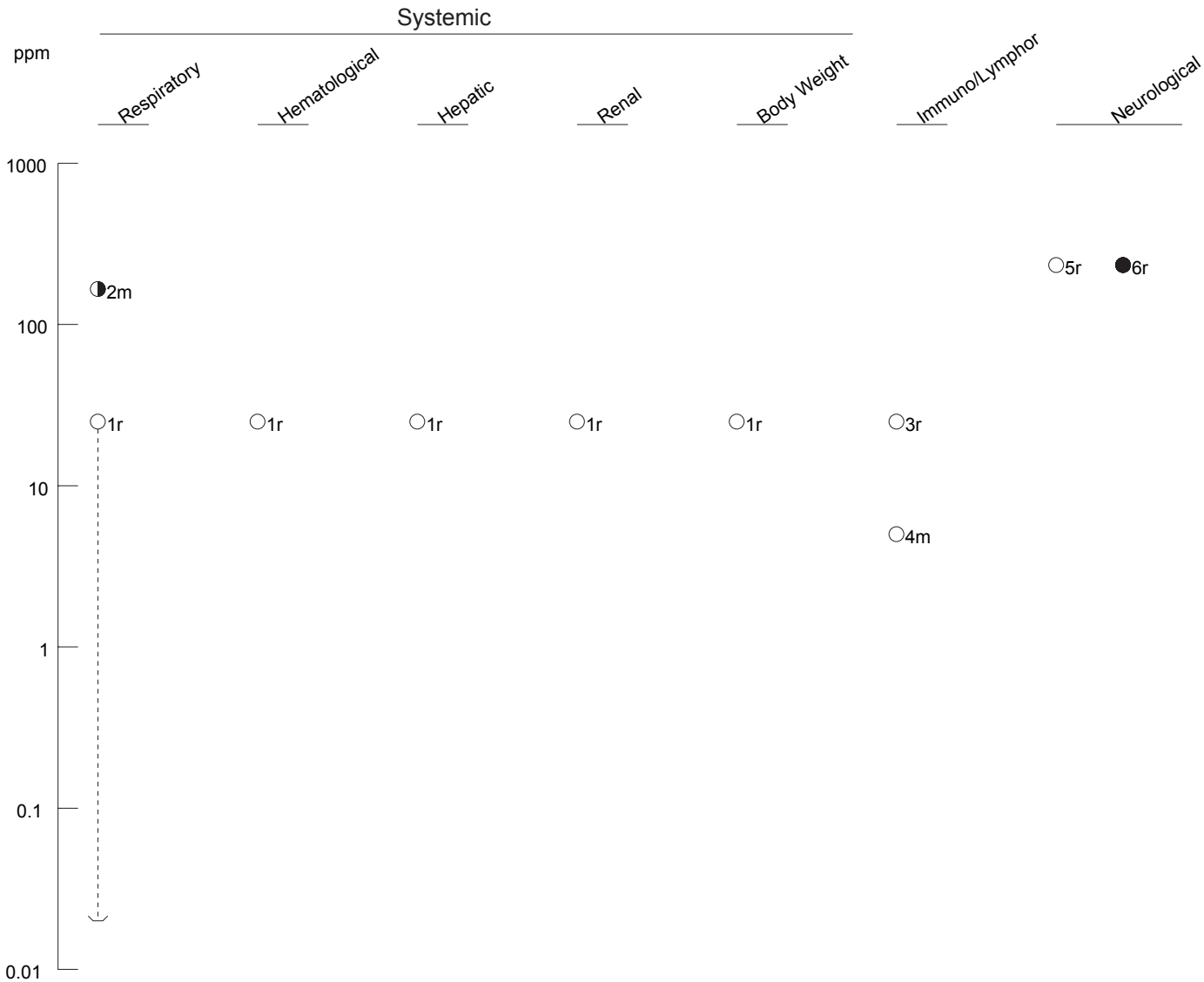
a The number corresponds to entries in Figure 3-1.

b Used to derive and acute-duration inhalation MRL of 0.02 ppm; the MRL was derived by dividing the NOAEL[HEC] of 0.6 ppm by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustment and 10 for human variability).

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

Figure 3-1 Levels of Significant Exposure to Phenol - Inhalation

Acute (≤14 days)



c-Cat -Humans f-Ferret n-Mink
d-Dog k-Monkey j-Pigeon o-Other
r-Rat m-Mouse e-Gerbil
p-Pig h-Rabbit s-Hamster
q-Cow a-Sheep g-Guinea Pig

◆ Cancer Effect Level-Animals
● LOAEL, More Serious-Animals
◑ LOAEL, Less Serious-Animals
○ NOAEL - Animals

▼ Cancer Effect Level-Humans
▲ LOAEL, More Serious-Humans
◭ LOAEL, Less Serious-Humans
△ NOAEL - Humans

■ LD50/LC50
Minimal Risk Level for effects other than Cancer

Figure 3-1 Levels of Significant Exposure to Phenol - Inhalation *(Continued)*

Intermediate (15-364 days)

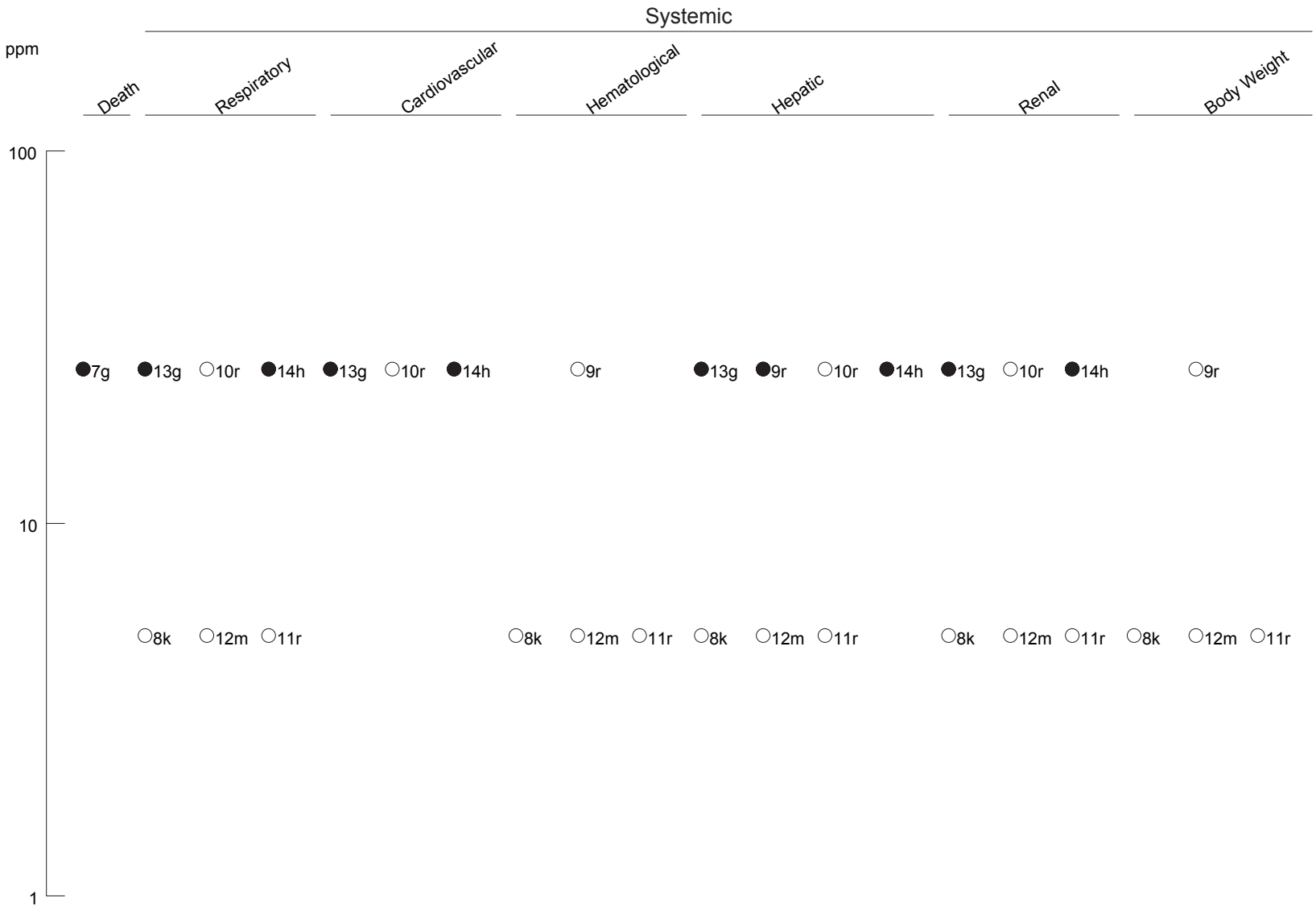
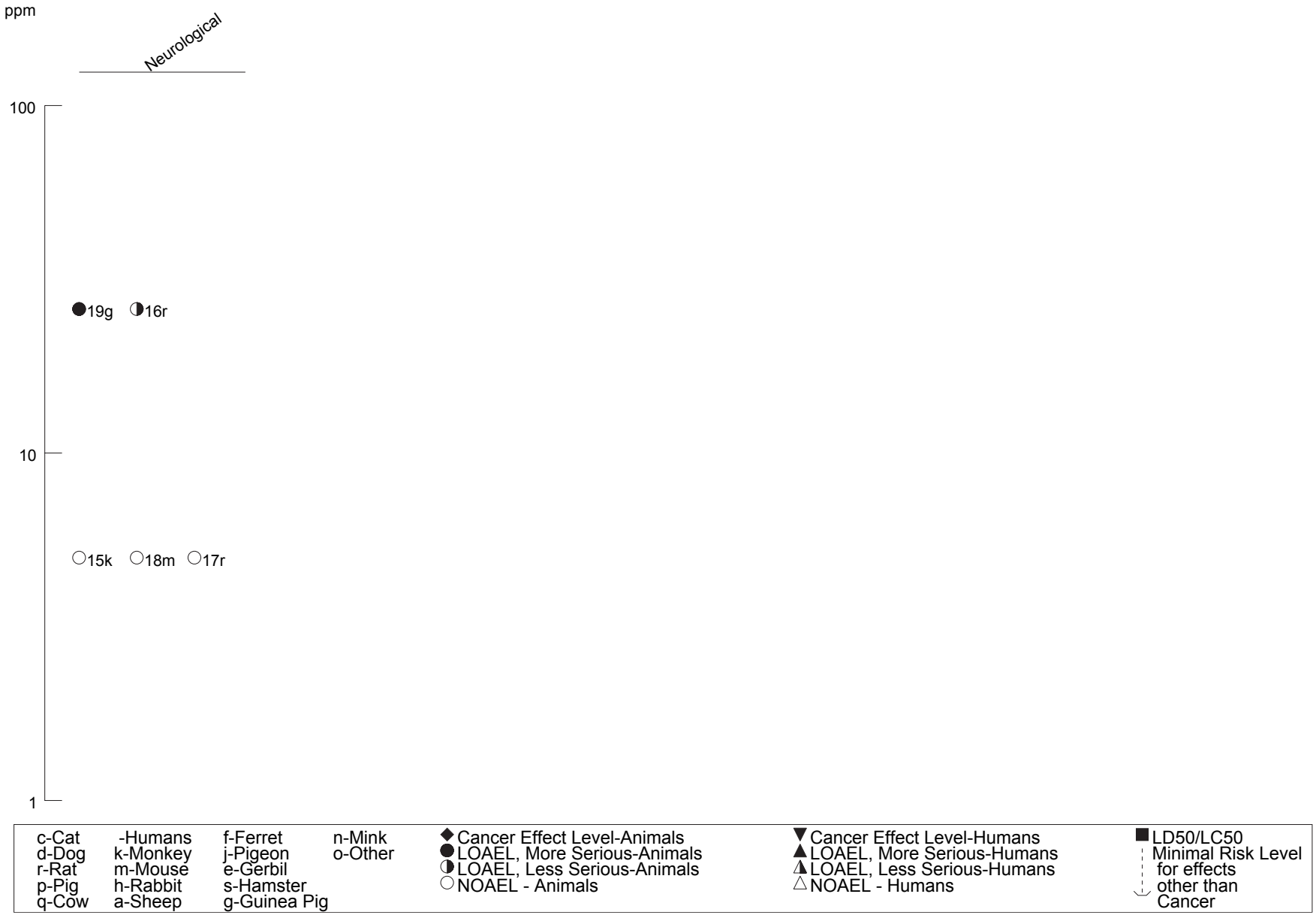


Figure 3-1 Levels of Significant Exposure to Phenol - Inhalation *(Continued)*

Intermediate (15-364 days)



the investigators to suggest that exposure to phenol could have a protective effect for diseases involving free radical damage.

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

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

In a study in which female Harlan Wistar rats were exposed for 1 hour to a phenol aerosol at a concentration of 234 ppm, then held for 2 weeks postexposure, Flickinger (1976) observed signs of nasal irritation during exposure. However, all animals exhibited normal behavior by postexposure day 1, and no abnormal lesions were observed upon gross autopsy. No histopathology was performed; thus, this study is not presented as a LOAEL for rats. A more recent study in which rats were exposed intermittently nose-only to up to 25 ppm phenol for 2 weeks found no significant gross or microscopic alterations in the respiratory tract, including the nasal turbinates (Hoffman et al. 2001). This study was used as the basis for derivation of an acute-duration inhalation MRL for phenol.

Inflammation, cellular infiltration, pneumonia, bronchitis, endothelial hyperplasia, and capillary thrombosis occurred in guinea pigs exposed by inhalation to 26–52 ppm phenol for 41 days (Deichmann et al. 1944). Rabbits exhibited qualitatively similar but less severe effects after 88 days of similar exposure. Rats exposed similarly showed no gross or microscopic alterations in the respiratory tract. Since only a range was given for the exposure level (26–52 ppm), the exact level of phenol in air that resulted in respiratory effects was not established and may be as low as 26 ppm or as high as 52 ppm. Interpretation of this study is further complicated by an apparent lack of controls. However, the lung pathology was so severe, particularly in the guinea pigs, that it is difficult to ascribe the effects to any source other than the phenol exposure. The lower limit of the exposure range, 26 ppm, can be considered a LOAEL for respiratory effects in guinea pigs and rabbits and a NOAEL for rats.

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

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

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

Myocardial injury was reported in guinea pigs exposed to 26–52 ppm for 41 days, rabbits exhibited qualitatively similar but less severe effects after 88 days of similar exposure, and rats showed no significant alterations after 54 exposures (Deichmann et al. 1944). The injury was characterized by myocardial inflammation, degeneration, and necrosis, interstitial fibrosis, and lymphocyte infiltration. Since only a range was given for the exposure level (26–52 ppm), the exact level of phenol in air that resulted in myocardial injury was not established and may be as low as 26 ppm or as high as 52 ppm. Interpretation of this study is further complicated by an apparent lack of controls. However, the heart pathology was so severe that it is difficult to ascribe the effects to any source other than the phenol

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

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

A cohort mortality study of workers in five phenol-formaldehyde resin manufacturing plants found that exposed workers showed a slight reduction in death rate due to cancers of the digestive system as compared to both non-exposed workers and the general population (Dosemeci et al. 1991).

In a study of rats exposed continuously for 15 days to 26 ppm phenol vapor, Dalin and Kristoffersson (1974) noted the absence of alterations in the digestive system and attributed this to the relatively low exposure levels (as compared to studies using oral dosing), but no further discussion was provided.

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

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

Workers (n=20) at an oil-refining plant in Egypt exposed to a time-weighted mean concentration of 5.4 ppm of phenol in air for a mean exposure period of 13.15 years showed small but significant increases in hemoglobin, hematocrit, mean corpuscular hemoglobin, and mean corpuscular volume, but red blood cell counts were not significantly altered relative to a group of 30 unexposed controls (Shamy et al. 1994). Other small, but significant changes relative to controls included increased basophils and neutrophils, decreased monocytes, and increased clotting time.

Hematocrit and hemoglobin concentrations were not affected in rats exposed to 26 ppm phenol in air continuously for 15 days (Dalin and Kristoffersson 1974). Detailed hematological evaluations including red and white blood cell, reticulocyte, and platelet counts; white cell differential; hemoglobin and sulfhemoglobin, and red cell fragility tests, as well as corpuscular volume, corpuscular hemoglobin, and corpuscular hemoglobin concentrations, did not reveal any effects in Rhesus monkeys, rats, or mice exposed continuously to 5 ppm phenol in air for 90 days (U.S. Air Force 1961). Comprehensive hematology testing of rats exposed nose-only to up to 25 ppm of phenol 6 hours/day, 5 days/week for 2 weeks showed no significant exposure-related deviations from control values (Hoffman et al. 2001).

Musculoskeletal Effects. A case of muscle pain and weakness was described in an individual after intermittent chronic inhalation and dermal exposure to vapors and solutions of phenol, cresol, and xylenol for >10 years (Merliss 1972). The symptoms lessened when the subject was removed from exposure. Although the exposure concentrations were not reported, the study author stated that the patient often detected heavy odors, and that phenol was often spilled on his clothes resulting in skin irritation. Since phenol is absorbed readily from the skin, dermal absorption of phenol may have contributed to the systemic effects that were observed. The above symptoms may represent neurological effects rather than injury to the muscle tissue.

Hepatic Effects. Enlarged liver and elevated serum levels of hepatic enzymes indicative of liver injury (lactate dehydrogenase, 2 times above normal; aspartate aminotransferase (AST), 21 times above

normal; alanine aminotransferase (ALT), 100 times above normal) were observed in an individual following chronic daily exposure to vapors and spills of phenol for >10 years (Merliss 1972). The symptoms lessened when the individual was removed from the site of exposure. Although the exposure concentrations were not reported, the study author stated that the patient often detected heavy odors and that phenol was often spilled on his clothes resulting in skin irritation. Since phenol is absorbed readily from the skin, dermal absorption may have contributed to the systemic effects that were observed. A study of 20 workers at an oil-refining plant in Egypt exposed to a time-weighted average concentration of phenol of 5.4 ppm for a mean exposure duration of 13.15 years found small, but significant increases in ALT and AST activities (approximately 65 and 54%, respectively) in serum collected at the end of the shift of the last working day of the week relative to 30 unexposed controls (Shamy et al. 1994).

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

Centrilobular degeneration and necrosis of the liver were reported in guinea pigs exposed intermittently by inhalation to 26–52 ppm phenol for 41 days, rabbits exhibited qualitatively similar but less severe effects after 88 days of similar exposure, whereas rats showed no significant alterations after 54 exposures (Deichmann et al. 1944). Since only a range was given for the exposure level (26–52 ppm), the exact level of phenol in air that resulted in hepatic injury was not established and may be as low as 26 ppm or as high as 52 ppm. Interpretation of this study is further complicated by an apparent lack of controls. However, the liver pathology was so severe, particularly in the guinea pigs, that it is difficult to ascribe the effects to any source other than the phenol exposure.

Elevated activities of liver enzymes (lactate dehydrogenase, AST, ALT, glutamate dehydrogenase) were found in the serum of rats exposed continuously to 26 ppm phenol vapor for 15 days (Dalin and Kristoffersson 1974). Increased concentration of these enzymes in serum is often associated with liver injury, but is not conclusive evidence for the type or severity of injury. Therefore, 26 ppm can be considered a less serious LOAEL in rats. Serum levels of magnesium were also increased in these rats, an effect the study authors suggested may also be a sign of liver injury. In a more recent study, rats exposed nose-only to up to 25 ppm of phenol 6 hours/day, 5 days/week for 2 weeks showed no evidence of liver effects as monitored by clinical chemistry tests and histopathological examination of the liver (Hoffman et al. 2001). No significant histological abnormalities were detected in the livers of Rhesus monkeys, rats, or mice exposed continuously to 5 ppm phenol in air for 90 days (U.S. Air Force 1961).

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

Renal proximal tubule and glomerular injury was reported in guinea pigs exposed intermittently by inhalation to 26–52 ppm phenol for 41 days, and rabbits exhibited qualitatively similar but less severe effects after 88 days of similar exposure; rats exposed similarly for 54 days showed no significant effects (Deichmann et al. 1944). Since only a range was given for the exposure level (26–52 ppm), the exact level of phenol in air that resulted in renal injury was not established and may be as low as 26 ppm or as high as 52 ppm. Interpretation of this study is further complicated by an apparent lack of controls. However, the kidney pathology was so severe, particularly in the guinea pigs, that it is difficult to ascribe the effects to any source other than the phenol exposure. The lower limit of the exposure range, 26 ppm, can be considered a LOAEL for renal injury in guinea pigs and rabbits. No significant histological abnormalities were detected in the kidneys of Rhesus monkeys, rats, or mice exposed continuously to 5 ppm phenol in air for 90 days (U.S. Air Force 1961). No kidney pathology was reported in a study in rats exposed intermittently nose-only to up to 25 ppm of phenol for 2 weeks (Hoffman et al. 2001); specific end points monitored included kidney histopathology, blood urea nitrogen (BUN), and serum creatinine and electrolytes.

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

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

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

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

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

Body weight effects were not observed in adult female Harlan Wistar rats exposed to an aerosol containing 234 ppm phenol for 8 hours (Flickinger 1976), in rats exposed continuously to 26 ppm phenol in air for 15 days (Dalin and Kristoffersson 1974), in Rhesus monkeys, rats, or mice exposed continuously to 5 ppm phenol in air for 90 days (U.S. Air Force 1961), or in rats exposed intermittently nose-only for 2 weeks to up to 25 ppm of phenol vapor (Hoffman et al. 2001).

Metabolic Effects. Dalin and Kristoffersson (1974) reported elevated serum concentrations of potassium and magnesium in rats exposed to 26 ppm phenol vapor continuously for 15 days. While not necessarily adverse, this effect may be related to the muscle tremors and neurological effects observed following inhalation exposure to phenol (see Section 3.2.1.4). No further information was located regarding metabolic effects of inhaled phenol in animals.

3.2.1.3 Immunological and Lymphoreticular Effects

A case-control study of office workers was conducted by Baj et al. (1994) to evaluate the risks of chronic exposures to "inhaled formaldehyde, phenol and isomers of organic chlorohydrocarbons from Ksylamit™" which is a widely used liquid wood preservative. Twenty-two workers (18 women and 4 men) exposed for at least 6 months were the cases, and 29 non-exposed, nonsmoking volunteers matched for age, sex, and place of residence were the controls. Using blood samples drawn after 6 months of exposure, cases and controls were compared on a variety of immunological parameters. The exposed group showed significantly decreased ($p<0.05$) levels of the CD3+, CD4+, and CD8+ subsets of T-lymphocytes, a significant decrease ($p<0.001$) in lymphocyte responsiveness to the mitogen phytohemagglutinin (PHA), a significant decrease ($p<0.05$) in natural killer (NK) cell cytotoxicity, and a significant decrease ($p<0.0001$) in the mixed lymphocyte response assay. Measurement of the office air

at the end of the 6-month period revealed a level of phenol of 0.34 ppm. Although the authors contend that their observations support the concern that chronic exposure to phenol could adversely affect the immune system, it is important to consider not only that other volatile chemicals, chlorinated organics, were present in the wood-preserving liquid, but also that the chemical composition provided for Ksylamit™ opens up the possibility that the effects being evaluated resulted from exposure to pentachlorophenol rather than phenol. This is particularly true since it was not possible to determine from the information presented if the analytical methods used would differentiate between phenol and pentachlorophenol.

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

3.2.1.4 Neurological Effects

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

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

Female Harlan Wistar rats exposed for 1 or 8 hours to 234 ppm phenol delivered in an aerosol demonstrated no neurological effects at 1 hour, a slight loss of coordination with spasm of the muscle groups at 4 hours, and frank tremors leading to a severe loss of coordination by 8 hours (Flickinger 1976). All animals were normal by postexposure day 1, and no abnormal lesions were observed upon gross autopsy performed at the end of a 14-day observation period. These exposure levels are recorded in Table 3-1 and are plotted in Figure 3-1 as a NOAEL, a less serious LOAEL, and a serious LOAEL.

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

Hindlimb paralysis was reported in guinea pigs exposed to 26–52 ppm phenol for 41 days (Deichmann et al. 1944). Rabbits and rats exhibited no overt neurological effects after 88 and 74 days of similar exposure, respectively. Since only a range was given for the exposure level (26–52 ppm), the exact level of phenol in air that resulted in hindlimb paralysis was not established and may be as low as 26 ppm or as high as 52 ppm. Interpretation of this study is further complicated by an apparent lack of controls. However, the neurological effect was so severe in the guinea pigs that it is difficult to ascribe the effects

to any source other than the phenol exposure. The lower limit of the exposure range, 26 ppm, is recorded in Table 3-1 and plotted in Figure 3-1 as a LOAEL for serious neurological effects in guinea pigs. Since the presence or absence of overt neurological effects such as paralysis is not a sensitive end point for detecting neurological effects, 26–52 ppm is not considered a reliable NOAEL for neurological effects in rats and rabbits.

There are several differences in the experimental designs of the Dalin and Kristoffersson (1974) and Deichmann et al. (1944) studies that may account for the different results regarding neurological effects in rats. Dalin and Kristoffersson (1974) reported subtle effects that may have been overlooked in the Deichmann et al. (1944) study. Furthermore, Dalin and Kristoffersson (1974) subjected the rats to a specific test for neurological impairment, the tilting plane test. Although exposure concentrations were the same in both studies, Dalin and Kristoffersson (1974) exposed rats continuously, while Deichmann et al. (1944) exposed rats intermittently. Because phenol is metabolized quite rapidly (see Section 3.4.3), rats exposed intermittently may not develop neurological effects.

Histopathological changes in the brain were not observed in Rhesus monkeys, rats, or mice exposed continuously to 5 ppm phenol in air for 90 days (U.S. Air Force 1961).

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

3.2.1.5 Reproductive Effects

The only relevant information located is that from a retrospective study of pregnancy outcome among university laboratory employees in Sweden (Axelsson et al. 1984). No significant increase in the rate of miscarriage was found in a group of 576 women exposed to organic solvent relative to 576 unexposed pregnancies. Specific mention of phenol was reported in only five cases, all of which were normal deliveries. No relevant information was found in animal inhalation studies.

3.2.1.6 Developmental Effects

Neither perinatal death rates nor prevalence of malformations were significantly increased in the study of laboratory workers conducted by Axelsson et al. (1984) mentioned above. 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. No further relevant information in humans was located. No developmental inhalation studies in animals were located.

3.2.1.7 Cancer

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

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

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

3.2.2 Oral Exposure

3.2.2.1 Death

There have been numerous reports of suicide or suicide attempts involving ingestion of large amounts of phenol. However, the lack of accurate documentation of dose levels in these cases makes it difficult to identify a minimal dose at which lethality occurs. Deichmann and Keplinger (1981), in summarizing the literature, indicated that an oral dose as low as 1 g could be fatal in humans, but that occasionally patients had survived doses as high as 65 g. Assuming that these patients were male with an average weight of 70 kg, the lower limit on the dose for death would be 14 mg/kg and the upper limit would be approximately 930 mg/kg. In a review of the toxicology of phenol, Bruce et al. (1987) summarized human oral lethality data from numerous case reports and estimated 140 mg/kg to be the minimal dose at which death occurs. Stajduhar-Caric (1968) reported a case in which a woman ingested ≈10–20 g of phenol and died within hours. The lower limit of the ingested dose was converted to 172 mg/kg, assuming a 58 kg body weight, to derive a dose for death, which is recorded in Table 3-2 and plotted in Figure 3-2. Boatto et al. (2004) described the case of a male who ingested a solution containing phenol and cresol and died approximately 30 minutes after ingestion. Toxicology tests revealed that the stomach content, blood, and urine of the individual contained 115.0, 58.3, and 3.3 μg/mL of phenol, respectively. Similar blood concentrations (56–130 μg/mL) were measured in fatal cases reported by Tanaka et al. (1998), Soares and Tift (1982), and Lo Dico et al. (1989).

The oral LD_{50} has been determined in rats treated by gavage with phenol in water; the LD_{50} was found to decrease with increasing concentration of phenol in the gavage fluid. The reported LD_{50} values were 340 mg/kg in rats gavaged with a solution of 200,000 ppm phenol and 530 mg/kg in rats gavaged with a solution of 20,000 ppm phenol (Deichmann and Witherup 1944). After rats were treated by gavage with 600 mg/kg in a 5% solution, 9 of 30 5-week-old rats, 18 of 20 10-day-old rats, and 12 of 20 adult rats died indicating that the 10-day-old rat is more sensitive to phenol than rats in the other age groups tested (Deichmann and Witherup 1944). In pregnant rats treated on gestation days (GDs) 6–15, 7 of 10 rats died at a dose of 125 mg/kg/day when treated with a volume of 1 mL/kg, while 1 of 6 rats died at a dose of 160 mg/kg/day when treated with a volume of 5 mL/kg (NTP 1983a). In a 1-day dosing regimen study, female rats were given 0, 12, 40, 120, or 224 mg/kg in order to determine a single-dose oral LD_{50} of 400 mg/kg (Berman et al. 1995). Mortality was observed only at the highest dose where two of eight rats treated died. All female rats treated for 14 days with a dose of 120 mg/kg/day died (Berman et al. 1995;

Moser et al. 1995). In a 14-day dosing regimen with the same doses (except the 224 mg/kg), all animals died at the dose of 120 mg/kg.

The oral LD_{50} of phenol has been estimated as 300 mg/kg in mice (von Oettingen and Sharpless 1946). Five of 10 rabbits treated with an oral dose of 420 mg/kg died (Deichmann and Witherup 1944). In pregnant mice treated on GDs 6–15, four of 35 mice died at a dose of 280 mg/kg/day (NTP 1983b).

Flickinger (1976) gave male Harlan-Wistar albino rats single doses of 0, 200, 398, 795, and 1,580 mg/kg phenol by gavage and held the animals for 14 days postdosing in order to determine an oral LD_{50}. No animals died following the 0, 200, or 398 mg/kg doses; four of five animals died the first day following the 795 mg/kg dose, and five of five animals died within 2 hours following 1,580 mg/kg dose. From these data, the investigators estimated an oral LD_{50} of 650 mg/kg.

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

In most studies, a specific cause of death was not reported, but common signs preceding death included convulsions, coma, and respiratory arrest. The LD_{50} values and doses resulting in death from each reliable study in each species in the acute-duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

Respiratory Effects. Stajduhar-Caric (1968) reported on a case in which a woman who ingested approximately 10–20 g of phenol, became comatose and died within a matter of hours. During the course of the poisoning and treatment, initially an increase in respiration was observed, then irregularities in

Table 3-2 Levels of Significant Exposure to Phenol - Oral

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
ACUTE EXPOSURE								
Death								
1	Human	once				172 F (death)	Stajduhar-Caric 1968	
2	Rat (Fischer- 344)	once (GW)				400 F (LD50)	Berman et al. 1995	
3	Rat (Fischer- 344)	14 d 1 x/d (GW)				120 F (8/8 died)	Berman et al. 1995	Dosing volume was 1 mL/kg.
4	Rat (Wistar)	once (GW)				340 (LD50)	Deichmann and Witherup 1944	
5	Rat (CD)	10 d Gd 6-15 1 x/d (GW)				125 F (7/10 maternal deaths)	NTP 1983a	Dosing volume was 1 mL/kg.
6	Mouse (CD-1)	10 d Gd 6-15 1 x/d (GW)				280 F (4/35 maternal deaths)	NTP 1983b	Dosing volume was 10 mL/kg.
7	Mouse (NS)	once (GO)				300 M (5/10 deaths)	Von Oettingen and Sharpless 1946	
8	Rabbit (White)	once (GW)				420 (5/10 deaths)	Deichmann and Witherup 1944	

Table 3-2 Levels of Significant Exposure to Phenol - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Systemic								
9	Rat (Fischer- 344)	once (GW)	Hepatic	224 F			Berman et al. 1995	Dosing volume was 1 mL/kg.
			Renal	120 F		224 F (renal tubular necrosis, protein casts, papillary hemorrhage)		
			Endocr	120 F	224 F (unspecified changes in the adrenal gland)			
			Bd Wt	224 F				
10	Rat (Fischer- 344)	14 d 1 x/d (GW)	Hepatic	40 F			Berman et al. 1995	Dosing volume was 1 mL/kg.
			Renal	12 F		40 F (renal tubular necrosis, protein casts, papillary hemorrhage in 3/8)		
			Endocr	40 F				
			Bd Wt	40 F				
11	Rat (Fischer- 344)	14 d Gd 6-19 (GW)	Resp			40 F (dyspnea, rales)	Narotsky and Kavlock 1995	Dosing volume was 1 mL/kg.
			Bd Wt			40 F (20% decrease in maternal body weight gain)		

Table 3-2 Levels of Significant Exposure to Phenol - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
12	Rat (CD)	10 d Gd 6-15 1 x/d (GW)	Hepatic	120 F			NTP 1983a	Dosing volume was 5 mL/kg.
			Bd Wt	120 F				
13	Rat (Sprague-Dawley)	10 d Gd 6-15 3 x/d (GW)	Bd Wt	60[b] F	120 F (11% reduced maternal body gain on Gd 6-16)		York 1997	Dosing volume was 10 mL/kg.
14	Mouse (Swiss CD-1)	once Gd 13 (GW)	Hemato		265 F (30-60% reduction in the ratio of poly/normo chromatic erythrocytes in the bone marrow of pregnant dams)		Ciranni et al. 1988	
15	Mouse (CD-1)	10 d Gd 6-15 1 x/d (GW)	Hepatic	280 F			NTP 1983b	Dosing volume was 10 mL/kg.
			Bd Wt	140 F		280 F (67% decrease in absolute maternal body weight gain)		
Immuno/ Lymphoret								
16	Rat (Fischer- 344)	once (GW)		120 F	224 F (necrosis or atrophy of the spleen or thymus)		Berman et al. 1995	Dosing volume was 1 mL/kg.

Table 3-2 Levels of Significant Exposure to Phenol - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
17	Rat (Fischer- 344)	14 d 1 x/d (GW)		40 F			Berman et al. 1995	NOAEL is for weight and histopathology of the spleen.
Neurological								
18	Rat (Sprague-Dawley)	once (G)				207 M (muscle twitching, convulsions, coma)	Liao and Oehme 1981	Dosing volume not reported.
19	Rat (Fischer- 344)	once (GW)		40 F		120 F (mild-to-severe whole-body tremors, decreased motor activity)	Moser et al. 1995	Dosing volume was 1 mL/kg.
20	Rat (Fischer- 344)	14 d 1 x/d (GW)		12 F	40 F (increased rearing)		Moser et al. 1995	Dosing volume was 1 mL/kg.
21	Mouse (CD-1)	10 d Gd 6-15 1 x/d (GW)		70 F	140 F (mild tremors on the first 3 days of dosing)	280 F (tremors, ataxia in pregnant dams)	NTP 1983b	Dosing volume was 10 mL/kg.
Developmental								
22	Rat (Fischer- 344)	14 d Gd 6-19 (GW)		40 F		53.3 F (significant decrease in the number of live-born pups, associated with severe respiratory effects in the dams)	Narotsky and Kavlock 1995	Dosing volume was 1 mL/kg.

Table 3-2 Levels of Significant Exposure to Phenol - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
23	Rat (CD)	10 d Gd 6-15 1 x/d (GW)		60 F	120 F (7% decrease in average fetal body weight)		NTP 1983a	Dosing volume was 5 mL/kg.
24	Rat (Sprague-Dawley)	10 d Gd 6-15 3 x/d (GW)		120	360 (decreased fetal weight and decrease ossification sites)		York 1997	Dosing volume was 10 mL/kg.
25	Mouse (CD-1)	10 d Gd 6-15 1 x/d (GW)		140 F		280 F (18% decreased fetal body weight, cleft palate 8/214)	NTP 1983b	Dosing volume was 10 mL/kg.

Table 3-2 Levels of Significant Exposure to Phenol - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
INTERMEDIATE EXPOSURE								
Systemic								
26	Rat (Fischer- 344)	13 wk ad lib (W)	Resp	1694 F			NCI 1980	NOAELs are for organs weight and histopathology.
			Cardio	1694 F				
			Gastro	1694 F				
			Musc/skel	1694 F				
			Hepatic	1694 F				
			Renal	1694 F				
			Endocr	1694 F				
			Dermal	1694 F				
			Bd Wt	467[c] M 508 F	1556 M (16% decrease in body weight gain associated with decreased water intake)	1694 F (26% decrease in body weight gain associated with decreased water intake)		
27	Rat (Sprague-Dawley)	10 wk 2-gen ad lib (W)	Hemato	321 F			Ryan et al. 2001	NOAELs are for histopathology of liver and kidney.
			Hepatic	321 F				
			Renal	321 F				

Table 3-2 Levels of Significant Exposure to Phenol - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
28	Mouse (CD-1)	28 d ad lib (W)	Resp	33.6 M			Hsieh et al. 1992	NOAELs are for histopathology.
			Cardio	33.6 M				
			Hemato			1.8 M (32% decrease in RBC count)		
			Hepatic	33.6 M				
			Renal	33.6 M				
			Bd Wt	33.6 M				

Table 3-2 Levels of Significant Exposure to Phenol - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
29	Mouse (B6C3F1)	13 wk ad lib (W)	Resp	2642 F			NCI 1980	NOAELs are for organs weight and histopathology.
			Cardio	2642 F				
			Gastro	2642 F				
			Musc/skel	2642 F				
			Hepatic	2642 F				
			Renal	2642 F				
			Endocr	2642 F				
			Dermal	2642 F				
			Bd Wt	741 M		2468 M (80% decrease in body weight gain associated with decreased water intake)		
Immuno/ Lymphoret								
30	Rat (Sprague-Dawley)	10 wk ad lib (W)		321 F			Ryan et al. 2001	NOAEL is for spleen and thymus histology and antibody production against immunization with SRBC.
31	Mouse (CD-1)	28 d ad lib (W)		1.8 M	6.2 M (decreased antibody production response to SRBC)		Hsieh et al. 1992	

Table 3-2 Levels of Significant Exposure to Phenol - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
Neurological								
32	Rat (Sprague-Dawley)	13 wk ad lib (W)		107 F	360 F (decreased motor activity on week 4)		Beyrouty 1998	
33	Mouse (CD-1)	28 d ad lib (W)			1.8 M (decreased levels of dopamine in the corpus striatum)		Hsieh et al. 1992	
Reproductive								
34	Rat (Fischer- 344)	13 wk ad lib (W)		1556[c] M 1694 F			NCI 1980	NOAEL is for histopathology of reproductive organs.
35	Rat (Sprague-Dawley)	10 wk 2-gen ad lib (W)		301[c] M 321 F			Ryan et al. 2001	NOAEL is for P males sperm parameters and F1 reproductive organs histology.
36	Mouse (B6C3F1)	13 wk ad lib (W)		2468[c] M 2642 F			NCI 1980	NOAEL is for reproductive organ histopathology.
Developmental								
37	Rat (Sprague-Dawley)	10 wk 2-gen ad lib (W)		93 F		321 F (decreased pup weight and percent live on day 4)	Ryan et al. 2001	

Table 3-2 Levels of Significant Exposure to Phenol - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
CHRONIC EXPOSURE								
Systemic								
38	Rat (Fischer- 344)	103 wk ad lib (W)	Resp	721 F			NCI 1980	NOAELs are for organs weight and histopathology.
			Cardio	721 F				
			Gastro	721 F				
			Musc/skel	721 F				
			Hepatic	721 F				
			Renal	721 F				
			Endocr	721 F				
			Dermal	721 F				
			Bd Wt		322[c] M (about 12% decrease in body weight associated with a 20% decrease in water intake)			
					721 F (about 17% decrease in body weight associated with a 10% decrease in water intake)			

Table 3-2 Levels of Significant Exposure to Phenol - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
39	Mouse (B6C3F1)	103 wk ad lib (W)	Resp	1204 F			NCI 1980	NOAELs are for organs weight and histopathology.
			Cardio	1204 F				
			Gastro	1204 F				
			Musc/skel	1204 F				
			Hepatic	1204 F				
			Renal	1204 F				
			Endocr	1204 F				
			Dermal	1204 F				
			Bd Wt	1204 F				
Immuno/ Lymphoret								
40	Rat (Fischer- 344)	103 wk ad lib (W)		721 F			NCI 1980	NOAEL is for weight and histopathology of lymphoreticular organs and tissues.
41	Mouse (B6C3F1)	103 wk ad lib (W)		1204 F			NCI 1980	NOAEL is for weight and histopathology of lymphoreticular organs. Immuno competence was not evaluated.
Neurological								
42	Rat (Fischer- 344)	103 wk ad lib (W)		721 F			NCI 1980	NOAEL is for weight and histopathology of the brain.

Table 3-2 Levels of Significant Exposure to Phenol - Oral (continued)

Key to Figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form	Comments
43	Mouse (B6C3F1)	103 wk ad lib (W)		1204 F			NCI 1980	NOAEL is for weight and histopathology of the brain.
Reproductive								
44	Rat (Fischer- 344)	103 wk ad lib (W)		721 F			NCI 1980	NOAEL is for weight and histopathology of reproductive organs of males and females. Fertility was not assessed.
45	Mouse (B6C3F1)	103 wk ad lib (W)		1204 F			NCI 1980	NOAEL is for weight and histopathology of reproductive organs of males and females. Fertility was not assessed.

a The number corresponds to entries in Figure 3-2.

b Used to derive an acute-duration oral MRL of 0.6 mg/kg/day; the MRL was derived by dividing the NOAEL of 60 mg/kg/day by an uncertainty factor of 100 (10 for animal to human extrapolation and 10 for human variability).

c Differences in levels of health effects and cancer effects between male and females are not indicated in Figure 3-2. Where such differences exist, only the levels of effect for the most sensitive gender are presented.

ad lib = ad libitum; Bd Wt = body weight; Cardio = cardiovascular; d = day(s); Endocr = endocrine; F = Female; (G) = gavage; Gastro = gastrointestinal; gd = gestational day; gen = generation; Gn pig = guinea pig; (GO) = gavage in oil; (GW) = gavage in water; Hemato = hematological; hr = hour(s); Immuno = immunological; LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; min = minute(s); Musc/skel = musculoskeletal; NOAEL = no-observed-adverse-effect level; NS = not specified; RBC = red blood cell; Resp = respiratory; SRBC = sheep red blood cells; x = time(s); (W) = drinking water; wk = week(s); yr = year(s)

Figure 3-2 Levels of Significant Exposure to Phenol - Oral

Acute (≤14 days)

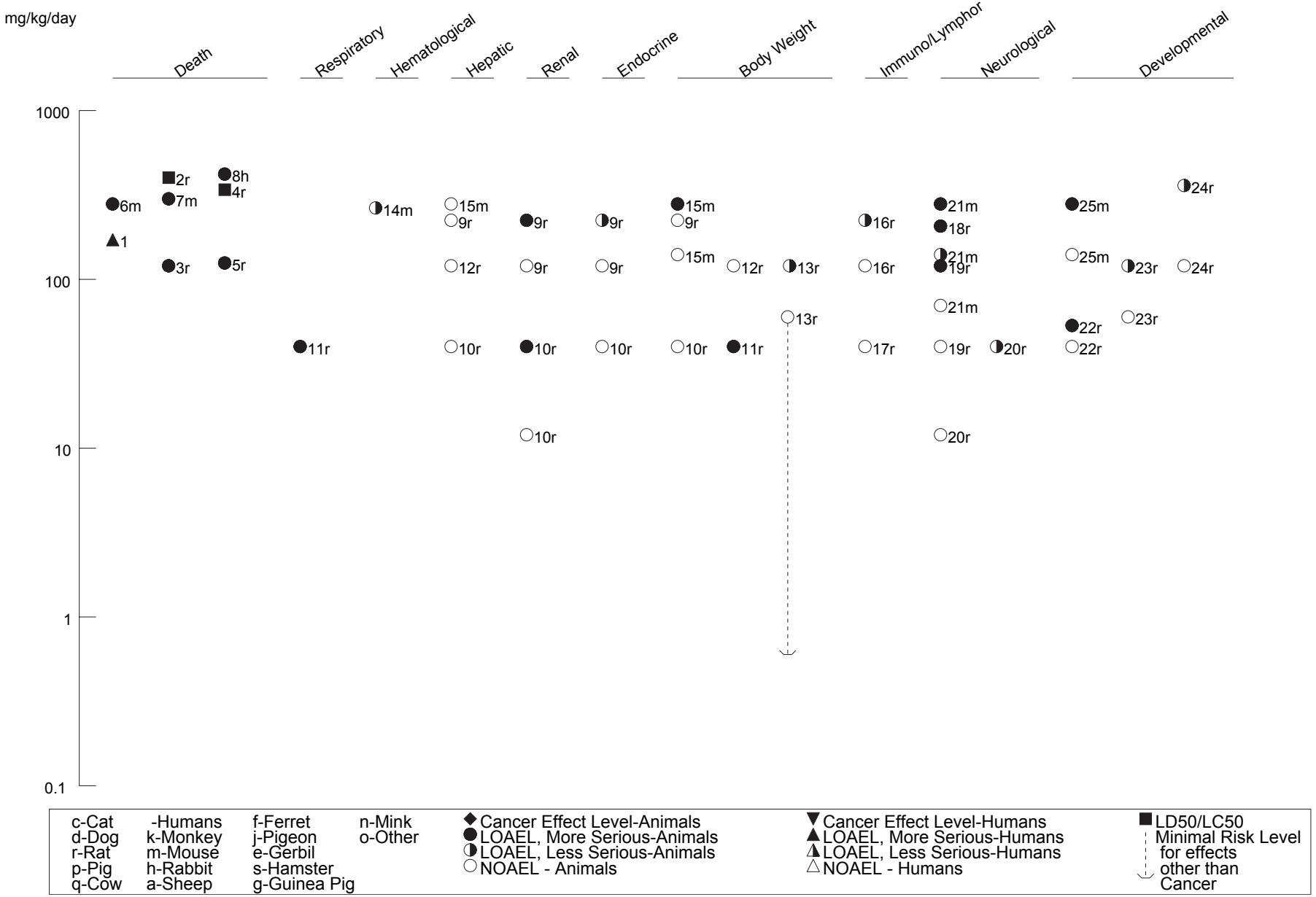


Figure 3-2 Levels of Significant Exposure to Phenol - Oral *(Continued)*

Intermediate (15-364 days)

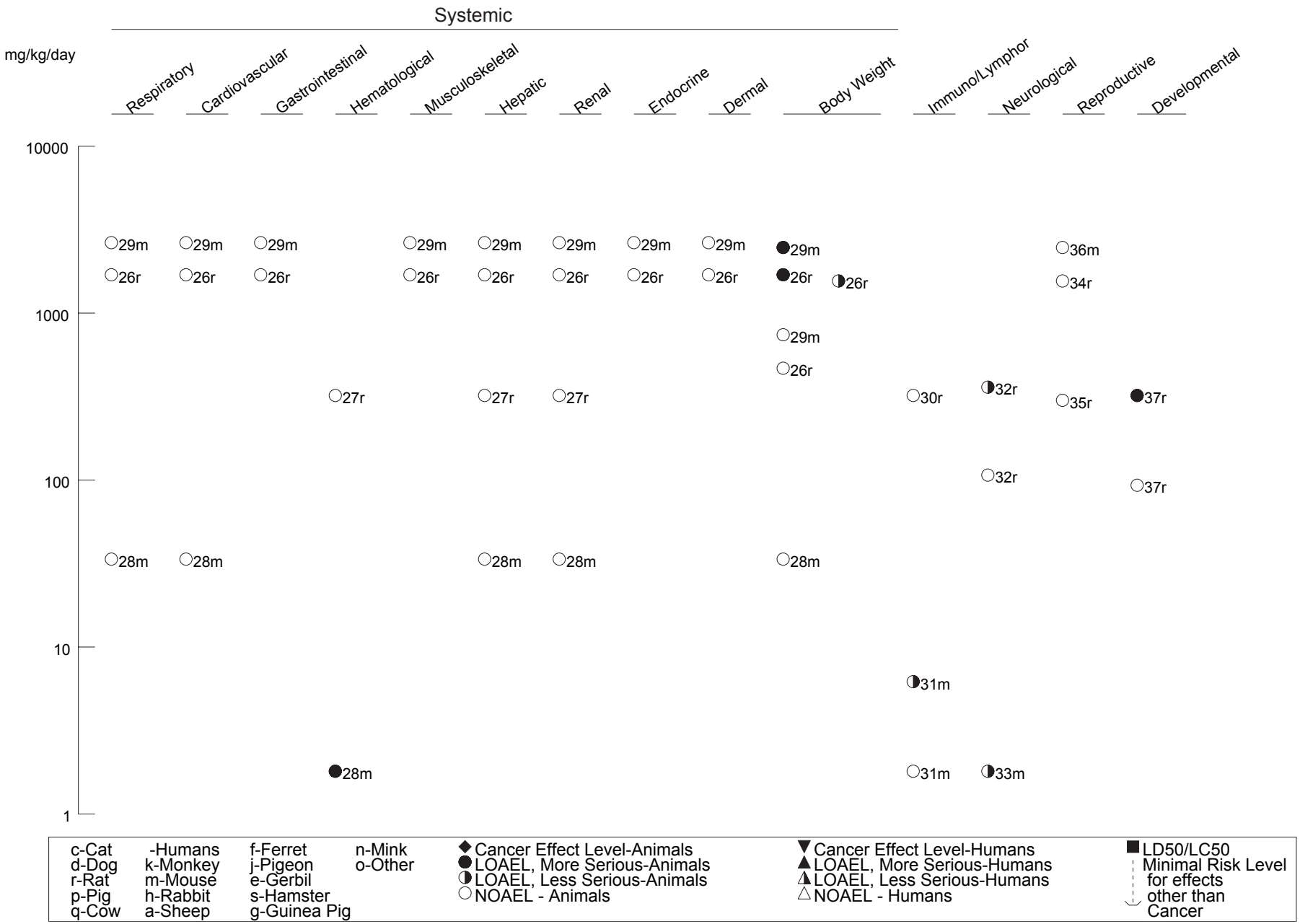
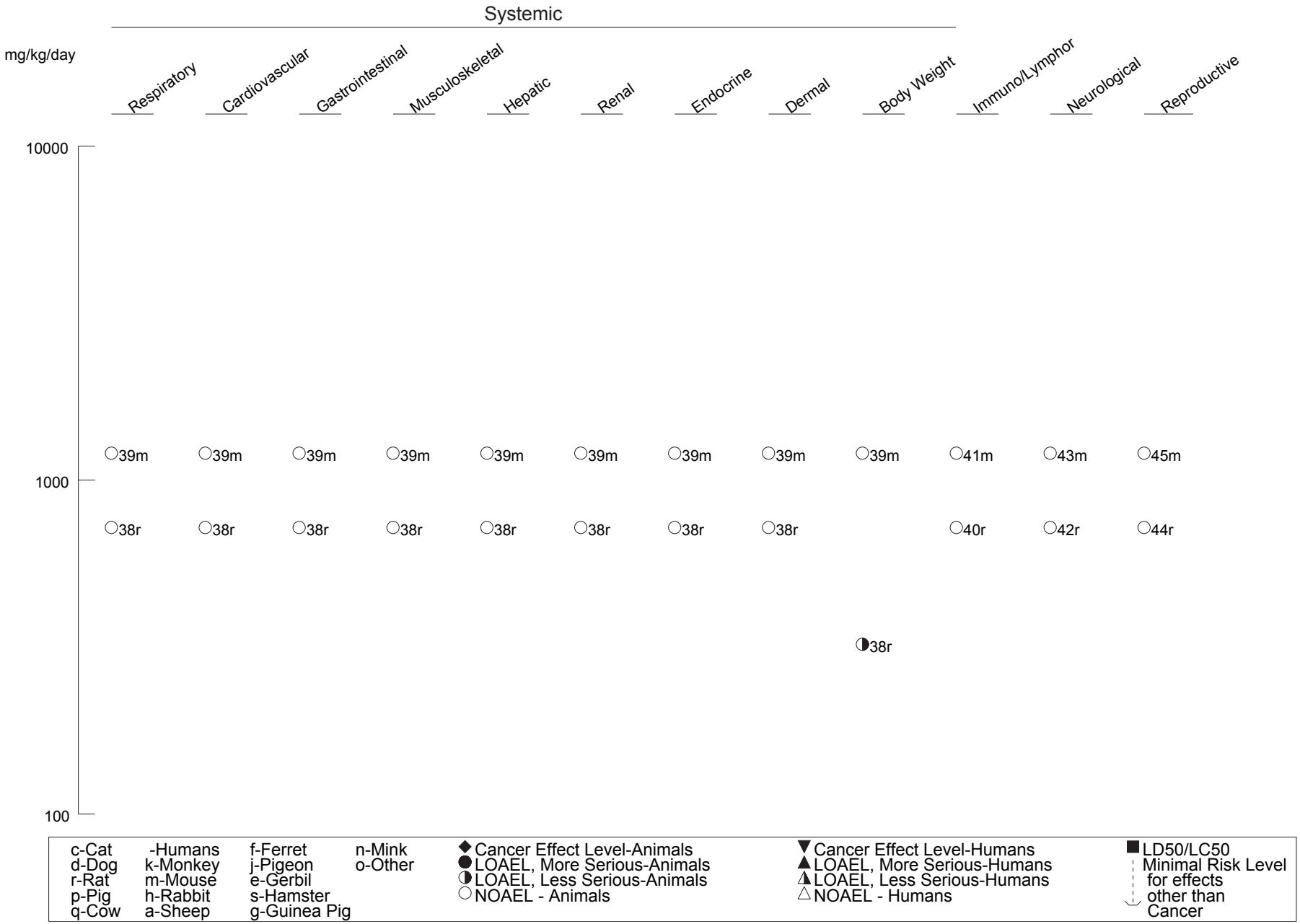


Figure 3-2 Levels of Significant Exposure to Phenol - Oral *(Continued)*

Chronic (≥365 days)



breathing, and finally cessation of respiration. An autopsy revealed marked hyperemia of the tracheal and bronchial mucous membranes, as well as pulmonary edema. According to Deichmann and Keplinger (1981), the progression of impacts on the respiratory system summarized above are typical of oral poisonings in humans, although often the intermediate stages are characterized by a decrease in respiration rate and magnitude. According to these authors, in acute intoxication, death usually results from respiratory failure. Pulmonary congestion and edema were reported in a man who died following phenol poisoning (Soares and Tift 1982). In another case of fatal ingestion of phenol, autopsy reported white froth in the nostrils, upper airway, trachea, and bronchi as well as edema and fluid in the lungs (Lo Dico et al. 1989). Inflammatory changes in the lungs also were observed in a more recent fatal case of ingestion of phenol (Tanaka et al. 1998).

Dyspnea and rales were observed in pregnant rats treated by gavage with phenol in water on GDs 6–19 (Narotsky and Kavlock 1995). The respiratory effects were observed at both 40 and 53.3 mg/kg/day. Gross pathological examinations did not reveal any adverse changes in the lungs of mice treated with phenol in drinking water at doses of 1.8, 6.2, or 33.6 mg/kg/day for 28 days (Hsieh et al. 1992).

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

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

Gross pathological examinations did not reveal any adverse changes in the hearts of mice treated with phenol in drinking water at doses of 1.8, 6.2, or 33.6 mg/kg/day for 28 days (Hsieh et al. 1992). In a study reported by the NCI (1980), rats exposed to 16–1,694 mg/kg/day (100–10,000 ppm) and mice exposed to 25–2,642 mg/kg/day (100–10,000 ppm) phenol in drinking water exhibited no indication of histopathological effects on the heart after 13 weeks of exposure. Histological abnormalities of the heart were not evident in rats after 103 weeks of exposure to 322 or 645 mg/kg/day for males or 360 or 721 mg/kg/day for females (2,500 or 5,000 ppm) or in mice after exposure to 590 or 1,180 mg/kg/day for males or 602 or 1,204 mg/kg/day for females (2,500 or 5,000 ppm). Cardiovascular function was not evaluated in these studies.

Gastrointestinal Effects. In a study on the clinical treatment of phenol poisoning, Langford et al. (1998) provide a summary of a case report in which a woman accidentally consumed an ounce of 89% phenol that had been mistakenly been given to her in preparation for an in-office procedure. Her immediate reaction upon consuming the phenol was to clutch her throat and collapse, and within 30 minutes, she was comatose and had gone into respiratory arrest. Treatment was initiated with an endotracheal intubation, which revealed her mouth and hypopharynx to be white. Esophagitis and upper gastrointestinal bleeding occurred in the first week, and an examination of the esophagus on day 8 revealed hyperkeratosis, erythema, and a friable mucosa. After a 15-day hospital stay, she was completely recovered with no evidence of impaired motility or compromised gastrointestinal system. A male who ingested a solution containing phenol and cresol and eventually died did not show macroscopic lesions of the esophagus and stomach, but histological examination revealed exfoliation of the mucosa of the esophagus and coagulative necrosis of the gastric mucosa (Boatto et al. 2004). Coagulation of the gastric mucosa was also reported in a fatal case of poisoning with phenol (Soares and Tift 1982). Erosive duodenal gastritis was also observed in a woman who ingested about 70 mL of a 42–52% phenol solution (Kamijo et al. 1999). Other fatal cases have described mucous changes in the digestive organs (Tanaka et al. 1998) and crusted corrugated appearance of the stomach (Lo Dico et al. 1989).

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

≤0.1 mg/L (0.003 mg/kg/day assuming 2 L water per day and a 70-kg body weight). Dermal exposure was not considered in these estimates of dose. A similar study was conducted by Jarvis et al. (1985) among 344 English households who had their drinking water contaminated with phenol. An unexposed group (250 households) served as control. The day of the contamination incident, the concentration of phenol in a high-exposure area (250 households) was estimated to be 10 µg/L, whereas in a low-exposure area (94 households), the concentration was 4.7 µg/L. The day after the incident, the phenol concentration in the water from both areas was 4.7 µg/L, and 2 days after the incident, it was 0.9 µg/L. Chlorophenols, which formed upon chlorination of the water, were detected at a higher concentration of phenol and followed a similar pattern as phenol. Since the concentration of phenol and chlorophenols were similar in the two exposed areas, the two exposed areas were combined in the analysis. Exposed individuals had significantly higher incidences of gastrointestinal illness (i.e., diarrhea, nausea, vomiting, and abdominal pain) than the unexposed group, and the onset of symptoms coincided with the period of elevated concentrations of phenol in the drinking water. Moreover, stronger associations were observed among those who reported drinking the water in the exposed areas than among those who reported not drinking the water in the same areas. The specific contribution of phenol to the adverse signs and symptoms reported is difficult to determine.

A case control study of 6,913 individuals living near a Korean river contaminated with 30 tons of 100% phenol found nausea, vomiting, diarrhea, and abdominal pain among 1,824 exposed subjects compared to 1,064 unexposed subjects (Kim et al. 1994). The level of phenol measured in the two reservoirs that served the community was 0.05 mg/L after the spill, while that in the chlorinated tap water was 0.0084 mg/L.

In a study reported by the NCI (1980), rats exposed up to 1,694 mg/kg/day and mice exposed up to 2,642 mg/kg/day phenol in drinking water exhibited no indication of histopathological effects on the gastrointestinal system after 13 weeks of exposure. No histological abnormalities of the gastrointestinal tract were observed in rats or mice exposed to phenol in drinking water that provided doses of approximately 720 and 1,200 mg/kg/day, respectively, for 103 weeks (NCI 1980).

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

A 30–60% decrease in the ratio of polychromatic to normochromatic erythrocytes was observed in the bone marrow of pregnant mice treated by gavage with a single dose of 265 mg/kg phenol in water on

GD 13 (Ciranni et al. 1988). Dose-related and significant decreases in red blood cell counts were observed in mice treated with phenol in the drinking water at doses of 1.8, 6.2, or 33.6 mg/kg/day for 28 days (Hsieh et al. 1992). Red blood cell counts in cells $x10^6/mm^3$ were 7.17 in controls, 4.9 at the low dose, 4.64 at the middle dose, and 3.23 at the high dose. A significant decrease in hematocrit was only observed at the high dose (48% control, 44.1% high dose), and no changes were observed in leucocyte numbers or leucocyte differentials.

No significant alterations in hematology parameters were observed in male or female rats dosed with up to 301 or 321 mg phenol/kg/day in the drinking water, respectively, for 10 weeks (Ryan et al. 2001).

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

Rats exposed up to 1,694 mg/kg/day and mice exposed up to 2,642 mg/kg/day phenol in drinking water exhibited no histological abnormalities of the bone after 13 weeks of exposure (NCI 1980). No histological abnormalities of the bone were observed in rats or mice up to 721 or 1,204 mg/kg/day, respectively, of phenol in drinking water for 103 weeks. (NCI 1980).

Hepatic Effects. Serum markers of liver effects, bilirubin, glucose, cholesterol, and AST activity were not affected in 39 persons exposed to phenol in the drinking water at an estimated dose of 0.14–3.4 mg/kg/day for several weeks (Baker et al. 1978). Because these examinations were completed 7 months after the spill, this study does not provide conclusive evidence that there was no reversible liver damage. Autopsy of a fatal case of ingestion of phenol revealed substantial toxic changes in the liver including extension of sinusoid lumens and centrilobular increase of cytoplasmic eosinophility (Tanaka et al. 1998).

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

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

In a study sponsored by the National Cancer Institute (NCI 1980), rats exposed up to 1,694 mg/kg/day and mice exposed up to 2,642 mg/kg/day phenol in drinking water exhibited no histological abnormalities of the liver after 13 weeks of exposure. Similar observations were made in rats dosed with up to 301–321 mg phenol/kg/day in the drinking water for 10 weeks (Ryan et al. 2001). No histological abnormalities of the liver were observed in rats or mice exposed up to 721 or 1,204 mg/kg/day respectively, of phenol in drinking water for 103 weeks (NCI 1980).

Renal Effects. Although not adverse, dark urine (as a result of oxidation products of phenol or a result of hemoglobin or its breakdown products in the urine) is a common symptom observed in humans exposed to phenol. In persons exposed to about 0.14–3.4 mg/kg/day phenol in drinking water for several weeks after an accidental spill, dark urine was reported by 17.9% of the most highly-exposed individuals, while only 3.4% of the controls reported the effect (Baker et al. 1978). This difference was not statistically significant. A 3.3-fold increase in the prevalence of dark urine was reported by persons exposed to unspecified doses of phenol after an accidental spill in Korea (Kim et al. 1994). Autopsy of an individual who ingested phenol showed interstitial edema and renal tubular hemorrhage (Tanaka et al. 1998). Extensive renal autolysis was also observed in a fatal case of poisoning with phenol (Soares and Tift 1982).

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

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

Rats exposed up to 1,694 mg/kg/day and mice exposed up to 2,642 mg/kg/day of phenol in drinking water exhibited no indication of histopathological effects on the kidney after 13 weeks of exposure (NCI 1980). Rats exposed to up to 301–321 mg phenol/kg/day in the drinking water for 10 weeks showed no significant histopathological effects in the kidneys (Ryan et al. 2001).

No compound-related histological changes in the kidneys were observed in rats or mice exposed up to 721 or 1,204 mg/kg/day, respectively, of phenol in drinking water for 103 weeks (NCI 1980). A higher incidence of inflammation of the kidney was reported in male rats exposed to 624 mg/kg/day (96%) than in controls (74%); however, because of the high incidence of inflammation in the controls, it is impossible to ascertain whether this was related to the exposure to phenol (NCI 1980). A high age-related incidence of inflammation is expected in male rats of the Fischer-344 strain used in this study. Kidney function, including glomerular filtration rate and glomerular sieving, however, was not evaluated in this study. Furthermore, histological examination was limited to standard light microscopic examinations which would not have detected functionally significant glomerular abnormalities like disruption of the glomerular basement membrane or immune complex deposition.

Endocrine Effects. Autopsy of a subject who died following ingestion of a solution containing phenol showed interstitial hemorrhage in the pancreas and adrenal glands (Tanaka et al. 1998). No further information regarding effects of phenol on endocrine-related end points was located.

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

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

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

contaminated by an accidental spill of phenol (Kim et al. 1994). Because the water was chlorinated before use, the effect may also have been a result of exposure to chlorophenol. Perioral chemical burns from phenol were observed in a woman who ingested approximately 70 mL of a 42–52% phenol solution (Kamijo et al. 1999). Spiller et al. (1993) also reported oral and esophageal burns in 17 out of 52 patients following ingestion of a disinfectant containing 26% phenol.

Rats exposed up to 1,694 mg/kg/day and mice exposed up to 2,642 mg/kg/day phenol in drinking water exhibited no histopathological changes in the skin after 13 weeks of exposure (NCI 1980). Exposure-related histopathological changes in the skin were also not observed in rats and mice exposed up to 721 or 1,204 mg/kg/day, respectively, phenol in drinking water for 103 weeks (NCI 1980).

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

Body Weight Effects. No effects on body weight were observed in rats treated with a single gavage dose of 224 mg/kg phenol in water or 14 daily gavage doses of 40 mg/kg (Berman et al. 1995; Moser et al. 1995). Maternal body weight gain was approximately 20% lower in rats treated by gavage with 40 or 53.3 mg/kg/day phenol in water on GDs 6–19 (Narotsky and Kavlock 1995). Maternal body weight gain was 67% lower than controls in mice treated by gavage with 280 mg/kg/day phenol in water on GDs 6–15, with no effects on body weight gain observed at 140 mg/kg/day (NTP 1983b). Body weight gain was not affected in pregnant rats treated by gavage with 120 mg/kg/day phenol in water on GDs 6–15 (NTP 1983a). Body weight gain was significantly reduced in pregnant rats dosed with 120 mg phenol/kg/day on GDs 6–15 (11% for GDs 6–16 and 19% for GDs 12–16) (York 1997). Doses of 360 mg/kg/day caused a reduction in body weight gain of 38% for GDs 6–16; the NOAEL for maternal weight gain in this study was 60 mg/kg/day. The reduction in maternal body weight gain in rats during pregnancy reported in the York (1997) study was used as the basis for derivation of an acute-duration oral MRL for phenol.

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

(467 mg/kg/day for males, 508 mg/kg/day for females). In mice provided with the highest concentration (10,000 ppm), body weight gain was decreased by 33% in females at 2,642 mg/kg/day, and by 80% in males at 2,468 mg/kg/day. An effect on body weight gain was not observed in mice at 3,000 ppm (741 mg/kg/day for males, 793 mg/kg/day for females). A significant decrease in body weight gain associated with a significant decrease in water consumption was also observed in male and female rats dosed with 301–321 mg/kg/day phenol in the drinking water for 10 weeks (Ryan et al. 2001).

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

3.2.2.3 Immunological and Lymphoreticular Effects

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

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

Hsieh et al. (1992) conducted a 28-day study of the immunotoxicologic impact of phenol in which CD-1 mice were given drinking water that provided doses of phenol of approximately 0, 1.8, 6.2, or 33.6 mg/kg/day. When challenged with sheep red blood cells (SRBC), a significant decrease was observed in the splenic concentration of anti-erythrocyte antibody-forming cells and in the anti-erythrocyte antibody titer at the two highest doses, while a significant decrease in the absolute number of anti-erythrocyte antibody-forming cells present in the spleen was observed only at the top dose. In contrast to the results of Hsieh et al. (1992), Ryan et al. (2001) reported no immunologic alterations in male rats in a drinking water study. Rats were dosed for 10 weeks with up to 301 mg phenol/kg/day and

then immunized intravenously with sheep red blood cells. Eighteen hours later, splenocytes were prepared in cell culture medium for enumeration of plaque-forming cells. Treatment with phenol had no significant effect on antibody-forming cells, and there were no significant effects on spleen or thymus weight, spleen cellularity, or spleen and thymus histology.

Rats exposed up to 1,694 mg/kg/day and mice exposed up to 2,642 mg/kg/day phenol in drinking water exhibited no histopathological changes in the bone marrow, spleen, or lymph nodes after 13 weeks of exposure (NCI 1980). Exposure-related histopathological changes in the bone marrow, spleen, or lymph nodes were also not observed in rats or mice exposed to estimated doses of up to 721 or 1,204 mg/kg/day, respectively, for 103 weeks (NCI 1980).

The highest NOAEL values and all LOAEL values from each reliable study for immunological and lymphoreticular effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.4 Neurological Effects

Headaches were reported 6 times more frequently by persons using drinking water contaminated with phenol than by controls (Kim et al. 1994). The water was used after chlorination; therefore, chlorophenol may have contributed to the observed effects. Fine, rapid, rhythmic, perioral movements, as well as signs of Parkinson's syndrome were observed in a woman who ingested approximately 70 mL of a 42–52% solution of phenol (Kamijo et al. 1999). Central nervous system depression was described in 11 out of 52 patients who ingested amounts ranging from 2 to 90 mL of a disinfectant solution containing 26% phenol (Spiller et al. 1993).

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

mild tremors on the first 3 days of dosing at 140 mg/kg/day, and no adverse neurological effects at 70 mg/kg/day (NTP 1983b).

In contrast with results from oral gavage studies, phenol administered in the drinking water was much less toxic. For example, male rats exposed to up to 309 mg phenol/kg/day in the drinking water for 13 weeks showed no significant alterations in tests of motor activity or a functional observation battery conducted throughout the exposure period (Beyrouty 1998). However, females dosed with 360 mg phenol/kg/day showed a significant reduction in motor activity on week 4 of the study; no significant alterations were seen in females at 107 mg/kg/day. Gross and microscopic evaluation of the brain, spinal cord, and peripheral nerves was unremarkable (Beyrouty 1998).

Mice exposed for 28 days to phenol in drinking water exhibited a significant reduction in dopamine level in the corpus striatum at the 1.8 mg/kg/day dose, and significantly decreased levels of norepinephrine, serotonin, and 5-hydroxyindoleacetic acid in the hypothalamus at the 6.2 mg/kg/day dose (Hsieh et al. 1992). Levels of neurotransmitters in other brain regions were also significantly altered at higher doses of phenol.

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

The highest NOAEL values and all LOAEL values from each reliable study for neurological effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.5 Reproductive Effects

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

No evidence of impaired reproduction was found in rats exposed to phenol in drinking water at <5,000 ppm (estimated 571 mg/kg/day) for three generations or at <1,000 ppm (estimated 114 mg/kg/day) for five generations (Heller and Pursell 1938). Data regarding breeding habits, controls,

and the methods used to evaluate the rats for reproductive impairment were not reported in sufficient detail to establish reliable NOAELs or LOAELs for presentation in Table 3-2 and Figure 3-2.

Rats exposed up to 1,694 mg/kg/day and mice exposed up to 2,642 mg/kg/day of phenol in drinking water exhibited no histopathological changes in the prostate, testes, uterus, or ovaries after 13 weeks of exposure (NCI 1980). Exposure-related histopathological changes in the prostate, testes, uterus, or ovaries were also not observed in rats or mice exposed up to 721 or 1,204 mg/kg/day, respectively, phenol in drinking water for 103 weeks (NCI 1980).

In a two-generation study in which rats were administered phenol in the drinking water (up to 301–321 mg/kg/day), there was a significant decrease in absolute seminal vesicle weight in parental males at 301 mg/kg/day and in absolute ovaries weight in parental females at 321 mg/kg/day, but 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 estrus frequency, testicular sperm count, or sperm motility or morphology. Significant reductions in prostate and uterine weights in all F_1 treated groups were not considered adverse effects of phenol by Ryan et al. (2001) on the basis of the absence of histological alterations and functional reproductive effects, and based on the fact that only a few animals had organ weights outside the range of concurrent control values.

Information on the effects of exposure to phenol on the genetic material of germinal cells is presented in Section 3.3, Genotoxicity.

The highest NOAEL values from each reliable study for reproductive effects in each species and duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

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

In a multi-generational study of the effect of various levels of phenol administered orally in water, Heller and Pursell (1938) saw no effect on growth, reproduction, and normal rearing of young over 5 generations of rats given concentrations of ≈1,000 mg/L phenol in drinking water (estimated dose of 114 mg/kg/day) nor over three generations of rats given concentrations of ≈5,000 ppm (estimated dose 571 mg/kg/day).

Phenol in water was administered to pregnant rats by gavage (5 mL/kg) at dose levels of 0, 30, 60, or 120 mg/kg/day on GDs 6–15 (NTP 1983a). A dose-related decrease in fetal body weight with increasing dose was observed, with 60 mg/kg/day established as the NOAEL and 120 mg/kg/day as the LOAEL. The mean reduction in fetal body weight relative to controls was approximately 7%. Concurrent controls provide the most appropriate comparison for experimental data; however, it is worth noting that the weights of control fetuses in this study were 22% higher than those of historical controls. As litter size is known to influence fetal weight, it is possible that a larger litter size in the high-dose group may have contributed to the smaller fetal weights in that group. The data were not specifically analyzed for that potential effect. Teratogenic effects were not observed and no signs of maternal toxicity were observed at any dose level. In a preliminary range-finding study conducted by NTP (1983a), a decrease in maternal weight gain and an increased incidence of maternal mortality were observed at >160 mg/kg. Tremors, a typical symptom of phenol toxicity, were also observed.

In a study of the developmental toxicity of phenol and structurally-related chemicals, Kavlock (1990) examined the effects of 0, 100, 333, 667 and 1,000 mg/kg phenol given by gavage on day 11 of gestation. Phenol was administered in a 4:4:1:1 mixture of water, Tween 20, propylene glycol, and ethanol. Five variables were examined: maternal weight change (at 24 and 72 hours postdosing), litter size (postnatal day [PND] 1 and 6), perinatal loss, pup weight (on PND 1 and 6), and litter biomass (in g on PND 1 and 6).

Within these five parameters, a significant decrease in maternal weight gain was seen at the two highest doses. At these same doses, malformations involving the limbs and tail were seen. At a dose of 667 mg/kg, pups in 21% of the litters were affected. (At a dose of 1,000 mg/kg, pups in 27% of the litters were affected.) The effect on tails was one of shortening or crimping (i.e., ‘kinky’ tails). The hindlimb effect consisted of paralysis and/or palsy. In animals with palsy, the limb function would alternate between normal strides and a several second-long period of tetany. Because limb function matures postnatally, this effect was not evident in the newborn but required 7–10 days to become obvious.

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

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

York (1997) conducted a study in which phenol was administered in three daily gavage doses in water to Sprague-Dawley pregnant rats in dosing volumes of 10 mL/kg on GDs 6–15. The total daily doses were 0, 60, 120, or 360 mg phenol/kg/day. Maternal end points evaluated included clinical signs, body weight, and food consumption. Dams were also observed for abortions and premature deliveries. Dams were sacrificed on GD 20 and a gross necropsy was conducted. The uterus was examined for pregnancy, number and distribution of implantations, live and dead fetuses, and early and late resorptions. Fetuses were weighed and examined for sex and gross external alterations. Half of the fetuses were examined for soft tissue alterations and the remaining fetuses were examined for skeletal alterations. In the mid-dose group, maternal body weight gain was reduced 11% for GDs 6–16 and 19% for GDs 12–16, whereas in the high-dose group, body weight gain was reduced 38% for GDs 6–16. Maternal final body weight in the high-dose group was reduced, but <10% relative to controls. Dose-related decreases in food consumption were also observed during the dosing period. Mean fetal weight in the high-dose group was reduced 5–7% relative to controls. In addition, there was a significant decrease in ossification sites on the hindlimb metatarsals in the high-dose group, which the investigators considered of minimal biological significance. At the mid- and high-dose levels, there were increases in litters with fetuses with “any alteration” and with “any variation”, but neither reached statistical significance and there were no clear dose-response relationships. No significant effects were seen regarding corpora lutea, implantations, litter sizes, live fetuses, early and late resorptions, and percent resorbed conceptuses. Based on the reduced fetal weight and delayed ossification in the high-dose group, the dose of 360 mg/kg/day is a developmental LOAEL; the developmental NOAEL is 120 mg/kg/day. Based on the reduction in body weight gain, the maternal LOAEL is 120 mg/kg/day and the NOAEL is 60 mg/kg/day.

In a two-generation reproduction study, administration of phenol in the drinking water to the parental generation (301–321 mg/kg/day) resulted in a significant reduction in F_1 pup weight (30% by PND 21 relative to controls) and F_2 pup weight (37% by PND 21 relative to controls) (Ryan et al. 2001). There

was also a decrease in percent live pups on day 4 in both generations and for days 7–21 in the F_2 generation at the high-dose level. In addition, preputial separation and vaginal patency were significantly delayed at the high dose in F_1 males and females, respectively. In this study, water consumption was significantly reduced at the high dose, including in females during gestation and lactation, and this was accompanied by reduced food consumption and body weight gain. A LOAEL of 321 mg/kg/day can be defined in this study for developmental toxicity; the NOAEL for developmental toxicity was 93 mg/kg/day.

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in each species in the acute-duration category are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

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

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

3.2.3 Dermal Exposure

3.2.3.1 Death

Application of phenol to the skin can be lethal. Death occurred within 10 minutes after ≈25% of an individual's body surface was exposed to liquid phenol (Griffiths 1973). The cause of death was reported to be respiratory depression and cardiac arrest. In another report, an individual died after being painted

with a brush that had been soaked in a solution of phenol and thoroughly washed before use (Lewin and Cleary 1982). In neither case was the dose known with sufficient accuracy to establish a lethal dose.

A 10-year-old boy was hospitalized with serious burns; during the next 2.5 days, his burns were treated by applying 7.5 L of an antiseptic solution containing 2% phenol; his urine became dark, respiration became labored, he fell into a coma, and died. Postmortem analysis of urine showed the presence of 200 mg/L of conjugated phenol (Cronin and Brauer 1949). Soares and Tift (1982) described two fatal cases attributed to absorption of phenol through intact skin. One was a 17-year-old male who died within 30 minutes of splattering a solution containing 30% phenol over portions of his face, neck, and right trunk. The other case was a 4-week-old female who was mistakenly treated with undiluted Castellani's paint (a mixture of phenol, basic fuchsin, resorcinol, acetone, ethanol, and water) to treat seborrheic dermatitis and died 5 hours later.

Lethality associated with dermal exposure to phenol is greatly influenced by the surface area exposed as well as the concentration of the applied solution. Mortality can vary depending on concentration; a dose of 100% phenol may be less toxic than the same dose of phenol given as a diluted solution. When an undiluted dose of 0.5 mL/kg was applied to the shaved backs of groups of five rats; one rat died, a 1/3 dilution killed three rats, a 1/2 dilution killed four rats, and a 2/3 dilution killed all five rats (Conning and Hayes 1970). Conning and Hayes (1970) speculated that an undiluted solution may produce a coagulative necrosis, which would slow further penetration of phenol resulting in a smaller number of deaths than with more diluted solutions. In rats treated with 3,000 mg/kg phenol in a 6% solution over 1/6 of the total body surface, all 22 treated animals died (Deichmann and Witherup 1944). Increased lethality with decreased concentration has also been observed in rabbits treated dermally with 2,000 mg/kg; 95% phenol resulted in the death of 53% of treated rabbits, while 10% phenol in water resulted in the death of 100% of treated rabbits (Deichmann and Witherup 1944). The cause of death was not stated in these studies.

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

The dermal LD_{50} of undiluted phenol in rats was reported to be 669 mg/kg (Conning and Hayes 1970). The LD_{50} of an unspecified concentration of phenol in rabbits was reported to be 1,400 mg/kg (Vernot et

al. 1977). Flickinger (1976) determined a dermal LD_{50} by exposing male albino rabbits to 0, 252, 500, 1,000, or 2,000 mg/kg phenol which was placed "in contact" with "abraded and intact skin for a maximum period of 24 hours." No animals died in the 0, 252, or 500 mg/kg groups whereas three of four in the 1,000 mg/kg group and all in the 2,000 mg/kg group died the first day following dosing. From these data, the authors estimated a "single dose skin penetration LD_{50}" of 850 mg/kg.

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

No effects on survival were observed in mice treated dermally with an unspecified volume of 5% phenol (3 times/week) or 10% phenol (2 times/week) in acetone for 12 months (Wynder and Hoffmann 1961). Pretreatment with a single dose of 7,12-dimethylbenz[a]anthracene (7,12-DMBA) followed by phenol resulted in increased skin tumors and decreased survival.

All LOAEL and LD_{50} values from each reliable study are recorded in Table 3-3.

3.2.3.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for systemic effects in each species and duration category are recorded in Table 3-3.

Respiratory Effects. Pulmonary edema was observed in two fatal cases of dermal poisoning with phenol (Soares and Tift 1982). A 79-year-old man who mistakenly instilled into his nose 0.5–10 mL of a 89% phenol solution (approximately 0.4–9 g) showed erythema and sloughing of the nasal mucosa 3 days after the accident (Durback-Morris and Scharman 1999). No further relevant information was located regarding respiratory effects in humans following dermal exposure to phenol.

Dyspnea was reported in pigs treated with a single dose of 500 mg/kg of undiluted phenol over 35–40% of the total body surface area (0.44 $mg/cm^2/kg$) (Pullin et al. 1978). This treatment resulted in the death of two of the three treated pigs.

Table 3-3 Levels of Significant Exposure to Phenol - Dermal

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form	Comments
				Less Serious		Serious		
ACUTE EXPOSURE								
Death								
Rat (Alderly Park)	24 hr				669.4 F mg/cm²/d	(LD50)	Conning and Hayes 1970	
Rat (Wistar)	once				3000 mg/cm²/d	(13/20 deaths 10-day-old, 5/20 deaths 5-week-old, 9/20 deaths adult)	Deichmann and Witherup 1944	
Rabbit (New Zealand)	NS				1400 F mg/cm²/d	(LD50)	Vernot et al. 1977	
Pig (Mixed breed)	24 hr				0.44 F mg/cm²/d	(2/3 died)	Pullin et al. 1978	
Systemic								
Human	1 hr	Cardio			75 M mg/cm²/d	(cardiac arrhythmia)	Warner and Harper 1985	

Table 3-3 Levels of Significant Exposure to Phenol - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL				Reference Chemical Form	Comments
				Less Serious			Serious		
Rat (Alderly Park)	24 hr	Renal				107.1 F mg/cm²/d	(severe hemoglobinuria, hematin casts in the tubules)	Conning and Hayes 1970	
		Dermal				107.1 F mg/cm²/d	(severe edema, coagulative necrosis, erythema)		
Mouse (ICR)	once	Dermal	12 F mg/cm²/d	15 F mg/cm²/d	(skin irritation indicated by thickening of treated ear)			Patrick et al. 1985	
Rabbit (NS)	once	Cardio				23.8 M mg/cm²/d	(cardiac arrhythmias, ventricular tachycardia)	Wexler et al. 1984	

Table 3-3 Levels of Significant Exposure to Phenol - Dermal (continued)

Species (Strain)	Exposure/ Duration/ Frequency (Route)	System	NOAEL	LOAEL			Reference Chemical Form	Comments
				Less Serious		Serious		
Pig (Mixed breed)	24 hr	Resp			0.44 F mg/cm²/d	(dyspnea)	Pullin et al. 1978	
		Dermal			0.44 F mg/cm²/d	(necrosis of the skin)		
Neurological								
Rat (Alderly Park)	24 hr				107.1 F mg/cm²/d	(severe muscle tremors, marked twitching, generalized convulsions, loss of consciousness and prostration)	Conning and Hayes 1970	
Pig (Mixed breed)	24 hr				0.44 F mg/cm²/d	(twitching, tremors)	Pullin et al. 1978	

Cardio = cardiovascular; d = day(s); F = Female; hr = hour(s); LD50 = lethal dose, 50% kill; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; NS = not specified; Resp = respiratory

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

Cardiac arrhythmia and bradycardia were reported in a man that splashed an unspecified concentration of a phenol-water solution over his face, chest wall, hand, and both arms (Horch et al. 1994). The cardiac effects were noted during the first 6 hours after exposure. The serum levels of phenol in μg/L were 11,400 after 1 hour, 17,400 after 4 hours, and 6,000 after 8 hours. Premature heartbeats and arterial fibrillation were reported in a male who experienced a 4.5-hour occlusive exposure to 90% phenol (Bentur et al. 1998); the concentration of phenol in serum reached a peak of 21.6 mg/L.

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

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

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

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

Hemoglobinuria and hematin casts were reported in the renal tubules of rats treated dermally with 108 mg/kg phenol (Conning and Hayes 1970). These observations are indicative of red blood cell hemolysis; however, this was not confirmed with hematological examinations.

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

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

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

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

Renal Effects. Renal tubule cell vacuolization was described in a fatal case of dermal poisoning with phenol (Soares and Tift 1982). A case of acute renal failure was reported by Foxall et al. (1989) in a worker who accidentally fell into a shallow vat containing a mixture of phenol (40%) in dichloromethane. The worker was partially immersed for only a few seconds and avoided ingesting any of the solution. He showered immediately, subsequently collapsed and was admitted to the hospital with surface burns over 50% of his body (involving the face, chest, genitals, and both legs). Following admission he became anuric and plasma creatinine levels rose. He was transferred to the regional renal unit where he was diagnosed with phenol- induced burns, acute tubular necrosis, and fluid overload. For the first 2 weeks, the patient demonstrated amino aciduria, glycosuria, and lactic aciduria consistent with renal cortical necrosis. This was followed by a period of polyuria revealing a biochemical pattern consistent with renal papillary damage. Treatment consisted of administration of a diuretic intravenously and hemodialysis

daily for a week followed by an additional 18 days of hemodialysis at gradually increasing intervals. The patient was discharged 42 days after admission once renal clinical chemistry values had return to normal, although nuclear magnetic resonance (NMR) spectroscopic analysis still revealed abnormalities consistent with renal papillary damage. One year after the incident, the patient was still polyuric.

Dark urine was reported in a case of chronic phenol poisoning (Merliss 1972). The man worked in a laboratory for 13.5 years where he distilled phenol several times a day. During the process, heavy odors were detectable, phenol was often spilled on his clothes, and he noted skin irritation. The study authors indicated that the urine was so dark that it suggested hemoglobinuria. Glucose was present in the urine, although the urine was negative for homogentistic acid (a substance whose presence can cause urine to darken upon standing) and urobilinogen. The urine cleared 2–3 months after the subject was removed from phenol exposure. Dark urine was also observed in a man who spilled 90% phenol over an occluded area of the skin and kept the area unattended for 4.5 hours (Bentur et al. 1998).

Hemoglobinuria and hematin casts in the distal convoluted tubules and tubular lumens located in the medulla and papilla were reported in rats after a single dermal exposure to 107 mg/kg liquid phenol (Conning and Hayes 1970). These phenomena are probably related to red blood cell lysis and increased glomerular filtration of hemoglobin. Hemoglobinuria is characteristic of lethal or near-lethal exposures by the dermal route.

Dermal Effects. Application of phenol to the skin of humans results in dermal inflammation and necrosis (Horch et al. 1994; Merliss 1972; Truppman and Ellenby 1979). Data concerning minimal effective exposure levels in humans were not found. NIOSH (1984) conducted a survey in an Oregon hospital in response to concerns about respiratory problems and contact dermatitis in housekeeping staff members who were exposed frequently to germicidal solutions containing phenol and other solvents (formaldehyde, cellosolve, ethanolamine). The housekeeping staff reported significantly more symptoms of cough, itching, sinus problems, and dermatitis than did other employees. Air concentrations of phenol in the work areas were below the limit of detection (<0.01 ppm). Urinary phenol levels in the housekeeping staff members were not significantly different from those of the other employees. Thus, while it is likely that the employees came into contact with irritants, the cause of the reported symptoms could not be attributed to phenol or any other specific substance in the work environment. Therefore, this study is not recorded in Table 3-3.

Application of 0.1 mL of molten phenol/kg (≈100 mg/kg) (Brown et al. 1975) or 107 mg/kg (Conning and Hayes 1970) to the skin of rats for 24 hours (surface area not reported) produced severe edema, erythema, and necrosis. In pigs, application of 500 mg/kg molten phenol to 35–40% of the body surface (0.44 mg/cm^2/kg) resulted in skin discoloration after 20–30 minutes of exposure and severe necrosis after 8 hours of exposure. Two of three pigs died within 95 minutes after exposure (Pullin et al. 1978). Necrosis, hyperemia of superficial dermal vessels, and dense perivascular infiltration of lymphocytes and neutrophils were noted in the skin of pigs treated dermally with an unspecified amount of 89% phenol (Hunter et al. 1992). The dose-effect relationship and time course for skin irritation and inflammation have been studied in mice (Patrick et al. 1985). The end point examined was swelling (increased thickness) of the ear after dermal application to the ear pinna. Application of 12 mg/cm^2/kg of phenol to the ear resulted in swelling in four of nine mice within 1 hour after application. Severity of skin irritation increased as the concentration of the applied phenol solution increased. Swelling persisted for 6 weeks after application of 18 mg/cm^2/kg. Swelling was observed in only one of eight mice treated with 12 mg/cm^2/kg phenol. Application of an unspecified amount of a 1:6 or 1:9 phenol:water solution to the skin of guinea pigs for 1 minute resulted in erythema and increased skin vascular permeability indicated by dye permeability (Steele and Wilhelm 1966).

Skin crusts were reported on mice exposed repeatedly to 5 mg phenol as a 5% (w/v) solution for 32 weeks, whereas skin ulceration was observed in mice exposed to 5 mg phenol as a 20% (w/v) solution (Salaman and Glendenning 1957). The skin ulceration healed in 4 weeks after the end of the exposure. In a 52-week study, mice were exposed 2 times each week to 42 or 83 mg/kg of phenol in a 5 or 10% solution in benzene (Boutwell and Bosch 1959). Severe skin damage was reported after 36 weeks in the mice exposed to 83 mg/kg. Skin papillomas were reported in mice exposed at 42 mg/kg. Because phenol was applied in benzene which is also a skin irritant, this study is not presented in Table 3-3.

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

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

A modified Draize test was used to assess ocular damage resulting from application of 5% phenol to the center of the cornea in New Zealand rabbits (Murphy et al. 1982). The eyes of one group of rabbits were

irrigated with water 30 seconds after exposure, while the eyes of another group were unirrigated. Conjunctivitis developed in all treated groups and lasted through the 7 days of observation. Corneal opacities became apparent in four of nine rabbits 24 hours after phenol application in unirrigated eyes, but only 1 hour after application in four of nine rabbits receiving irrigation. The opacities lasted through the 7-day observation period in the unirrigated eyes, but were cleared by day 7 in the irrigated eyes. Based on these observations, phenol was designated as a severe eye irritant in unirrigated eyes, and as a moderate eye irritant in irrigated eyes (Murphy et al. 1982).

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

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

3.2.3.3 Immunological and Lymphoreticular Effects

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

3.2.3.4 Neurological Effects

Fatal dermal exposure to an 80% phenol solution in a 24-year-old man being treated for skin rash was characterized by severe convulsions prior to death (Lewin and Cleary 1982). A child who suffered accidental dermal poisoning with phenol became listless and developed seizures before death (Soares and Tift 1982). Seizures were also reported in a young adult who splattered a solution containing 30% of phenol over portions of his face, neck, and right trunk and later died (Soares and Tift 1982). A man who spilled 90% phenol over his foot and shoe had hypalgesia and hypoesthesia of the affected area in addition to confusion, vertigo, and faintness (Bentur et al. 1998).

Muscle tremors and convulsions are characteristic effects of acute dermal phenol toxicity in laboratory animals. Tremors that developed into convulsions and prostration were reported in rats exposed to

107 mg/kg liquid phenol; application surface areas were not reported (Conning and Hayes 1970). In pigs, application of 500 mg/kg over 35–40% of the body surface (0.44 mg/cm^2/kg) resulted in muscular tremors in the head region within 3–5 minutes of exposure (Pullin et al. 1978). This was followed by dilation of the pupils, loss of coordination, and excess salivation and nasal discharge within 5 minutes of exposure. It was followed by convulsions, coma, and death 5–7 minutes after exposure in two of three pigs. Direct application of a dose of 38 mg/kg phenol to the inner ear resulted in a reduced threshold for auditory brainstem response (Schmidt et al. 1990).

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

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

3.2.3.7 Cancer

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

In a study of the promoting effects of phenol, mice were exposed to 9,10-dimethyl-1,2-benzanthracene (9,10-DMBA) (300 μg) followed by weekly dermal exposure to 5 mg phenol in either a 5 or 20% phenol solution in acetone for 32 weeks (Salaman and Glendenning 1957). Exposure to 9,10-DMBA followed by phenol (5 or 20%) resulted in a significantly greater incidence of tumors, including carcinomas, than exposure to 20% phenol alone; tumors, but no carcinomas, resulted from exposure to 20% phenol, and no tumors resulted from exposure to 5% phenol. Application of 5% phenol alone resulted in skin "crusting" at the site of application, whereas 20% phenol resulted in skin ulceration. The study authors concluded that phenol was an effective tumor promoter after a single application of 9,10-DMBA. Although this study did not include a group of animals that had been exposed to 9,10-DMBA alone, the authors indicated that previous work done in their laboratory provided the data from such animals and that it was thus the comparison between such historical information and the information from this study which led to their conclusion about the promotional effects of phenol.

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

Additional studies indicate that phenol applied to the skin is a cancer promoter and possibly a complete carcinogen (i.e., promoter and initiator) in mice. Boutwell and Bosch (1959) examined the carcinogenic effects of phenol in several strains of mice. Mice were exposed to a single dermal application of 9,10-DMBA (75 mg) followed by repeated dermal applications of a 5 or 10% phenol solution in benzene (42 or 83 mg/kg/treatment), twice each week for 52 weeks. Two other experimental groups of mice were exposed to 9,10-DMBA alone or phenol alone. Severe skin damage, decreased body weight, and increased mortality were observed in phenol-treated animals. Sutter strain mice (inbred for three generations for susceptibility to the initiator 9,10-DMBA) treated with 9,10-DMBA followed by 10% phenol developed papillomas (95% in 13 weeks) and carcinomas (43% in 42 weeks) at a much higher incidence than mice treated with 9,10-DMBA alone (14% with papillomas at 42 weeks; no carcinomas), or phenol alone (36% with papillomas at 52 weeks; no carcinomas). One fibrosarcoma was observed after 52 weeks of exposure to phenol alone. An elevated incidence of papilloma was also observed in CAF1, C3H, and Holtzmann mice exposed to 9,10-DMBA followed by phenol, and in Holtzmann mice exposed to 10% phenol alone. The promoting effect of phenol was dose related; application of 5% phenol (41.7 mg/kg) following 9,10-DMBA treatment resulted in fewer tumors than a similar protocol using 9,10-DMBA followed by 10% phenol (83.3 mg/kg). Phenol elicits skin tumors in mice even without treatment with 9,10-DMBA. Ten out of 30 albino mice treated twice weekly for 12 weeks with a 20% phenol solution in dioxane developed papilloma of the skin; also, 8 out of 30 mice treated with 10% phenol solution in benzene for 15 weeks developed papilloma, and 3 developed carcinoma of the skin (Boutwell and Bosch 1959). Because the phenol was administered in benzene or dioxane, both of which are skin irritants and/or de-fatting agents, this study is not presented in Table 3-3.

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

3.3 GENOTOXICITY

Phenol has been evaluated for genotoxicity in both *in vivo* (Table 3-4) and *in vitro* (Table 3-5) test systems. End points evaluated in *in vivo* mammalian test systems include chromosomal aberrations, micronucleus, and deoxyribonucleic acid (DNA) synthesis. Several different cell types have been monitored, including bone marrow, liver, and renal cell. Both positive and negative results have been reported for *in vivo* genotoxicity tests. *In vitro* studies have been conducted in prokaryotic and eukaryotic test systems. Results for various end points (gene mutation, chromosomal aberration, micronuclei, DNA damage, sister chromatid exchanges, and unscheduled DNA synthesis) have been both positive and negative. The mixed results in both the *in vivo* and *in vitro* assays indicate that under certain conditions, especially at higher doses, phenol has the potential to be genotoxic. However, at the exposure levels likely to occur near hazardous waste sites, phenol is not anticipated to be genotoxic.

Positive and negative results have been reported for phenol in *in vivo* chromosomal aberration tests. Increases in chromosomal aberrations have been reported in bone marrow (Shelby and Witt 1995) and in spermatocytes (Bulsiewicz 1977) from mice treated with phenol. Chromosomal aberrations were reported in the bone marrow of male B6C3F_1 mice exposed to phenol through intraperitoneal injection (Shelby and Witt 1995). Bulsiewicz (1977) also reported results of a five-generation study with Porton strain inbred mice. Chromosomal aberrations were monitored in spermatogonia and spermatocytes of gavage treated mice. Dose dependent increases in aberrations were observed with succeeding generations. The investigator attributed the observed chromosomal effects to interactions of phenol with the spindle apparatus. Other studies have not observed chromosomal aberrations in bone marrow from mice treated with phenol (Barale et al. 1990; Chen and Eastmond 1995a; Pashin et al. 1987). In tests of feeding and injection exposures of *Drosophila* to phenol, results were negative in sex-linked recessive lethal assays (Gocke et al. 1981; Sturtevant 1952).

Positive (Ciranni et al. 1988; Li et al. 2005; Shelby and Witt 1995) and negative (Barale et al. 1990; Gocke et al. 1981) results were reported for *in vivo* micronucleus assays in bone marrow isolated from mice treated with phenol. Bone marrow micronucleus tests were positive for male B6C3F_1 mice exposed to phenol through intraperitoneal injection (Shelby and Witt 1995). In a study of pregnant CD-1 mice receiving doses of phenol, maternal bone marrow micronuclei were studied. Pregnant mice were treated by gavage with a single dose of 265 mg/kg of phenol on GD 13. Observed effects included an increase in bone marrow micronuclei and cytotoxicity. Micronuclei were not observed in fetal liver tissue (Ciranni et al. 1988). Bone marrow of Kunming mice exposed to concentrations of 20, 40, or 80 mg/kg of phenol

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

Species (test system)	End point	Results	Reference
Mammalian cells:			
Mouse bone marrow	Chromosomal aberration	–	Barale et al. 1990; Chen and Eastmond 1995a; Pashin et al. 1987
Mouse bone marrow	Chromosomal aberration	+	Shelby and Witt 1995
Mouse spermatocytes	Chromosomal aberration	+	Bulsiewicz 1977
Bone marrow from pregnant mice	Micronucleus	+	Ciranni et al. 1988
Mouse fetal liver cells	Micronucleus	–	Ciranni et al. 1988
Mouse bone marrow	Micronucleus	+	Li et al. 2005; Shelby and Witt 1995
Mouse bone marrow	Micronucleus	–	Barale et al. 1990; Gocke et al. 1981
Mouse tubular renal and liver epithelial	DNA synthesis	+	Amlacher and Rudolph 1981
Rat testes	DNA synthesis	–	Skare and Schrotel 1984
Rat liver	DNA synthesis	–	Miyagawa et al. 1995
Insects:			
Drosophila	Micronucleus	–	Gocke et al. 1981; Sturtevant 1952

+ = positive response; – = negative response; DNA = deoxyribonucleic acid

Table 3-5. Genotoxicity of Phenol *In Vitro*

Species (test system)	End point	Results		Reference
		With activation	Without activation	
Prokaryotic organisms:				
Salmonella typhimurium	Gene mutation	–	–	Florin et al. 1980; Haworth et al. 1983; Kubo et al. 2002; Pool and Lin 1982
S. typhimurium	Gene mutation	+	–	Gocke et al. 1981
Escherichia coli	Gene mutation	–	–	Nagel et al. 1982
E. coli	Gene mutation	No data	+	Demerec et al. 1951
Eukaryotic organisms:				
Aspergillus	Chromosomal aberration	No data	+	Crebelli et al. 1987
V79 Chinese hamster cells	Gene mutation	+	–	Paschin and Bahitova 1982
Chinese hamster ovary cells	Micronuclei	+	+	Miller et al. 1995
Chinese hamster ovary cells (DNA strand breaks)	Chromosomal aberration	No data	–	Sze et al. 1996
Crucian (goldfish) erythrocytes	DNA damage	No data	+	Li et al. 2005
Mouse lymphoma (DNA strand breaks)	Chromosomal aberration	No data	–	Pellack-Walker and Blumer 1986
Mouse spermatocytes	DNA damage	No data	+	Li et al. 2005
Rat liver mitochondria	DNA synthesis	No data	–	Schwartz et al. 1985
Syrian hamster embryo cells	Gene mutation	No data	+	Tsutsui et al. 1997
Syrian hamster embryo cells	Chromosomal aberration	No data	+	Tsutsui et al. 1997
Syrian hamster embryo cells	Sister chromatid exchanges	No data	+	Tsutsui et al. 1997
Syrian hamster embryo cells	Unscheduled DNA synthesis	No data	+	Tsutsui et al. 1997
Human lymphocytes	Sister chromatid exchanges	+	+	Morimoto and Wolff 1980; Morimoto et al. 1983
Human lymphocytes	Sister chromatid exchanges	No data	–	Jansson et al. 1986
Human lymphocytes	Sister chromatid exchanges	No data	+	Erexson et al. 1985
Human lymphocytes	DNA damage	No data	+	Li et al. 2005

Table 3-5. Genotoxicity of Phenol *In Vitro*

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

+ = positive response; – = negative response; DNA = deoxyribonucleic acid

through intraperitoneal injection showed increased frequency of micronuclei at dose levels of 40 and 80 mg/kg (Li et al. 2005). However, exposures of male CD-1 mice to maximum intraperitoneal injections of 160 mg/kg resulted in negative micronucleus tests (Barale et al. 1990). Results were also negative for micronucleus assays in male and female NMRI mice dosed twice by intraperitoneal injections of 188 mg/kg of phenol (Gocke et al. 1981).

Phenol increased DNA synthesis in tubular renal and liver epithelial cells from mice (Amlacher and Rudolph 1981). Skare and Schrotel (1984) reported the results of experiments where Sprague-Dawley rats were dosed with single intraperitoneal injections of 79 mg/kg or five daily intraperitoneal injections of 39.5 mg/kg/day. Single strand breaks were not observed in testicular cells. A DNA synthesis test in male $B6C3F_1$ mice dosed by gavage with concentrations of 0, 300, and 600 mg/kg of phenol also was negative (Miyagawa et al. 1995).

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).

In vitro studies regarding chromosomal aberrations in eukaryotic cells have been positive in *Aspergillus* (Crebelli et al. 1987), and in SHE cells (Tsutsui et al. 1997), and negative in mouse lymphoma cells (Pellack-Walker and Blumer 1986) and CHO cells (Sze et al. 1996). Tsutsui et al. (1997) reported dose-dependent increases in the frequencies of chromosome aberrations in SHE cells exposed to phenol. Single strand breaks were not observed in mouse lymphoma L5178YS cells (Pellack-Walker and Blumer 1986).

The report of an *in vitro* micronucleus study with CHO cells was positive with and without S9 activation, with stronger results observed with S9 activation (Miller et al. 1995).

Results of *in vitro* sister chromatid exchange tests were reported as positive and negative. Phenol produced dose-related increases in sister chromatid exchanges in human lymphocytes at doses of

≥500 μM (Erexson et al. 1985). In contrast, sister chromatid exchanges were not observed in human lymphocytes incubated with 0–2,000 μM phenol (Jansson et al. 1986). Incubation of human lymphocytes with 1,000,000 μM, but not 200,000 μM phenol for 72 hours resulted in an increase in sister chromatid exchanges (Morimoto and Wolff 1980). Exposures of human lymphocytes to 3,000 μM phenol with S9 activation also resulted in an increase in sister chromatid exchanges (Morimoto et al. 1983). Phenol induced sister chromatid exchanges in SHE cells at doses of 1,000 and 3,000 μM (Tsutsui et al. 1997).

In vitro assays for DNA synthesis have been negative in rat liver mitochondria (Schwartz et al. 1985), and positive in human fibroblasts (Poirier et al. 1975) and HeLa cells (Painter and Howard 1982). However, unscheduled DNA synthesis was induced to the same degree in SHE cells incubated with phenol in concentrations ranging from 1 to 30 μM (Tsutsui et al. 1997).

An *in vitro* study of DNA damage using the comet assay indicated that phenol induced DNA damage in human lymphocytes, mouse spermatocytes, and crucian erythrocytes. In these tissues, amounts of DNA damage increased in conjunction with increasing doses. Observed DNA damage to mouse spermatocytes and crucian erythrocytes was more significant than DNA damage to human lymphocytes (Li et al. 2005).

3.4 TOXICOKINETICS

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

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

Phenol is absorbed readily after inhalation exposure. Eight subjects were exposed to phenol vapors (1.6–5.2 ppm) for 8 hours (Piotrowski 1971). Subjects were exposed through a face mask in order to eliminate the possibility of percutaneous absorption. The concentration of phenol in inhaled and exhaled air was determined, and urine was analyzed for total phenol (phenol and phenol conjugates). Steady-state appeared to be achieved within 3 hours after initiating exposure; steady-state retention was 60–88%. Urinary recovery of phenol that had been retained in the lungs was 99±8% within 24 hours after initiating exposure.

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

Rats exposed by intratracheal instillation to [^{14}C]-labeled phenol also demonstrated rapid absorption kinetics, with most of the radioactivity being excreted within 72 hours (Hughes and Hall 1995). Rats exposed for 6 hours nose-only to 25 ppm [^{14}C]-labeled phenol demonstrated rapid absorption. Greater than 90% of phenol-derived radioactivity was measured in the urine 30 minutes after initiation of exposure (Hiser et al. 1994).

3.4.1.2 Oral Exposure

Based on the rapid excretion of phenol and its metabolites in urine, it has been concluded that phenol is readily absorbed by the oral route in humans (Capel et al. 1972) and a variety of mammalian species including monkeys (Capel et al. 1972), rodents (Capel et al. 1972; Edwards et al. 1986; Hughes and Hall 1995; Kao et al. 1979; Kenyon et al. 1995), dogs (Capel et al. 1972), rabbits (Capel et al. 1972), cats (Capel et al. 1972; French et al. 1974), and pigs (Capel et al. 1972; Kao et al. 1979).

In three men given a single oral dose of 0.01 mg/kg [^{14}C]-labeled phenol in food or drink, about 90% (range 85–98%) of the dose was excreted in the urine in 14 hours (Capel et al. 1972). In this same study,

urinary recovery of orally administered [^{14}C]-labeled phenol was determined in 18 other mammalian species; mean 24-hour recoveries of ^{14}C ranged from 95% in the rat to 31% in the squirrel monkey. Rats exposed orally to radiolabeled phenol demonstrated rapid absorption and excretion, with most of the radioactivity being excreted within 72 hours (Hughes and Hall 1995). The gastrointestinal absorption of phenol has also been studied in rats with *in situ* preparations. The absorption kinetics of [^{14}C]-labeled phenol administered directly into the small intestines of rats were described as first-order, with a rate constant for intestinal absorption of 0.127±0.003 minute^{-1} (or half-life of 5.5±0.5 minutes from t½=0.693k) (Humphrey et al. 1980). Two hours after [^{14}C]-labeled phenol was injected into the small intestines of anesthetized rats, recoveries in the urine were 77.9±2% after a 12.5-mg/kg dose, and 76.9±5.8% after a 25-mg/kg dose (Kao et al. 1979).

Hiser et al. (1994) reported results of the kinetics of oral doses of phenol in rats. Exposures included single and multiple bolus and drinking water doses of different concentrations. Peak blood concentrations of free phenol of 0.02 µg/g blood in rats receiving 1.5 mg/kg bolus dose were reached 1–3 minutes after receiving the dose. A terminal half-life of about 8 minutes was calculated for phenol following low doses. Peak blood concentrations of phenol of 46.4 µg/g blood in rats receiving 150 mg/kg bolus dose were reached 1 minute after receiving the dose. Since the doses were separated by only a factor of 100 and the blood peak concentration by a factor of 2,320, these results suggest saturated absorption or saturated metabolism and excretion. After 24 hours, concentrations of administered [^{14}C]-radioactivity were >90% in the urine, regardless of the dosing method or concentration.

3.4.1.3 Dermal Exposure

Phenol is absorbed quite readily through the skin, and the skin is considered the primary route of entry during occupational exposure (ACGIH 2005). Whole-body skin exposures studies were conducted in volunteers lightly clothed and unclothed (Piotrowski 1971). The subjects were exposed to phenol vapor (35% humidity, 26 °C) at concentrations of 1.3, 2.6, or 6.5 ppm for 6 hours. Fresh air was supplied to the subjects through a face mask in order to prevent absorption of phenol through the lungs. The total amount of phenol excreted in urine during and after exposure (minus baseline excretion) was used as a measure of absorption. Absorption increased proportionately with exposure level. Percutaneous clearance (mg phenol absorbed through the skin per hour/mg phenol per m^3 of air) was estimated to be 0.35 m^3/hour. Thus, an amount of phenol equivalent to that contained in 0.35 m^3 of air was absorbed through the skin each hour.

The data reported by Piotrowski (1971) provide a basis for comparing the relative contributions of lung and percutaneous absorption during exposures to phenol vapor. Assuming a ventilation rate for the human of 0.8 m^3/hour (EPA 1986a) and a steady-state lung retention of inhaled phenol of 0.7 m^3/hour (Piotrowski 1971), clearance of airborne phenol through the lung is ≈0.6 m^3/hour. Thus, an amount of phenol equivalent to that contained in 0.6 m^3 of air was absorbed through the lungs each hour. It can be concluded that at any given exposure level within the range of 5–25 mg/m^3 (1.3–6.4 ppm), percutaneous absorption (0.35 m^3/hour) will be about half that of absorption through the lungs (0.6 m^3/hour).

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

When human skin was treated *in vitro* with 0.0013–0.0027 mg/cm^2 [^{14}C]-labeled phenol and left unoccluded, 20% of the radioactivity was absorbed when analyzed 72 hours later, while 7% remained on the skin surface (Hotchkiss et al. 1992). Covering the skin with a teflon cap resulted in the absorption of 47%, with 3% recovered in the skin. When rat skin was subjected to the same exposure regime in this study, 72 hours later, 24% of the radioactivity was absorbed with 22% recovered in the skin when the skin was unoccluded, and 36% was absorbed with 3–4% recovered in the skin when the skin was occluded.

In rats in which a 0.03-mg/kg dose of [^{14}C]-labeled phenol was placed on the skin, only 1–5% of the dose remained in the body 72 hours later (Hughes and Hall 1995). The dermal absorption of phenol was studied in three pigs in which undiluted phenol was placed on the skin for 1 minute, and the peak plasma level was determined (Pullin et al. 1978). Plasma levels were not measurable in one pig treated with a dose of 90 mg/kg over a surface area of 91.6 cm^2. In pigs treated with a dose of 500 mg/kg, peak plasma levels of 0.9 and 30.5 ppm were reported in pigs treated over surface areas of 91.6 and 1,135.5 cm^2, respectively.

Permeability coefficients for phenol in isolated skin patches from nude mice have been determined (Behl et al. 1983). The permeability coefficient increased as the concentration of the applied aqueous phenol solution increased; doubling the concentration from 20 to 40 g/L resulted in a 12-fold increase in mean permeability coefficient (0.007–0.085 cm/hour). The value obtained for the permeability coefficient when 60 g/L was applied to the skin patch (0.169 cm/hour) was similar to that obtained for skin patches

in which the stratum corneum had been removed. It was concluded that phenol concentrations exceeding 20 g/L may destroy a diffusion barrier normally provided by the intact stratum corneum, permitting increased percutaneous absorption.

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

3.4.1.4 Other Routes of Exposure

Nomoto et al. (1987) studied the absorption of phenol after injection into 20 patients as part of lumbar or thoracic sympathetic blockades. Patients were injected with 5–10 mL 7% phenol. The concentrations of unconjugated and conjugated phenol (sulfate esters and glucuronic esters) were monitored in blood and urine samples. Unconjugated phenol reached a mean peak concentration in blood of 3.01±0.28 μg/mL 18.8±2.5 minutes after the injection. The mean peak concentration of conjugated phenol in the blood was 4.15±0.25 μg/mL 54.9±4.5 minutes after the injection. The authors concluded that uptake times indicated rapid absorption of phenol after injection. The lag time of unconjugated phenol was 5.3±1.6 minutes, indicating that phenol remained at the injection site before being taken up into the blood. The lag time of conjugated phenol was 9.9±5.9 minutes.

There is also indirect evidence of phenol being absorbed following phenol injection sclerotherapy for hemorrhoids. Suppiah and Perry (2005) reported the case of a 43-year-old man who developed jaundice after an unspecified number of injections of 2 mL of a 5% solution of phenol at hemorrhoidal tissue during several months. Liver function tests returned to normal after 6 months.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

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

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

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

In a study conducted by Hiser et al. (1994), rats were exposed 6 hours nose-only to 25 ppm ^{14}C-phenol for either 1 or 8 days. Mean percent of administered dose/g were reported for several tissues. Radioactivity was quantified in blood, bone, brain, fat, heart, kidney, liver, lung, muscle, skin, spleen, testes, ovaries, and carcass 24 hours after exposure. No single tissue seemed to preferentially accumulate phenol-derived radioactivity and, in all cases, concentrations were <0.02% administered dose/g tissue. No significant differences were seen between the 1- and 8-day exposure experiments.

3.4.2.2 Oral Exposure

Limited information in humans is available from cases of accidental or intentional ingestion of phenol that resulted in fatalities. One case involved ingestion of a mixture of phenol and cresol. The concentrations of phenol measured in the blood, urine, and stomach content were 58.3, 3.3, and 115 μg/mL, respectively (Boatto et al. 2004). Another case involved ingestion of a mixture of phenol and chloroform. Phenol was measured at 60 μg/mL in the blood and 208 μg/mL in the urine. Concentrations in the brain, lungs, liver, and kidney were 106, 116, 166, and 874 μg/g, respectively (Tanaka et al. 1998).

The third case involved ingestion of phenol, which resulted in the following tissue concentrations of phenol: blood, 130 μg/mL; urine, 47 μg/mL; bile, 187 μg/mL; brain, 486 μg/g; kidney, 331 μg/g; muscle, 204 μg/g; liver, 228 μg/g; and stomach content, 668 mg (Lo Dico et al. 1989).

In animals, information is available for rabbits (Deichmann 1944) and rats (Hiser et al. 1994; Hughes and Hall 1995; Liao and Oehme 1981). In rabbits, distribution is rapid, with peak tissue concentrations achieved in most tissues within 1 hour after dosing. The highest peak concentrations and fraction of administered dose are found in the liver; >90% of the administered dose is eliminated from tissues within 24 hours.

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

The kinetics of tissue distribution of [^{14}C]-labeled phenol in rats given 207 mg/kg of [^{14}C]-labeled phenol, a sublethal (≈0.5xLD_{50}) oral dose, were studied (Liao and Oehme 1981). Although all rats survived for 16 hours, signs of systemic toxicity were observed including twitching of muscles around the eyes and ears, convulsions, and coma persisting for 15–30 minutes. Thirty minutes after dosing, 28.4% of administered ^{14}C was recovered in tissues (liver, kidney, adrenal, thyroid, spleen, blood, lung, thymus, brain, testes, heart, muscle, and fat). Sixteen hours after dosing, 0.3% of the administered dose was recovered in tissues. Concentrations of ^{14}C were highest in all tissues 30 minutes after dosing, with the exception of the thyroid gland, in which peak concentrations were achieved after 2 hours. The highest concentration and fraction of administered dose were found in the liver; 42% (range 29–56%) of the administered dose was recovered in the liver 30 minutes after dosing. Approximately 67–85% of the ^{14}C in blood was present in the plasma fraction, of which 41–50% was bound to plasma proteins or other macromolecules. The elimination half-time for ^{14}C was <4 hours. Based on their results, the study authors suggested that blood flow determines the tissue uptake of the radiolabel from phenol.

Rats exposed orally to radiolabeled phenol were sacrificed 72 hours later and analyzed for tissue distribution of the radioactivity (Hughes and Hall 1995). Of the radioactivity remaining in the body, a

majority was distributed in the muscle (0.08%), skin (0.07%), fat (0.02%), liver (0.02%), and blood (0.02%).

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

In a study conducted by Hiser et al. (1994), rats were exposed to ^{14}C-phenol via single gavage doses of 1.5, 15, or 150 mg/kg, multiple gavage doses of 1.5 mg/kg/day, 5,000 ppm in drinking water for 1 day, or 5,000 ppm in drinking water for 8 days. In all cases, phenol-derived radioactivity was detected in blood, bone, brain, fat, heart, kidney, liver, lungs, skin, spleen, testes, ovaries, and carcass 24 hours after exposures. Regardless of the dosing method or dose level, no single tissue seemed to accumulate radioactivity, with all measured concentrations being <0.02% of the administered dose/g tissue.

3.4.2.3 Dermal Exposure

Limited information is available in humans from a fatal case. Tissue samples (liver, blood, lung, urine, and stomach contents) from an individual who was painted with benzyl benzoate with a brush that had been soaked in 80% phenol were analyzed for phenol. The blood contained 4.7 µg/mL phenol and unhydrolyzed and hydrolyzed liver samples contained 3.3 and 7.1 µg/g phenol, respectively. Phenol was not detected in the lung, urine, or stomach contents (Lewin and Cleary 1982).

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

3.4.2.4 Other Routes of Exposure

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

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

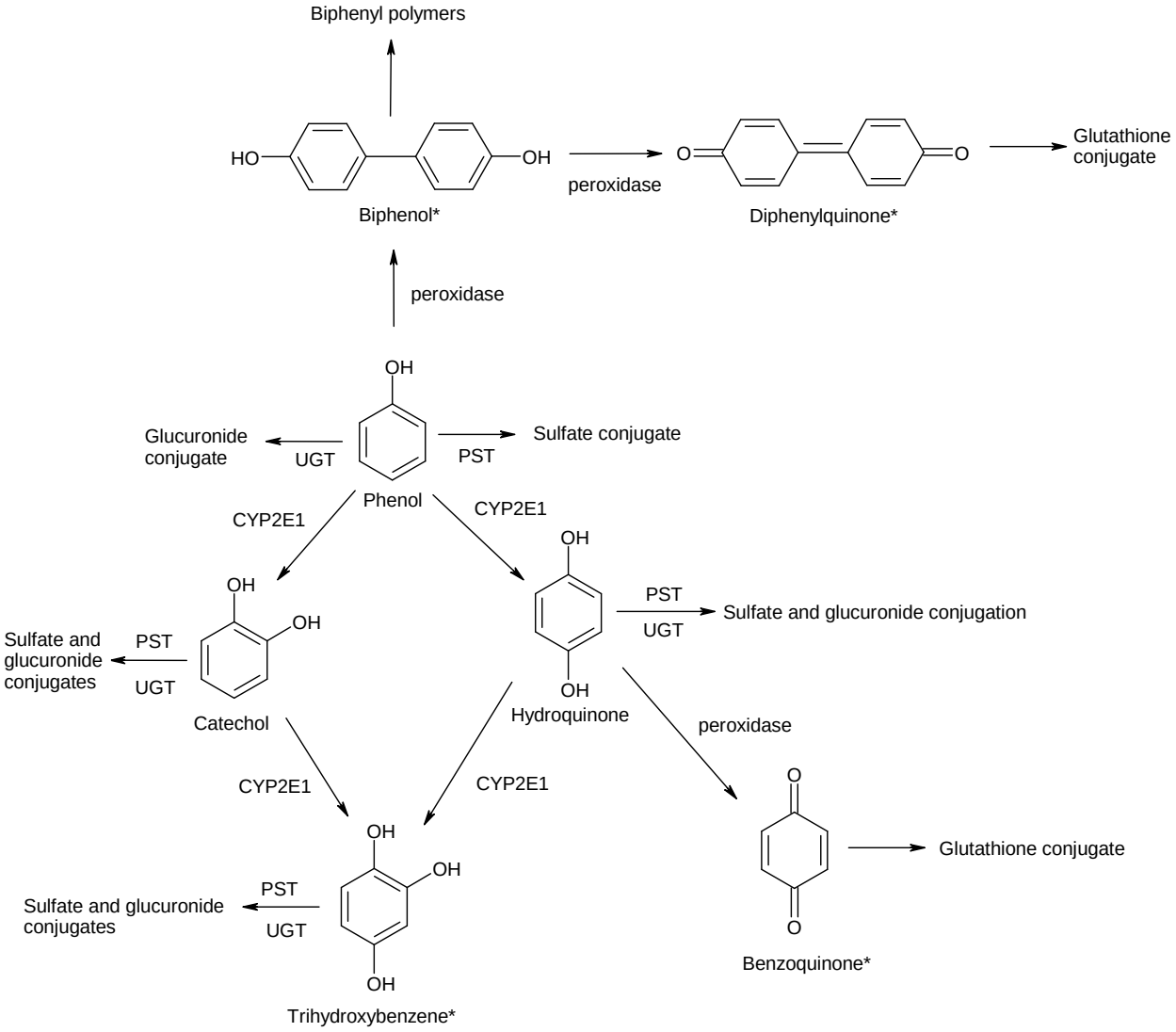
The distribution of phenol in the liver has been studied in mice treated intravenously with 31.4 mg/kg phenol (Davies and Lunte 1996). Microdialysis probes used to monitor the distribution of phenol metabolites in three regions of the liver (anterior, median, posterior) indicated that phenol-glucuronide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

3.4.3 Metabolism

Figure 3-3 shows the general metabolic pathways that transform phenol prior to its excretion in the urine. Three different enzymes systems catalyze the reactions that transform phenol. Cytosolic phenol sulfotransferases catalyze the transfer of inorganic sulfur from the activated 3'-phosphoadenosine-5'-phosphosulfate donor molecule to the hydroxyl group on phenol. Microsomal membrane-located uridine diphosphate (UDP) glucuronosyltransferases catalyze the transfer of an activated glucuronic acid molecule to the hydroxyl moiety of phenol to form an O-glucuronide conjugate. Cytochrome P4502E1, also microsomally located, catalyzes the hydroxylation of phenol to form hydroquinone (and to a much lesser extent, catechol), which is then acted upon by the phase II enzymes (Benet et al. 1995; Campbell et al. 1987; Gut et al. 1996; Koop et al. 1989; McFadden 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.

Cytochromes other than CYP2E1 also seem to be involved in the metabolism of phenol as demonstrated by Powley and Carlson (2001) in experiments utilizing chemical inhibitors of CYP2E1, CYP2B, CYP2F2, and CYP2E1 knockout mice. The investigators found that CYP2E1 was responsible for only approximately 50% of phenol metabolism in liver, suggesting the participation of other cytochromes.

Figure 3-3. Metabolism of Phenol



PST = phenol sulfotransferase; UGT = UDP-dependent glucuronosyl transferase

*Indicates metabolites identified *in vitro* only

Source: EPA 2002

Experiments in pulmonary microsomes showed that both CYP2E1 and CYP2F2 played important roles in the metabolism of phenol.

Phenol can also undergo peroxidation to form 4,4'-biphenol and diphenoquinone. This has been demonstrated in studies that used *in vitro* cell preparations with high peroxidase activity (Eastmond et al. 1986; Post et al. 1986), purified peroxidase enzymes (Smart and Zannoni 1984; Subrahmanyam and O'Brien 1985), or cell lines that have high myeloperoxidase activity (Kolachana et al. 1993). Thus far, there is no direct evidence that these peroxidation reactions occur *in vivo*.

In vivo, the gastrointestinal tract, liver, lung, and kidney appear to be the major sites of phenol sulfate and glucuronide conjugation of simple phenols (Cassidy and Houston 1984; Powell et al. 1974; Quebbemann and Anders 1973; Tremaine et al. 1984). Experiments conducted by Cassidy and Houston (1984) in rats injected intra-arterially, intravenously, or intraduodenally (doses ranged from 0.5 to 15 mg/kg) allowed them to evaluate the first-pass metabolism by different tissues. It was assumed that phenol that was systemically available had not been conjugated or metabolized and, therefore, the doses at which this occurred reflected the doses at which metabolic reactions were saturated. The investigators found that metabolism became nearly saturated in the liver at doses 10 times lower than in the endothelial lung, whereas metabolism in the gut was not saturated even at the highest dose tested. They also observed that the endothelial lung had a much lower affinity for phenol than the liver and gut. However, caution should be exercised when interpreting the results of the metabolic capacity of the lung because normal exposure results in exposure of the epithelial respiratory tract rather than the endothelial surface, as occurred in this study.

Four principal metabolites have been identified in mammals: two phenol and two hydroquinone conjugates (of sulfate and glucuronide) (Capel et al. 1972; Hoffmann et al. 1999; Kenyon et al. 1995; Wheldrake et al. 1978). In humans, rats, and mice given low doses of phenol orally, sulfate conjugates of phenol were found to predominate. However, in guinea pigs, pigs, and fruit bats, the glucuronide conjugates were dominant (Capel et al. 1972). In humans given an oral dose of 0.01 mg/kg, 77% of the urinary ^{14}C was identified as phenyl sulfate, 16% as phenyl glucuronide, and trace amounts (<1%) as the sulfate and glucuronide conjugates of hydroquinone (Capel et al. 1972).

In mice, phenyl sulfate was the predominant urinary metabolite for low doses (1–21 mg/kg) of phenol administered either by gavage and intravenously; however, as the dose increased, a decrease in phenol sulfation and a concomitant increase in glucuronidation of both phenol and hydroquinone was seen

suggesting saturation of the sulfation pathway (Kenyon et al. 1995). The degree of saturation appeared to be slightly greater following gavage administration, and intravenous administration resulted in higher proportions of the products of oxidative metabolism, with male mice being more sensitive than female mice. These latter observations suggest that the oxidative pathway become more prominent when phenol is introduced directly into the circulation, bypassing an initial intestinal sulfate conjugation process, and also suggests that the sulfate conjugation process saturates at a lower concentration in males than in females.

Similarly, in the rat, the ratio of phenyl sulfate/glucuronide conjugates in urine decreased from 2.6 to 0.7 when the intravenous dose level is increased from 1.2 to 25 mg/kg (Weitering et al. 1979). This phenomenon appears to be, at least in part, the result of differences in K_m in the two pathways, in relation to their respective V_{max} (Koster et al. 1981; Weitering et al. 1979). The range of substrate concentrations over which the reaction rate remains a linear function of concentration narrows as V_{max}/K_m decreases. A shift toward glucuronide formation as a function of dose would be expected in V_{max}/K_m, for the sulfation pathway was lower than that of the glucuronide pathway. Treatment of rats with an intraperitoneal dose of phenol (23–188 mg/kg) has also been shown to result in dose-dependent decreases in hepatic 3'-phosphoadeonsine 5'-phosphosulfate (PAPS), the co-substrate for the sulfate conjugation of phenol, as well as sulfate (Kim et al. 1995). The depletion of PAPS may also contribute to the saturation of sulfation at high doses of phenol. In another study of rats exposed to single and multiple bolus and drinking water doses of different concentrations, metabolites in the urine were primarily conjugates of phenol, showing dose-dependant concentrations (Hiser et al. 1994). For bolus doses, the ratios of glucuronide to sulfate phenol conjugates were 0.61 for 1.5 and 15 mg/kg doses and 1.16 for 150 mg/kg doses. Drinking water exposures resulted in a similar ratio of glucuronide to sulfate as observed for the 150 mg/kg bolus dose, with a ratio of 0.60. For inhalation exposures, ratios ranged from 0.24 to 0.39. Small amounts of an unidentified metabolite (2–4% total urinary radioactivity) were also detected.

All three enzyme systems involved in phenol metabolism have other substrates, which can competitively inhibit the metabolism of phenol, thereby changing the balance among metabolites. Inhibition of phenol sulfotransferase with chlorinated phenols (e.g., pentachlorophenol) results in increased glucuronide conjugation of simple phenols (Mulder and Scholtens 1977). Similarly, benzene is metabolized by CYP2E1; thus, high exposures to benzene may competitively inhibit phenol metabolism, resulting in decreasing hydroquinone production (and its corresponding sulfate and glucuronide conjugates) (Medinsky et al. 1995; Schlosser et al. 1993). Further information regarding the shift between sulfation, glucuronidation, and oxidation reactions is presented in Section 3.5.1, Pharmacokinetics Mechanisms.

Age- and sex-related changes in phenol sulfoconjugation were studied in hepatic cytosolic preparations from fetal, newborn, and adult rats (Iwasaki et al. 1993). Phenol sulfoconjugation activity was higher in adult males (1.94±0.1 nmol/mg/minute) than females (1.07±0.03 nmol/mg/minute), although there were no sex-related differences in the younger rats. Activity in fetal rats was very low (0.04±0.01 nmol/mg/minute). Activity at 2 days after birth was half that in adult females and a quarter of that in adult males, and remained constant until 25 days after birth. At 2 years of age, activity was intermediate between young adult male and female activities, and there were no sex-related differences. Heaton and Renwick (1991) found that young rats have a higher production of oxidative metabolism than adult rats. If this were the case in humans, children might be potentially more sensitive to the systemic effects of phenol, if a reactive intermediate is responsible for phenol toxicity. However, since glucuronidation does not appear to be limited in the young, production of oxidative products may be a smaller risk than anticipated. Caution should be exercised when extrapolating from adolescent rats to children, since rodents are well known to undergo a number of changes in xenobiotic-metabolizing enzymes during sexual development (Waxman et al. 1985).

3.4.4 Elimination and Excretion

Phenol, in its free and conjugated forms, is a normal constituent of human urine. Piotrowski (1971) reported 8.7±2.0 mg/day as the daily excretion rate of total phenol (free plus conjugates) in human subjects with no known exposure to phenol. Others have reported a range of values. In a study of workers employed in the distillation of high-temperature phenolic fractions of tar, mean values of phenol in the urine of 13.8 mg/L in 26 male non-exposed workers and 67.8 mg/L in 89 exposed workers were reported (Bieniek 1994). The highest concentration was found 2 hours after the end of the work shift. Quint et al. (1998) evaluated the urinary phenol concentration before and after using phenol to chemically cauterize the lesion created by excision of chrondroblastoma in 11 patients. Preoperatively, the average urinary concentration of phenol was 5.1 mg/L. Ling and Hanninen (1991) studied the effect of phenol on serum and urinary concentrations in patients who switched from a conventional diet to an uncooked “vegan” diet. Patients were tested at week 0, were on the vegan diet for 4 weeks, and then were on the regular diet for the second month. Urinary and serum levels of phenol were measured at weeks 0, 2, 4, and 9. A significant decrease in both urinary and serum concentrations of phenol was seen within 2 weeks of adopting the vegan diet. At 2 weeks, the serum concentration had dropped from about 0.75 to 0.5 mg/L (about 30%), and levels in urine had dropped from about 7 mg/L to about 3 mg/L (about 60%).

These data indicate that phenol is a natural product of metabolism that may vary significantly depending at least on diet, but probably also due to other factors.

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

3.4.4.1 Inhalation Exposure

Phenol absorbed through the lungs is excreted rapidly in urine in its free and conjugated forms. Within 24 hours after human subjects inhaled phenol at concentrations of 6–20 mg/m^3 (1.5–5.1 ppm), 99±8% of the phenol retained in the lungs was excreted (Piotrowski 1971). The urinary excretion of phenol was studied in 106 men occupationally exposed to phenol, cresols, xylenols, and other phenolic derivatives, and 26 unexposed controls (Bieniek 1994). Urine samples were taken after 4 hours at work, and in 16 workers every 2 hours for 24 hours after an 8-hour shift. The mean level of phenol in urine of the exposed workers was 87.3 mg/L, compared to 11.7 mg/L in controls. The highest phenol concentrations were recorded between 8 and 10 hours after the beginning of the exposure. Exposure concentrations were not reported in this study.

A study of workers in a Bakelite factory reported a linear correlation between concentrations of phenol in the air (up to 12.5 mg/m^3 or 3.25 ppm) and urinary excretion of total phenol (free plus conjugated) (Ohtsuji and Ikeda 1972). However, the urinary concentration of free phenol seemed to be independent of the environmental phenol, suggesting that under the exposure conditions, the maximum capacity to conjugate phenol had not been reached.

Urinary excretion of total phenol (free and conjugates) is considered a biomarker of exposure for phenol. The biological exposure index (BEI) for phenol, for exposure to 5 ppm in air, is 250 mg/g creatinine when measured at the end of the shift (ACGIH 2001).

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

In a study conducted by Hiser et al. (1994), rats were exposed via nose-only inhalation for 6 hours to 25 ppm ^{14}C-phenol for either 1 or 8 days. Thirty hours after initiation of exposure, mean percentages of phenol-derived radioactivity were measured in urine and feces. In rats exposed for 1 day, values in urine were 94.48% (males) and 90.92% (females). In rats exposed for 8 days, values in urine were 97.40% (males). In rats exposed for 1 day, values in feces were 3.33% (males) and 2.02% (females). In rats exposed for 8 days, values in feces were 0.81% (males). Less than 1% remained in tissues and carcass. These results indicate rapid elimination of phenol in urine after inhalation exposure.

3.4.4.2 Oral Exposure

Phenol absorbed from the gastrointestinal tract is excreted rapidly in urine as free phenol or conjugates (Capel et al. 1972; Deichmann 1944; Edwards et al. 1986; French et al. 1974; Kao et al. 1979; Kenyon et al. 1995; Liao and Oehme 1981). In three human subjects who received a single oral dose of 0.01 mg/kg [^{14}C]-labeled phenol, the mean 24-hour urinary recovery of ^{14}C was 90% (range 85–90%) of the administered dose (Capel et al. 1972). In this same study, urinary recovery of orally administered [^{14}C]-labeled phenol was determined in 18 other mammalian species; the mean 24-hour recoveries of ^{14}C ranged from 95% in the rat to 31% in the squirrel monkey. In three separate fatal cases of ingestion of phenol at unknown quantities, phenol was detected in the urine at concentrations of 3.3 μg/mL (Boatto et al. 2004), 208 μg/mL (Tanaka et al. 1998), and 47 μg/mL (Lo Dico et al. 1989).

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

Hiser et al. (1994) reported results of rats exposed to single and multiple bolus and drinking water doses of different concentrations of ^{14}C-phenol. After 24 hours, concentrations of administered ^{14}C radioactivity were >90% in the urine, regardless of the dose method or concentration. Less than 1% remained in tissues and carcass. This indicates rapid elimination of phenol in urine after oral exposure.

3.4.4.3 Dermal Exposure

Phenol absorbed through the skin is rapidly excreted in urine as free phenol or conjugates. A 4.5-hour occlusive exposure of one foot of an adult male to 90% phenol resulted in an elimination half-life of 13.86 hours. When admitted to the hospital, the phenol urine concentration was 7,909 mg/g in creatine. Over the next 12, 20, 43, 58, and 82 hours, phenol concentrations in the urine were measured at 13,416, 721, 80, 62.8, and 35.7 mg/g creatine, respectively (Bentur et al. 1998). Following an industrial accident in which a phenol-water solution was splashed over a man's face, chest wall, hand, and both arms, phenol in the urine decreased from 566 mg/L after 4 hours to 0.75 mg/L 46 hours after the exposure (Horch et al. 1994). Subjects exposed to dermally applied reservoirs containing phenol solutions (2.5–10 mg/L) excreted 80% (range 58–98%) of the absorbed phenol in the urine within 24 hours (Baranowska-Dutkiewicz 1981). Another study in which human subjects were dermally exposed for 7 hours to phenol vapors, both clothed and unclothed, while breathing clean air to avoid inhalation exposure, found that almost 100% of the absorbed phenol was excreted in the urine within 1 day, with clothing providing no apparent protection (Piotrowski 1971).

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

3.4.4.4 Other Routes of Exposure

Observations of elimination of phenol (5–10 mL 7%) after injection into 20 patients were carried out as part lumbar of thoractic sympathetic blockade treatments. Apparent elimination half-lives were 30.3±2.8 minutes for unconjugated phenol and 64.0±7.3 minutes for conjugated phenol. Urinary excretion of conjugated phenol was 52±5% after 8 hours (Nomoto et al. 1987).

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

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry

models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

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

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parameterization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) are adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994). PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-4 shows a conceptualized representation of a PBPK model.

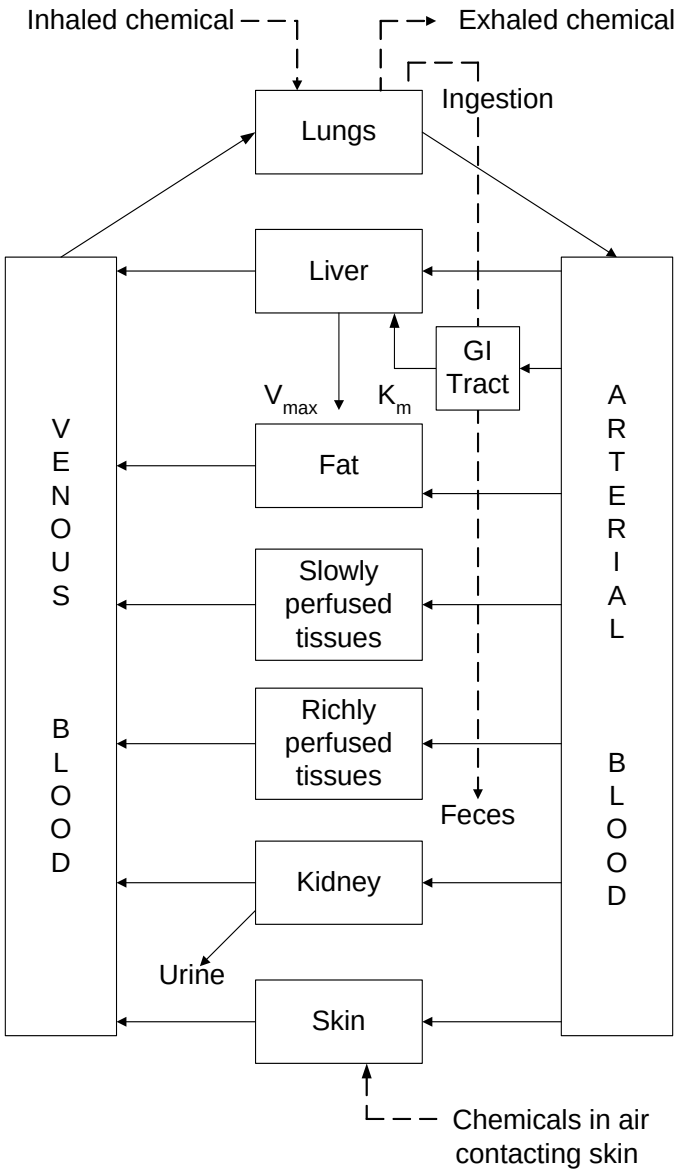
If PBPK models for phenol exist, the overall results and individual models are discussed in this section in terms of their use in risk assessment, tissue dosimetry, and dose, route, and species extrapolations.

3.4.5.1 Summary of PBPK Models

A PBPK model simulating phenol disposition has been developed as part of the attempt to understand the toxicity of benzene, of which phenol is the primary metabolite (Bois et al. 1991). Human exposure to benzene is widespread, and much of the toxicity of benzene is due to the action of its metabolites. Thus, while no studies were located involving PBPK models developed specifically for phenol exposure, the benzene model of Bois et al. (1991) is capable of predicting the pharmacokinetics of phenol and is appropriate to this discussion.

Two empirical compartmental models for benzene have also been developed, which predict the production and subsequent metabolism of phenol. A two-compartment model for quantifying benzene hepatic metabolism to phenol and other metabolites in an *in vitro* microsome system was developed by Schlosser et al. (1993) and enhanced by Medinsky et al. (1995). This model does not predict benzene (or phenol) absorption, disposition, or excretion from the body of animals or humans. A one-compartment model of phenol in humans was developed for assessing the variability of worker biomarkers related to occupational exposures (Pierrehumbert et al. 2002). Methods for model calibration and validation data were not reported. Both of these models are limited for use in phenol risk assessment since they do not reduce uncertainties associated with extrapolation animal internal dosimetry to humans or high exposure levels to low levels.

Figure 3-4. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

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

3.4.5.2 Discussion of Models

The Bois et al. (1991) Model

A PBPK model for benzene and phenol was developed by Bois et al. (1991) to explore differences in metabolite formation and distribution from benzene or phenol exposures to clarify why benzene, but not phenol, is carcinogenic in rats and humans.

Description of the model. The model represents the male rat as a series of flow-limited compartments interconnected by arterial and alveolar blood flow. The disposition of benzene and phenol was predicted in the liver, fat, bone marrow, and well- and poorly-perfused tissues. In addition, phenol distribution to the gut and lung was included. Routes of exposure included oral gavage dosing, inhalation, and intravenous injection of both compounds. Elimination of benzene was accomplished by exhalation and metabolism in the liver and bone marrow. Additionally, phenol was conjugated in the liver, lung, and gut. Hepatic and bone marrow metabolism of benzene to phenol was described by Michaelis-Menten generation of benzene oxide followed by first-order production of phenol. Michaelis-Menten kinetics described the transformation of benzene oxide to diols or glutathione conjugates and phenol to hydroquinone and sulfo- and glucurono-conjugates. Physiological flow and metabolic rates and constants were allometrically scaled to body weight. Instead of using point estimates of physiological and metabolic parameters values, uniform or log-uniform distributions (e.g., ranges) of parameter values were defined for all 64 model parameters. The model was executed using Monte Carlo techniques, in which individual random values were sampled from each parameter distribution during iterative model runs to produce distributions of model outputs rather than single values. This was done to accommodate variability and uncertainty in the parameter values. The parameter distributions were taken from the literature.

The model was calibrated to rat data for gavage (Sabourin et al. 1987, 1989) or inhalation (Sabourin et al. 1987, 1989) of benzene and intravenous, intra-arterial, intra-duodenal, and hepatic portal injection of phenol (Cassidy and Houston 1984) by adjusting the bounds of alveolar ventilation and other nonspecified parameter distributions. Different compartments pertaining to separate metabolic systems were assessed by selective injection as follows: jugular vein to assess first-pass metabolism across lung, hepatic portal vein to assess hepatic first-pass metabolism, duodenum to assess intestinal mucosa metabolism, and carotid artery to assess immediate tissues distribution.

Validation of the model. Validation of this model against empirical data was not done, introducing uncertainty into the ability of the model to predict other data. Of particular interest is the prediction that hydroquinone production is greater following phenol administration as compared to benzene administration. This is in opposition to the prediction of Medinsky et al. (1995).

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

Species extrapolation. Extrapolation of this model from rats to other animals or humans has not been done.

Interroute extrapolation. The model included parameter values for intestinal absorption and pulmonary partitioning of phenol, which enable simulation of oral and inhalation exposures, respectively. However, calibration and validation of these routes was not performed against empirical data. Predictions of phenol metabolism and distribution following injection into various sites were used to illustrate possible consequences of first-pass metabolism following oral exposure to phenol.

Risk assessment. This model has not been applied to a quantitative risk assessment of benzene or phenol. The predicted blood and bone marrow phenol and total hydroquinone levels were substantially higher after phenol administration than after benzene administration. This finding is counter to the hypothesis that phenol or hydroquinone plays a direct role in the carcinogenicity of benzene, suggesting that other metabolites must be involved. The study authors suggest that catechol, a potentially genotoxic oxidation metabolite produced in much larger amounts following benzene, as opposed to phenol administration, may contribute to benzene's carcinogenicity.

3.5 MECHANISMS OF ACTION

3.5.1 Pharmacokinetic Mechanisms

Absorption of phenol occurs fairly rapidly via the inhalation (Hughes and Hall 1995; Ohtsuji and Ikeda 1972; Piotrowski 1971), oral (Capel et al. 1972; Edwards et al. 1986; French et al. 1974; Hughes and Hall 1995; Kao et al. 1979; Kenyon et al. 1995), and dermal (Baranowska-Dutkiewicz 1981; Hughes and Hall 1995; Piotrowski 1971) routes. Because it is an irritant, tissue damage, inflammation, or other irritation

effects may occur at the sites of absorption. Because of its high pK_a, ionization will not occur within the acid environment of the gut. The action of gut microflora on phenol breakdown is not expected to be significant.

When it is absorbed through the lungs, gut, or skin, phenol conjugated at the portal-of-entry and free phenol, if the conjugation capacity of the tissue has been saturated by a high dose, enter the bloodstream where it can then be distributed throughout the body. The dilution of phenol in water enhances the dermal absorption of phenol, as indicated by the greater toxicity of a water-phenol solution compared to neat phenol (Conning and Hayes 1970). Conning and Hayes (1970) speculated that an undiluted solution may produce a coagulative necrosis, which would slow further penetration of phenol resulting in less phenol absorbed than with more diluted solutions.

As described in Section 3.4.3, Metabolism, conjugation with glucuronic acid and conjugation with sulfate are the main routes of detoxification of phenol. In most species tested, including humans, sulfation predominates at lower doses. As doses increase, glucuronidation increases, as does the formation of oxidative metabolites. Some have suggested that the shift from sulfation to glucuronidation is 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). An alternative explanation for the dose-dependent metabolic profiles for phenol is that the activities of metabolizing enzymes vary across areas of the liver (Medinsky et al. 1995). As blood flows into the liver from the periphery of the lobule towards the central vein, it encounters first a zone in which both sulfotransferases and glucuronosyltransferases are present (periportal zone 1), the former predominating. Glucuronosyltransferases predominate in zone 2, whereas both glucuronosyltranferases and monooxygenases are present in pericentral zone 3. In this zonal arrangement, phenol would be metabolized first by sulfotransferases, and at low doses, little free phenol would be available for glucuronide conjugation and oxidation. However, at increasing phenol doses, unconjugated phenol that reaches zone 2 is available for glucuronidation. At even higher doses that exceed the conjugation capacities of zones 1 and 2, oxidative metabolites are generated (Kenyon et al. 1995). Studies in isolated perfused liver from rats (Ballinger et al. 1995) and mice (Hoffmann et al. 1999) have validated the ‘enzyme zonation’ model.

The influence of enzyme localization on intestinal metabolism of phenol has also been studied (Kothare and Zimmerman 2002). In an *in situ* perfused intestine preparation from rat, the investigators showed that sulfation was the predominant metabolic pathway after vascular administration of phenol, whereas

luminal dosing produced greater glucuronidation. These results were consistent with the sulfotransferases being cytosolic enzymes (Burchell and Coughtrie 1997) and glucuronyltransferase being located between the nuclear and apical membrane of the epithelial cell (Inoue et al. 1999) and showing a decreasing expressional gradient from the villus to the crypt (Chowdhury et al. 1985).

Phenol that is absorbed is rapidly excreted in the urine as free phenol or conjugates (Baranowska-Dutkiewicz 1981; Capel et al. 1972; Deichmann 1944; Edwards et al. 1986; French et al. 1974; Hughes and Hall 1995; Kao et al. 1979; Kenyon et al. 1995; Liao and Oehme 1981; Piotrowski 1971).

3.5.2 Mechanisms of Toxicity

Limited information is available regarding the mechanism(s) of toxicity of phenol. Phenol is irritating and corrosive at high concentrations as evidenced by numerous cases of accidental dermal exposure or intentional or accidental ingestion of phenol. Phenol impairs the stratum corneum and produces coagulation necrosis by denaturing and precipitating proteins.

Phenol is a hydroxylated metabolite of benzene and it further undergoes oxidative metabolism to produce other compounds; however, it is still unknown with certainty whether the parent compound or a metabolite(s) is responsible for phenol's systemic toxicity. 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). A study by Chapman et al. (1994) provided 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. However, 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. Chapman et al. (1994) also found that adding together phenol and hydroquinone resulted in more-than-additive embryotoxicity which, according to the investigators, suggested the involvement of a peroxidative mechanism for phenol bioactivation.

Several studies in animals have reported tremors following exposure by oral gavage (Moser et al. 1995; NTP 1983b). The mechanism by which phenol or metabolites exert this effect is unknown. 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. It has been suggested that phenol exposure results in cardiac effects because it blocks the cardiac sodium channel subtype, with little effect on sodium channels in skeletal muscle (Zamponi et al. 1994). A preferential block by phenol of sodium channels in inhibitory pathways would be consistent with a net result of increased activity or even tremors, but there is no experimental support for this hypothesis.

3.5.3 Animal-to-Human Extrapolations

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

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Thomas and Colborn (1992), was also used in 1996 when Congress mandated the EPA to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), and in 1998, the EDSTAC completed its deliberations and made recommendations to EPA concerning *endocrine disruptors*. In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to

the health of humans, aquatic animals, and wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwerceman et al. 1993; Hoel et al. 1992).

Based on the available information, there is no clear evidence that phenol is an endocrine disruptor in humans or in animals. 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 (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. Significant reductions in prostate and uterine weights in all F_1 treated groups were not considered adverse effects of phenol by Ryan et al. (2001) on the basis of the absence of histological alterations and functional reproductive effects, and based on the fact that only a few animals had organ weights outside the range of concurrent control values.

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. However, historical control data showed that the concurrent control fetal weight for the CD rat was much higher (22%) than the historical control weight. In addition, a larger litter size in the high-dose group may have contributed to the smaller fetal weight in the high-dose group.

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). A substance was considered positive when its activity was >10% of the activity of 10^{-7} M 17β-estradiol. For phenol, that concentration was $>1x10^{-3}$ M.

3.7 CHILDREN'S SUSCEPTIBILITY

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

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

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life, and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water, and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth

and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

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

IARC (1989), citing Hinkel and Kintzel (1968), indicated that a newborn infant whose umbilicus had been bound with a bandage containing 2% phenol, died after 11 hours. Another newborn whose skin ulcer was treated with a solution of 30% phenol/60% camphor developed circulatory failure, cerebral intoxication, and methemoglobinemia, but recovered after a blood transfusion. Rogers et al. (1978) evaluated the percutaneous absorption of phenol in 16 infants, aged 2–5 months, who were treated for seborrhoeic eczema with Magenta Paint B.P.C., a medicine containing 4% phenol. The treatment consisted of twice daily painting of the napkin and skin folds (representing about 11–15% of the body surface) with the Magenta paint over 48 hours, with an average of 32 mL of paint (approximately 1,300 mg of phenol) applied to each child. Phenol was detected in the urine of four of the infants; however, no information on concentration was presented. Liver function tests run on 8 of the 16 treated infants showed no abnormalities. The study was initiated because of the observation of signs of central

nervous system depression in a 6-month-old who had been treated over a much larger area (all of the body except the face).

A study of 2,075 infants exposed to phenolic disinfectants used to clean hospital nursery surfaces reported a significant increase in mean third-day microbilirubin level and an increase in the proportion of infants with a microbilirubin level >10 mg/dL (Doan et al. 1979). However, no cases of severe jaundice were observed. Since infants did not come into direct contact with the cleaned surfaces, exposure was assumed to have occurred by inhalation of fumes.

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

Warner and Harper (1985) reported the case of a 10-year-old male developed cardiac arrhythmias following a chemical peeling procedure initiated to remove a 12x17 cm hairy nevus of the left scapula and nape. An hour into the procedure, which involved the application of a solution of phenol (60% phenol, 0.8% croton oil in hexachlorophene soap and water) to the entire surface of the nevus, multifocal and coupled premature ventricular complexes developed in the electrocardiogram, but subsided after infusion of bretylium sulfate. Although this was a severe reaction, it is difficult to determine, based on just one case, whether it reflects a special sensitivity based on age. In an additional case report, another 10-year-old boy was hospitalized with serious burns; during the next 2.5 days his burns were treated by applying 7.5 L of antiseptic solution containing 2% phenol; his urine became dark, respiration became labored, he fell into a coma, and died. Postmortem analysis of urine revealed 200 mg/L of conjugated phenol (Cronin and Brauer 1949).

In a review of the use of phenol as a neurolytic agent, Wood (1978) summarized the results of a number of studies including one in which children with cerebral palsy were given nerve blocks with 3% phenol in water as a treatment for spasticity. Out of 150 blocks on 46 children, 9 were associated with

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

Only one study in animals was located that compared the age-dependency toxicity of phenol. Deichmann and Witherup (1944) administered phenol orally and subcutaneously to three age groups of rats: 10 days old, 5 weeks old, and adults. At a dose of 600 mg/kg orally, death occurred in 90% of 10-day-old rats, in 30% of 5-week-old rats, and in 60% of adult rats. Similarly, 3,000 mg/kg administered subcutaneously caused death in 65% of 10-day-old rats, 25% of 5-week-old rats, and 45% of adult animals. These results suggested that neonates are more sensitive than adults, and that adults are more sensitive than young rats, but these findings have not been confirmed.

Extremely limited data regarding possible adverse developmental effects in humans exposed to phenol provide no evidence for effects. As mentioned in Section 3.6, standard developmental toxicity studies in rats and mice, with one exception (NTP 1983a), have reported fetotoxicity at doses that were 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 pharmacokinetics of phenol in children. As discussed in Section 3.4.3, 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. If microsomal oxidation transforms phenol into a toxic metabolite, a reduced CYP2E1 activity, as it seems to occur in neonates, would result in decreased toxicity. However, the ability of the liver to sulfonate phenol, and consequently facilitate elimination, also develops with age (Iwasaki et al. 1993). Thus, a lower ability to conjugate could result in more phenol available for oxidative metabolism. Heaton and Renwick (1991) found that young rats have a higher production of oxidative metabolism than adult rat. If this were the case in humans, children might be potentially more sensitive to the systemic effects of phenol. Glucuronide conjugation reactions also are considerably reduced in the young and reach adult values only after the age of 3 in humans. This would play a role at high doses where the glucuronide metabolites of phenol predominate. As previously mentioned, caution should be exercised when extrapolating from adolescent rats to children, since rodents are known to undergo a number of changes in xenobiotic-metabolizing enzymes during sexual development (Waxman et al. 1985).

It is not known whether phenol can cross the placenta and there are no reports on levels of phenol in maternal milk.

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

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

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

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself, substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures

from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to phenol are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by phenol are discussed in Section 3.8.2.

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

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Phenol

Biological monitoring for exposure to phenol is possible by measuring blood or urine levels of the parent compound. However, it should be noted that phenol and metabolites of phenol may also come from other sources. For example, phenol is a metabolite of benzene and of protein metabolism. Urine samples taken from male workers employed in the distillation of high-temperature phenolic fractions of tar revealed a phenol excretion rate of 4.20 mg/hour compared to a control rate of 0.53 mg/hour for non-exposed workers (Bieniek 1994). Samples were taken 4 hours into the workers' workday, but the worker exposure levels were not reported. A study of workers in a Bakelite factory reported a linear correlation between concentrations of phenol in the air (up to 12.5 mg/m^3 or 3.25 ppm) and urinary excretion of total phenol (free plus conjugated) (Ohtsuji and Ikeda 1972). However, the urinary concentration of free phenol

seemed to be independent of the environmental phenol, suggesting that under the exposure conditions, the maximum capacity to conjugate phenol had not been reached.

The biological exposure index (BEI) for occupational exposure to 5 ppm phenol is 250 mg total phenol in urine/g creatinine (ACGIH 2005). The urine should be collected at the end of the 8-hour work shift. The sample can be stored in the refrigerator for 4 days or frozen for at least 3 months before analysis. ACGIH (2005) warns that the test is nonspecific and should not be used when workers are exposed to benzene or to household products or medications that contain phenol. Dermal exposure may result in overestimation of inhalation exposure.

Phenol can also be measured in the urine after oral exposure, although a dose-response relationship between oral exposure to phenol and phenol in the urine has not been established. In persons not exposed to phenol or benzene, the total phenol concentration in the urine does not exceed 20 mg/L and is usually <10 mg/L (ACGIH 2005).

3.8.2 Biomarkers Used to Characterize Effects Caused by Phenol

Specific biomarkers used to characterize effects caused by phenol have not been identified. Dark urine has been reported in persons exposed to phenol (orally, dermally, or by inhalation) (Baker et al. 1978; Bentur et al. 1998; Cronin and Bauer 1949; Kim et al. 1994; Merliss 1972) and following oral exposure. The dark urine may be a result of an oxidation product of phenol or hemoglobin or hemoglobin breakdown products. Further research is required to identify the cause of the dark urine. If it is the result of an oxidation product of phenol, it should be considered a biomarker of exposure.

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

3.9 INTERACTIONS WITH OTHER CHEMICALS

Phenol is a tumor promoter in laboratory animals. In mice, dermal exposure to phenol in benzene (Boutwell and Bosch 1959) or in acetone (Salaman and Glendenning 1957; Wynder and Hoffmann 1961) increased the incidence of tumors resulting from dermal exposure to the tumor initiator, 9,10-DMBA.

The mechanism of phenol promotion activity is not known, but may be related to the dermal damage that it causes and subsequent rapid cell division that may take place to repair the damage. When injected with mixtures of phenol and hydroquinone, a hydroxylated metabolite of phenol, mice exhibited significantly depressed bone marrow erythropoiesis compared to injection with phenol alone (Chen and Eastmond 1995a). The involvement of peripheral acetylcholine in phenol-induced tremors was implicated by studies in which mice were injected with phenol and pentobarbital, an inhibitor of acetylcholine release (Itoh 1995).

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

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

Potentially, individuals with low activities of the enzymes phenol sulfotransferase and glucuronyl-transferase may be more susceptible to phenol toxicity. Persons with ulcerative colitis may have an impaired capacity to sulfate phenol (Ramakrishna et al. 1991), which may increase the amount of unchanged phenol that is absorbed following oral exposure. Neonates may also be more susceptible to toxicity from dermally-applied phenol because of increased skin permeability and proportionately greater surface area. A study in which 10-day-old rats were more sensitive to lethality following oral exposure to phenol than 5-week-old or adult rats (Deichmann and Witherup 1944) further suggests that the young may be more sensitive to phenol. (For a more detailed discussion, please see Section 3.7.) 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.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to phenol. However, because some of the treatments discussed may be experimental and

unproven, this section should not be used as a guide for treatment of exposures to phenol. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. The following texts provide specific information about treatment following exposures to phenol:

Goldfrank LR, Flomenbaum NE, Lewin NA, et al. 2002. Goldfrank's toxicologic emergencies. 7th ed. New York, NY: McGraw-Hill.

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

Viccellio P. 1998. Emergency toxicology. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers.

3.11.1 Reducing Peak Absorption Following Exposure

Human exposure to phenol may occur by inhalation, ingestion, or dermal contact. Mitigation methods for reducing exposure to phenol include the general recommendation of separating contaminated food, water, air, and clothing from the exposed individual. Externally, phenol can produce mild irritation; acute exposure may produce dermatitis and abnormal pigmentation (HSDB 2006). Dermal exposure to relatively low concentrations of phenol (5–6%) over a sufficient surface area can result in death. Therefore, speed in removing phenol from the skin is important (HSDB 2006). Following dermal exposure, washing the skin with undiluted polyethylene glycol is recommended. 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.

Emesis is not recommended following oral ingestion of phenol 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. Lavage is contraindicated if esophageal injury is suspected.

3.11.2 Reducing Body Burden

Phenol is excreted in the breath, urine, and feces. Mitigation strategies to increase urinary output and dilute the chemical once it is in the bloodstream may be useful. One method for this may be increased hydration of the individual in order to stimulate diuresis. Hemodialysis is not effective in removing phenol. Information on the distribution of phenol is limited and provides little insight on how distribution might be altered to facilitate any attempts at mitigation of effects.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

The mechanism of action of phenol in the body is not well understood. Reports of cardiac arrhythmias resulting from phenol exposure are not uncommon (Gross 1984; Horch et al. 1994; Truppman and Ellenby 1979; Warner and Harper 1985). Specific methods to interfere with the mechanism of action for phenol were not identified. Treatment of phenol toxicity is essentially supportive. Patients exposed by inhalation should be removed from the contaminated area and given 100% humidified oxygen and ventilatory assistance. Cardiovascular support includes the use of intravenous saline and vasopressors to support the blood pressure. Lidocaine can be used to treat ventricular dysrhytmias and bretilium for lidocaine-refractory arrhythmias. Administration of sodium bicarbonate intravenously may rapidly reverse central nervous system depression in the presence of metabolic acidosis. Also, if methemoglobinemia is >30%, ingestion of methylene blue may be warranted.

3.12 ADEQUACY OF THE DATABASE

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

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

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

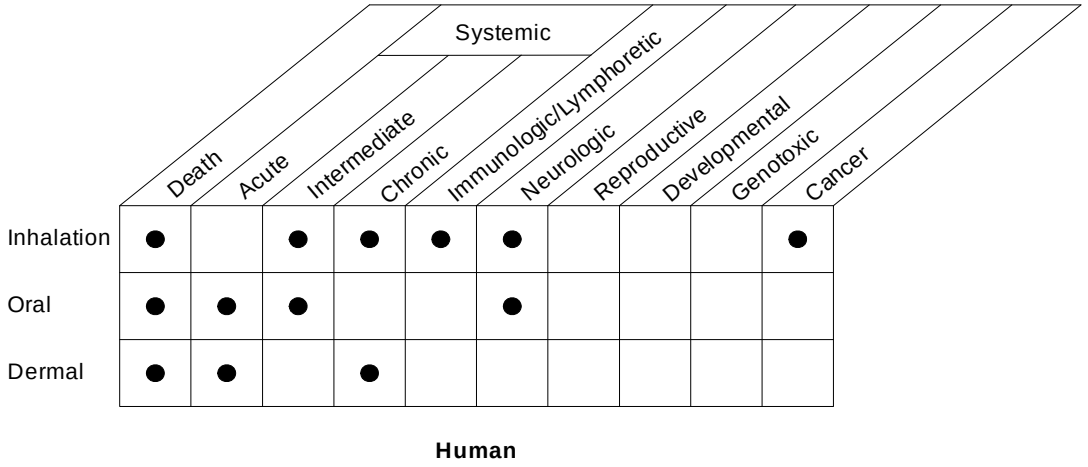
3.12.1 Existing Information on Health Effects of Phenol

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to phenol are summarized in Figure 3-5. The purpose of this figure is to illustrate the existing information concerning the health effects of phenol. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

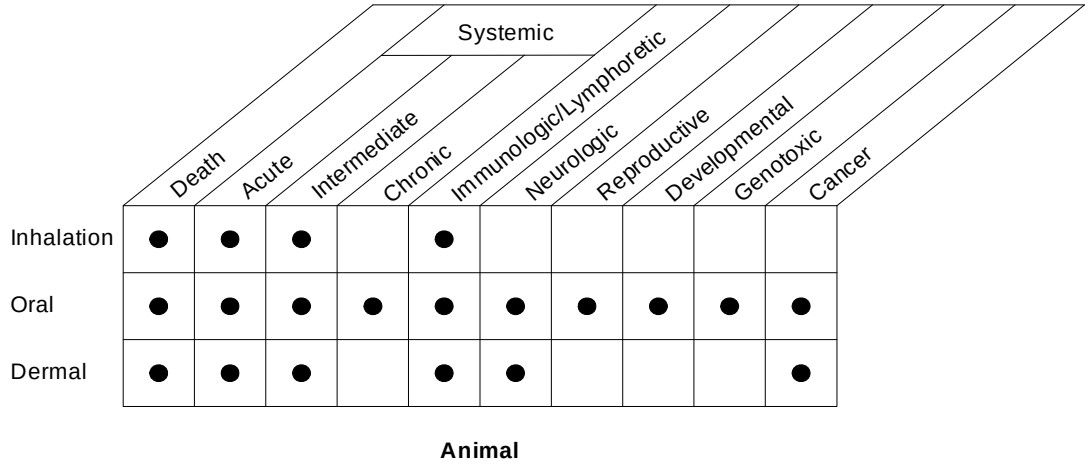
The existing information on the health effects of phenol in humans comes from case reports of people who accidentally or intentionally swallowed phenol-containing substances or whose skin came in contact with phenol, subjects exposed to phenol (and possibly to other substances at the same time) at work, and populations whose drinking water was contaminated with phenol (and other substances). Acute oral and dermal exposure to high amounts of phenol caused serious systemic effects and even death in humans due phenol's irritant and corrosive properties.

Acute- and intermediate-duration inhalation studies in animals are available, but only one of these studies can be considered a modern study. Inhalation studies in animals showed adverse respiratory, cardiovascular, liver, renal, and neurological effects. Phenol administered by oral gavage is much more toxic than in drinking water; this is related to differences in toxicokinetics between the two means of administration. Phenol exhibited relatively little toxicity in drinking water studies, including studies of reproductive and developmental end points. Of special interest is a study that reported hematological, immunological, and neurological effects in mice exposed to low concentrations of phenol in the drinking water for 28 days. Longer-term studies examined mostly systemic end points. Data are extensive regarding genotoxicity of phenol in bacterial systems and mammalian systems. Data regarding the oral carcinogenicity of phenol in rats and mice are available, as well as data on the dermal carcinogenicity, and tumor-promoting and tumor-inhibiting activities of phenol.

Figure 3-5. Existing Information on Health Effects of Phenol



Human



Animal

● Existing Studies

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Case reports of humans exposed to high doses of phenol, either orally or dermally, have provided acute toxicity information. 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 phenol (Langford et al. 1998) and cardiac arrhythmia and bradycardia were reported following acute dermal exposure to phenol (Gross 1984; Horch et al. 1994; Truppman and Ellenby 1979; Warner and Harper 1985). Two acute-duration inhalation studies in animals of limited scope indicated that the respiratory tract and the nervous system are targets for phenol toxicity (De Ceaurriz et al. 1981; Flickinger 1976). A more recent well-conducted study that used modern methodology to evaluate a number of relevant end points, including upper and lower respiratory tract histology, defined a study NOAEL of 25 ppm, the highest exposure level tested (Hoffman et al. 2001). This study was used as the basis for derivation of an acute-duration inhalation MRL of 0.02 ppm for phenol. Since the MRL based on a free-standing NOAEL may be overly conservative (the true NOAEL may be higher), additional studies may be necessary to construct dose-response relationships that can be analyzed with modern methods for risk assessment.

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. A need for additional acute-duration oral studies is not apparent at this time. Phenol is a well known skin irritant and further acute-duration dermal studies in animals are unlikely to provide new key information.

Intermediate-Duration Exposure. 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). 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). Only three studies were identified that exposed animals to airborne phenol for intermediate durations (Dalin and Kristoffersson 1974; Deichmann et al. 1944; U.S. Air Force 1961). These studies provided evidence of respiratory, heart, liver, kidney, and neurological effects, but had numerous limitations including poor control of exposure levels, unclear scope of the evaluations, and limited reporting, and were inadequate for MRL derivation. Therefore, a well-conducted 90-day inhalation study that examines a comprehensive number of end points would provide valuable information for dose-response analyses and possibly MRL derivation. Since phenol is well absorbed through the skin, a nose-only exposure protocol may be considered.

Several studies provided information on the effects of phenol following intermediate-duration oral exposure and all of them used drinking water to administer phenol. 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). A two-generation reproduction study found no evidence of reproductive effects in male or female rats, but reported decreased pup weight and reduced viability (Ryan et al. 2001). A specialized 13-week neurotoxicity study reported decreased motor activity in female rats (Beyrouty 1998). In these three studies, the doses tested were higher than doses tested in acute-duration oral studies. The most significant findings in the intermediate-duration oral database were those of Hsieh et al. (1992) who reported hematological, neurochemical, and immunological effects in mice at dose levels much lower than those used in other studies that tested similar end points. The Hsieh et al. (1992) study was not used for derivation of an intermediate-duration oral MRL largely due to the unconfirmed nature of findings and because only five mice comprised each dose group. NTP is currently conducting a comprehensive series of tests to evaluate the potential immunotoxicity of phenol in mice. Once the NTP study is completed and evaluated, a decision can be made regarding the use of the findings of Hsieh et al. (1992) or NTP for MRL derivation. Skin ulcerations were reported in mice treated dermally with 20% phenol in acetone once each week for 24–32 weeks (Salaman and Glendenning 1957). Because humans are more likely to be dermally exposed to phenol in water, and phenol is readily absorbed through the skin, additional intermediate-duration studies examining the effects of dermal exposure to different concentrations of phenol in water may fill a data gap.

Chronic-Duration Exposure and Cancer. 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 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. 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. This constitutes a data gap that may need to be filled.

The only chronic-duration animal studies are the NCI (1980) 103-week studies in rats and mice. NCI (1980) evaluated clinical signs, organ weights, and gross and microscopic appearance of organs and tissues. Under the conditions of the study, phenol showed essentially no systemic toxicity. A chronic-duration oral drinking water study with emphasis on immunological end points may be necessary if the intermediate-duration immunotoxicity study that NTP is currently conducting confirms that immunocompetence is the most sensitive end point for phenol toxicity. Since, as previously mentioned, phenol is readily absorbed through the skin and the possibility exist of dermal exposure via contaminated water (bathing or showering) at or near waste sites, a chronic-duration dermal study of phenol in water may be considered if the results of a shorter-term study suggest that adverse effects might happen.

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, 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. 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. Additional bioassays do not seem necessary at this time.

Genotoxicity. Phenol has been tested extensively for genotoxicity in a variety of *in vivo* (Amlacher and Rudolph 1981; Barale et al. 1990; Bulsiewicz 1977; Chen and Eastmond 1995a; Ciranni et al. 1988; Gocke et al. 1981; Li et al. 2005; Miyagawa et al. 1995; Pashin et al. 1987; Shelby and Witt 1995; Skare and Schrotel 1984; Sturtevant 1952) and *in vitro* (Crebelli et al. 1987; Demerec et al. 1951; Erexson et al. 1985; Florin et al. 1980; Gocke et al. 1981; Haworth et al. 1983; Jansson et al. 1986; Kubo et al. 2002; Li et al. 2005; Miller et al. 1995; Morimoto and Wolff 1980; Morimoto et al. 1983; Nagel et al. 1982; Painter and Howard 1982; Paschin and Bahitova 1982; Pellack-Walker and Blumer 1986; Poirier et al. 1975; Pool and Lin 1982; Schwartz et al. 1985; Sze et al. 1996; Tsutsui et al. 1997) tests. The results of these assays have been equivocal. Phenol appears to be potentially genotoxic, although this may be more a result of the action of its metabolites than the parent compound. Additional genotoxicity studies of phenol do not seem to be necessary.

Reproductive Toxicity. Extremely limited data regarding possible adverse reproductive effects in humans following exposure to phenol provide no evidence for effects (Axelsson et al. 1984). 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 estrus frequency, testicular sperm count, or sperm motility or morphology. Significant reductions in prostate and uterine weights in all F_1 treated groups were not considered adverse effects of phenol by Ryan et al. (2001) on the basis of the absence of histological alterations and functional reproductive effects, and based on the fact that only a few animals had organ weights outside the range of concurrent control values. Additional reproductive toxicity studies by the oral route do not seem necessary. Studies by the inhalation or dermal route also do not seem necessary since there is no indication that reproductive effects would be route-dependent.

Developmental Toxicity. Extremely limited data regarding possible adverse developmental effects in humans following exposure to phenol provide no evidence for effects (Axelsson et al. 1984). 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 occurs only at dose levels that are also toxic to the mother. The study by York (1997) was used to derive an acute-duration oral MRL of 0.6 mg/kg/day for phenol. Additional developmental studies by the oral route of exposure do not seem necessary at this time. Also, studies by

the inhalation or dermal route also do not seem necessary since there is no indication that developmental effects would be route-dependent.

Immunotoxicity. Immunological effects were reported in workers exposed for 6 months to a mixture of phenol, formaldehyde, and organic chlorohydrocarbons, although there is some question whether the exposure was due to phenol or a substituted phenol (Baj et al. 1994). Increased susceptibility to bacteria was not observed in mice exposed by inhalation to phenol (Aranyi et al. 1986). Necrosis or atrophy of the spleen or thymus, which was not described further, was observed in rats given a single dose of phenol by oral gavage (Berman et al. 1995). Effects on the spleen or thymus were not observed in rats given 14 daily doses of phenol (Berman et al. 1995). Decreased antibody production in response to immunization with SRBC was observed in mice treated with phenol in the drinking water for 28 days (Hsieh et al. 1992). Ryan et al. (2001) conducted similar tests in rats in the two-generation reproductive study and found no significant effects of phenol. NTP is currently conducting immunotoxicity studies in mice in order to confirm or refute the findings of Hsieh et al. (1992). In longer-term studies, histopathologic changes in the spleen or thymus were not observed in rats or mice exposed to phenol in the drinking water for 13 or 103 weeks, but immunocompetence was not assessed (NCI 1980). Depending on the results of the assessment of immunotoxicity by the NTP, it may be desirable to evaluate the potential immunotoxicity of phenol in a long-term oral study. Studies by the inhalation and dermal routes are not necessary since there is no evidence of route-dependency.

Neurotoxicity. 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). As reported in a retrospective review (Spiller et al. 1993), 11 patients with oral exposures to phenol-based disinfectants experienced rapid central nervous system depression, but no seizures occurred. Neurological effects (muscle tremor, loss of coordination) have been reported in laboratory animals after single exposures to high concentrations of phenol in the air (Flickinger 1976), continuous exposure in the air (Dalin and Kristoffersson 1974), repeated intermittent exposures in the air (Deichmann et al. 1944), and oral gavage dosing (Deichmann and Witherup 1944; Liao and Oehme 1981; Moser et al. 1995; NTP 1983b). In contrast, no such effects were observed in rats and mice in drinking water studies of longer durations and with higher doses of phenol (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 toxicity studies is not apparent, but studies aimed at elucidating the mechanism(s) of phenol neurotoxicity are needed.

Epidemiological and Human Dosimetry Studies. As previously mentioned, information about the health effects of phenol in humans is derived from studies of workers and members of the general population following inhalation, oral, and dermal exposure. Specific effects and references are mentioned in previous sections. Doses were generally not available, but Deichmann and Keplinger (1981) estimated that an oral dose as low as 1 g could be fatal in humans, but also pointed out that patients occasionally survived doses as high as 65 g. Other than the skin and mucosal membranes, the liver and cardiovascular system might by considered targets for phenol toxicity. Wilcosky and Tyroler 1983 studied workers in the rubber industry and found that 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. Cardiac arrhythmia and bradycardia were reported following acute dermal exposure to phenol (Gross 1984; Horch et al. 1994; Truppman and Ellenby 1979; Warner and Harper 1985) and supraventricular and ventricular dysrhythmias were reported in a case of acute ingestion of phenol (Langford et al. 1998). 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. Prolonged exposure to low levels of phenol may occur at or near waste sites via contaminated water. Since such contamination may lead to inhalation exposure (evaporation of phenol when bathing or showering, particularly if the water is acidic), dermal exposure (absorption through the skin), and oral exposure (ingestion of water or cooking with contaminated water), a dosimetric model that predicts total exposure and intake of phenol from contaminated water would be valuable. The specific end points that should be monitored under such exposure scenario (prolonged low level) are not immediately apparent. Phenol administered in the drinking water to rats and mice for 2 years showed almost no systemic toxicity (NCI 1980).

Biomarkers of Exposure and Effect.

Exposure. Measurement of total phenol in the urine is the most useful biomarker following inhalation exposure to phenol (ACGIH 2001). The test is nonspecific and should not be used when workers are exposed to benzene, to household products, or to medications containing phenol. Dermal exposure may also result in overestimation of inhalation exposure. In persons not exposed to phenol or benzene, the total phenol concentration in the urine does not exceed 20 mg/L and the mean is usually <10 mg/L (ACGIH 2001). Phenol can also be measured in the urine after oral exposure, although a dose-response relationship between oral exposure to phenol and phenol in the urine has not been established. Benzene metabolism yields not only phenol, 1,4-dihydroxybenzene, and their sulfates and glucuronides, but also

the benzene-specific *t,t*-muconic acid. For both *t,t*-muconic acid and *S*-phenylmercapturic acid, significant correlations were shown with benzene concentrations in air and in blood (Popp et al. 1994; Stommel et al. 1989). Thus, determination of urinary concentrations of these metabolites allows delineation of the portion of metabolites stemming from phenols and the portion derived from benzene exposure. Further research on the relationship between exposure doses and urinary levels of phenol is needed.

Effect. Specific biomarkers used to characterize effects caused by phenol have not been identified. Dark urine has been reported in persons occupationally exposed to phenol (inhalation, dermal) (ACGIH 2001; Merliss 1972), and following oral exposure (Baker et al. 1978; Kim et al. 1994). The dark urine may be a result of an oxidation product of phenol or hemoglobin. Further research is required to identify the cause of the dark urine.

Absorption, Distribution, Metabolism, and Excretion. The toxicokinetics of phenol have been studied extensively in laboratory animals and humans. Phenol is readily absorbed from the lungs, gastrointestinal tract, and skin. A study that examined the absorption of phenol vapor through the skin indicates that it is readily absorbed and clothing does not serve as a barrier (Piotrowski 1971). Dermal absorption is considered the primary route of entry for vapor, liquid, and solid phenol (ACGIH 2001). Conjugation of phenol with glucuronic acid and sulfate are the main detoxification pathways. Conjugation occurs predominantly in the lungs, gastrointestinal tract, liver, and kidneys. The skin has relatively low potential to detoxify phenol. Therefore, absorption through the skin may represent the greatest hazard from phenol because it readily passes through the skin and because there is no first-pass metabolic effect as is observed following oral exposure. Further studies regarding the metabolism of phenol following dermal exposure are needed. *In vitro* studies of phenol metabolism have demonstrated that reactive intermediates are produced during the metabolism of phenol (Chapman et al. 1994; Eastmond et al. 1986; Lunte and Kissinger 1983; Subrahmanyam and O'Brien 1985). These reactive compounds may be involved in mediating phenol toxicity. Further investigation of these compounds in tissues suspected of being targets for phenol toxicity (i.e., the lungs, skin, liver, kidney, and heart) are needed to provide information for extrapolating from animals to humans.

There is no PBPK model specifically designed for phenol, although phenol, as a major metabolite of benzene, has been considered in a PBPK model of benzene discussed in this profile (Bois et al. 1991). The model does not adequately explains the differences in carcinogenicity observed between benzene and

phenol, and needs additional refinements in order to incorporate all the observations and be validated. Additional efforts to develop a PBPK model for phenol are needed.

Comparative Toxicokinetics. The metabolism and excretion of orally administered phenol in 18 animal species have been compared to metabolism and excretion in humans (Capel et al. 1972). The rat was the most similar to the human with respect to the fraction of administered dose excreted in urine in 24 hours (95%) and the number and relative abundance of the four principal metabolites excreted in urine (sulfate and glucuronide conjugates of phenol and 1,4-dihydroxybenzene). The rat excreted a larger fraction of the orally administered dose than the guinea pig or the rabbit (Capel et al. 1972) and appears to be the least susceptible of the three species to respiratory, cardiovascular, hepatic, renal, and neurological effects of inhaled phenol (Deichmann et al. 1944). More rapid metabolism and excretion of absorbed phenol may account for the lower sensitivity of the rat to systemic effects of phenol. More information on the relative rates of metabolism of phenol in various species is needed to identify the most appropriate animal model for studying potential health effects in humans.

Methods for Reducing Toxic Effects. Removing a person from phenol exposure is the most important method for reducing toxic effects of phenol. This is especially important following dermal exposure, after which speed in removing phenol from the skin is important (HSDB 2006). Because a study has shown that dilution in water increases the dermal absorption of phenol (Conning and Hayes 1970), it has been recommended that polyethylene be used to remove dermal contamination with phenol (Viccellio 1998). Because water is readily available, others believe that its use is more appropriate for the decontamination of skin following phenol exposure (Pullin et al. 1978). Further research on the best way to remove phenol from the skin without increasing absorption is needed. The general recommendations for reducing the absorption of phenol following acute oral exposure are well established and have a proven efficiency (HSDB 2006). No additional investigations are considered necessary at this time.

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

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

Deichmann and Witherup (1944) found that 10-day-old rats were more sensitive to lethality following oral exposure to phenol than 5-week-old or adult rats; however, this work has never been repeated and there was little other information evaluating the toxicity of phenol at various ages. Such studies need to be conducted in order to follow up this earlier observation. However, caution should be exercised when extrapolating from adolescent rats to children, since rodents are known to undergo a number of changes in xenobiotic-metabolizing enzymes during sexual development (Waxman et al. 1985).

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

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

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

3.12.3 Ongoing Studies

No ongoing studies pertaining to phenol were identified in the Federal Research in Progress database (FEDRIP 2006).