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Summary Review of the Health Effects Associated with Phenol:

Health Issue Assessment

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I. INTRODUCTION

The purpose of this overview is to provide a brief summary of the data base available concerning health effects associated with exposure to phenol [monohydroxybenzene; carbolic acid]. Emphasis is placed on determining whether or not evidence exists which suggests that phenol exerts effects on human health at concentrations commonly encountered by the general public under ambient air exposure conditions. Both acute and chronic health effects are addressed, including general toxicity, reproductive toxicity, teratogenicity, mutagenicity, and carcinogenicity. This report also reviews certain air quality aspects of phenol in the United States, including sources, distribution, fate, and concentrations associated with rural, urban, and point source areas as background for placing the health effects discussion in perspective.

Phenol [CAS no. 108-85-2], sometimes referred to as carbolic acid, is a monohydroxy derivative of benzene which is a clear, colorless (light pink in the presence of impurities), hygroscopic, deliquescent, crystalline solid at 25°C. It has a molecular formula of C_6H_5OH and a molecular weight of 94.1. At 25°C, the specific gravity is 1.071 and the vapor pressure is 0.35 mm Hg. Pure solid phenol has a melting point of 43°C and a boiling point of 182°C at standard pressure. It has a very sweet tarry odor which is detectable at a recognition threshold (100% response) of ~0.05 ppm. Phenol has a water solubility of 6.7 g/100 ml at 16°C; its solubility, however, is variable between 0-65°C. Above 65.3°C, phenol and water are miscible in all proportions. Phenol is very soluble in most organic solvents: ethyl ether, methyl alcohol, ethyl alcohol, carbon tetrachloride, acetic acid, glycerol, liquid sulfur dioxide, and benzene.

Monohydroxybenzene, generically known as phenol, is the simplest member of a class of organic compounds known collectively as phenols. Members of this class contain one or more hydroxyl groups attached to an aromatic ring. This latter attachment causes delocalization of the oxygen electron pair into the benzene ring due to the electronegativity. This so-called "resonance" phenomenon of phenol(s) is responsible for their acidity and in this respect they also differ from alcohols. Phenol is slightly acidic with pKa of 9.9 in aqueous solutions at 25°C ($Ka = 1.3 \times 10^{-10}$). With the exception of phenol [monohydroxybenzene], most phenols are not soluble in water; however, they readily ionize in strong bases to form salts collectively referred to as phenoxides, phenolates, and phenates. Many of these phenoxides, especially those produced from the alkali earth metals, are soluble in water.

Aside from acidity, the most striking chemical property of phenol(s) is the extremely high reactivity of the aromatic ring towards electrophilic substitution, especially the hydrogen atoms that are *ortho* and *para* to the hydroxyl group. This property, like acidity, is due to the electronic interaction between the hydroxyl and phenyl groups. Phenols undergo not only electrophilic substitution reactions that are typical of most aromatic compounds, but also react in ways that are uniquely due to the presence of the hydroxyl group. Some of the more important reactions are the formation of salts, ethers and esters, and ring substitution. The latter encompasses nitration, sulfonation, halogenation, alkylation, acylation, nitrosation, coupling with diazonium salts, aldehyde formation, and reaction with formaldehyde. The most important commercial reaction of phenol is its condensation with formaldehyde to produce phenolic resins. This reaction accounts for approximately 40 percent of U.S. phenol usage.

Phenol was first isolated from coal tar in 1934. The first synthetic method developed just prior to World War II involved the sulfonation of benzene and subsequent hydrolysis. Today, the majority of phenol is produced synthetically and very little (1-2 percent) is recovered by the fractional distillation of coal tar. The two most widely used synthetic processes for phenol production are cumene hydroperoxidation and toluene oxidation. Among the top fifty chemicals listed in terms of production for 1983, phenol ranked thirty-fourth; this ranking did not include data from coke and gas retort ovens (Anonymous, 1984a).

As a result of large production volume and natural sources, occupational and environmental exposure to phenol is likely; however, the inhalation of phenol vapors appears to be largely restricted to the occupational environment and/or populations living in the immediate vicinity of point sources. The National Institute for Occupational Safety and Health (NIOSH) estimated that as many as 10,000 workers are potentially exposed to phenol. This figure encompasses people who are employed in the production of phenol, its formulation into products, and the distribution of concentrated phenol products (National Institute for Occupational Safety and Health, 1976).

The American Conference of Governmental Industrial Hygienists (1952) recommended as early as 1952 that air concentrations of phenol vapor in the workplace be limited to 5 ppm (19 mg/m^3). Due in part to its low volatility, phenol does not frequently constitute a serious respiratory hazard in industry (Elkins, 1959). A skin notation was added in 1961, and there has been no change in the TLV (5 ppm) through 1985 by ACGIH (American Conference of Governmental Industrial Hygienists, 1961, 1984). According to Thomas and Back (1964), the TLV of 5 ppm provides a sufficiently large safety factor to prevent systemic poisoning if skin absorption is avoided. The present short-term exposure limit (STEL) for phenol is 10 ppm (38 mg/m^3). Compared to the TLV, the general ambient levels of phenol, based on monitoring data, are extremely low, with the possible exception of concentrations in the immediate vicinity of phenol manufacturing and/or processing plants. Although data on phenol in soil and water are plentiful, information on the fate of phenol once it is released into the ambient air is limited. Estimates of reaction rates, based on data derived from structure-activity relationships, suggest that reactions with atmospheric radicals are the dominant removal processes. As a result, the half-life of atmospheric phenol is less than one day.

Phenol is known to be absorbed readily by animals and man after oral, inhalation, or dermal exposure. The disposition of phenol by the body is primarily by Phase II conjugation reactions, secondarily by Phase I oxidative reactions to dihydroxy products, and thirdly by urinary excretion of unchanged phenol. The relative importance of these elimination processes, and in particular the nature of the conjugates (predominantly sulfates and glucuronides), differs across species. The conjugation and oxidative products are in general less toxic than phenol and are excreted into the urine.

Regardless of the route of exposure, the signs and symptoms of acute toxicity in man and experimental animals are similar. Muscle weakness, convulsions, and coma are the predominant symptoms associated with exposure to lethal concentrations of phenol. Dermal and oral LD_{50} values are reported in the literature, most falling within one order of magnitude according to the sensitivity of the species. Although LC_{50} values are not available in the literature, rats exposed to 236 ppm (900 mg/m^3) phenol vapor for 8 hr exhibited signs of irritation, loss of coordination, tremors, and prostration. Subchronic inhalation studies in animals have demonstrated species-to-species variation in sensitivity to phenol, with the guinea pig appearing to be most sensitive and the rat most resistant.

No chronic inhalation studies were found in the available literature on phenol; however, there are two chronic oral studies described. If these data are utilized along with some of the subchronic data, various effect levels (e.g., no-observed-adverse-effect level, NOAEL) can be derived for phenol. Teratogenic effects have not been associated with exposure to phenol by either the inhalation or oral route, although high doses of phenol are fetotoxic. Although a clear carcinogenic response is not available from long-term bioassay data, there were non-dose-related increases in the incidence of some tumor types. In addition, phenol has been shown to have tumor-promoting activity when large concentrations of phenol solution were painted on the skins of "S" strain albino mice.

II. AIR QUALITY: SOURCES, DISTRIBUTION, FATE, AND AMBIENT LEVELS

Sources of naturally occurring phenol are animal waste and decomposition of organic wastes (U.S. Environmental Protection Agency, 1983). Manmade sources of phenol include the fractional distillation of coal tar (Thurman, 1982), effluents from the conversion of coal (Parkhurst et al., 1979), and wastewater from manufacturing of resins, plastics, fibers, adhesives, iron and steel, aluminum, leather, and rubbers (U.S. Environmental Protection Agency, 1983). Other sources of environmental phenol for all media (air, water, soil) include spills during transport, storage, and use, and emissions during manufacturing processes (Delaney and Hughes, 1979). Based on emission factors for air, provided by Delaney and Hughes (1979), emission of phenol from its manufacture by the common oxidative process alone is estimated at 0.181×10^3 MT (0.4×10^6 lbs) for 1983.

Today, the two most widely used processes for phenol production utilize cumene hydroperoxidation and toluene oxidation (Thurman, 1982). According to SRI International (1984), the companies in the United States shown in Table 1 are the principal producers of phenol as of January 1984. The Monsanto Company stopped production of phenol at the Alvin, TX facility, reducing 1983 production capacity by 500×10^6 pounds (Greek, 1984). Including production from coke ovens and gas retort ovens, the 1983 production volume for phenol was 2638 million pounds (U.S. International Trade Commission, 1984).

Table 1. U.S. Companies Producing Phenol as of January 1984

Company	Annual Capacity (Millions of Pounds)
Allied Corp., Frankford, PA	*500*
Clark Chem. Corp., Blue Island, IL	*88*
Diamond Shamrock Corp., Tuscaloosa, AL	*10*
Dow Chem., Oyster Creek, TX	*465*
Ferro Corp., Sante Fe Springs, CA	*8*
General Electric Co., Mount Vernon, IN	*400*
Georgia-Pacific Corp., Bound Brook, NJ	*157*
Plaquemine, LA	*330*
Getty Oil Co., El Dorado, KS	*95*
Kalama Chem., Inc., Kalama, WA	*75*
Koppers Co., Inc., Follansbee, WV	*8*
Merichem. Co., Houston, TX	*20*
Shell Oil Co., Deer Park, TX	*500*
Stimson Lumber Co., Anacortes, WA	*2*
U.S. Steel Corp., Haverhill, OH	*520*
Total	*3178*

Source: SRI International (1984).

Of the total phenol produced, the consumption pattern is as follows: phenolic resins, 45 percent; bisphenol-A [2,2-bis-(4-hydroxyphenol) propane], 20 percent; caprolactam, 13 percent; alkyl-phenols, 57 percent; cresols and xylenols, 5 percent; aniline, 3 percent; miscellaneous usage, 5 percent; and export, 4 percent (Anonymous, 1984b).

In addition to natural and anthropogenic sources, phenol is also produced indirectly from other atmospheric chemicals via photochemical reactions. As a secondary source of pollution, phenol from these reactions appears to have minimal impact on the ambient budget, compared to that from primary sources. Based on limited available data, the median ambient atmospheric levels of phenol (based on estimated 24-hour averages) are 30 ppt (120 ng/m^3) for urban/suburban areas and 5000 ppt (19,000 ng/m^3) for source-dominated areas (Brodzinsky and Singh, 1982).

Relative to other environmental media (water, soil), the data base regarding the fate of phenol in the atmosphere is somewhat limited. The initial half-life of phenol in the atmosphere, based on estimated data derived from structure activity relationships, was 0.5 day (Hendry and Kenley, 1979). In polluted atmospheres, reactions with NO_3 radicals may dominate and the half-life of phenol would be less than one minute (Carter et al., 1981). The anticipated products formed from phenol in the atmosphere via photochemical reactions are dihydroxybenzenes, nitrophenols, and ring cleavage products. Most recently, Battelle Columbus Laboratories, under contract to EPA, have determined major reaction products (2-nitrophenol, 4-nitrophenol) and have experimentally estimated the half-life of phenol to be ~4 to 5 hr (disappearance rate of phenol 0.113 hr^{-1} corrected for dilution) under photochemically reactive conditions (1 ppm phenol; 1.0 ppm propylene, 3.0 ppm butane, and 0.5 ppm NO_2) using a smog chamber (Spicer et al., 1985). As for atmospheric removal mechanisms, Callahan et al. (1979) have speculated that phenol will undergo photodecomposition in the atmosphere and some phenol may be removed by wet deposition. Although atmospheric oxidation via the hydroxyl and nitrate radicals appears to be the dominant fate-determining pathway for atmospheric phenol, most recent data (Leuenberger et al., 1985) do indicate that with respect to wet deposition, gas scavenging is much more important than particle scavenging for phenols since the latter in air are virtually exclusively present in the gas phase. The efficiency of this removal process is clearly reflected in the high concentrations of phenol in rain water.

III. HEALTH EFFECTS

Pharmacokinetics

Absorption and Distribution

Phenol is readily absorbed upon contact with intact or abraded skin, and from the gastrointestinal tract and lungs of animals and man (Deichmann and Keplinger, 1981; Babich and Davis, 1981). Regardless of the route of exposure, absorption is rapid, as illustrated by the fact that acute doses of phenol can produce symptoms of toxicity within minutes of administration.

Reports of occupational exposure and controlled human exposure studies showed that phenol can enter the human body by inhalation and through the skin by adsorption, and is rapidly detoxified and eliminated by conjugation and excreted in the urine. Studies by Piotrowski (1971) in which dermal absorption was precluded (facemask) have demonstrated that phenol in air (6-20 mg/m^3) is rapidly absorbed and efficiently (60-88 percent) retained in the lungs of human volunteers. Phenol vapor readily penetrates the skin with an absorption rate somewhat lower than that of inhalation but approximately proportional to the vapor concentration in the air (Piotrowski, 1971). The predominant route of elimination is through the urine; however, small amounts are excreted in the feces or in exhaled air. Ohtsuji and Ikeda (1972) demonstrated that the urinary concentration of total phenol (free plus conjugated) in Bakelite® factory workers was a good index of exposure to atmospheric levels of phenol. This linearity between environmental phenol concentrations and total urinary phenol is attributable to changes in concentrations of conjugated phenol since the levels of free phenol remained essentially unchanged regardless of exposure. The concentration of conjugated phenol increased during the working shift, but decreased to pre-exposure levels the following morning, suggesting that these employees readily conjugated and eliminated the phenol absorbed as a result of their combined inhalation and skin exposure. These results are in agreement with and appear to support similar conclusions made by Piotrowski (1971), who separately investigated the inhalation and skin absorption of phenol vapor. As in adults, phenol was detected in the urine of infants (2-5 months) when they were skin-painted twice daily for 48 hours with Magenta Paint BPC (4 percent phenol, w/v) for treatment of seborrhoeic eczema (Rogers et al., 1978).

In vitro studies of phenol absorption through human abdominal skin obtained from autopsy demonstrated that 10.9 percent of the applied dose was absorbed (Franz, 1975). *In vitro* studies by Hogg et al. (1981) using ^{14}C-phenol, excised trachea-lung preparations, and isolated perfused lung from rats support the observation from *in vivo* human studies that phenol is rapidly and efficiently absorbed through the lungs.

Once absorbed, phenol is rapidly distributed to all tissues in animals. In rabbits, after 15 minutes of an oral dose of 0.5 g/kg body weight, the highest concentrations were found in the liver, followed by the heart, kidneys, lungs, blood, and muscle (Deichmann, 1944; Table 2). Additional studies on rats demonstrated that the liver, spleen, kidney, and adrenal gland consistently exhibited phenol concentrations greater than that observed in plasma (Liao and Oehme, 1981). Elevated levels of ^{14}C-phenol (phenol plus metabolites) were also found in the thyroid glands and the lungs compared to the plasma. The majority of the radioactivity (65-85 percent) detected in the whole blood of rats was found in the plasma as phenol and phenol conjugates. Even though phenol

Table 2. Distribution of Phenol in the Organs of Rabbits After an Oral Dose of 0.5 g/kg

Tissue	Phenol	Concentration of Phenol in mg/100 g Tissue				
		Died After 15 min	Died After 82 min	Killed After 2 hrs	Killed After 2½ hrs	Killed After 6 hrs
Liver	Free	63.7	22.4	3.4	13.5	0.5
	Conjugated	0.9	4.2	3.2	6.0	9.4
	Total[b]	64.6	26.6	6.6	19.5	9.9
Blood	Free	30.8	22.4	5.8	11.3	6.5
	Conjugated	0.9	5.3	8.0	10.2	9.8
	Total	31.7	27.7	13.8	21.5	16.3
Kidneys	Free	35.3	13.4	4.8	11.2	2.6
	Conjugated	0.8	7.4	22.8	12.9	30.0
	Total	36.1	20.8	27.6	24.1	32.6
Lungs	Free	34.2	20.8	5.4	12.2	1.5
	Conjugated	1.8	4.7	6.7	5.1	3.0
	Total	36.0	25.5	12.1	17.3	4.5
Heart, Thymus, Testes, Spleen	Free	53.0	21.0	6.8	14.0	7.5
	Conjugated	0.6	2.3	5.7	5.1	7.7
	Total	53.6	23.3	12.5	19.1	15.2
Brain & Cord	Free	31.3		6.8	10.4	2.5
	Conjugated	0.5		0.7	0.3	0.4
	Total	31.8		7.5	10.7	2.9

Table 2. (Continued)

Tissue	Phenol	Concentration of Phenol in mg/100 g Tissue: Died After 15 min	Died After 82 min	Killed After 2 hrs	Killed After 2½ hrs	Killed After 6 hrs
Muscle	Free	19.0	8.2	9.2	12.0	10.1
	Conjugated	0	0.5	1.1	0.8	1.4
	Total	19.0	8.7	10.3	12.8	11.5
Urine	Free		0.5		11.6	11.0
	Conjugated	no sample	14.0	no sample	52.0	12.3
	Total		14.5		63.6	23.3
Exhaled Air	Free	0	0.1[a]	0.7[a]	0.1[a]	0.2[a]
	Conjugated					
	Total	0	0.1	0.7	0.1	0.2

[a]*Phenol in total air exhaled.*
[b]*Total phenol obtained by summation of free and conjugated fractions.*
Source: Adapted from Deichmann (1944).

is very soluble in organic solvents and fats (Deichmann and Keplinger, 1981), its uptake by tissues high in lipids (fat, testes, brain) was very low, based on total radioactivity.

The kinetics of phenol distribution were studied by Oehme (1969) in a number of species and in the desert rodent *Notomys alexis* by Wheldrake et al. (1978). Intravenously injected ^{14}C-phenol disappeared most rapidly in goats and most slowly in cats. The half-life of the disappearance of ^{14}C-phenol (phenol plus metabolites) from the blood of the desert rodent *N. alexis* was 14.1 min (5 mg/kg) and 19.4 min at 100 mg/kg. Within 30 minutes after injection, a minimum of 95 percent of the ^{14}C-phenol had been metabolized. In rabbits (Deichmann, 1944) roughly 77 percent of the administered dose was excreted in the urine during the first 24 hours, and approximately 20 percent was completely metabolized to CO_2 and water plus other trace substances (Figure 1).

Even though the study by Piotrowski (1971) does not provide distributional data for various organs, it does indicate a rapid rate of clearance of phenol in man in inhalation experiments (6-20 mg/m^3) near the TLV (Figure 2).

Figure 1. ***Fate of a sublethal oral dose of phenol analyzed over 24 hours. Source: Deichmann and Keplinger (1981).***

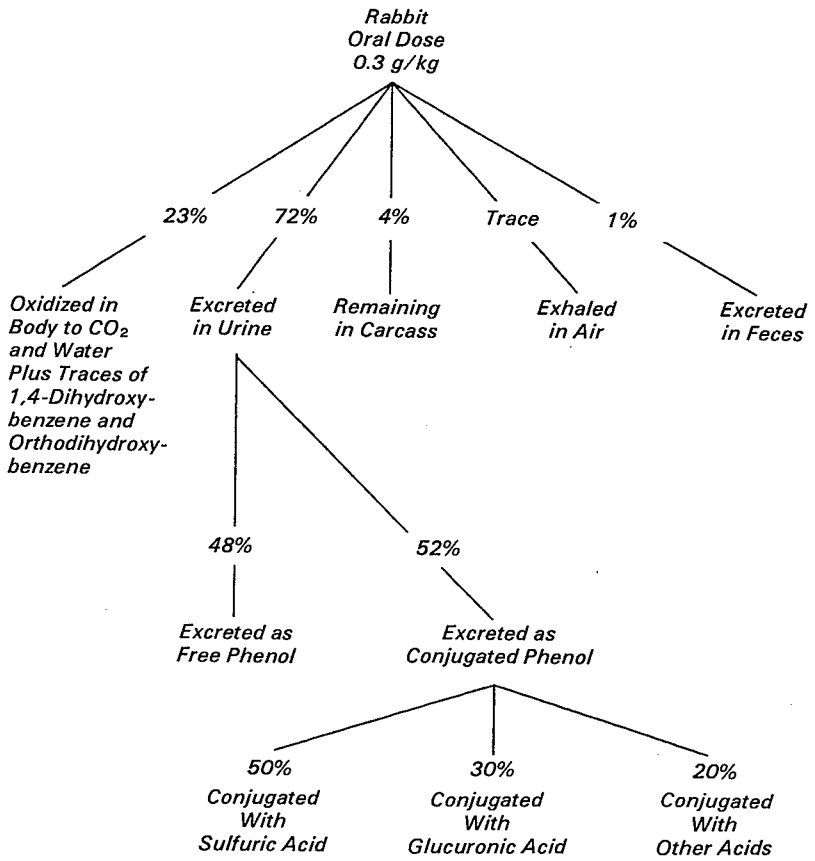
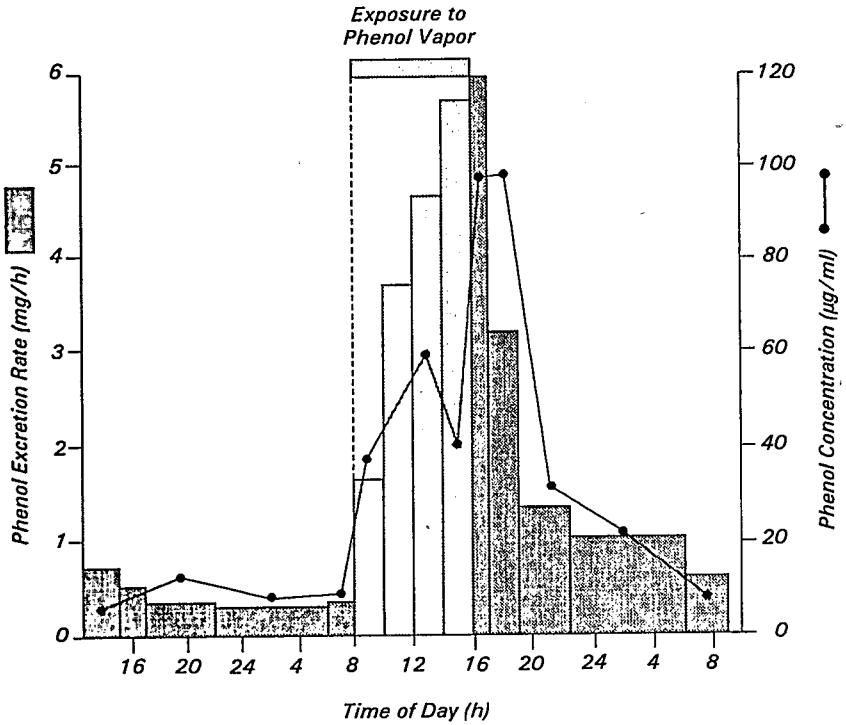


Figure 2. ***Concentrations and excretion rates of phenol in urine in a human subject exposed to phenol vapor in a concentration of 18.3 mg/m³ by inhalation for 6 hr.***
Source: Piotrowski (1971).

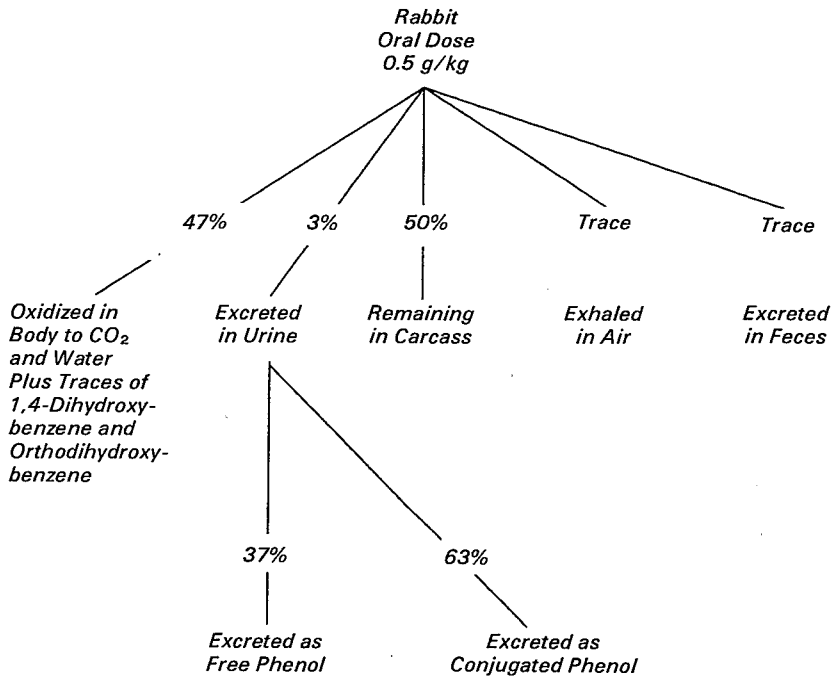


Metabolism

It is well known that man and mammalian species, even with no known exposure to phenol or its metabolic precursors, excrete phenolic compounds into urine (Williams, 1959, 1964). These phenolic compounds may be derived from dietary aromatic amino acids or food components (Van Haaften and Sie, 1965). The normal range reported for phenol levels in human blood differs markedly among various investigators, principally because of analytical methodology (Ikeda and Ohtsuji, 1969; Adlard et al., 1981) and the amount of dietary protein, which increases urinary phenol excretions (Folin and Denis, 1915).

Exogenous sources of urinary phenol include environmental chemicals (e.g., benzene) and medicines containing phenylsalicylate (Kociba et al., 1976) such as Pepto-Bismol® and Chloraseptic® lozenges. Although phenol is a well-known metabolite of the leukemogen benzene, phenol *per se* fails to exhibit any potential for myeloclastogenicity compared to benzene or the mildly clastogenic benzene metabolite hydroquinone (Gad-El-Karim et al., 1985). The metabolism of exogenous phenol has been extensively studied qualitatively and quantitatively by Deichmann and Keplinger (1981) in rabbits at lethal and sublethal oral doses. Results from these studies are summarized in Figures 1 and 3. A

Figure 3. ***Fate of a lethal oral dose of phenol analyzed over 5 hours. Source: Deichmann and Keplinger (1981).***



detailed review of the metabolic fate of phenol is provided by Williams (1964), and a systematic study of phenol metabolism in various animal species and man has been described by Capel et al. (1972a,b). In the majority of mammals, including man, four major metabolites of phenol have been reported, namely phenyl sulfate, phenyl glucuronide, quinol (or 1,4 benzenediol) sulfate, and quinol glucuronide (Table 3). Their relative importance, however, depends on the species and dose level being considered. Urine analysis by paper chromatography showed that eight of the treated species excreted all four metabolites, six species excreted only three metabolites, four species excreted two, and one species excreted only one. In the majority of these animals, phenyl glucuronide and phenyl sulfate were the principal end products of metabolism. However, there are certain species such as the cat, pig, and brush-tailed opossum that give rise to interesting quantitative differences in metabolic end products. The pig was found to be virtually unable to use the sulfate conjugation mechanisms. Similarly, the cat was found to produce only small amounts of the glucuronide conjugate.

Results comparable to Capel et al. (1972a,b) on the metabolism of phenol and recovery of radioactivity in urine were also obtained by other investigators for the rat, pig, and cat. Kao et al. (1979) reported that phenyl glucuronide and phenyl sulfate were the major metabolites for the rat and sheep, with sulfate and glucuronide conjugates of quinol as the minor constituents. Unlike rodents, sheep were found to excrete phenyl and quinol phosphates. In the pig, phenyl glucuronide was the major metabolite (83 percent), compared to 1

Table 3. Species Variation in the Conjugation of Phenol. Dose of ^{14}C-Phenol = 25 mg/kg Orally (in Man 1 mg/Person or 17 μg/kg)

Species	No. of Metabolites	% of ^{14}C Excreted in 24 hrs as the Glucuronide of Phenol	Glucuronide of Quinol	Sulfate of Phenol	Sulfate of Quinol	Remarks
Pig*	1	100	0	0	0	no sulfate
Indian fruit bat	2	90	0	10	0	
Rhesus monkey	2	35	0	65	0	
Cat*	2	0	0	87	13	no glucuronide
Man	3	23	7	71	0	
Squirrel monkey	3	70	19	10	0	
Ring tail monkey	3	65	21	11	0	two glucuronides and one sulfate
Guinea pig	3	78	5	17	0	
Hamster	3	50	25	25	0	
Rat	3	25	7	68	0	
Ferret	3	41	0	32	28	two sulfates and one glucuronide
Rabbit	3	46	0	45	9	
Gerbil	3	15	0	69	15	
Hedgehog	3	15	0	75	10	
Lemming	4	38	15	35	12	
Mouse	4	33	14	43	5	
Jerboa	4	26	4	61	12	

**The sulfate conjugation of phenol in the pig and the glucuronic acid conjugation of phenol in the cat are very small (about 2%). From Capel et al. (1972a,b).*

percent for the phenyl sulfate conjugate. It should be noted that this sulfate conjugation deficiency is not common to all phenols, since the pig is capable of conjugating 1-naphthol with sulfate to an appreciable extent (Capel et al., 1974). Miller et al. (1973, 1976) confirmed previous findings that the cat lacks the ability to conjugate phenol as glucuronide. Phenyl sulfate and quinol sulfate were detected as the major metabolites. Even the desert-adapted rodent *N. alexis*, like the jerboa and gerbil (Capel et al., 1972a,b), is similar to hamsters and laboratory rats and mice. *N. alexis* also fails to diverge from the typical pattern of four phenolic metabolites. Therefore, the metabolism of

compounds such as phenol, which are rapidly conjugated to soluble form, are the same and independent of low water turnover (Wheldrake et al., 1978).

When phenol conjugation was studied *in vitro* using liver preparations from *N. alexis*, the formation of phenyl sulfate was found to predominate over formation of phenyl glucuronide at low phenol concentrations (Ramili and Wheldrake, 1981), an observation also recorded in intact animals (Wheldrake et al., 1978). The preferential formation of phenyl sulfate over phenyl glucuronide at low phenol dose levels is suggested by the authors to be due to a higher affinity, for phenol, of sulfotransferase ($Km = 1.9 \times 10^{-5}M$) compared to glucuronyl transferase ($Km = 6.4 \times 10^{-4}M$). The reduction of phenyl sulfate formation seen at high phenol concentrations is due to the depletion of a cosubstrate in the reaction, 3'-phosphoadenosine-5'-phosphosulfate (PAPS). The formation of PAPS becomes rate-limiting at high phenol concentrations. When the phenol dose was increased, a similar decrease in the ratio of formation of sulfate to glucuronide was observed by Weitering et al. (1979) as they studied the incorporation of ^{35}S-sulfate into phenyl sulfate in male Wistar rats. No significant depletion of the inorganic sulfate pool was observed.

Even though hepatic metabolism continues to be accepted as quantitatively the most important route of elimination for drugs and other xenobiotics, the role of extrahepatic biotransformation in the disposition and toxicity of foreign compounds is receiving increasing attention. Several *in vitro* studies utilizing the intestines and lung as semipurified tissue homogenates, isolated cells, and isolated perfused organs have been used to indicate potential extrahepatic sites of phenol metabolism (Cassidy and Houston, 1984). In the rat trachea-lung preparation, the amount of conjugation was inversely dose-dependent, ranging from 83 percent at the lowest dose to 65 percent at the highest dose. Phenyl glucuronide and phenyl sulfate were present in approximately equal proportions, with small amounts of quinol sulfate detected. A similar degree of conjugation (85 percent) was found for the isolated perfused rat lung. Isolated, perfused segments of small intestine from the rat were able to convert ^{14}C-phenol to phenyl sulfate (5 percent) and phenyl glucuronide (95 percent). Similar results were found in rat gut segments perfused *in situ*; the radioactivity that appeared in the portal blood was all associated with ^{14}C-phenol conjugates. No free phenol was detected.

Additional knowledge concerning the intestine as a major site of phenol detoxification derives from *in vivo* studies by Powell et al. (1974). Whole-body autoradiography of young rats given ^{14}C-phenol either orally or intraperitoneally did not indicate any accumulation of phenol in the liver relative to blood levels. These results strongly support the view that free phenol is not transported as such from the intestinal lumen but in conjugated form. It therefore follows that the role of the liver is minimal in the detoxication of orally ingested phenol. Extensive intestinal metabolism, as suggested by the observation that isolated, perfused segments of rat small intestine were able to convert ^{14}C-phenol to phenyl sulfate (5 percent) and phenyl glucuronide (95 percent), may explain the results obtained by oral administration but not by intraperitoneal injection. When the gastrointestinal tract is bypassed by i.p. administration of free phenol, however, conjugation with sulfate and glucuronide and subsequent excretion of these conjugates in the urine nevertheless take place (Capel et al., 1972a,b).

Using whole-animal evaluations, Cassidy and Houston (1984) developed a procedure to assess the relative *in vivo* capacity of hepatic and extrahepatic tissues (intestinal mucosa, lung) to metabolize xenobiotics. Phenol, because of its high metabolic clearance in the rat and its extensive first pass metabolism, was chosen as the model compound. The ability of intestinal mucosa, liver, and lung to conjugate phenol was investigated over a 35-fold dose range by employing a judicious choice of route of administration. Comparison of blood

phenol concentration-time profiles, following intravenous administration into the jugular and the hepatic portal veins, indicates extensive hepatic conjugation of phenol at low doses. The relatively poor capacity of the liver to conjugate phenol was confirmed using isolated perfused livers over a similar dose range. Comparison of blood phenol concentration time profiles, following vascular administration into the carotid artery and the jugular vein, indicates substantial pulmonary conjugation of phenol. Although the extent of pulmonary conjugation is less than the hepatic contribution, pulmonary conjugation is evident over a wider dose range. Intestinal conjugation of phenol is assessed by comparison of data from intraduodenal and hepatic portal venous administration. At low doses of phenol (<1 mg/kg), capacities of intestinal and hepatic enzymes to conjugate phenol were comparable; however, as dose increased, the intestine, unlike the lung and liver, maintained efficient conjugation over a wide dose range. At large doses (>5 mg/kg), intestinal conjugation far exceeds the contribution of the hepatic and pulmonary enzymes. The relative capacity of the three organs to conjugate phenol may be related to the relative need for physiological mechanisms to cope with different routes of environmental exposure to phenolic compounds. Efficient conjugation in intestinal mucosa over a wide dose range drastically reduces amounts of ingested phenol reaching the circulatory system. Similarly, an effective array of enzymes in the lung, another portal of entry for the volatile phenols, provides the body with a defense barrier. Consequently, amounts of phenols penetrating enzymic barriers at the portals of entry are minimized. The main source of phenols in the liver is of endogenous origin, because of mixed function oxidase activity. The slow rate of phenol production by these oxidative enzymes (MFO) does not exceed the capacity of the liver to detoxify phenol via conjugation as the glucuronide and/or sulfate.

Excretion

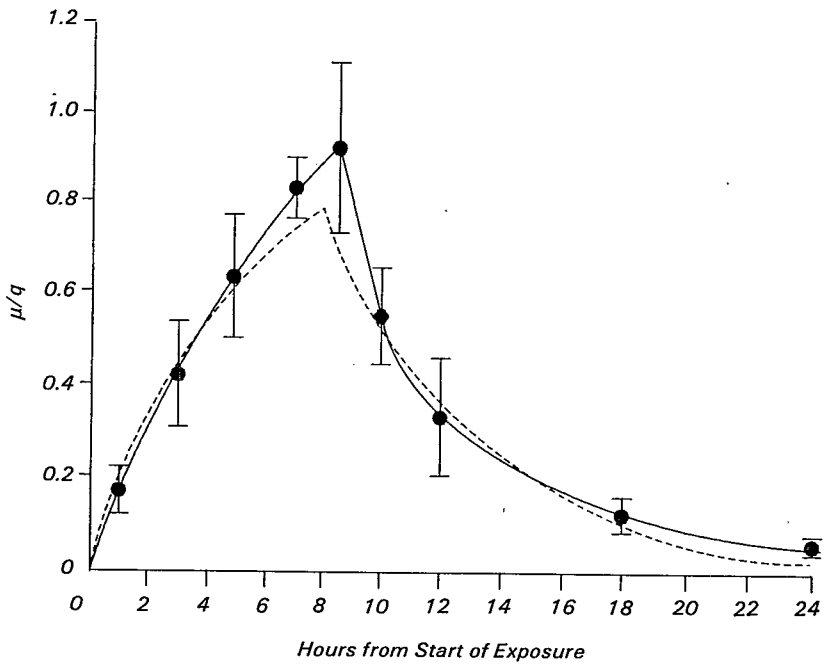
The contribution of the lungs, intestines, and liver to the conjugation of phenol(s) *in vivo* has been well established. In man and all other mammals that have been tested, nearly all of the phenol and its metabolites are excreted in the urine. The amounts excreted in feces and exhaled air are very minimal (Deichmann and Keplinger, 1981). Twenty-four hours after administering 300 mg phenol/kg body weight orally to rabbits, Deichmann (1944) reported finding less than 1 percent of the administered dose in the feces. Kinetic results from controlled human exposure studies by Piotrowski (1971) via inhalation and skin absorption showed that phenol is quickly excreted from the human body and that this process may be described with sufficient exactness by a simple one-compartment open model with an excretion rate constant, K, of 0.2 hr^{-1}. This rate corresponds to a half-life of approximately 3.5 hours (Figures 2 and 4).

Acute, Subchronic, and Chronic Toxicity

Sudden collapse and unconsciousness in humans exposed to phenol are generally associated with the impact of this agent on the central nervous system. Human responses to phenol at various airborne concentrations and durations are listed in Table 4. Based on unpublished data submitted to American Conference of Governmental Industrial Hygienists in 1971 by the Connecticut Bureau of Industrial Hygiene, intermittent industrial exposure (5 to 10 minutes per hour, 8 hr per day) inside a conditioning room for phenol-impregnated asbestos resulted in marked irritation of the nose, throat, and eyes. The average phenol concentration in the room was 48 ppm, although formaldehyde (8 ppm) also was found. This level of formaldehyde alone has

Figure 4. ***Excretion rate of "excess" phenol in relation to absorption in human subjects during and after 6 hr. inhalation exposures. Means ± S.D. Dotted Line -- theoretical curve for K = 0.2 Hour^{-1}.***

Source: Piotrowski (1971).



been shown to cause such irritation (National Institute for Occupational Safety and Health, 1976). Workers at the same plant continuously exposed to an average concentration of 4 ppm during winding operations experienced no respiratory irritation, although the odor of phenol was noticeable. Under controlled human exposure conditions (1.5-5.2 ppm for 8 hr with two 30-min breaks), Piotrowski (1971) described no adverse effects upon inhalation and/or skin absorption of phenol at the present TLV of 5 ppm. Under both exposure conditions, urinary phenol concentrations returned to normal within 16 hours after termination of exposure. Petrov (1963) reported 29 poisonings during a three-year period in a group of employees in Russia who quenched coke with waste water containing 0.3 to 0.8 mg of phenol per liter. Air samples in the work area indicated phenol vapor concentrations of the order of 2 to 3 ppm. Although these levels could possibly have been associated with the intoxications, the observed conditions were most likely produced by some substance in the effluents from either the waste water or the coking process. Thus, it is inappropriate to assume that these conditions were produced by phenol *per se*.

Additional studies of human responses were carried out by Mukhitov (1964). Six 5-minute inhalation exposures to phenol at 0.004 ppm produced an increased sensitivity to light in each of three dark-adapted subjects. Further tests revealed that 15-second exposures to phenol (0.006 ppm) elicited the

Table 4. Human Responses to Phenol at Various Durations and Airborne Concentrations

Concentration		Duration of Exposure	N	Response	References
ppm	mg/cu m				
48 + 8 ppm HCHO	185 + 9.8 HCHO	5-10 min/hr, 8 hrs/day	?	Marked irritation of the nose, throat, and eyes. HCHO may be primary cause.	American Conference of Governmental Industrial Hygienists (1980)
1.5-5.2	6-20	8 hrs with two 30-min breaks	8	No ill effects. 60-88% of phenol absorbed by lungs. Rise in urinary excretion of phenol during exposure with a return to preexposure levels within 24 hrs.	Piotrowski (1971)
0-3.3	0-12.5	8 hrs/day	?	No ill effect. Rise in urinary phenol.	Petrov (1963)
2.3-3.2 (in coke quench effluent)*	8.8-12.2 (in coke quench effluent)*	8 hrs/day	29	"Poisoning"	Petrov (1963)
0.047	0.18	Minutes	4	Odor threshold average	Leonardos et al. (1969)
0.006-0.048	0.022-0.184	"	14	Odor threshold range	Mukhitov (1964)
0.006-0.024	0.022-0.094	"	19	Odor threshold range	Makhinya (1972)

Table 4. (Continued)

Concentration		Duration of			
ppm	mg/cu m	Exposure	N	Response	References
0.006	0.024	15 sec	4	Conditioned electrocortical reflex in all	Mukhitov (1964)
0.004	0.0155	5 min	3	Increased sensitivity to light in dark adapted people	Mukhitov (1964)

*mg/liter of effluent (1 ppm).
Source: National Institute for Occupational Safety and Health (1976).

formation of conditioned electrocortical reflexes in 4 subjects. In animals, these effects are generally preceded by muscular twitchings and severe clonic convulsions due to the action of phenol on the central nervous system motor mechanism. Regardless of route of exposure, the signs and/or symptoms (physiological responses) induced by phenol in man and animals are similar. Subsequent to absorption of an acutely toxic dose, heart rate first increases, then becomes slow and irregular and, after an initial rise, blood pressure rapidly declines. Salivation and labored breathing may be evident along with a decline in body temperature. Death may occur within minutes of an acute exposure and is usually due to respiratory failure (Deichmann and Keplinger, 1981; Sollmann, 1957).

With respect to odor threshold, Leonardos et al. (1969) reported an average value for 100 percent recognition at 0.047 ppm, which agrees well with the upper limit of the range reported by Mukhitov (1964). However, in some sensitive individuals odor recognition has been reported as low as 0.006 ppm (Mukhitov, 1964; Makhinya, 1972). Such studies certainly demonstrate that phenol has warning properties by odor at concentrations far below the concentrations at which toxic effects occur.

Only limited information exists by which to estimate lethal phenol exposure levels for humans. Even though phenol has long been used in suicide attempts, a lack of accurate documentation makes it difficult to estimate the LD_{50} for oral exposure to man. Assuming a standard 70-kg body weight and using reported oral toxicity data, estimated ingestion doses for phenol associated with lethal or near-lethal outcomes can be calculated (Table 5). The human lowest lethal dose (LDL_0) for phenol is estimated to be 140 mg/kg. No published information was found concerning lethal exposure levels for humans via the inhalation route.

The acute toxicity of phenol in terms of a lethal dose necessary to kill 50 percent of test animals (LD_{50}) has been evaluated for various species and various routes of exposure (Table 6). The majority of the LD_{50} values fall within one order of magnitude, with the cat being most sensitive and the guinea pig most resistant. No LC_{50} values associated with acute exposure were found in the available literature for animal inhalation studies; however, Flickinger (1976) did report that rats exposed to 236 ppm phenol vapor (900 mg/m^3) for 8 hours developed ocular and nasal irritation, loss of coordination, tremors, and prostration. Also, subsequent to dermal application of reagent grade phenol, rats developed severe skin lesions, with edema followed by necrosis (Conning and Hayes, 1970).

Prolonged administration of phenol to animals can lead to pathological changes in the skin, mucous membranes, esophagus, lungs, liver, kidney, heart, and genitourinary tract. Subchronic inhalation studies (Table 7) for various species of animals were reported at 25-52 ppm, 5 ppm, and 1 ppm by Deichmann et al. (1944), Sandage (1961) and Mukhitov (1964), respectively. Deichmann et al. (1944) exposed guinea pigs, rabbits, and rats to phenol at 25 ppm (100 mg/m^3) for 7 hours per day, 5 days per week. Extensive mortality (42 percent) occurred for guinea pigs after 28 days of exposure. Rabbits, however, (exposed for 88 days) showed no external signs of toxicity but pathological changes were noted in the lungs, liver, and kidney. Rats were most resistant, with no internal or external signs of toxicity with 74 days of exposure.

Sandage (1961) did not find any significant adverse toxic effects when various animal species (rats, mice, monkeys) were exposed to 5 ppm (19 mg/m^3) phenol, 8 hr/day, 5 days/wk, for 90 days (this corresponds to the present TWA-TLV recommended by the American Conference of Governmental Industrial Hygienists, 1984). Also, Mukhitov (1964) reported changes in blood enzyme (cholinesterase) activity, time for excitation of extensor muscles (~0.02 ppm and 1 ppm), and decreased rate of weight gain (1 ppm) for rats

Table 5. Oral Toxicity of Phenol in Humans

Total Dose (g)	Estimated* (g/kg)	Effect	Reference
5	0.07	Survived	Willhard, 1886
10-20	0.14-0.29	Died	Stajduhar-Carić, 1968
15	0.21	Survived	Model, 1889
15	0.21	Died	Krönlein, 1873
25-30	0.36-0.43	Died	Geill, 1888
50	0.71	Survived	Geill, 1888
53	0.75	Survived	Bennett et al., 1950

*Assuming a standard 70-kg body weight.
Source: U.S. Environmental Protection Agency (1980).

Table 6. The Acute Toxicity of Phenol[a] to Nonhuman Mammals

Species	Route	LD_{50} (g/kg)	Reference
Cat	Subcut.	0.09	Tollens, 1905
Cat	Oral	0.1	Macht, 1915
Dog	Oral	0.5	Macht, 1915
Guinea pig	Subcut.	0.68	Duplay and Cazin, 1891
Mouse	Subcut.	0.3	Tollens, 1905
Rabbit	I.V.	0.18	Deichmann & Witherup, 1944
Rabbit	Subcut.	0.5-0.6	Tauber, 1895; Tollens, 1905
Rabbit	Oral	0.6	Clarke & Brown, 1906
Rabbit	Oral	0.4-0.6	Deichmann & Witherup, 1944
Rabbit	I.P.	0.5-0.6	Deichmann & Witherup, 1944
Rat	Subcut.	0.45	Deichmann & Witherup, 1944
Rat	Oral	0.53	Deichmann & Witherup, 1944
Rat	Oral	0.34 (20% emuls.)	Deichmann & Witherup, 1944
Rat	I.P.	0.25 (In olive oil)	Farquharson et al., 1958
Rat	Dermal	2.5	Deichmann & Witherup, 1944
Rat	Dermal	0.67	Conning & Hayes, 1970

[a]In dilute aqueous solution, unless noted otherwise.
Source: U.S. Environmental Protection Agency (1980).

Table 7. Subchronic Inhalation Toxicity of Phenol

Species	No. of Animals	Dose	Length of Exposure	Effects	Reference
Mice	100 treated, 100 controls	19 mg/m^3 (5 ppm)	8 hours/day, 5 days/week, 90 days	Increased stress test endurance ($p < 0.05$), no significant differences seen in any other parameters studied (hematology, urinalysis, blood chemistry, kidney function, rate of weight gain, pathological examination).	Sandage, 1961
Rats	15 treated, no controls	100-200 mg/m^3 (26-52 ppm)	7 hours/day, 5 days/week, 74 days, 53 exposures	No external or internal signs of toxicity.	Deichmann et al., 1944
Rats	50 treated, 50 controls	19 mg/m^3 (5 ppm)	8 hours/day, 5 days/week, 90 days	Slight weight gain with respect to controls ($p < 0.05$), no significant differences seen in any other parameters studied (hematology, urinalysis, blood chemistry, kidney function, stress tests, pathological examination).	Sandage, 1961
Guinea pigs	12 treated, no controls	100-200 mg/m^3 (26-52 ppm)	7 hours/day, 5 days/week, 29 exposures	Decreased activity, weight loss, respiratory difficulties, hind quarter paralysis; histological changes included myocardial necrosis, acute lobular pneumonia, liver and kidney damage; 5/12 deaths.	Deichmann et al., 1944

Table 7. ***(Continued)***

Species	No. of Animals	Dose	Length of Exposure	Effects	Reference
Rabbits	6 treated, no controls	100-200 mg/m^3 (26-52 ppm)	7 hours/day, 5 days/week, 88 days, 63 exposures	No external signs of toxicity, histological changes included lobular pneumonia, purulent bronchitis, myocardial degeneration and necrosis, liver and kidney damage.	Deichmann et al., 1944
Monkeys	10 treated, 10 controls	19 mg/m^3 (5 ppm)	8 hours/day, 5 days/week, 90 days	Slight weight gain with respect to controls ($p < 0.05$), no significant differences seen in any other parameters studied (hematology, urinalysis, blood chemistry, kidney function, stress tests, pathology).	Sandage, 1961

exposed to phenol vapors continuously for 2 months. However, insufficient details were produced by which to evaluate the validity of the reported findings.

Effects of repeated oral exposure of humans to phenol were reported after an accidental spill of phenol in 1974 caused groundwater contamination, which resulted in consumption by 17 people of amounts of phenol estimated at 10-240 mg/day for about one month (Baker et al., 1978). Several symptoms were reported, the most significant ($p < 0.01$) compared to controls being diarrhea, mouth sores, and dark urine. No long-term sequelae were observed six months after exposure.

The only subchronic oral study in animals found in the available literature is an unpublished study conducted by Dow Chemical Company in 1944 and mentioned in a 1976 review (Dow Chemical Company, 1976). Phenol was administered to rats by gavage over a six-month period (135 doses; 50 or 100 mg/kg/day). Slight liver changes and slight to moderate kidney damage was observed in high-dose animals. Low-dose animals (50 mg/kg/day) exhibited slight kidney damage. No effects were noted on the growth rate of treated rats.

No inhalation studies for chronic toxicity were found in the available literature. Only two chronic oral studies are available (Heller and Pursell, 1938; National Cancer Institute, 1980). Heller and Pursell (1938) administered phenol to rats via drinking water at levels ranging from 0-12,000 ppm for periods lasting up to 5 generations, although the exact duration of exposure was not reported. Variables observed included growth, fecundity, and general condition. All were normal at exposures of 100-1,000 ppm for 5 generations or 3,000 or 5,000 ppm for 3 generations. At ≥8,000 ppm, many offspring died due to maternal behavioral disturbances, and at 12,000 ppm no reproduction occurred. The National Cancer Institute (1980) bioassay study is described in more detail in the section on carcinogenicity. The only effect observed was a dose-related decrease in weight gain in the group exposed to 10,000 ppm, thought to be associated with decreased water consumption.

Teratogenicity and Reproductive Toxicity

The only available pertinent data concerning teratogenicity or reproductive toxicity associated with inhalation exposure to phenol was found in an abstract in the Russian literature (Korshunov, 1974). In this study, an increased incidence of preimplantation loss and early postnatal death was observed among the offspring of rats exposed (exposure regimen not reported) throughout pregnancy to air containing ~1.3 ppm and 0.13 ppm phenol.

The work of Heller and Pursell (1938) demonstrated adverse effects on reproduction when phenol was administered in the drinking water of rats at levels of >5,000 ppm; but the credibility of these results has been questioned given inadequacies in design as a teratogenicity study. More recent gavage studies by Jones-Price et al. (1983a,b) on CD rats and CD-1 mice yielded similar results. CD rats (23/group) given phenol in water at doses of 0, 30, 60 or 120 mg/kg/day on days 6-15 of gestation exhibited dose-related signs of fetal toxicity (average fetal body weight per litter showed a significant dose-related [$p < 0.001$] decrease; the difference between the high-dose group and controls was significant [$p < 0.01$]), even at dosages below the maternally toxic range, but failed to significantly increase the incidence of structural malformations. In addition there was no evidence of maternal toxicity in these rats. These results appear to coincide with those of Minor and Bechard (1971) which revealed fetal toxicity, but no teratogenic effect following exposure of Sprague-Dawley rats to phenol (20, 63, or 200 mg/kg/day, i.p.) on days 9-11 or 12-14 of gestation. More recently, CD-1 mice given phenol orally at doses of 0, 70, 140 and 280 mg/kg/day on days 6-15 of gestation revealed no teratogenic effects; however, signs of maternal and fetal toxicity were observed. Although no

statistically significant evidence for a teratogenic effect of phenol in CD-1 mice was observed under the conditions of the present study, data from the preliminary investigation suggest that increased malformations (primarily cleft palate) may occur with high dose exposure (i.e., ≥200 mg/kg/day) to phenol in conjunction with compromised maternal status.

In vitro studies on the ability of lipophilic acids to inhibit growth in *Bacillus subtilis* cultures and on several mammalian tissue culture lines have shown phenol to be strongly inhibitory (Freese et al., 1979). The authors hypothesized that the inhibitory potency of a compound may provide an indication of its potential teratogenicity. Based on their data, the authors suggest that phenol could be teratogenic if it can reach the embryo.

A proposed *in vitro* assay system presently under development is designed to be predictive for teratogenicity based upon the ability of a chemical to inhibit the attachment of ascites tumor cells to plastic surfaces coated with concanavalin A (Braun et al., 1982). The authors tested 102 chemicals and found that the tumor-cell attachment assay correctly determined the teratogenic potential of 79 percent of the compounds. The relationship between the lowest reported *in vivo* teratogenic dose of a compound and the concentration of that compound in the *in vitro* assay which reduced cell attachment by 50 percent was found to have a correlation coefficient of 0.69. In this assay, phenol gave a positive response even though the compound has not been found to be teratogenic *in vivo.*

Mutagenicity

Demerec et al. (1951) reported that phenol produced reverse-mutations in *E. coli*, B/Sd-4 from streptomycin dependence to non-dependence. Significant reverse mutations occurred from 0.1 to 0.2 percent phenol; however, at these concentrations, the mortality of bacteria was 95-98 percent. Phenol did not induce filamentation in a lon$^-$ mutant of *E. coli* (Nagel et al., 1982). More recently, the standard Ames test, employing four tester strains of *Salmonella typhimurium* with or without metabolic activation, indicated that phenol was not mutagenic (Florin et al., 1980; Pool and Lin, 1982; Haworth et al., 1983). In another study, however, phenol showed mutagenic effects after metabolic activation with S-9 preparations in *Salmonella* tester strains sensitive to frame-shift mutations, specifically strain TA 98 (Gocke et al., 1981). In the same study, Gocke et al. (1981) performed a sex-linked recessive lethal test in Drosophila and the micronucleus test on mouse bone marrow, both of which gave negative results.

In testing the mutagenicity of phenol toward the HGPRT locus of the V79 Chinese hamster fibroblast cell line, phenol was found (analyzed by Student t-test) to significantly increase the frequency of 8-azaguanine-resistant mutants at concentrations of 250-500 μg/ml (Paschin and Bahitova, 1982). In a chromosomal study, Morimota et al. (1983) observed an increase in the frequency of sister-chromatid exchange (SCE) when human lymphocyte cultures were exposed to phenol. Without metabolic activation, a 3 *m*M solution of phenol gave a small but significant increase ($P < 0.01$) in SCE. Metabolic activation with S-9 mix (from Aroclor-1254 induced rats) produced an even greater increase in SCE ($p < 0.001$).

Other tests indicative of genetic damage and applied to phenol include inhibition of DNA synthesis in Helen Lake (HeLa) cells, inhibition of DNA replication synthesis and DNA repair synthesis in cultured human diploid fibroblast. The inhibition of DNA synthesis in HeLa cells was produced by a 2 *m*M solution of phenol upon addition of an S-9 mix from Aroclor-induced rats (Painter and Howard, 1982). DNA replication synthesis was inhibited (>50%) by a 1.0 *m*M solution of phenol, and DNA repair synthesis was inhibited by a 10

*m*M solution of phenol subsequent to damage of cultured human diploid fibroblast cells with N-acetoxy-2-acetylaminofluorene (Poirier et al., 1975).

Levan and Tjio (1948) reported C-mitotic effects in the root tips of *Allium cepa* when exposed to phenol. Chromosome fragmentation was very rare.

Carcinogenicity

In a tumor promotion study involving many different phenolic compounds, various strains (Sutter, Holtzman, CAF, and CH3) of mice were pretreated with a single dermal application of 7,12-dimethylbenz(a)anthracene (DMBA; 75 mg/kg) and subsequently given repeated dermal applications of selected phenols (Boutwell and Bosch, 1959). In one experiment of this series, Sutter strain mice (specially inbred for three generations for susceptibility to development of tumors after a single application of DMBA followed by croton oil) received a single application of 75 mg/kg DMBA via skin painting. After one week, these sensitive mice were treated twice weekly with dermal applications of phenol (as a 10 percent solution in benzene) for 42 consecutive weeks; severe skin damage, decreased body weight, and increased mortality were observed in the mice. Also, the mice developed papillomas (95 percent of the animals by the thirteenth week of treatment) and carcinomas (73 percent by 42 weeks) at a much higher incidence than mice receiving either DMBA alone (14 percent had papillomas at 42 weeks; no carcinomas) or phenol alone (36 percent had papillomas at 52 weeks; no carcinomas). However, after 72 weeks of skin painting with phenol alone, one fibrosarcoma was observed. Strains of mice other than Rusch's special breed of Sutter mice also developed papillomas after pretreatment with a 10 percent phenol solution (w/v), but the incidence was lower. Even the incidence for papillomas and carcinomas decreased in the Sutter strain upon diluting the 10 percent solution to half strength. No carcinomas occurred in standard breeds of mice exposed to phenol (10 percent, w/v) without pretreatment with the polycyclic aromatic hydrocarbon DMBA. However, when the phenol concentration was increased to 20 percent (5 mg phenol in benzene), many animals died due to systemic toxicity.

Similar experiments by Salaman and Glendenning (1957) demonstrated that phenol exhibited a weak carcinogenic and strong tumor-promoting activity in "S" strain albino mice after repeated skin painting with a high, skin-ulcerative concentration (20% w/v in acetone) of phenol. The polycyclic aromatic hydrocarbon DMBA (0.3 mg) was used as the tumor initiator in the tumor promotion studies. A lesser, non-ulcerative concentration of 5% phenol was found to have moderate promoting but no carcinogenic activity.

Unlike Boutwell and Bosch (1959) and Salaman and Glendenning (1957), Van Duuren and colleagues (1968, 1971) utilized a different polycyclic aromatic hydrocarbon, benzo(a)pyrene, in their two-stage (tumor-promoting) and cocarcinogenesis studies on phenol.

In their tumor-promotion studies (Van Duuren et al., 1968), 20 female ICR/Ha Swiss mice were treated first with 100 μg of benzo(a)pyrene, single dose, followed by applications of 3 mg phenol in acetone, three times weekly for one year. Four animals bore papillomas and one a squamous carcinoma. There were no tumors in the control groups which received initiator alone, phenol alone (both at same doses as above), acetone alone, or no-treatment control groups. Because of the negative results obtained in the same study with 17 other phenols and the clearly positive results obtained in the same study with the phorbol esters of croton oil, it can be concluded that phenol in this test is a weak promoting agent.

In subsequent experiments on cocarcinogenesis, 20 female ICR/Ha Swiss mice were treated with 5 μg benzo(a)pyrene and 3 mg of phenol, applied in the same acetone solution, three times weekly for the duration of the test, which

lasted 460 days. At the conclusion of the test, there were three mice with papillomas and one with carcinoma. There were no tumors in the group receiving phenol alone. Benzo(a)pyrene alone resulted in eight mice with papillomas and one with squamous carcinoma. From this it was concluded that phenol was not a cocarcinogen but that at the dose used it showed an inhibitory effect on the mouse skin carcinogenicity of benzo(a)pyrene (Van Duuren et al., 1971). This partial inhibitory effect of phenol was subsequently confirmed by Van Duuren and Goldschmidt (1976) and Van Duuren et al. (1973) using a larger group of 50 mice.

The most recent chronic study on phenol was that performed by the National Cancer Institute in 1980. Fischer-344 rats and B6C3F1 mice (50 rats, 50 mice) of each sex were given drinking water containing 2,500 and 5,000 ppm phenol for 103 weeks. Matched controls (50 rats, 50 mice) received tap water. Statistically significant increases in pheochromocytomas of the adrenal medulla and leukemias or lymphomas were observed in low-dose male rats, compared to controls, and may have been associated with exposure to phenol; however, the incidences were not significantly different between high-dose males and the matched controls (Table 8). Therefore, because of the high spontaneous tumor rate observed in the matched controls (36%) compared to previous 103 to 104-week bioassays conducted by the NCI testing program and the lack of an association between increasing dose and the incidence of tumor development, phenol does not appear to be carcinogenic for male and female Fischer-344 rats or male and female B6C3F1 mice when administered via gavage in drinking water.

Table 8. Tumor Incidence in Rats and Mice Exposed to Phenol Via Drinking Water

Exposure Route	Species/ Strain	Sex	Concentration (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound %	Vehicle	Target Organ	Tumor Type	Tumor Incidence (p value)[a]
Oral	rat/ F344	M	0 2500 5000	103	105	98.47	drinking water	hematopoietic system	monocytic leukemia	18/50(NS) 30/50 (p=0.014) 24/50 (NS)
Oral	rat/ F344	M	0 2500 5000	103	105	98.47	drinking water	hematopoietic system	all leukemias	18/50(NS) 30/50 (p=0.014) 25/50 (NS)
Oral	rat/ F344	M	0 2500 5000	103	105	98.47	drinking water	hematopoietic system	leukemia or lymphoma	18/50(NS) 31/50 (p=0.008) 25/50 (NS)
Oral	rat/ F344	M	0 2500 5000	103	105	98.47	drinking water	adrenal	pheochromo-cytoma	13/50(NS) 22/50 (p=0.046) 9/50 (NS)
Oral	rat/ F344	M	0 2500 5000	103	105	98.47	drinking water	thyroid	C-cell carcinoma	0/50(NS) 5/49 (p=0.027) 1/50 (NS)
Oral	rat/ F344	M	0 2500 5000	103	105	98.47	drinking water	testis	interstitial cell tumor	42/48(NS) 49/50 (p=0.050) 47/50 (NS)
Oral	rat/ F344	F	0 2500 5000	103	105	98.47	drinking water	No significant increased incidence of tumors in any tissue examined.		

Table 8. (Continued)

Exposure Route	Species/ Strain	Sex	Concentration (ppm)	Duration of Treatment (weeks)	Duration of Study (weeks)	Purity of Compound %	Vehicle	Target Organ	Tumor Type	Incidence (p value)[a]
Oral	mouse/ B6C3F1	M	0 2500 5000	103	105	98.47	drinking water	No significant increased incidence of tumors in any tissue examined.		
Oral	mouse/ B6C3F1	F	0 2500 5000	103	105	98.47	drinking water	No significant increased incidence of tumors in any tissue examined.		

Quality of Evidence

Strengths of study: Adequate numbers of experimental and control animals of each sex were studied. Complete autopsies and histologic examinations were performed. Animals were exposed for a significant portion of their lifespan. Two species were studied at two exposure levels.

Weakness of study: The high spontaneous tumor rate noted for leukemias and lymphomas in male rats (36%, compared with the 15% historical incidence seen in other bioassays) was unexplained.

Overall adequacy: Adequate.

Comments: The primary reviewer of this report recommended that phenol be considered for retesting because of the equivocal results obtained in male rats.

Source: National Cancer Institute, 1980.

[a]*The level of significance appearing beside incidences in the control group reflects the results of the Cochran-Armitage Test for dose-related increase. The p values appearing beside the incidences in low-dose male rats reflect the results of Fisher's Exact Test.*

NS = Not significant.

IV. SUMMARY AND CONCLUSIONS

Phenol is one of many aromatic compounds present in the atmosphere. In addition to natural and anthropogenic sources, phenol is also produced indirectly as a secondary pollutant from atmospheric photochemical reactions. However, as a secondary pollutant, it appears to have minimal impact on the ambient budget, compared to primary sources. As a result of large volume production and natural sources, occupational and environmental exposure to phenol is likely; however, the inhalation of phenol vapors appears to be largely restricted to the occupational environment and/or to populations living in the immediate vicinity of point sources. Compared to the threshold limit value (TLV, 5 ppm, 19 mg/m^3) as recommended by the American Conference of Governmental Industrial Hygienists (1984) for occupational settings, the general ambient levels of phenol are extremely low. The odor recognition threshold (100% response) of phenol is ~0.05 ppm, a concentration far below the levels where toxic effects have been reported. The median ambient atmospheric level of phenol, based on an estimated 24-hour average, is 30 ppt (120 ng/m^3) for urban/suburban areas. However, concentrations in source-dominated areas near phenol manufacturing and/or processing plants have been estimated from 24-hour average monitoring data to be on the order of 5,000 ppt (19,000 ng/m^3) as a median level. Estimates of rates of reactions with atmospheric radicals, based on data derived from structure-activity relationships, suggests that these reactions are the dominant removal process, resulting in a half-life of less than one day. In polluted atmospheres, reactions with nitrate radicals may dominate, and the half-life of phenol would be less than one minute. The anticipated products formed from phenol in the atmosphere via photochemical reactions are dihydroxybenzenes, nitrophenols, and ring cleavage products. Most recently, Battelle Columbus Laboratories, under contract to EPA, have determined major reaction products (2-nitrophenol, 4-nitrophenol) and have experimentally estimated the half-life of phenol to be ~4 to 5 hr under photochemically reactive conditions.

Phenol poisoning can occur by skin absorption, vapor inhalation, or ingestion. The primary route of entry is typically the skin, for vapors readily penetrate the skin surface with an absorption efficiency close to that for inhalation. Absorption of phenol from solutions in contact with the skin may be very rapid, and death can result from collapse within 30 minutes to several hours. In those cases where death is delayed, damage to the kidneys, liver, pancreas, and spleen, and edema of the lungs may result. Phenol vapors are also well absorbed by the lungs. Inhalation causes dyspnea, cough, cyanosis and pulmonary edema. Ingestion of even small amounts of phenol causes severe burns of the mouth and esophagus, as well as abdominal pain.

The human body behaves almost like a single compartment with respect to phenol absorption and clearance, with an excretion rate constant of 0.2 hr^{-1}, which corresponds to a half-life of approximately 3.5 hr. After absorption, exogenous phenol is extensively metabolized, principally by the liver but also at portals of entry such as the intestinal mucosa and lung. In man and all mammals that have been tested, virtually all of the phenol and/or its metabolites are excreted into the urine; the amounts excreted in the feces and exhaled air are very minimal. Depending upon exposure dose and species, the urine may contain free phenol, conjugates of phenol (primarily glucuronide and/or sulfate), and hydroxy derivatives (such as quinol and catechol) and their conjugates. With very high exposure doses, the conjugation reactions resulting

in conjugation of phenol with glucuronide and sulfate, the principal metabolic process, may become saturated and rate-limited by availability of endogenous glucuronic acid and/or active sulfate. With low exposure levels in man, the kinetics of phenol metabolism and renal excretion can be adequately described by a first-order single compartment model with a biological half-life of about 3.5 hr.

Sudden collapse and unconsciousness of humans exposed to phenol is generally associated with the impact this agent has on the central nervous system. In animals, these effects are generally preceded by muscular twitchings and severe clonic convulsions due to the action of phenol on the central nervous system motor mechanisms. Regardless of the route of administration, the signs and/or symptoms induced by phenol in man and animals are similar. With respect to humans, no acute or chronic inhalation data were available in the literature. No epidemiologic study of an employee population exposed to phenol by inhalation has been reported. Based on a standard 70-kg-man body weight and reported oral toxicity data, a human oral LDL_o (140 mg/kg) has been estimated for phenol.

With respect to animals, the acute toxicity of phenol in terms of lethal dose necessary to kill 50 percent of the test animals (LD_{50}) has been evaluated for various species and routes of exposure. The majority of observed LD_{50} values fall within one order of magnitude, with the cat the most sensitive and the guinea pig most resistant. Although no LC_{50} values were found for animal inhalation studies, exposure of rats to phenol at 236 ppm for 8 hours resulted in ocular and nasal irritation, loss of coordination, tremors, and prostration. Subsequent to dermal application of phenol, rats developed severe skin lesions, with edema followed by necrosis.

Several subchronic toxicity studies via inhalation and the oral route have been reported for various species of animals. With respect to inhalation, a frank-effect-level based on the sensitivity of the guinea pig (42 percent mortality) can be established at 25 ppm. Additional inhalation studies on rats, mice, and monkeys demonstrated a no-observed-adverse-effect level (NOAEL) at 5 ppm, i.e., no significant adverse toxic effects were observed at 5 ppm (a level corresponding to the present phenol TWA-TLV recommended by the ACGIH for occupational settings) (American Conference of Governmental Industrial Hygienists, 1984). One abstract in the Russian literature reported changes in blood enzyme activity, excitation of extensor muscles, and decreased body weight at low concentrations (0.02 to 1 ppm) when rats were exposed to phenol vapor. Additional Russian studies attempted to associate the toxicity observed among employees with the phenol present in the work environment at 2.3 ppm as a result of quenching coke with phenol-contaminated waste water. These studies, as with most of the Russian studies cited in this report, are not well documented and the results are not consistent with other, better known studies at similar exposure levels. Studies by the Dow Chemical Company in 1944 (Dow Chemical Company, 1976) demonstrated slight kidney damage at 50 mg/kg, which can be used to establish an oral exposure LOAEL (lowest-observed-adverse-effect level). No effects were noted on the growth rate of treated rats.

No inhalation studies for chronic toxicity were found in the available literature. The only chronic oral studies were those reported by Heller and Pursell (1938) and the National Cancer Institute (1980). The drinking water study by Heller and Pursell (1938) demonstrated that growth, fecundity, and general condition were normal for rats up to 5,000 ppm, the NOAEL. Above 5,000 ppm, the growth of the rats was affected, and at 12,000 ppm there was no reproduction. The only effect observed in the National Cancer Institute (1980) study was a dose-related decrease in weight gain, thought to be associated with decreased water consumption.

The present data base concerning the genotoxicity of phenol indicates no evidence of maternal toxicity or structural teratogenicity in rats exposed via gavage from 30 to 120 mg/kg/day of phenol on days 6-15 of gestation compared to controls. With increasing doses, average fetal body weight/litter decreased ($p < 0.001$). Although no teratogenic effects were noted, 30 mg/kg/day could be regarded as a LOAEL for fetotoxic effects. Adverse effects on reproduction were demonstrated for rats only when the phenol concentration in the drinking water exceeded 5,000 ppm. The only available inhalation study (Russian literature) demonstrated increased incidence of preimplantation loss and early postnatal death in the offspring of rats exposed to phenol concentrations in air of 0.13 and 1.3 ppm throughout pregnancy. Similar results were obtained for mice exposed via gavage to phenol at doses of 70, 140 and 280 mg/kg/day on days 6-15 of gestation. Like the rats, the mice revealed signs of fetal toxicity with no evidence of teratogenic effects. Unlike the rats, the mice in the high-dose group exhibited statistically significant signs of maternal toxicity (i.e., reduced maternal body weight and reduced weight gain), increased maternal mortality and clinical signs, including tremors and ataxia, during phenol treatment.

Phenol has been evaluated in a variety of test systems for its ability to induce gene mutations, chromosomal aberrations, sister chromatid exchanges (SCE), and inhibition of DNA replication and repair synthesis. In the *Salmonella*/microsome assay both negative and positive results have been reported. In *E. coli*, phenol induced mutations involving filamentation, but not reverse mutation for streptomycin non-dependence. Positive results in mammalian *in vitro* test systems were reported for gene mutation in Chinese hamster fibroblast (V79) cells, for SCE in human lymphocytes, and for inhibition of DNA replication and repair synthesis in human fibroblasts. Negative results were reported for the *Drosophila* sex-linked recessive lethal test and the mouse micronucleus test. Because of the positive findings in mammalian *in vitro* tests and in certain bacterial tests, phenol may have mutagenic potential.

Phenol may be a promoter and/or weak skin carcinogen in specially inbred sensitive strains of mice. Studies by Boutwell and Bosch (1959) and Salaman and Glendenning (1957) demonstrated strong tumor-promoting activity of phenol in Sutter strain mice and "S" strain albino mice after pretreatment with the polycyclic organic DMBA, followed by repeated skin applications of 20 percent phenol in various solvents including acetone, ethanol in acetone, benzene, and dioxnea. A lesser concentration of phenol (5 percent) was found to have a moderate promoting action, but no carcinogenic action. Van Duuren et al. (1968), utilizing ICR/Ha Swiss mice, demonstrated that phenol is at best a weak promoting agent on mouse skin. With respect to cocarcinogenesis experiments, Van Duuren et al. (1971), using the same strain of Swiss mice, demonstrated that the tumorigenic response normally exhibited by benzo(a)-pyrene (BaP) is slightly inhibited by phenol. This partial inhibitory effect that phenol has on the carcinogenic activity of BaP was also confirmed by Van Duuren and Goldschmidt (1976) and Van Duuren et al. (1973). However, all of these studies did not provide for evaluation of effects produced by the solvents used and, in some cases, for the pretreatment of the albino mice with a known carcinogen, either DMBA or BaP. These mice studies suggest that phenol may function primarily as a nonspecific irritant and may be capable of promoting tumors. It should be pointed out here that tumor promotion represents a special case of cocarcinogenesis (Berenblum, 1985). The latter corresponds more closely to the environmental situation, i.e., humans are not ordinarily exposed sequentially to chemicals, but simultaneously and for prolonged periods of time to mixtures of large numbers of chemicals, some of which may be carcinogens and other cocarcinogens.

The most recent gavage study by the National Cancer Institute (1980) demonstrated an increased incidence of some types of tumors (leukemia, lymphomia, interstitial cell of the testes) in male rats in a low dose group, but there was no clear dose-response association between carcinogenicity and the administration of phenol under the conditions of the bioassay in that tumor incidence was not significantly elevated in the high-dose group. Therefore, based on the skin-painting studies of mice and the gavage studies on mice and rats by the National Cancer Institute, there is no clear evidence that phenol acts as a complete carcinogen—particularly at low exposure concentrations. Accordingly, phenol is classified as a Group D compound using the new EPA weight-of-evidence criteria for cancer data (F.R., 1984). Group D means that the data are inadequate for evaluating the carcinogenic potential.

In conclusion, the available toxicity data are rather limited, making it difficult to characterize fully the toxic potential of phenol to humans, especially in regard to inhalation exposure effects. The weight of evidence for phenol's carcinogenicity is inadequate in humans; however, the fact that the National Cancer Institute study did not demonstrate a clear association between the incidence of cancer in phenol-exposed animals compared to controls does not necessarily imply that phenol is not a carcinogen, inasmuch as the experiments were conducted under a limited set of conditions (i.e., drinking water). Also, given evidence suggesting that phenol may be a tumor promoter, it would be prudent to carry out additional evaluations of the carcinogenic potential of phenol. It is recommended, therefore, that a long-term bioassay study for phenol via the inhalation route be nominated for inclusion in the National Toxicology Program (NTP) or a similar testing program.

In addition, it seems appropriate to further evaluate the reproductive toxicity and teratogenicity associated with exposure to air containing phenol in view of the effects reported in the offspring of rats at low levels by the Russians and in view of the dose-related signs of fetal toxicity exhibited by mice at dosages below the maternal toxic level.

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