III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

The term "phenol" as used in this document refers specifically to monohydroxybenzene, C6H5OH, [1] which is a clear, colorless, hygroscopic, deliquescent, crystalline solid at 25 C. [1,2,3] Impurities may impart a light pink color to phenol samples. [1,2,4] Such impurities were not considered in the development of the recommended standard. Although "phenol" and "phenolics" are terms often used to describe compounds containing one or more hydroxyl groups attached to an aromatic ring, [1] it is not intended here to develop a standard for compounds other than C6H5OH.

The chief chemical and physical properties of phenol are given in Table XII-1. Phenol readily forms aqueous solutions and emulsions with the amount of phenol actually dissolved in an aqueous solution increasing with temperature. [1] In solution, phenol can be oxidized, forming a variety of products including benzenediols, benzenetriols, and diphenyls. Reduction with removal of the hydroxyl group to form benzene occurs on distillation with zinc. [1] Phenol undergoes esterification and can form an ether by reactions characteristic of an alcohol. [1] The hydroxyl group is ortho- or para-directing in nucleophilic substitution reactions of the aromatic ring, [1] and the hydroxyl group participates and is highly reactive in condensation reactions with formaldehyde. The aromatic ring can be nitrated by nitric acid. [1]

In the US, phenol is produced either synthetically or by the fractional distillation of coal tar. [1,5] Synthetic processes are the most significant commercially, and production of phenol may be accomplished

by the following processes: (1) cleavage of cumene hydroperoxide to form phenol and acetone, (2) the sulfonation of benzene followed by the fusion of sodium benzene sulfonate with NaOH to form phenol, (3) hydrolysis of chlorobenzene to form phenol in an aqueous sodium hydroxide solution, or (4) oxidation of toluene to benzoic acid and then to phenol. The 1972 US production capacities by process are listed in Table XII-2. Demand for phenol in the US was 1,900 million pounds in 1972, and demand has been estimated at 2,500 million pounds for 1976. [5]

Phenol is supplied commercially either as a solid or as an aqueous solution. [1,2] The USP [6] specification for phenol requires a phenol content of not less than 98%, but in practice nearly all synthetic phenol has a purity in excess of 99.5%. [1] Commercial grades of phenol obtained from distillation of coal tar are either 90-92% phenol or 80-82% phenol, the remaining constituents being water and cresol. [1,2] Solid phenol is shipped in tank cars, tank trucks, wooden barrels, wooden boxes, aluminum drums, nonreturnable metal drums, and small containers. [2] Phenol solutions are shipped in tank cars, tanks, returnable barrels or drums, nonreturnable metal drums, boxed glass carboys, and small containers for laboratory use. [2]

About 90% of the phenol produced in the US is ultimately used (Table XII-3) in the manufacture of phenolic resins, caprolactam, bisphenol-A, alkylphenols, and adipic acid. [5,7] A more complete list of uses is found in Table XII-4. [8-48] Phenol has also been identified in automobile exhaust [49,50] and in cigarette smoke. [49,51]

Occupations in which employees may encounter exposure to phenol are listed in Table XII-5. The number of employees who may be exposed to

phenol has been estimated by NIOSH to be 10,000. This essentially reflects that population of employees engaged in commercial production, formulation of products, or distribution of concentrated products. A substantial but uncertain number of employees indicated by occupation in Table XII-5 may be intermittently exposed.

Historical Reports

Historical reports, described below essentially in chronologic order, indicate that phenol has long had significant chemical and physical properties of commercial interests. Phenol has been used in numerous products and processes, and applications are expected to continue and to increase. [5] According to Stevens [52] and Wilbert, [53] phenol was discovered by Runge who called it "carbon oil acid." Stevens [52] also reported that in 1841 Laurent synthesized phenol in pure form and called it "hydrate de phenyle," but Gerhardt who prepared phenol from salicylic acid later in the mid-nineteenth century was the first to introduce the name phenol.

Cook [54] reported that Lemaire was the first to use phenol as a disinfectant on wounds. In 1867, Lister [55] reported a new treatment using lint soaked in phenol and applied as a covered dressing for compound fractures. Tissue was eroded by phenol in all of the 11 cases treated, and gas gangrene occurred in 8. One death occurred when the application of phenol damaged tissue sufficiently to rupture a femoral artery. There were no complaints of pain as a result of the progressive tissue degeneration. This was an early report indicating the anesthetic property of phenol.

Lister [55] also used phenol as a spray for disinfecting operating rooms and in solutions for storing catgut sutures.

In 1869, Fuller [56] gave phenol to healthy individuals and to patients suffering from a variety of disorders. Oral doses from 0.5 to 1 g phenol in 48 ml of an aqueous solution containing 8% glycerol administered 3 - 4 times/day produced complaints of coldness and a burning sensation in the throat upon swallowing. In addition, signs of giddiness, profuse perspiration, and a weak pulse were observed in most of the subjects. Urine collected from those tested was greenish. Some individuals, especially those characterized as heavy alcohol drinkers, were able to tolerate phenol at similar doses from solutions containing as much as 2% phenol concentration before these signs were observed or symptoms developed. Female subjects tolerated only about half the dose tolerated by males. Some individuals became faint after inhaling aerosols of phenol aspirated directly from 1-2% aqueous phenol, at which time the subjects were advised to cease inhalation of the aerosol. Fuller's experiments preceded a report of the germicidal action of phenol described by Koch in 1881. [57]

Many of the effects which have been associated with phenol exposures are presented in Table XII-6. In addition to the numerous injurious effects of phenol exposure, repeated application of dressings impregnated with 5-10% solutions of phenol has produced acquired ochronosis, a discoloration of collagenous tissue, which was described in 4 reports. [58-61] The discoloration occurred when phenol dressings were used to treat skin ulcerations associated with the development of varicose veins. The dressings were applied over periods ranging from 3 to 24 years.

Prior to the 1940's, only a few cases of exposure to phenol in the workplace had been reported. [20,29,62-66] Among these were 3 cases of prolonged inhalation of phenol [63-65] with possible additional contact with the spilled liquid in 1 case [64] and 4 cases of contact with spilled liquid on the skin [20,29,62] including 1 fatal exposure. [20]

In 1872, Unthank [63] described the case of a farmer who inhaled phenol vapor at unknown concentrations for 3 hours. The victim had symptoms of giddiness and euphoria followed by convulsions and coma. Additional signs were stertorous breathing, lividity of face and neck, cold extremities, and a weak, irregular pulse. Following treatment and return to consciousness, the patient complained of giddiness, pain in the face and neck, gastric irritation, and a phenol taste. There was a gradual improvement with recovery in 4 days.

Hamilton, [20] in a 1917 report, attributed 2 poisonings, 1 fatal, to the absorption of phenol through the intact skin. The fatality occurred as a result of a chemist accidentally stepping into a phenol waste solution. The victim experienced tinnitus, dyspnea, vertigo, euphoria, and hysteria. The victim was allowed to leave in this condition, but he evidently soon lost consciousness as he was found dead on the road the next morning. Examination of the body revealed a gangrenous leg below the knee.

In 1922, an employee wiping up the fluid spilled as a result of dropping a bushel of crude phenol developed signs and symptoms associated with absorption of phenol. [65] The victim collapsed a few minutes after a brief exposure. Thirty minutes later, the patient was comatose and cyanotic with stertorous breathing, subnormal temperature, cold extremities, slight burns on the right hand, and the odor of phenol on his

breath. After treatment, recovery was complete in 2 days.

A report by McCord and Minster [29] in 1924 described the exposure of a shoe worker to phenol contained in a marking ink spilled on her clothing. Injuries were second-degree burns on the face, neck, and breasts, followed by depression, fatigue, headache, a weak and rapid pulse, and collapse. Recovery was speedy following institution of treatment.

In 1939, Winkler [62] described a case in which a chemical worker was sprayed with a liquid containing 50% phenol, 35% cresol, and 10% xylene. The victim received severe burns of the hands, chest, face, and eyes. Examination of the eyes revealed edematous conjunctivae, corneal opacities, insensitivity to light, and hemorrhaging beneath the conjunctivae. Application of fluorescein dye produced intense coloration. The victim was euphoric, complained of headache, and passed a darkened urine which contained phenol and albumin. Winkler concluded that the patient had suffered transitory kidney damage. The red blood cell count was initially normal but decreased markedly to 2.3 million/cu mm in 10 days. Aside from anemia, Winkler postulated damage to the blood-forming organs based upon an increased bilirubin concentration in the serum, slightly increased leukocyte count of 17,000/cu mm, lymphocytosis, and monocytosis. Blood and kidney abnormalities disappeared upon treatment.

Prior to the early 1900's, phenol taken orally was a popular suicidal agent. [25,67-74] Its popularity declined markedly after 1900 because other poisons were considered to be less painful and were also more accessible. [26] Reid et al [59] noted that, in 1909 in the US, of the 3,376 fatal poisonings in which the agents were known, 1,621 (48%) were due to phenol. Of the 1,621, 1,466 (88%) were suicides. With the decline of

phenol as a suicidal agent since 1900, [26] cases of phenol poisoning by oral exposure have diminished. Since 1940, there have been two reports [75,76] involving three deaths from intentional phenol ingestion.

Effects on Humans

The most frequent adverse effects of phenol reported in humans are those from skin contact. Since the early 1940's, numerous investigators [27,76-99] have reported the injurious effects of phenol following inhalation, [88, 92,95,97,98], ingestion, [75,76] contact with the skin, [76-99] direct contact with the trachea during a tracheotomy, [91] and percutaneous injection. [81] Injurious effects following skin contact with resins containing phenol have been reported. [100-105] These signs and symptoms are listed in Table XII-6.

Early investigators [29,56,58,62,63,68,69,71,106-112] reported certain signs and symptoms which are not found in the more recent literature. These included abortion, [69,109] acquired ochronosis, [58-61] difficulty in swallowing, [56,68,69,71,106,107,111] and tinnitus. [58] Symptoms such as euphoria, delirium, and giddiness are reported as increased excitability by more recent investigators [86,88] while symptoms of depression have been more recently reported as stupor. [75]

Effects not found in earlier reports but noted by current investigators [77,85,89,93] include pigmentary changes in the skin, [93] damage to the pancreas, [84] skin cancer, [89] loss of weight, [92] and leukocytosis. [76] These reports probably reflect changes in medical terminology.

(a) Effects of Inhalation

Aside from Fuller's [56] 1869 report, only 5 reports were found

[88,92,95,97,98] on the inhalation of phenol. In 1971, Piotrowski, [97] in controlled experiments, exposed 7 men, aged 25-42, and 1 woman, aged 30, to phenol vapor at various concentrations either by inhalation or by absorption through the intact skin. The subjects passed a thorough medical examination prior to exposure. In 12 separate experiments, phenol at 6-20 mg/cu m (1.5-5.2 ppm) was inhaled using a face mask connected to a chamber in which airborne phenol was generated dynamically from a vessel heated in a constant temperature bath. During each experiment, the concentration of phenol was determined hourly by sampling air directly from the inhalation and exhalation channels of the exposure masks and analyzing for phenol. The only dermal exposure to phenol during the inhalation studies was inside the masks. Subjects were exposed for 8 hours with 2 breaks of 0.5 hour each, one occurring 2.5 hours and the other 5.5 hours after the start of exposure. A 24-hour urine sample was collected prior to exposure. Urine samples were taken every 2 hours during exposure and ad libitum until the next morning after the exposure ceased.

Skin absorption studies [97] were carried out inside the previously mentioned exposure chambers at phenol concentrations of 4.8-5.3 mg/cu m (1.2-1.4 ppm), 9.3-9.7 mg/cu m (2.4-2.5 ppm), 24.8-25.3 mg/cu m (6.4-6.6 ppm), and 22.3-26.1 mg/cu m (5.8-6.8 ppm), as determined by hourly sampling of chamber air. The subjects were clothed in underwear and denim overalls and placed in hammocks during the first, second, and fourth series of experiments and were naked during the third. In each case, subjects breathed fresh air through a face mask to exclude the inhalation of phenol vapor. Exposures were for 6-hour periods with 1 short break in the middle. Urine samples were collected as in the inhalation experiments. Urine

samples in both series of experiments were analyzed for total phenol using the method of Porteous and Williams [113] as modified by Teisinger et al. [114] Phenol was collected from air, using 0.1 N NaOH in fritted bubblers, and analyzed by distillation of phenol in a manner similar to that used in the analysis of urine. The standard error of a single measurement was $\pm$ 4% of the mean, and phenol recovery from air in 1 bubbler exceeded 95%.

Piotrowski [97] found that individuals exposed by inhalation retained 60-88% of the inhaled dose. This percentage did not vary significantly with airborne phenol concentration but did decrease from about 80% at the beginning of exposure to about 70% at the end. There was a slight tendency for retention of phenol to increase after each 30-minute break in exposure. Urinary excretion increased rapidly during exposure and returned to normal within 16 hours after termination of exposure. Calculations showed that 99 $\pm$ 8% of the inhaled dose was excreted in the urine. Individuals exposed through skin absorption excreted amounts similar to those exposed by inhalation, and excretion rates were about the same by either route of exposure. In the skin absorption experiments, clothed and naked subjects showed about the same excretion rates. The author [97] did not describe any adverse effects for any of the test subjects.

In 1972, Merliss [92] reported a gradual deterioration of the health of a 44-year-old laboratory technician who had been exposed to vapor containing phenol, cresol, and xylenol and who had often spilled phenol on his trousers. Spills resulted in skin irritation. Signs and symptoms noted included loss of appetite, darkened urine, and muscle pain in the legs and arms. He stayed away from his job for several months during which time his health gradually improved. He returned to the laboratory for a

period of 45 minutes and had an immediate recurrence of muscle pain and subsequent darkened urine. He lost weight and exhibited an enlarged liver which was slightly tender to the touch. His urine remained dark for several weeks. His condition gradually improved over the next 3 months. Although his liver size and urine color had returned to normal and he had gained weight, it was reported that he had not completely recovered.

Petrov [88] reported 29 poisonings during a 3-year period in a group of employees who quenched coke with a waste water solution containing 0.3-0.8 g phenol/liter. Concentrations for phenol in air samples collected in work areas ranged from 0.5 to 12.2 mg/cu m (0.1-3.2 ppm). The author felt that phenol at concentrations from 8.8 to 12.2 mg/cu m (2.3-3.2 ppm) may have been implicated in the intoxications. No other measurements were reported in this area, and the nature of the phenol poisoning was not further characterized. The observed conditions were most likely produced by some substance in the effluents from either the waste water or the coking process, but it is inappropriate to assume that these conditions were produced by phenol.

In documenting their Threshold Limit Value for phenol, [95] the American Conference of Governmental Industrial Hygienists cited data given to them as a personnal communication by the Connecticut Bureau of Industrial Hygiene. These data indicated that employees inside a conditioning room for phenol-impregnated asbestos suffered marked irritation of the nose, throat, and eyes when exposed for intermittent periods of 50 minutes to a mixture of phenol at 48 ppm (about 200 mg/cu m) and formaldhyde at 8 ppm. Formaldehyde alone at 8 ppm has been shown to cause such irritation. [115-122]

Ohtsuji and Ikeda [98] measured exposures to airborne phenol and urinary phenol concentrations in samples from a group of Bakelite factory employees. Airborne phenol concentrations ranged from 0 to 12.5 mg/cu m. Samples of phenol in air were obtained at a rate of 2 liters/minute using two midget impingers containing 15 ml of 0.1 M borate buffer (pH 10.0). Total air volumes sampled ranged from 5 to 10 liters. Analyses for phenol were performed using Gibbs reagent. [98,123] Urine samples were collected before and after exposure and analyzed for total, free, and conjugated phenol using the Ikeda modification [124] of the Gibbs method. Urine samples were also analyzed for ethereal glucuronides and sulfates using the method of Bertolacini and Barney [125] as modified by Ohmori and Hara. [126] In addition, the specific gravity and creatinine concentration of urine were measured, the latter by the method of Ikeda and Ohtsuji. [127] Urinary conjugated phenol and total phenol adjusted to an average urine specific gravity of 1.018, due largely to the conjugated phenol fraction, increased with airborne phenol concentrations, but the concentration of free phenol varied little with changes in airborne phenol concentrations. Ethereal sulfates in the urine generally increased with increasing airborne phenol concentrations. These increases were observed during the shift, but decreases in these constituents to preexposure concentrations the following morning suggested that these employees readily conjugated and eliminated the phenol absorbed as a result of their combined inhalation and skin exposures. These results are in agreement with and appear to support similar conclusions made by Piotrowski, [97] who separately investigated the inhalation and skin absorption of phenol vapor.

(b) Effects of Ingestion

Bennett et al [75] reported 2 suicide cases. The first case involved a 50-year-old morphine addict who had swallowed 2 oz (approximately 60 ml) of an 88% aqueous phenol emulsion. Forty-five minutes later, he was stuporous with cold and clammy skin and had a rapid and weak pulse, stertorous breathing with a phenol odor on the breath, constricted pupils which did not react to light, and rales in his lungs. An electrocardiogram showed auricular flutter with a variable auriculoventricular block. Lumbar puncture revealed normal spinal fluid. His urine was greenish with no albumin but, 12 hours later, there was marked albuminuria and cylindruria. Albuminuria persisted for 10 days. The patient responded to treatment except for nausea, vomiting, and diarrhea which continued during the first week. He recovered in 20 days. Constriction of the pupils may have been due to the intravenous injection of 0.5 g of morphine prior to phenol ingestion.

The second case [75] involved a 19-year-old woman who had ingested 15 ml of liquefied phenol. Ninety minutes later, she complained of severe nausea and burning in the throat and epigastrium. Laryngoscopic examination revealed superficial burns and slight edema of the hypopharynx. Despite gastric lavage with olive oil and intravenous saline administration, she continued to be nauseated. One hour later, she began to vomit blood and to have diarrhea, passing copious amounts of blood with clots. She gradually became cyanotic and stuporous. Her blood pressure decreased markedly and her extremities became cold. She experienced periods of relapse and recovery during treatment but died 17.5 hours after the ingestion.

In another report, [76] a woman committed suicide by ingesting 10-20 g of phenol. She became comatose with partial absence of reflexes, pallor of the skin, accelerated respiration, weak and rapid pulse, and dilated pupils which did not react to light. Almost one hour after the ingestion, her heart and respiration stopped and, in spite of repeated attempts at resuscitation for two hours, she died. Autopsy revealed marked hyperemia of the tracheal and bronchial mucous membranes. Histologic examination revealed pulmonary and liver edema as well as hyperemia of the intestines.

(c) Effects of Skin Exposure

The skin represents a primary route of entry for phenol vapor, [97] liquid phenol [76,77,84,86,87,89,90,93,94,96] and solid phenol. [79] Phenol vapor readily penetrates the skin with an absorption efficiency approximately equal to that for inhalation. [97] Skin absorption can occur at low vapor concentrations, [97] apparently without discomfort. [79,96]

Liquid phenol in contact with the skin rapidly enters the bloodstream [77-79,82,84-87] and is responsible for the variety of signs and symptoms listed in Table XII-6. These signs and symptoms can develop rapidly with serious consequences, including shock, [76,82,84,85] collapse, [76,81,85] coma, [77,86] convulsions, [80,128] cyanosis, [76,78,83] and death. [76,79,84,86,87] Damage to internal organs has also been described. [76,79,82,85] In addition, the skin is often a site of contact for production of chemical burns and absorption of solid [79] or liquid phenol. [77-79,82,84-86,90,93,94,96,105] There is no evidence that allergic dermatitis results from exposure to phenol, but exposure to resins containing phenol has produced allergic dermatitis results. [100-105] Such allergic reactions can be caused by other agents such as formaldehyde

in the resins, [100,102] the resin itself, [100,101 103,104] or some other product. [104] Discussions of phenolic resins are included in these criteria only when the resins are used or manufactured in such a way as to release free phenol. In such cases, phenol has been mentioned as the probable cause of the skin irritation. [105]

Gottlieb and Storey [129] have described pathologic findings in a 32-year-old somewhat obese man who accidentally spilled a strong solution of phenol over his scalp, face, neck, shoulders, and back. The authors stated that information on the onset of symptoms was not available but, had it been, in all probability it would not have been reliable. The victim, a chronic alcoholic, died within 10 minutes after contact with phenol. Pathologic findings related to phenol were coagulation necrosis of the skin and left eye, acute dermatitis venenata, acute phenol toxicosis, and acute passive congestion of the lungs, liver, spleen, and kidneys. There was moderate cerebral edema (possibly due to his chronic alcoholism). Other pathologic conditions, including chronic degeneration of the liver, kidneys, and heart, were also described. Samples of blood, brain, and stomach contents were analyzed for phenol. The blood contained 0.073% ethanol and 0.0037% phenol. The concentrations of phenol and ethanol in the stomach contents were nil. Skin and liver tissues were positive for phenol by Millon's test. The authors attributed the cause of death to a phenol toxicosis from absorption of phenol through the intact skin.

Caviness [84] reported the case of a 47-year-old diabetic woman who had been lax in her diet and insulin regimen for over 3 years. She developed an eczema on her toe to which she applied a 5% phenol in iodoform and zinc oxide ointment twice a day under a closed dressing. The toe

showed marked edema and erythema, which soon extended to the ankle. She complained of a throbbing pain. Five days later upon admission to the hospital, she had a fever, and increased respiratory rate, pulse rate, and blood pressure. The toe was blue in some areas and red and edematous in others. Later, gangrene developed, causing severe pain and associated periostitis. Following amputation, the woman recovered.

Noury [81] reported a suspected case of rabies in a 49-year-old man who was given prophylactic inoculations of antirabies vaccine in 5 cc of a 1% phenol solution every day for 15 days. The patient had a history of chronic alcoholism. For the first 10 inoculations, he did not notice any particular effect but, after the 11th, he collapsed. His pupils were constricted, his breathing was stertorous, and his pulse weak. He vomited, lost consciousness, and was taken to the hospital. He regained consciousness after 6 hours and remained in the hospital for 20 days. A permanent partial facial paralysis occurred as a result of the incident, but the author did not provide sufficient information to determine the cause of paralysis.

Satulsky and Halpern [90] described 3 cases of dermatitis venenata caused by the local application of a phenol-camphor ointment. The first case was that of a 28-year-old man who treated a self-diagnosed case of crab lice with a liquid preparation containing camphor and 4.75% phenol. Within two hours he felt a burning pain which increased in severity. The abdominal area was covered with a severe dermatitis with lurid erythema, marked edema, and numerous small, tense, clear vesicles throughout. Desquamation was evident around the umbilicus. The edges of the eruption were clearly marked. Also noted were a marked increase in local body

temperature, profuse serous exudation, maceration, and a tendency towards bullous formation. Covered and uncovered patch tests with the mixture on unaffected areas of the man's skin and on the skin of 2 volunteers elicited a primary irritant response in all cases within 30 minutes. The second case was that of a 26-year-old man who treated himself for tinea corporis on the abdomen with a phenol-camphor solution. In 1 hour, he had severe burning, stinging, and pruritus; all of these symptoms increased in severity until his hospitalization the following day. Severe erythema and serous exudation were present. The edges of the eruption were clearly demarcated and slightly raised. Vesiculation and bullae were also accompanied by the exudation of a thick, white serum. Edema, erythema, and crusting were also present. The third case was that of a 24-year-old man, who treated paronychia on his fingers and toes with a phenol-camphor mixture which caused burning and pain within 45 minutes and lasted for 1-5 hours. Erythema, vesiculation, crusting, fissuring, and oozing were present.

Hubler [78] cited the case of a 30-year-old woman who treated the ringworm between her toes with a camphor-phenol solution which caused marked edema and pain. One week later, her toes showed bilateral edema and a number of deep ulcerations. The patient was totally disabled for about a month.

In 1949, Cronin and Brauer [77] reported the case of a 10-year-old boy who had received first- and second-degree burns over 25-30% of his body surface. After being treated with a 2% phenol solution, he developed signs and symptoms of phenol poisoning, including darkened urine, increased pulse rate and body temperature, severe abdominal pain, stupor, cyanosis, local

tissue necrosis, stertorous breathing, dyspnea, rales, frothing, and "pink mucus arising from the lungs." Two and one-half days after the initiation of treatment, the boy was comatose, with irregular respiration, fever, and increased pulse rate; he died within 3 days. Post-mortem examination revealed burns, a yellow fluid in the pericardium, and spotty, firm, dark brown and red areas on the lungs, which also showed hypostatic pneumonia. Abnormal amounts of mucus were present in the trachea and bronchi, where the mucous membranes were hemorrhagic. The spleen was congested. The liver showed midzonal necrosis. The epithelial cells in the glomeruli of the kidneys showed marked parenchymatous degeneration, with loss of cellular configuration. The gastrointestinal tract showed acute congestion. A similar case was cited by Johnstone. [130]

Watorski [96] reported 2 cases of phenol poisoning in the workplace following skin contact with phenol. In the first case, a laboratory technician suffered burns on both hands after spilling a 97% phenol solution (containing cresol impurities). Shortly after the spill, he washed his hands with 98% methanol and then with 20% sodium thiosulfate solution followed by soap and water. Later, he was treated by topical application of 20% sodium carbonate and a dressing with 30% castor oil ointment. Six hours later, he suffered fatigue, general weakness, and blurred vision. A day later, he had severe pain and continued weakness. Recovery occurred within several weeks of the accident. In the second case, a man died 5-7 minutes after the explosion of a metal container of crystalline phenol which was being heated by a battery of Bunsen burners. Trauma produced by the explosion could have contributed to his death.

Evans [82] reported the case of an industrial employee who was involved in the spraying of weeds with a predominantly phenolic material which was the effluent of a chemical plant. This material contained 43.5% phenol, 20% water, 14% cresols, 11.5% low-boiling organics probably aldehydes, and 11% high-boiling organics--probably resinous material according to the author. The skin of both thighs (7 inch x 4 inch and 6 inch x 2 inch areas, respectively), of the scrotum, and of the penis was exposed to the spray. Washing with large amounts of warm water was started immediately and continued for 30 minutes. This was followed by swabbing with ethanol for 10 minutes. The warm water wash and ethanol swabbing were repeated. The employee developed symptoms of shock within 30 minutes after exposure. He had reduced body temperature, a weak and irregular pulse, an accelerated respiratory rate, stertorous breathing, and constricted pupils which showed a slow response to light and slow accommodation. His left leg had convulsive movements for 30 minutes. There was minimal liver damage, as indicated by an increased serum bilirubin at 1.7 mg% (approximately 1 mg % is normal) and by a positive Van den Berg reaction with a direct/indirect quotient of 40%. Other tests for liver function were normal. Urine was not analyzed for phenol until 4 days after exposure, at which time it was negative. Recovery was complete, and the patient was released from the hospital 7 days later.

Johnstone and Miller [85] described a case of industrial exposure to phenol in an ink-manufacturing plant where an employee spilled phenol on his leg, abdomen, and chest. Following immediate flushing with water, he went to a physician's office where he collapsed and died within 15 minutes. Post-mortem examination revealed extensive first- and second-degree burns

on his body, hyperemia and edema of the lungs, and marked hyperemia and edema of the kidneys, pancreas, and spleen.

Duverneuil and Ravier [86] reported that an employee accidentally spilled 4-5 liters of 78% aqueous phenol on himself. Despite immediate irrigation with alcohol, he became comatose and exhibited superficial skin burns. He died shortly thereafter.

Hinkel and Kintzel [87] observed 2 cases of newborn-babies exposed to phenol. One died 11 hours after the application of a bandage containing 2% phenol to the umbilicus. The other was treated for a skin ulcer with a 30% phenol-60% camphor mixture (Chlumsky's solution) and then experienced circulatory failure, cerebral intoxication, and methemoglobinemia. The infant recovered following a blood transfusion.

Telegina and Boiko [93] reported vitiligoid dermal changes in 12 employees in a motor-oil additives-production plant where concentrations of phenol vapor were 0.055-3.33 mg/cu m, hydrocarbons 3.3-24.6 mg/cu m, hydrogen sulfide 0.11-0.78 mg/cu m, sulfur chloride 0.05-0.28 mg/cu m, and carbon monoxide 3.3-26.6 mg/cu m, and where contact of the exposed skin surfaces of the employees with phenol and other irritating substances was a distinct possibility. One employee had been employed for 2.5 years, 1 for 3 years and 7 months, 9 for 6-10 years, and 1 for more than 10 years; 3 employees were 20-29 years, 6 were 30-39 years, and 3 were 40-49 years of age. In those employees in whom this pigmentation abnormality had existed for 2-5 years, the skin had vitiligoid depigmentation spots on the chest, the waist, and the dorsa of the hands and feet, with the largest spots occurring at skin folds. The edges of the spots were not clearly demarcated. Accompanying these large spots were numerous small white ones

distributed in clusters. In those individuals who had developed this depigmentation more recently, isolated maculae of depigmentation were evident. Pruritus was rarely reported. In dyschromic individuals, eosinophilia, monocytopenia, elevated local tissue temperature, susceptibility to prolonged spasms of the cutaneous capillaries of the hands, extensive prolonged dermographia of the chest, marbleization of the extremities, induration and turgescence of the larger and intermediate blood vessels, and excessive perspiration and cyanosis of the extremities occurred. Furthermore, the author noted that employees over 40 appeared to develop secondary and intercurrent skin diseases more readily than did younger employees. It also has been noted [131-134] that several other phenolic compounds can cause similar depigmentary changes.

Abraham [79] reported that an 18-year-old laboratory assistant developed gangrene of the thumb after a 30-minute exposure to crystals of pure phenol which were present inside a rubber glove. The phenol rendered his thumb insensitive. He did not receive treatment for 41 hours following exposure. A clear demarcation between the gangrenous area and the normal skin appeared 26 days after exposure. The necrotic tissue was removed surgically, and the patient recovered. No systemic disorders were noted.

In 1940, Stevens and Callaway [89] described a case involving an epithelioma with basal- and squamous-cell components which had resulted from the continued self-application of a salve made of phenol and ergot to an area on the back. The man, a 72-year-old druggist, had applied this "secret formula" daily to one area of the back where the eczematoid dermatitis was more resistant to treatment. His skin in the middle of the lower back was loose, wrinkled, and warm, and contained a large fungating

mass, 15 cm in diameter. Borders were rolled and, in some areas, there was deep ulceration. In other areas, epitheliomatous hyperplasia and granulations were evident. The lesion was extremely vascular and bled easily. A biopsy showed a neoplastic, invasive growth. Microscopic examination of the tissue revealed it to be a basal-cell and squamous-cell epithelioma. The authors reported that there was no evidence of metastasis. The patient refused treatment either by radiation or excision. The investigators properly attributed the cancer to the continued irritation of the skin rather than to any specific property of phenol.

(d) Thresholds of Perception

Leonardos et al [135] using an odor panel determined the phenol odor threshold to be 0.047 ppm. This threshold represented the lowest concentration to which all 4 trained panelists, selected from a pool of 15 experienced odor panelists, responded positively. Phenol was so tested for at least 5 different concentrations.

Makhinya [136] measured the phenol odor thresholds of 19 people and the lowest range of concentrations for the detection of phenol by odor was 0.022-0.094 mg/cu m (0.006-0.024 ppm). Phenol at concentrations of 0.016-0.078 mg/cu m (0.004-0.020 ppm) was not perceptible by odor for the group tested. Mukhitov [17] obtained similar results using a group of 14 people. The odor threshold for phenol ranged from 0.022 to 0.184 mg/cu m (0.006-0.048 ppm). The highest concentration of phenol not perceptible by odor was 0.0175 mg/cu m (0.005 ppm).

Six 5-minute inhalation exposures to phenol at 0.0155 mg/cu m (0.004 ppm) produced an increased sensitivity to light ($p < 0.01$) in each of 3 dark-adapted subjects [17] who were selected from an original group of 14,

based upon their minimal odor thresholds of 0.029, 0.073, and 0.184 mg/cu m, respectively. Further tests on the original group revealed that 15-second exposures to phenol at 0.024 mg/ cu m (0.006 ppm) elicited the formation of conditioned electrocortical reflexes in 4 additional subjects. Tests with 0.0155 mg phenol/cu m (0.004 ppm) elicited the latter response in 3 of the 4, while 0.0137 mg/cu m (0.0036 ppm) elicited no response. In these experiments, light was used as the unconditioned reflex stimulator which elicited alpha-rhythm desynchronization as measured on an electroencephalograph. Inhalation of phenol was used as the conditioned stimulator, and desynchronization was the index of reflex elicitation.

(e) Metabolism

Ruedemann and Deichmann, [137] using 1 group of 5 male medical students and 3 other groups made up of volunteers, conducted experiments on skin absorption of phenol. Each group member received 1 or more applications of 50 g calamine lotion containing 1 g of phenol (2% phenol) applied over 75% of the body. The medical students received a single application; the second group received 2 applications, 90 minutes apart; the third group received 3 applications, 90 minutes apart; the fourth group received 4 applications, 90 minutes apart. Blood samples were drawn at 2-hour intervals for 1-3 days and analyzed for phenol using the method of Deichmann and Schafer. [138] From the time of the final application, subjects did not remove their underwear for periods of 24-48 hours, at which time each took a shower and donned clean clothing. After allowing a 2- or 3-week period for their blood values to return to normal, these same subjects were similarily exposed to 1, 2, 3, or 4 1-g doses of phenol contained in 21 g of phenol-camphor-liquid petrolatum (4.75% phenol). In

both tests, preexposure concentrations or free phenol in the blood of all 20 subjects averaged 0.15 mg/100 ml and increased to an average of about 0.4 mg/100 ml during each of the tests. Preexposure concentrations of conjugated (protein-precipitated) phenol in the blood of all subjects averaged 0.35 mg/100 ml in both experiments. Conjugated phenol concentrations in blood increased to averages of 1.1, 1.65, 1.9, and approximately 1.9 mg/100 ml, respectively, for the groups receiving 1, 2, 3, and 4 calamine applications and to averages of 0.9, 1.2, 1.7, and 1.5 mg/100 ml, respectively, in the groups receiving 1, 2, 3, and 4 applications of phenol-camphor-liquid petrolatum. Both the free and the conjugated phenol concentrations in blood returned to preexposure values within 24 hours. The subjects noted a soothing and cooling sensation followed by a feeling of warmth after application of the test formulation. There were no indications of systemic intoxication at any time during or shortly after the tests. The investigators noted from these experiments that phenol readily penetrated the human skin, and that detoxication by conjugation apparently was initiated immediately.

There have been various estimates made of the "normal" concentrations of phenol in blood and urine. (see Table XII-10,11) Aside from the values cited by Ruedemann and Deichmann, [137] estimates of "normal" free phenol in blood ranged from none or traces to 4 mg/100 ml. For conjugated (protein-precipitated) phenol in "normal" human blood, estimates ranged from 0.1 mg/100 ml to 2 mg/100 ml, and for total phenol in "normal" human blood, values range from 0.15 to 7.96 mg/100 ml. [138-150] The concentrations of free and conjugated phenol in the blood of those exposed to dermal applications of 2% and 4.75% phenol lotions overlapped the range

of other reported norms. [137] However, with the exception of two reports, [137,138] data presented in Table XII-10 were reported prior to 1939. Based upon more recent work and the propensity for phenol to combine with protein, [137] one would expect the concentration of free phenol in the blood of unexposed subjects to be lower than the concentration of conjugated phenol. However, several investigators [145-148] have reported the opposite case. The variation in absolute amounts of phenol reported also depend on the analytical method used; however, even with the exclusion of results from dubious analytical methods, [141-146] "normal" blood values cover a considerable range and no precise estimates of normal, free, or conjugated blood phenol concentrations can be made.

Total phenol concentrations in "normal" urine have been found to range from 0.5 to 81.5 mg/liter. [97,128,151-158] The specific gravity used to correct for "normal" urine in the British literature is usually 1.016 g/cu cm, and in the US literature it is usually 1.024 g/cu cm. Some investigators use the average specific gravity for the urine obtained from a test population as "normal" urine. In some reports, there are no indications of which correction factor, if any, might have been used. The variation for urinary phenol concentrations in Table XII-11 can be attributed in part to individual variation between test subjects, variation between analytical methods, and the correction factor used. Single exposures to phenol vapor at up to 6.8 ppm via either inhalation or skin absorption for periods of up to 8 hours produced no more than about 100 mg total phenol/liter of urine. [97] By comparison, industrial exposures to phenol at 10 mg phenol/cu m (2.6 ppm) were reported to result in a urinary phenol concentration of 262 mg/liter. [98] Assuming respiration of 8 cu m

of air during the work shift and 100% absorption (80 mg), excretion of the total amount absorbed in approximately 300 cc of urine would result in the reported concentration. This suggests that phenol is rapidly collected and excreted in urine.

Ikeda and Ohtsuji [127] observed considerable variation in normal urinary phenol concentrations, depending upon the analytical method used. Folin and Denis [151] found differences in urinary phenol excretion between people on high- and low-protein diets and noted [159] that both salicylic acid and aspirin produced an increase in the concentration of phenol in human urine. The latter finding was recently substantiated in a report by Fishbeck et al. [160] Biologic monitoring of urinary phenol concentration as a precise index of exposure to phenol has limited usefulness because of the considerable variation and overlap in the ranges for urinary phenol output in individuals considered to be unexposed as well as in individuals considered to have been exposed. In addition, phenol is a metabolite associated with benzene exposure [161] and would not provide a specific biologic indicator.

Animal Toxicity

(a) Acute Exposure

Acute toxicity studies have been conducted on a variety of species including the cat, [162-164] dog, [162,165-167] goat, [167] guinea pig, [168], pig, [167] rabbit, [163,169-171] and rat. [163,169,172] Results of these studies by species, routes of administration, and conditions of exposure to phenol are summarized in Table XII-12.

In 1915, Macht [162] reported that oral administration of phenol to

cats at doses of from 50 to 100 mg/kg body weight caused death in all animals tested. Intravenous injection of phenol in water at a dose of 50 mg/kg also killed all animals tested. [164] Subcutaneous injections of phenol in 0.9% sodium chloride solution were administered to cats at doses of from 1.2 to 15 mg/kg each day for 5 days. One of 3 cats administered phenol at a dose of 30 mg/kg each day for 3 days died 2 days after the final dose while the surviving cats experienced inappetence and diarrhea. [164] Lesser doses of phenol caused loss of appetite. Phenol at 80 mg/kg administered by subcutaneous injection of 10% phenol in olive oil killed approximately 50% of a test group of cats. [163]

Macht [162] conducted experiments to determine the minimal dose of phenol which would cause death in cats and dogs in from 1 to 2 hours. For cats this dose was from 50-100 mg/kg while for dogs it was about 500 mg/kg. All animals left untreated died at these doses. However, comparisons of immediate treatments by lavage using plain water, a strong solution of sodium sulfate, or a solution of 10% ethanol in water showed that sodium sulfate was most effective, followed in effectiveness by plain water. Treatment with ethanol aggravated the apparent effects and hastened death. The author recommended that use of alcohol to treat cases of phenol ingestion be strongly discouraged.

Bond and Haag [165] found that 300 mg of camphor administered orally to 3 fasted dogs along with doses of phenol at 54 - 64 mg/kg body weight resulted in death for all animals while administration of phenol at doses of 37-83 mg/kg in 3 fasted dogs produced no fatalities. A seventh dog given 300 mg of camphor alone also survived. In a separate experiment using 14 dogs fasted for 24 hours and given a dose of 20 mg of morphine

sulfate, 10 of 11 dogs died when given phenol at doses from 3 to 8 g/kg while 2 of 3 dogs survived when given doses from 1 to 2 g/kg. Haskell et al [166] administered oral doses of liquified phenol at 320-420 mg/kg to healthy adult dogs. The dogs were fasted for the immediately previous 24 hours, but were allowed free access to water. Prior to phenol administration, each dog was given a subcutaneous injection of morphine sulfate. Two dogs survived, and the remaining dogs died in 1-6 days.

Oehme and Davis [167] observed neuromuscular irritability, coma, and convulsions (but no deaths) as toxic effects of phenol given orally at 100 mg/kg to dogs, goats, and pigs. They also reported frequent intravascular hemolysis and darkened urine containing protein, hemoglobin, and bilirubin. The authors considered these findings indicative of kidney damage.

Chassevant and Garnier [168] gave intraperitoneal injections of phenol to 6 guinea pigs at doses of 30-300 mg/kg using a 10% aqueous solution of the sodium salt of phenol. The average dose was 170 mg/kg. At high doses, the guinea pigs died in a few hours but, at low doses, deaths occurred in 1-5 days. A few minutes after injection, there was usually a crisis which began with a generalized shaking that developed into broader movements until the animal could no longer stand. This was followed by a complete muscular atonia. Hypothermia was a constant observation. Autopsies performed immediately after death revealed intense congestion of the visceral and parietal peritoneum, the abdominal viscera, and particularly of the kidneys and adrenals. In another series of experiments, 5 guinea pigs were given intraperitoneal injections of phenol at doses of from 200 to 1000 mg/kg using 10% phenol solution in olive oil. While 2 of the 5 animals survived, the physiologic responses of the guinea

pigs to phenol and the pathologic findings were similar to those for the sodium salt of phenol. [168]

Cosgrove and Hubbard [171] conducted experiments to determine the effects of phenol on the eyes of rabbits and to test the efficacy of decontamination techniques. One drop of phenol at either 87%, 50%, 20%, or 10% in glycerin was applied to the eyes of rabbits. The eyes were completely destroyed by 1 drop of 87% phenol, and applications of one drop of the more dilute solutions of phenol produced similar destructive effects. When the eyes of the test animals were irrigated immediately with either water or 4% sodium sulfate, there was no damage. Immediate irrigations with 25% ethanol in water resulted in some slight permanent opacities. If irrigation with water was delayed for 10 seconds or longer after application, corneas became opaque in 40% of the animals treated with 87% phenol. However, 70% of the animals developed opacities when treated with 50% phenol followed by delayed irrigation. The authors also reported that animals treated with either 20% or 10% phenol had responses similar to those of the animals treated with 50% phenol, but this observation of more opacities produced by weaker solutions was not further explained. Delayed irrigations with 4% sodium sulfate were less effective than water in preventing opacities.

Experiments to establish a range of toxicity were carried out on the rabbit using a variety of oral doses of phenol in water. [173] The studies indicated that there was no difference in the toxicity of phenol when the same amount was administered in either a concentrated or a dilute solution. Administration of phenol at a dose of 620 mg/kg caused death in all rabbits tested. An intraperitoneal (ip) LD50 of 620 mg/kg was found

for rabbits injected with 5% aqueous solutions of phenol, and the intravenous (iv) LD50 for rabbits was approximately 180 mg/kg. [173] In other experiments, the abdominal skin of rabbits was exposed for one hour to aqueous phenol solutions or emulsions under a latex covering. [173] Blood phenol concentrations were determined after exposure using the diazotized p-nitroaniline method of Deichmann and Schafer. [138] The concentration of phenol in blood did not show a proportional increase relative to the amount of phenol contained in the exposure solutions, and phenol concentrations in blood were 1.1-5.2 mg/100 ml using 7% phenol, 1.2-5.1 mg/100 ml using a 75% emulsion of phenol, and 2.2-6.0 mg/100 ml using a 95% emulsion of phenol. In a range-finding experiment, [170] rabbits were clipped of body hair, and the skin of individual rabbits was exposed to phenol at single doses ranging from 10 to 6,400 mg/kg using 1.0, 5.0, or 20% solutions of phenol applied under an impervious cuff and allowed to remain for 24 hours. Large doses involved application of from 70 to 100 ml of solution to each rabbit under the cuff which covered the entire portion of the body between the appendages. Three rabbits receiving doses of 1,600, 3,200, or 6,400 mg/kg of phenol died within two hours of application. Rabbits exposed to phenol at 10 to 800 mg/kg survived.

Deichmann and Witherup [163] conducted experiments on rats, rabbits, and cats to determine the acute effects of phenol. Equal numbers of males and females were used in the individual experiments. The 100% lethal dose for cats given subcutaneous injections of a 10% phenol solution in olive oil was 80 mg/kg. In experiments using rats to determine differences in susceptibility to phenol as a function of age, 10-day-old rats were more susceptible to phenol administered either cutaneously or by ingestion when

compared to 5-week-old or to adult rats. Cutaneous applications of 3,000 mg phenol/kg were lethal to 9 of 20 (45%) adult rats, to 5 of 20 (25%) 5-week-old rats, and to 13 of 20 (65%) 10-day-old rats. Oral administrations of 600 mg phenol/kg were lethal to 12 of 20 (60%) adult rats, to 9 of 30 (30%) 5-week-old rats, and to 18 of 20 (90%) 10-day-old rats. An LD50 for adult rats given 10% phenol in olive oil was found to be 1,500 mg/kg. In several experiments with rabbits, the effects of phenol either by oral intubation, injection into the stomach through the abdominal wall, intravenous injection, or by skin contact were investigated. Oral doses of phenol ranged from 280 to 940 mg/kg as either melted crystals or as solutions containing from 2 to 90% phenol. There was little difference in the toxicity of either dilute or concentrated solutions when administered in similar amounts orally. Lethal effects were generally produced by phenol at a dose of 620 mg/kg and occasionally by phenol at a dose of 420 mg/kg.

Ernst et al [164] dipped the tails of 10 rats in a 4.75% phenol-camphor-liquid petrolatum solution 1 hour/day for 30 of 42 days. Tails were washed and dried after each exposure. Another group of 10 rats was similarly exposed to water. Both groups showed occasional mild hyperemia, which was less noticeable in controls. No other significant difference between the two groups was observed.

Deichmann and Witherup [163] exposed four rabbits to 4.75% phenol-camphor-petrolatum solutions (250 mg/kg) for 5 hours/day, 5 days/week, for 18 days. Two of the rabbits were wrapped in bandages. After each 5-hour period the bandages were removed, and all rabbits were washed with soap and water. A mild hyperemia developed but disappeared after washing. Mild

tremors occurred during the 18-day period. In a continuation of the experiments, 24 rabbits were divided into 6 groups of 4 each and exposed to aqueous solutions containing phenol at 1.18, 2.37, 3.56, 4.75, 5.93, and 7.12% concentrations. These exposures were equivalent to doses of phenol at 64, 130, 190, 250, 320, and 380 mg/kg, respectively. Two of the four rabbits in each of the groups exposed to the four lowest concentrations were bandaged, while no bandages were used in the two highest exposure groups. Rabbits exposed to 1.18% phenol showed no signs of irritation or of systemic effect. The group exposed to 2.37% showed no signs of skin irritation, but occasional mild tremors were observed. Those rabbits exposed to 3.56% and 4.75% phenol had hyperemia and mild tremors which developed one hour after the start of each exposure for all animals in the group. Hyperkeratosis was observed in one of the four animals in the 4.75% group. Those animals exposed to the two higher concentrations of 5.93 and 7.12% phenol had local tissue necrosis and severe tremors. One of the four exposed to 7.12% phenol died after the sixth application.

In 1950, Deichmann et al [169] found that approximately 50% of the rats whose tails were dipped in 6.6% aqueous phenol solutions for 8 hours died; 2.75% phenol in aromatic liquid petrolatum and 12.5% phenol with 10.86% camphor in aromatized liquid petrolatum produced similar results. They also found that tails dipped in 1.78% phenol in liquid petrolatum or in 4.15% aqueous phenol for 8 hours became gangrenous.

In 1970, Conning and Hayes [172] determined the LD50 to be 0.625 ml/kg (670 mg/kg) for percutaneous exposure of rats to liquified phenol (melted at 40 C) by both occlusive and nonocclusive techniques (shorn back). Severe muscle tremors with twitching developed into generalized

convulsions with subsequent loss of consciousness and prostration 5-10 minutes after administration of the dose in all animals. Severe hemoglobinuria developed 45-90 minutes after the application with severity increasing as a function of the administered dose. In addition, all animals developed skin lesions and edema with subsequent tissue necrosis and discoloration. Pathologic examinations revealed evidence of severe kidney damage in all animals. The lowest dose applied was 0.1 ml/kg.

(b) Chronic Exposure

Various investigators have conducted experiments to determine effects produced in animals by chronic exposure to phenol by inhalation, [17,28,174] ingestion, [173] or skin contact. [175-179] Data from these experiments are presented in Tables XII-13-18.

(1) Inhalation

In 1944, Deichmann et al [174] exposed 12 guinea pigs, 6 rabbits, and 15 rats to phenol vapor at concentrations ranging from 100 to 200 mg/cu m (26-52 ppm) for 7 hours/day, 5 days/week. No control animals were used. All animals were exposed in a single 600-liter chamber with phenol vapor generated from 2 gas-washing bottles containing a phenol solution and immersed in an oil-coated, constant-temperature water bath maintained at 25 C. Airborne phenol concentrations were estimated by analysis of grab samples using a colorimetric diazotization procedure. After 20 exposures over a period of 28 days, 5 guinea pigs died and the remaining 7 were killed on the 29th day. Prior to termination of the exposures, some animals showed weight loss, respiratory difficulty, and signs of paralysis. At autopsy, pathologic examinations revealed evidence of extensive necrosis of the myocardium, acute lobular pneumonia, vascular

damage, and hepatic and renal damage. Analysis of blood at autopsy by the method of Deichmann and Schafer [138] showed average free phenol concentrations of 1.0 mg/100 ml, average conjugated phenol concentration of 0.4 mg/100 ml, and average total phenol concentration of 1.4 mg/100 ml.

In a continuation of the inhalation experiments, [174] 6 rabbits exposed 63 times in 88 days did not show signs of distress. After 27 exposures (37 days), average blood concentrations were 0.5 mg free phenol/100 ml, 0.7 mg conjugated phenol/100 ml, and 1.2 mg total phenol/100 ml. When the animals were killed at 88 days, blood phenol analyses were essentially unchanged. Microscopic examinations revealed evidence of lobular pneumonia, chronic purulent bronchitis, degenerative changes in pulmonary blood vessels, myocardial degeneration, and indications of liver and kidney damage. In general, damage was less severe than that found in the guinea pigs.

Rats exposed 53 times in 74 days showed no signs of distress and upon autopsy revealed no evidence of adverse effects. No blood analyses were reported for rats. [174]

In 1961, Sandage [180] exposed 10 monkeys, 50 rats, and 100 mice to phenol at 5 ppm (19 mg/cu m), 8 hours/day, 5 days/week, for 90 days. An equal number of animals of each species, housed in identical chambers, served as controls. Phenol vapor was introduced using sintered glass gas washing bottles maintained at elevated temperature. Phenol vapor air streams were reduced in temperature, and the air saturated with phenol was introduced into the chambers by mixing with fresh air. Phenol concentrations were determined by absorbing the phenol from 2 liters of air in 20 ml of 0.1 N NaOH and analyzing this solution colorimetrically with

diazotized p-nitroaniline and sodium carbonate. Periodically hematology tests, urinalysis, blood chemistry measurements, kidney function tests, stress tests, and measurements of body weight were performed. Pathologic examinations upon autopsy at the termination of exposure showed no differences between exposed and control animals (with 95% confidence) with the exception of a slight weight gain in exposed rats and monkeys and an increased stress test endurance for exposed mice.

(2) Reproduction and Growth

Heller and Pursell [173] reported the results of controlled oral exposures to phenol, in which 10 groups of rats were allowed 0, 100, 500, 1,000, 3,000, 5,000, 7,000, 8,000, 10,000, and 12,000 ppm phenol in their drinking water. For the groups allowed water containing from 0 to 8,000 ppm phenol, volumes of water consumed were noted and food was analyzed for phenol content. Phenol from food represented a significant fraction of dietary phenol intake, especially in the lower exposure groups. Growth, fecundity, and general condition were noted for 5 generations of rats in the groups receiving 100, 500, and 1,000 ppm phenol, for 3 generations in the 3,000- and 5,000-ppm groups, for 2 generations in the 7,000- and 8,000-ppm groups, and for 1 year in the 10,000- and 12,000-ppm groups. All observations were within normal limits in the groups allowed 5,000 ppm or less. The growth of young from the group allowed 7,000 ppm in water was stunted. At concentrations of 8,000 ppm and above, mothers did not provide the ordinary care for their young, and many of the young died. At 10,000 ppm, the offspring died at birth. At 12,000 ppm, there was no reproduction and, in the summer, the older rats allowed 10,000 or 12,000 ppm died sooner than did controls.

Mukhitov [17] exposed 3 groups of 15 rats continuously for 61 days to phenol vapor at approximately 0.011 mg/cu m (0.003 ppm), 0.11 mg/cu m (0.03 ppm), and 5.2 mg/cu m (1.4 ppm), respectively. A fourth group of 15 rats served as controls. Animals were exposed dynamically in 100-liter chambers. The air was sampled once or twice each day. The general condition and the weight of the animals were determined daily, and motor chronaxy, urinary coproporphyrins, and whole blood cholinesterase activities were measured periodically. Animals exposed to phenol at 0.011 mg/cu m were of good general health and their condition was indistinguishable from controls in all categories. Rats exposed to phenol at 0.11 mg/cu m (0.03 ppm) were also in excellent health, but exhibited a slightly shorter extensor muscle chronaxy ($p < 0.01$) and an increase in whole blood cholinesterase activities in comparison with controls. Rats exposed to 5.2 mg phenol/cu m were more sluggish than controls and showed a lower rate of weight gain ($p < 0.05$), had a shortened extensor and lengthened flexor muscle chronaxy ($p < 0.01$), and showed increased whole blood cholinesterase activities ($p < 0.01$).

(3) Skin Cancer

Salaman and Glendenning [175] performed experiments to test the effect of phenol as a sclerosing agent on the production of skin tumors in 4 groups of 20 male mice using "S" strain albinos. Two groups were pretreated by application to the whole back of 0.2 ml of 0.15% 9,10-dimethyl-1,2-benzathracene (DMBA) in acetone. Three weeks after the DMBA application, one of the pretreated groups and one untreated control group were treated with 0.1 ml of 5% phenol in acetone at two alternating sites on the lower back once a week for 32 weeks. The second group receiving

DMBA pretreatment was treated with 0.025 ml of 20% phenol in acetone at four sites on the back in rotation once a week for 24 weeks while a control group was treated with 20% phenol in a similar manner for 32 weeks. All mice were inoculated on the tails with sheep lymph vaccine as a precaution against ectromelia. The hair from the back was clipped before treatment and at intervals when necessary. Throughout treatment, 20% phenol in acetone continued to produce local ulcerations in both the test and the control groups. The ulcerations required almost the entire 4 weeks to heal before the next application scheduled for the site. Tumors began to appear in the group treated with DMBA after 8 applications of 20% phenol in acetone while tumors appeared in the control group after 24 applications of 20% phenol. No tumors developed in the group exposed only to 5% phenol in acetone. The group pretreated with DMBA and exposed to 5% phenol in acetone developed 13 tumors after 13 weeks, and there were 9 tumors on 4 mice out of 14 surviving after 45 weeks. Tumor yields and the experimental conditions are summarized in Table XII-15. The authors [175] concluded that, under the conditions of these experiments, a solution of 20% phenol in acetone produced skin ulcerations and had a strong promoting action on tumor development and a weak carcinogenic action. A solution of 5% phenol in acetone was found to have a moderate promoting action, but no carcinogenic action. No unexposed controls, no controls with DMBA alone, and no controls for application of acetone were reported.

Boutwell and Bosch [176] conducted experiments with one group of albino male mice of the Sutter strain and several groups of albino female mice of the Sutter, Holtzman, CAF1, and CH3 strains to evaluate the skin tumor-promoting potential of phenol following a single application of 9,10-

dimethyl-1,2-benzanthracene (DMBA). Sutter strain mice were selectively bred for three generations for susceptibility to development of tumors after a single application of DMBA followed by croton oil. [181] Benzene solutions of phenol or DMBA were applied to the backs of mice by test group as indicated in Table XII-16, and tumor yields were noted for periods of up to 52 weeks. DMBA was applied in a single application of 75 μg (0.025 ml of a 0.3% solution in benzene) one week prior to initiation of treatments with phenol. For DMBA applications, the fur was shaved from the test area of the back. Because of the possibility of mechanical irritation and damage to papillomas, the mice were not shaved after initiation of phenol exposures. Phenol was applied at concentrations of 5% or 10% in benzene 2 times/week while one group received only DMBA with no subsequent treatment with phenol or benzene and a second group received DMBA pretreatment followed by 0.025 ml of benzene 2 times/week for 20 weeks.

One group receiving treatment with 10% phenol in benzene 2 times/week for 52 weeks did not receive pretreatment with DMBA. Repeated application of 10% phenol in benzene following pretreatment with DMBA caused benign tumors to appear rapidly and in large numbers while carcinomas appeared late. Phenol alone was capable of inducing tumors in females of the DMBA/croton oil-tumor-susceptible Sutter mice, and in female mice of the Holtzman strain. Using female mice of the DMBA/croton-oil-tumor susceptible Sutter strain, Boutwell and Bosch [176] conducted additional experiments in which a single application of 75 μg of DMBA in 0.025 ml of a 0.3% solution in acetone was used as an inititator for tumor formation, and phenol was applied 2 times/week in concentrations from 5% to 20% in various solvents including acetone, 30% ethanol in acetone, benzene, and dioxane.

Tumor yields, survival, duration of observations, and treatment conditions are given in Table XII-17. Tumor yields increased with increasing phenol content of solvents and total amounts of phenol applied. Tumor yields were zero for acetone, benzene, or 30% ethanol in acetone solvent controls using mice pretreated with a single application of DMBA and observed over a 12-week period

Wynder and Hoffmann [177] conducted experiments to compare the tumor promoting action of phenol and phenol derivatives identified in tobacco smoke. The phenol used in their initial test was especially prepared and "chemically pure" while in later experiments, phenol was purified by distillation over zinc dust. Reagent grade acetone was used as a solvent for the administration of either phenol, 3,4-benzo[a]pyrene (BaP), or DMBA. Six-week-old Swiss Millerton mice were used in seven experiments in which acetone containing phenol at either 5% or 10% concentration was applied 2 or 3 times/week to the backs of animals which had been treated with a single application of DMBA one week prior to the start of the phenol tests. The dorsal hairs of the mice were shaved before the single DMBA application.

In other experiments, [176] about 5 μg of BaP at a concentration of 0.005% in acetone was applied 3 times/ week to the backs of 6-week-old-Swiss Millerton mice. On alternate days, 5% phenol in acetone was applied to one group 2 times/week, and 10% phenol in acetone was applied to a second group 2 times/week. No phenol or acetone was applied to a third group maintained as a BaP-exposed control. The dorsal hair of these mice was not shaved to avoid any additional skin irritation. Tumor yields and conditions for these experiments are presented in Table XII-18. With a

single application of DMBA, exposure to phenol increased the yield of tumors and caused an earlier onset of tumors. In addition, tumor yield was greater and tumor onset was earlier for each of the 2 DMBA-exposed groups receiving 10% phenol when compared to a DMBA-exposed group receiving applications of 5% phenol. Applications of phenol caused earlier onset of tumors compared to time of onset in the control group exposed to BaP alone.

Van Duuren et al [178] treated the shaved dorsal skin of 20 female ICR/Ha Swiss mice with 0.3 mg phenol in 0.1 ml acetone 3 times/week for 1 year beginning 4 days after pretreatment with a single application of 150 μg DMBA in 0.1 ml of acetone. Twenty female ICR/Ha Swiss mice serving as controls were subjected to a single application of 150 μg DMBA. Four of the phenol-exposed mice (20%) developed papillomas during the year with observation of the first papilloma after 167 days of exposure. One animal developed a squamous carcinoma after 355 days of exposure. The DMBA controls had two (10%) papillomas, with observation of the first papilloma after 247 days and one carcinoma (5%) observed after 373 days. Results and conditions of these experiments are presented in Table XII-18.

Van Duuren et al [179] reported an additional experiment in which 3 mg of phenol in 0.1 ml acetone and 5 μg of 3.4-benzo(a)pyrene in 0.1 ml acetone were applied 3 times/week over a 460-day period to the backs of female ICR/Ha Swiss mice. When compared to a control group receiving only BaP in acetone, the phenol treatment produced fewer tumors. Tumor yields and conditions for this experiment are also presented in Table XII-18.

(c) Metabolism

Once phenol enters the body, it may be rapidly eliminated in the urine [167,173,182-192] as the conjugated phenylglucuronide [167,173,182-

192] or phenylsulfuric acid products. [167,182,183,187-192] It may also be oxidized to catechols [191], quinones, [191] and carbon dioxide and water, [182,185] or excreted unchanged in the urine, [167,182,183,185,189,190,192] feces, [173,183,193] or exhaled air. [183] Conjugation occurs primarily in the liver, [183,184,190, 191,193-195] but it also occurs in the intestine, [184,193,195] kidneys, [194, 195] spleen, [195] pancreas, [193] and extracellular fluid. [184,193] Oxidation to catechols and quinones occurs primarily in the liver. [191] Deichmann and Keplinger [196] presented two figures (see Figures XII-1 and XII-2) which combine the findings of Deichmann [183] and Parke and Williams [191] to show the respective fates of sublethal and lethal oral doses of phenol in the rabbit.

The extent and nature of the conjugation of phenol have been shown to be functions of diet, [173,184,189,194,197] dose, [183,187], route of entry, [184] degree of animal fatigue, [198] and body temperature. [199] The metabolism of tyrosine [173,184,189,193,197] or metabolism of salicylic acid [160,192] can result in significant endogenous production of phenol. Williams [187] has stated that the extent of conjugation to phenylsulfuric acid decreases rapidly with increasing dose, and he expressed the opinion that the formation of phenylsulfuric acid was largely a function of available sulfate. [187]

In general, signs of intoxication appear only after absorption of phenol in amounts sufficient to overwhelm the capacity of the body to detoxify or otherwise eliminate phenol. The precise dosage at which adverse effects begin to occur is uncertain. Excessive doses of phenol in animals have been shown to depress the vasomotor centers of the brain,

[164,167,172,200,201] producing, in some studies, motor disturbances and blood pressure changes of sufficient magnitude to induce cardiac arrest, respiratory failure, [167,172,185, 190,192] and coma followed by death. [162,163,165,166,169,170,172]

Correlation of Exposure and Effect

Solutions of phenol were shown (see Table XII-6) to rapidly penetrate human skin. [81,86,96,111,202,203] Skin contact by humans with solutions, emulsions, or pure preparations containing 80-100% phenol for as little as 5-20 minutes (see Table XII-6) resulted in death. [96,115,202,204] Exposure of eczematous skin to a phenol solution as dilute as 2.5% caused coma in 3 minutes. [111] Contact with a 43.5% phenol solution for a period of less than 1 minute produced shock despite repeated 30-minute irrigations with copious amounts of water followed by swabbing with ethanol. [81] Seventeen daily dermal applications of a 1% phenol solution resulted in coma in an 82-year-old woman. [128] Exposure of skin contact areas as small as a portion of a thumb for 30 minutes caused gangrene, [79] while contact of "pure carbolic" with a portion of the scalp and cheek caused death in 5-10 minutes. [204] Thus, repeated contact with dilute phenol solutions or even brief contact with concentrated phenol solutions posed a hazard to life, even if the contact area was relatively small.

Chronic skin contact with 5% phenol in oil was reported to have caused acquired ochronosis [58-61] over periods of 3-30 years, [58,59] and death after a period of 12 years. [60] In addition, Stevens and Callaway [89] reported a single case of an invasive squamous cell epithelioma in a

72-year-old man who had applied a salve of phenol and ergot to his back daily for 20 years.

Reports of occupational exposure and of controlled experiments (see Table XII-6) showed that phenol vapor can enter the human body both by inhalation [17,95,97,98,135,136] and through the intact skin [97] (see Table XII-6), and is rapidly detoxified and eliminated by conjugation [95,97,98] and excreted in the urine. [95,97,98] Conjugation has been associated with the formation of ethereal sulfates [95,98] and glucuronides. [98] Ohtsuji and Ikeda [98] reported that concentrations of conjugated phenol in the urine increased following exposure of humans to phenol from as little as 0.6 mg/ cu m (0.16 ppm) to as much as 12.5 mg/cu m (3.3 ppm) without any significant increase in the concentration of free phenol. Piotrowski [97] conducted experiments on inhalation and skin exposure to phenol vapor separately. He found that humans exposed to phenol at vapor concentrations of 6-20 mg/cu m by inhalation showed increased total urinary phenol. Skin exposure to phenol vapor at 5-25 mg/cu m also caused an increase in total urinary phenol. The increase of urinary phenol was about the same for inhalation as for skin exposure. In both cases, urinary phenol concentration returned to normal within 16 hours after termination of exposure. Denim overalls or other clothing did not hinder the absorption of phenol vapor through the skin. [97] No ill effects were reported from the combined skin and inhalation exposures to phenol at 12.5 mg/cu m (3.3 ppm), [98] from inhalation of phenol at 25 mg/cu m (6.8 ppm) phenol, or from skin exposure to phenol at 20 mg/cu m (5.2 ppm) for up to 8 hours. [97]

Skin absorption from human contact with solid phenol produced tissue destruction and gangrene at the site of contact following 30 minutes of direct contact with the solid. [79]

Cosgrove and Hubbard [171] reported that the eyes of rabbits were completely destroyed by 1 drop of 87% phenol in glycerin. If, however, the eyes were irrigated immediately with water, corneas remained clear. If irrigation of the eyes was delayed 10 seconds or longer after application, corneas were damaged in 40% of the animals tested. One drop of 50% phenol in glycerin left in the eyes 10 seconds or longer before irrigation with water resulted in only 30% of the animals recovering and having transparent corneas within 3 or 5 days. Use of 20% or 10% phenol in glycerin gave similar results. In general, if the eyes of treated animals were irrigated immediately with water or 4% sodium sulfate, all animals had transparent corneas. Using 25% ethanol for immediate irrigation resulted in some slight permanent opacities. Delayed irrigations with 4% sodium sulfate were less effective than water in preventing opacities.

Ingestion of phenol by humans caused abdominal pain and numerous signs and symptoms listed in Table XII-6. Principal effects of ingestion included at least one or more of the following: a burning sensation in the throat [68,69,77,205] followed by abdominal pain, increased irritability, headache, absence of corneal reflexes, collapse, convulsions, [68] coma, and death. [70,75,76] The amounts of phenol required to produce such severe reactions in humans were relatively small, and data in Table XII-9 show that ingestion of as little as 4.8 g of pure phenol caused death in 10 minutes. [205] The ingestion of 4.3 g phenol 3-4 times in a single day caused a burning sensation in the throat, giddiness, cold and profuse

perspiration, a weak pulse, and darkened urine, [56] while by contrast a single ingestion of 1.3 g phenol [206] or 0.96 g phenol taken 3-4 times/day [56] produced no immediate ill effects.

No report was found of acute or chronic human exposure to phenol vapor or aerosol by inhalation. No epidemiologic study of an employee population exposed to phenol by inhalation has been reported.

Phenol can be derived from endogenous as well as exogenous sources, and animal experiments provided a more precise definition of the metabolic fate of phenol. As shown in Figure XII-1, subacute doses of phenol were rapidly eliminated largely by conjugation to phenylsulfuric acid and phenylglucuronic acid, by oxidation to catechols and quinones or to carbon dioxide and water, [182,185] or by excretion as free phenol. [167, 182,183,187,189,190,192] Excretion occurred primarily in the urine [167,173,182-192] with small amounts being excreted in the feces [173,183,193] or in exhaled air. [183] When the functional capacity for detoxification was exceeded, vasomotor centers of the brain could be depressed [164,167,172,200,201] producing alteration of blood pressure [200,207,208] and motor disturbances [164,167,172,200,201] capable of inducing cardiac arrest with respiratory failure [172,185,190,192] followed by death. [162-170,172]

The lowest doses producing death in animals as shown in Table XII-12 were 50-100 mg/kg by oral administration [162] and 20 mg/kg by intravenous injection in the cat, [164] 320 mg/kg by ingestion in the dog, [166] 150 mg/kg by intraperitoneal absorption in the guinea pig, [168] 380 mg/kg by skin absorption in the rabbit, [169] and 420 mg/kg by ingestion in the rabbit. [163] The LD50 for the rat through skin absorption is 670 mg/kg.

[172] Deichmann and Witherup [163] reported the lethal dose for approximately 50% of the animals as 80 mg/kg by subcutaneous injection in the cat, 620 mg/kg by subcutaneous injection or 620 mg/kg by intraperitoneal injection in the rabbit; 340 mg/kg by ingestion in the rat, and as 2.75% phenol in petrolatum applied to the skin of a rat for 1 hour/day for 3 days. The lowest doses of phenol to attack the vasomotor center and produce signs were 4.9 mg/kg by intravenous injection [164] and 1.2 mg/kg by subcutaneous injection in the cat, [164] 700 mg/kg by intravenous injection in the dog, [167] 100 mg/kg by intravenous injection in the goat, [167] 150 mg/kg by intraperitoneal injection in the guinea pig, [168] 100 mg/kg by intravenous injection in the pig, [167] 130 mg/kg by skin contact, [169] 280 mg/kg by ingestion, [163] and 26-52 ppm (100-200 mg/cu m) by inhalation in the rabbit, [174] and 107 mg/kg by skin absorption in the rat. [172]

Inhalation exposures (see Table XII-13) of 26-52 ppm (100-200 mg/cu m) phenol 7 hours/day, 5 days/week, produced 5 (42%) deaths in a group of 12 guinea pigs after 29 exposures. [174] Upon autopsy, pathologic examination revealed necrosis of the myocardium, lobular pneumonia, vascular damage, and hepatic and renal damage. Rabbits similarly exposed 63 times in 88 days showed no signs of illness or discomfort but had lobular pneumonia, chronic bronchitis, vascular damage, myocardial degeneration, liver damage, or kidney damage at post mortem examination. [174] Rats exposed at 26-52 ppm (100-200 mg/cu m) phenol 53 times in a period of 74 days showed no microscopic evidence of adverse effects. [174] No controls, however, were used. Monkeys, mice, and rats were exposed to phenol at 5 ppm for 8 hours/day, 5 days/week, for 90 days without any

adverse effects. None of 15 rats receiving 53 exposures showed any signs of illness or discomfort, and no pathologic findings were reported. [180] In contrast, Mukhitov [17] found a significant ($p < 0.01$) decrease in rate of weight gain for rats exposed to phenol at 1.4 ppm (about 6 mg/cu m). Heller and Pursell [173] found that phenol at 7,000 - 12,000 ppm in drinking water adversely affected growth, fecundity, and general conditions of rats.

Odor thresholds for phenol in air in all persons so tested (see Table XII-7) were found to be 0.091 mg/cu m, [136] 0.178 mg/cu m, [135] and 0.182 mg/cu m. Phenol has warning properties by odor at concentrations far below the concentrations at which toxic effects occur. Mukhitov [17] obtained similar results finding an odor threshold for phenol ranging from 0.022 to 0.184 mg/cu m (0.006-0.048 ppm).

Carcinogenicity, Mutagenicity, and Teratogenicity

Heller and Pursell [173] (see Table XII-14) allowed groups of rats to drink water containing phenol at 0-12,000 ppm. The group allowed phenol at 5,000 ppm in water had no adverse effects over 3 generations. Stunted growth was evident in the young of the group exposed to phenol at 7,000 ppm in water over 2 generations. In the group allowed phenol at 8,000 ppm in water for 2 generations, mothers would not care for their young which then died prematurely. The offspring of the rats allowed phenol at 10,000 ppm in water died at birth. The group allowed phenol at 12,000 ppm in water did not reproduce, and many adults died prematurely in hot weather. This study did not indicate any specific teratogenic properties of phenol.

Salaman and Glendenning, [175] Boutwell and Bosch, [176] Wynder and Hoffmann, [177] and Van Duuren et al [178] showed that phenol promotes skin cancer in mice. In addition, Boutwell and Bosch [176] and Wynder and Hoffmann [177] reported that phenol is a weak skin carcinogen in mice. 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. Conditions of these experiments, [175-179] do not reflect industrial experience with phenol, and the studies were carried out with phenol dissolved in various organic solvents, including benzene, acetone, dioxane, and a mixture of 30% ethanol in acetone. Results of these mice studies suggest that phenol functions primarily as a nonspecific irritant and may be capable of promoting tumors. There is no evidence that phenol acts as a specific carcinogen or as a mutagen, particularly at low concentrations within normal physiologic limits.