## III. BIOLOGIC EFFECTS OF EXPOSURE

### Extent of Exposure

The cresol isomers ($CH_3C_6H_4OH$) are monomethyl derivatives of phenol (or hydroxy derivatives of toluene) that have the methyl group ortho, meta, or para to the hydroxyl group. The three isomers can occur alone or in various mixtures, either with each other or with other compounds. A mixture containing all three isomers is often referred to as tricresol and has a boiling range between 191 and 203 C. Commercial cresylic acids usually contain cresol in combination with phenol and xylenols and are generally defined as mixtures in which 50% of the material boils above 204 C. The cresol isomers are usually the major components of cresylic acids. Some important chemical and physical properties of cresol are listed in Table XI-1 [1-7]. Although some of these properties differ among the isomers, the oil/water partition coefficients suggest that their biologic distribution may be similar.

Most nonsynthetic cresol used in industry is derived from petroleum or coal tar acids. Petroleum-based cresol is a byproduct of the naphtha-cracking process and is present in the spent caustic liquor used to wash petroleum distillate [8]. Coal tar acids are obtained from coke oven byproducts, gas-retort oven tars, and distilled tar byproducts [8]. The initial fractionation of petroleum or coal tar acids yields a phenolic mixture composed mainly of cresol, phenol, and xylenols. Pure o-cresol can be obtained by further distillation of this mixture, but because of their similar boiling points, the meta and para isomers of cresol must be

separated by other methods. Generally, these two isomers are used industrially as a mixture containing 40-65% m-cresol. Only small amounts of pure natural meta and para isomers are produced. There also are several methods of synthesizing the cresol isomers, particularly p-cresol. The catalyzed methylation of phenol is one of the methods used most often.

It is estimated that 151 million pounds of cresol and cresylic acids were produced in the United States in 1975, down 21% from 1974 [8]. The consumption of synthetic cresol varies to some extent from that of the natural products. Industry sources [8] estimated that, in 1975, 28% of natural cresol was used for production of wire enamel solvents, 20% for phosphate esters, 18% for phenolic resins, 6% for agricultural chemicals, 3% for disinfectants, 3% for ore flotation, 10% for miscellaneous purposes, and 12% for export. In 1969, 29% of synthetic cresol was consumed for phenolic resins, 26% for tricresyl phosphate, 11% for disinfectants, 17% for antioxidants and automotive products, 7% for ore flotation, and 10% for other purposes [8]. A major use of o-cresol is in the manufacture of the herbicides dinitro-o-cresol (DNOC) and 2-methyl-4-chlorophenoxyacetic acid (MCPA) [8]. p-Cresol is used largely to produce the antioxidant 2,6-di-tert-butyl-p-cresol (BHT), which is added to plastics and to food [8]. Cresylic acids and m,p-cresol mixtures are used to make phenolic resins, tricresyl phosphate, and cresyl diphenyl phosphate, the latter two used mainly as plasticizers [8]. Some minor uses of cresols are in the production of azo dyes and as perfume additives, nylon solvents, metal degreasing agents, and synthetic tanning agents [9].

NIOSH estimates that 11,000 people in the United States are occupationally exposed to cresol. This estimate is low, however, because

it does not include workers who are intermittently exposed to a widely used commercial degreasing agent that contains cresol. Some representative occupations are listed in Table XI-2 [8-10].

## Historical Reports

Historical reports have described the dangers of exposure to cresol by ingestion and skin and eye contact. Such exposures have produced toxic effects on the central nervous system (CNS), lungs, liver, kidneys, pancreas, vascular system, skin, and eyes. Many attempted and successful suicides resulted from the ingestion of Lysol Disinfectant, which was introduced in 1860. It originally contained phenol, but, in 1872, a new Lysol preparation was introduced, which contained cresol (6-50%) as the active ingredient generally in glycerin or saponified linseed oil. Cresol was removed from Lysol preparations in the United States in 1951 and replaced by o-phenylphenol. Several other cresol solutions similar to Lysol, such as Compound Cresol Solution, U.S.P. and Cresol, N.F., are available and contain 15-50% cresol in saponified linseed or other suitable oil.

In 1922, Isaacs [11] described 52 cases of cresol poisoning, 2 of which were fatal. Most of the cases involved attempts at suicide by ingestion of Lysol, which the author reported as containing 25-50% cresol. Individuals had taken between 4 and 120 ml of the cresol preparation. The first signs of intoxication included abdominal pain and cramps, vomiting, and burning sensations of the mouth, throat, esophagus, and epigastrium. In the severe cases, cyanosis, unconsciousness, and respiratory failure

resulted. Body temperature was generally unaffected by cresol, but it was as low as 94.4 F in some individuals and as high as 99-100 F in others. The pulse of some patients became weak and rapid (100-136 beats/minute), but in others it was slow (66-80). Respiratory rates varied from 16 to 52/minute. Some cases involved dermal contact with cresol, which caused chemical burns. In cases where the eyes were exposed to cresol, the eyelids, corneas, and palpebral conjunctivae swelled and became congested.

Burg [12], in 1929, reported the effects of cresol on the lungs of a 24-year-old man who had attempted suicide by drinking 25 ml of Lysol. The man was found unconscious 2 hours later. He survived but developed pneumonia in both lungs, which the author believed was caused by aspirated Lysol that irritated the mucous membranes of the respiratory tract.

Dellal [13] reported in 1931 that a 31-year-old woman had died 4 days after she drank an unknown amount of Lysol. At autopsy, the pancreas showed acute hemorrhagic degeneration. Extensive fatty necrosis was found in the abdominal cavity, especially in the mesentery of the small intestine, and some congestion was present in the kidneys. This was the earliest mention found in the literature of a possible link between cresol and acute pancreatitis.

In 1933, Herwick and Treweek [14] stated that severe facial burns had developed in a 16-year-old girl exposed to Compound Cresol Solution. The girl had been hospitalized for a spinal graft. During anesthesia, she was placed in a prone position with her face resting for 2 hours in a rubber-cushioned mask. Afterward, her face had marked erythema where it had contacted the rubber on the mask. The skin condition worsened, and blistering developed. Disfiguring scars were still evident 1 year later.

One week before the girl was anesthetized, the mask apparently had been left overnight in a 10% solution of Compound Cresol Solution for sterilization.

Vance [15], in 1945, described the case of a 26-year-old woman, 4.5 months pregnant, who had introduced an unknown quantity of Lysol (50% cresol in saponified linseed oil) into her uterus to terminate the pregnancy. She was admitted to the hospital in a state of collapse. She was also cyanotic and semicomatose and had an extremely low blood pressure. Her breathing was rapid and labored, loud moist rales were detected in her lungs, and she was coughing up a bloodstained fluid. The woman died 75 minutes after being hospitalized. From the results of an autopsy, the author attributed death to pulmonary oil embolism and the action of cresol. He thought the latter may have caused erosion of the blood vessels and tissue necrosis that permitted the oil to enter the bloodstream.

Effects on Humans

The effects of cresols on humans in both occupational and nonoccupational situations have been observed after exposure by various routes, including skin and eye contact, inhalation, and ingestion.

(a) Dermal Exposure

Medical data from industrial plants where cresols are manufactured indicate that skin and eye contact are the major concerns in occupational exposure to cresols and are the cause of most worker injuries related to cresols [16(p 3)]. Effects recorded in the medical departments of these companies included skin and eye burns and irritation, dermatitis, and

conjunctivitis. One manufacturer reported 13 cases of chemical burns from exposure to cresols during 1970-1976 that required employees to miss one or more days of work. A company involved in the synthesis of p-cresol had 11 cases of burns from skin and eye contact in 1976. Maintenance workers and those involved in collecting cresol samples for analysis were at the greatest risk of exposure. The signs and symptoms related to skin contact with cresols were a burning sensation, erythema, localized anesthesia, and a brown discoloration of the skin. Although overt effects were reported, micro biochemical changes were not assessed.

The only report found in the published literature of a death from occupational exposure to cresols was one published by Cason [17] in 1959. It involved a 47-year-old male worker who fell into a vat of "ardrox," which the author called a derivative of cresylic acid. His clothing was removed immediately, and he was washed thoroughly before being taken to a hospital. He suffered burns on 15% of his body. Anuria developed 36 hours after the accident, and his blood urea nitrogen and potassium levels were elevated. On the 7th day, the man developed generalized rhonchi in both of his lungs, a pericardial rub, and precordial pain. He became comatose, developed congestive heart failure on the 10th day, and died 18 hours after becoming unconscious. No autopsy was performed.

In 1945, Klinger and Norton [18] described a case involving a one-time occupational exposure of a 41-year-old man who cleaned torpedo gear trains with a solvent containing 30% cresylic acid, 45% vegetable oil, and 25% water. The solution was diluted fivefold before use. The man worked for 5-6 hours with his unprotected hands and wrists immersed in the solvent most of the time. Later, the skin of his hands became dry and stiff, and

his right eye became watery. On the next day, the skin of his hands began to crack and peel, and the right side of his face and the area around the right ear became painful; his symptoms worsened, and he was hospitalized. The examining physician observed paralysis on the right side of the face, eversion and drooping of the right lower eyelid, sagging of the right corner of the mouth and elevation of the left corner, lacrimation of the right eye, and impaired speech. The skin of the hands and wrists was still dry and peeling, and the underlying tissue was erythematous. The patient's condition was diagnosed as facial peripheral neuritis. Results from red, white, and differential blood cell counts, a hemoglobin determination, and a urinalysis all were normal. The patient was treated with ointments applied to the hands and wrists and with "anti-neuritic vitamins" for the facial neuritis. The authors reported that the prognosis was good.

Goodman [19] reported, in 1933, the effects of skin contact with cresols on silkmill employees. A 21-year-old man developed reddened, ulcerated areas on the fingers of both hands. The redness had been present for 4 of the 8 months he had worked in the mill. Through a series of patch tests, the author concluded that the dermatitis was caused by contact with an antimildew solution that contained the cresol isomers and cresylic acid. After further investigation, nine other workers were identified with dermatitis caused by contact with the antimildew solution.

Zalecki [20] examined employees of several factories in Poland to determine the prevalence of occupational skin disorders. Some of the workers had been exposed to cresol in a cable plant, a rubber plant, and several plants manufacturing synthetic chemicals. Dermatitis, observed most often, was present in 0.75 and 1.3% of the workers in the cable and

rubber plants, respectively. Since many other chemicals were used in these factories, dermatitis could not be attributed specifically to cresol exposure. In a plastics plant, 6 of 30 people examined had dermatitis that was localized on the hands. During the summer months, dermatitis also developed on the face of an unspecified number of workers. The author attributed the dermatitis chiefly to exposure to cresol and phenol.

Nonoccupational dermal exposure to cresol has also resulted in injury and death. In 1975, Green [21] described the case of a male infant who had about 20 ml of a 90% cresol solution in water accidentally poured over his head. Within 5 minutes, the baby was unconscious and cyanotic. He died 4 hours later. Chemical burns were evident on about 7% of his skin. Examination of the internal organs revealed edema, hemorrhagic effusions from the peritoneum, pleura, and pericardium, and congestion in the brain and kidneys. The blood contained 12 mg of cresol/100 ml. Microscopic examination of the tissues revealed destruction of the epidermis with loss of the stratum corneum, extensive centrilobular and midzonal necrosis of the liver, edema of the brain, and signs of early acute tubular necrosis of the kidneys.

These reports of dermal exposures [17-21] show that cresols can produce chemical burns and dermatitis following skin contact. Cresols are rapidly absorbed through the skin and produce effects on the CNS, liver, kidneys, and vascular system.

(b) Inhalation

Because the cresol isomers have low vapor pressures, inhalation of appreciable amounts of their vapors in working environments under normal conditions is unlikely. However, at high process temperatures, vapors can

be produced and may lead to adverse effects upon inhalation. In addition, inhalation of particulate cresol as an aerosol is possible.

In 1939, Corcos [22] presented a study of 34 French workers who were involved in the manufacture of synthetic resins used to produce automobile brake linings. The resins were prepared by combining cresol with formaldehyde in the presence of a condensation agent (ammonia). Because of the high process temperature, cresol vapor was produced and inhaled by the workers. No temperature and vapor concentration data were reported. Seven workers were examined. They were 23-32 years old and had been working for 18 months to 3 years in a plant where resins were prepared in an open tank located in a poorly ventilated room. Blood pressure, Ambard's constant (the ratio of the urea concentration in the blood to that in the urine), and Chvostek's sign (a test for facial muscle spasms, possibly related to blood calcium imbalance) were determined in these workers. During the medical examination, the seven workers complained of headaches that were most severe at the start of the working day and of nausea that was often accompanied by vomiting. Four of the seven workers were hypertensive, as indicated by blood pressure readings of 170/130, 180/120, 170/100, and 160/120. Two of these workers had elevated Ambard's constants, three had marked tremors, and two had positive Chvostek's signs. Radiography showed that the four hypertensive workers also had slightly enlarged hearts, although they were within normal limits.

About 6 months later, after additional ventilation had been installed in the factory, Corcos [22] reexamined these seven workers. Although their arterial pressures had returned to normal and their tremors were less marked, the workers still had digestive disorders, which the author

attributed to continued exposure to cresol vapor because of inadequate ventilation in the plant.

In another study of the same plant, Corcos [22] observed 27 male and female workers (age range not specified) and noted similar but less severe effects than those previously mentioned.

In 1974, NIOSH conducted a Health Hazard Survey of maintenance shop workers exposed to degreasing agents that contained cresol and phenol [23]. Samples taken from the general room air adjacent to the degreaser vats had concentrations of 0.02-10 ppm (0.08-38 mg/cu m), expressed as total phenols. (See Chapter IV for details on environmental data.)

Medical interviews were conducted with several of the shop mechanics at the end of the workday [23]. Questions were directed towards finding whether there were any problems with dermatitis or any effects on the eyes, nose, or throat. One employee complained about the cresol-phenol odor released when the degreaser vat was refilled. No adverse health effects were determined from the interviews. However, the cresol/phenol concentration of 10 ppm (38 mg/cu m), measured as an area sample, was not representative of the true work procedure. Normal procedure required degreaser vats to remain covered. Covers of these vats were removed for the purpose of placing material to be degreased into them and then replaced. The report did not indicate that the workers remained in the area of the degreaser vats for any lengthy period. Thus, the association of the area sample measured as total phenol (38 mg/cu m cresol/phenol) with no health effects is diminished greatly.

Uzhdavini et al [24,25], in two reports that concentrated on the toxicity of cresol in animals (see Animal Toxicity), briefly mentioned the

irritant effects of o-cresol on the nasal mucosa of humans. Ten subjects were exposed to o-cresol vapor at a concentration of 6 mg/cu m (1.4 ppm). Eight individuals had complaints that included dryness and constriction in the nose, irritation of the throat, and an unspecified taste sensation. The authors did not specify the duration of exposure or how the cresol vapor was generated or sampled.

The reports [22-24] on exposure to cresol by inhalation, described above, indicate that cresol vapor has an unpleasant odor, can cause irritation of the upper airways, and may be responsible for nervous system and vascular disturbances.

(c) Other Routes of Exposure

Reports have also described the effects of cresol solutions used in suicide attempts and as abortifacients. In 1956, Presley and Brown [26] presented the cases of four women, 18-35 years old, who had Lysol-induced abortions. When the women were hospitalized because of vaginal bleeding, it was discovered that Lysol, which the authors described as a mixture of 50% cresol and saponified linseed oil, had been introduced into the uterus of each one. One of the women, who reportedly had been given Lysol by her physician 2 days before, had an elevated temperature (104 F), pulse rate (100), and white blood cell count (35,000), a low hemoglobin value (7.5 g%), blood and albumin in her urine, and extensive hemolysis at the time she was hospitalized. The authors stated that the white blood cell count and hemoglobin value were probably inaccurate because of hemolysis. The woman developed abdominal cramps, moist rales in both lungs, hyperpnea, and pulmonary edema and died 12 hours after entering the hospital. Autopsy revealed massive hemolysis in all tissues, especially the liver and

kidneys, acute hemoglobinuric nephrosis, focal necrosis of the liver, and pulmonary oil embolism.

The other three women examined by Presley and Brown [26] survived the abortions. They all had elevated body temperatures and pulse rates. Two had extremely low hematocrits (27% and 11%) and hemoglobin values (7.0 g% and 3.3 g%), while the third had a hematocrit of 34% and a hemoglobin value of 11.1 g%. The white blood cell counts were elevated in two women (14,250 and 24,000) and were not reported for the third.

The most recent case of pancreatic damage from cresol ingestion found in the literature was described by Klimkiewicz et al [27] in 1974. A 49-year-old woman ingested 250 ml of 40% ethyl alcohol and 250 ml of Lysol, which the authors reported contained 50% cresol in potassium soap. She was unconscious when admitted to the hospital and suffered from respiratory disturbance. A medical examination revealed high blood pressure, rapid pulse rate, low hemoglobin concentration, and a low red cell count. Kidney problems, which worsened during the next 3 days, were indicated by the presence of blood in the urine, oliguria with accompanying metabolic acidosis, accumulation of nitrogen metabolites in the blood, and blood electrolyte imbalance. Dialysis was performed, but the patient's condition remained serious. There were also indications (strong stomach pains, no peristaltic sounds) that either the stomach or the intestinal wall had been perforated, but surgery revealed acute inflammation of the pancreas with peritoneal involvement. The woman was treated with diuretics, which gradually relieved the excess nitrogen metabolites, electrolyte imbalance, oliguria, and acidosis. In 3 weeks, the patient's general condition began to improve, although she had developed lobar pneumonia in the left lung.

The authors attributed the kidney malfunction to the direct action of cresol and the pancreatitis to the irritant action of both the cresol and alcohol, including the alcohol that had been consumed prior to the incident. They suggested that these compounds, by directly irritating the mucous lining of the duodenum, constricted the sphincter of the pancreatic and bile ducts and thereby disrupted drainage of pancreatic fluid. The authors attributed the woman's survival, despite pancreatic complications, to the early dialysis, which they thought had quickly reduced the amount of circulating cresol.

The reports [11,12,15,26,27] dealing with the ingestion of Lysol and with its introduction into the uterus demonstrate that it can produce vascular effects, necrosis of the liver and kidneys, and pancreatic involvement. These effects were attributed to the cresol contained in Lysol.

## Epidemiologic Studies

No reports of epidemiologic studies of workers exposed to cresol were found in the literature.

## Animal Toxicity

Animal studies have investigated the local and systemic effects of exposure to cresols by skin contact, by inhalation, and by oral, subcutaneous, and intravenous administration.

(a) Dermal Exposure

In 1941, Campbell [28] described the toxicities of cresol and several cresylic acids derived from petroleum or coal tar. The chemical constituents of the cresylic acids were not specified. In one experiment, groups of two to six rats of unstated sex and age were dermally exposed to various coal tar-derived mixtures or to high-boiling, petroleum-derived cresylic acids. The mixtures and the doses applied are given in Table III-1. Each dose was placed on a 1-sq-cm gauze patch, which was applied to the clipped abdominal skin and covered with adhesive plaster. The patch and plaster were kept in place for 1 hour, and then they were removed and the skin was washed. The survivors received another similarly applied dose the following day and were observed for 1 week.

TABLE III-1

DOSES OF CRESOL SOLUTIONS APPLIED TO RATS

| Solution | Dose* (ml/kg) |
|---|---|
| Coal tar-derived mixtures | |
| (1) Commercial cresylic acid | 1.0 or 2.0 |
| (2) Soluble cresylic disinfectant | 1.0 or 2.25 |
| (3) Commercial soluble cresylic disinfectant | 1.0 or 3.5 |
| (4) Saponified Cresol Solution, U.S.P | 1.0 or 1.7 |
| Petroleum-derived cresylic acids | 1.0 |

*Each rat was given one of the specified amounts once or twice, depending on whether it survived the first application.

Adapted from Campbell [28]

The petroleum-derived cresylic acid mixtures were less toxic than the others [28]. They caused, at most, slight skin discoloration and occasional superficial erosion of the skin. The other four mixtures caused convulsions and death, as well as skin discoloration ranging from a reddish brown to a dark bluish brown. Convulsions, beginning 5-30 minutes after application and lasting up to 4 hours, occurred after two applications of mixtures 1 and 4, after the first application of 2.25 ml/kg of mixtre 2, and after each of two applications of 1 ml/kg of mixtures 2 and 3. Rats that recovered from the convulsions appeared practically normal the next day. Deaths occurred 0.5-2 hours after a single application of 1.0 or 2.0 ml/kg of mixture 1, 1.0 ml/kg of mixture 2, 3.5 ml/kg of mixture 3, and 1.7 ml/kg of mixture 4. Death also followed the second application of 1.0 ml/kg of mixture 2 and the second application of 1.0 ml/kg of mixture 3. The author concluded that coal tar-derived cresols were more irritating to the skin than petroleum-derived cresols.

Uzhdavini et al [25], as part of a study of various cresol and xylenol isomers (see also sections (b) and (c) in Animal Toxicity), reported on the toxicities of these compounds after application to the skin of rats and mice. The three cresol isomers and 2,4-xylenol, which is a liquid isomer, were applied to the skin of rats. The solid xylenol isomers, 2,6-, 3,4-, 3,5-, and 2,5-, were applied to the skin of rats in crystalline form. Also, 2,6-xylenol in a solution of ethyl alcohol was applied to the skin of mice. The LD50 values were 620, 1,100, and 750 mg/kg for o-, m-, and p-cresol, respectively. 2,4-Xylenol had an LD50 of 1,040 mg/kg in rats, while the LD50 for 2,6-xylenol in ethyl alcohol was 920 mg/kg in mice. No deaths resulted from exposure to any of the other

solid xylenol isomers. All of the xylenols were said to have produced necrosis following skin contact.

Back and colleagues [29] determined the LD50 value for a cresol mixture containing the three isomers in unspecified concentrations. The mixture was applied to the skin of female albino New Zealand rabbits weighing about 5 pounds each. Cresol was administered as an undiluted liquid to the clipped back and sides of rabbits and kept in place with a gauze patch covered by latex rubber or vinyl plastic for 24 hours. Mortality was recorded for 14 days. The authors determined that the dermal LD50 was 1,782 mg/kg.

The dermal LD50 values of the three cresol isomers were determined in albino rabbits (sex unspecified) by a commercial laboratory [30]. The undiluted cresol isomers at four dose levels were each applied to groups of five rabbits weighing between 2.3 and 2.7 kg. Each compound was applied to clipped skin, which was covered with a plastic sleeve for 24 hours. The animals were observed for signs of poisoning, including mortality and evidence of dermal irritation, for 14 days. Gross autopsies were performed on all rabbits.

The LD50 values for o-, m-, and p-cresol were 1,380, 2,050, and 301 mg/kg, respectively [30]. It is not known why in this particular study the reported LD50 value for p-cresol was greatly different from the values for o- and m-cresol. This disparity in LD50 values for the isomers was not indicated in other studies [25,30,31]. Rabbits exposed to m-, o-, and p-cresol at concentrations that ranged from 1,000 to 3,160, 681 to 2,150, and 215 to 618 mg/kg, respectively, exhibited signs of skin irritation,

hyperemia, convulsions, tremors, and death. No abnormalities were observed in animals that survived 14 days after exposure.

In 1972, Shelley and Raque [32] reported that topical application of black laundry ink, which they had used to mark experimental groups of mice, produced depigmentation of the hair in these animals. Two years later, Shelley [33] published the results of a study that investigated the various components of the laundry ink to determine which ones were responsible for pigment loss. Female CBA/J agouti mice were exposed, in groups of five, to various compounds, including phenol and o-, m-, and p-cresol, each at a 0.5% concentration in acetone, or to acetone alone. The hair of the lower back of the animals was plucked or clipped, and each compound was applied topically three times/week for 6 weeks as a mist spray from a tuberculin syringe. Thirty black 6-week-old male mice of the C57 BL/6J strain were similarly exposed to p-cresol at a concentration of 0.5% in acetone. All animals were observed for 6 months after the last dose for any changes in hair color.

p-Cresol produced patterned depigmentation in two of five agouti mice in both the plucked and clipped groups [33]. In two other mice in the plucked group, new hair was totally white. Both the plucked and clipped mice showed what the author described as "occult loss of pigment in the hair." The surface color remained and hid the fact that there was pigment loss in 90% of the hair shaft. Only the tip of the new hair contained pigment. This change was still noted 6 months after the last application of p-cresol. Patches of pigment loss were also observed in the C57 BL/6J mice following application of p-cresol. In the C57 BL/6J strain, a local corrosive effect and a depigmentation of the epidermis were also seen after

repeated applications of p-cresol. Phenol was the only other compound tested that produced the "occult" loss of pigment. The effect from phenol, however, was scarcely apparent after 6 months. Neither o- nor m-cresol produced any changes in hair color. The results of the experiment thus indicated to the author that p-cresol was the chemical responsible for producing hair depigmentation after application of the laundry ink.

Boutwell and Bosch [34] reported on the tumor-promoting action of cresol and xylenols in 2- to 3-month-old tumor-susceptible female mice of the Sutter strain. The fur was shaved from the mid-dorsal region of the mice with electric clippers 1 week prior to application of 9,10-dimethyl-1,2-benzanthracene (DMBA). The mice were not shaved again because of the possibility of mechanical irritation and damage to papillomas. Solutions of DMBA, cresol, and xylenol were applied to the backs of mice as indicated in Table III-2. A single application of DMBA in benzene or acetone was given 1 week prior to the start of xylenol or cresol treatment. The cresol and xylenol isomers, as 20% solutions in benzene, were applied twice weekly for 11 and 19 weeks, respectively. Some mice were given m- or p-cresol two times/week for 19 weeks after a single application of DMBA in benzene, and xylenols were applied to some mice twice weekly for 20 weeks with no prior DMBA treatment. Mice were inspected for tumors once a week, and tumor diagnosis was confirmed by microscopic identification. Tumor yields and survival rates for the various groups of mice are given in Table III-2.

Application of each of the three cresol isomers in benzene after treatment with DMBA in benzene or acetone resulted in a large increase in the number of surviving mice with papillomas compared to the number after

TABLE III-2

CARCINOGENESIS PROMOTING EFFECTS OF CRESOL AND XYLENOL IN MICE

| DMBA Solution (25 μl) | Test-agent Solution (25 μl) | Duration (Weeks) | No. of Survivors/ Original | Percent Survivors with Pa* | Average Pa/ Survivor | Percent Survivors with Ca* |
|---|---|---|---|---|---|---|
| 0.3% in acetone | None (benzene control) | 12 | 12/12 | 0 | 0 | 0 |
| " | 20% o-cresol in benzene | 12 | 17/27 | 59 | 1.35 | 0 |
| " | 20% m-cresol in benzene | 12 | 14/29 | 50 | 0.93 | 0 |
| " | 20% p-cresol in benzene | 12 | 20/28 | 35 | 0.55 | 0 |
| 0.3% in benzene | None (benzene control) | 20 | 18/20 | 0 | 0 | 0 |
| " | 5.7% m-cresol in benzene | 20 | 17/20 | 24 | 0.24 | 0 |
| " | 5.7% p-cresol in benzene | 20 | 14/20 | 29 | 0.36 | 0 |
| " | None (control) | 15 | 16/20 | 13 | 0.13 | 0 (6 at 53 wk) |
| " | 20% 2,4-xylenol in benzene | 15 | 28/30 | 50 | 1.21 | 11 (18 at 23 wk) |
| " | 20% 2,6-xylenol in benzene | 15 | 27/30 | 30 | 0.44 | 4 (11 at 23 wk) |
| " | 20% 3,4-xylenol in benzene | 15 | 21/30 | 95 | 2.66 | 0 (14 at 23 wk) |

TABLE III-2 (CONTINUED)

CARCINOGENESIS PROMOTING EFFECTS OF CRESOL AND XYLENOL IN MICE

| DMBA Solution (25 μl) | Test-agent Solution (25 μl) | Duration (Weeks) | No. of Survivors/ Original | Percent Survivors with Pa* | Average Pa/ Survivor | Percent Survivors with Ca* |
|---|---|---|---|---|---|---|
| 0.3% in benzene | 20% 3,5-xylenol in benzene | 15 | 20/30 | 40 | 0.90 | 0 (5 at 23 wk) |
| None | 10% 2,4-xylenol in benzene | 20 | 26/29 | 31 | 0.66 | 0 (12 at 28 wk) |
| " | 10% 2,5-xylenol in benzene | 20 | 25/30 | 24 | 0.40 | 0 (8 at 28 wk) |
| " | 10% 2,6-xylenol in benzene | 20 | 26/30 | 8 | 0.15 | 0 |
| " | 10% 3,4-xylenol in benzene | 20 | 28/29 | 50 | 0.71 | 4 (14 at 28 wk) |
| " | 10% 3,5-xylenol in benzene | 20 | 22/30 | 55 | 0.91 | 5 (14 at 28 wk) |

*Pa=papilloma; Ca=Carcinoma

Adapted from Boutwell and Bosch [34]

application of only DMBA in benzene or acetone, but there were no carcinomas due to cresol [34]. Application of the xylenols in benzene after DMBA produced a higher incidence of papillomas and carcinomas than treatment with just DMBA in benzene. When the xylenols in benzene were given with no prior DMBA treatment, both papillomas and carcinomas

developed. Although benzene alone was not evaluated, no tumors were produced when benzene was given after initial application of DMBA. This would indicate that the xylenols, not benzene, produced tumors in the test mice. Cresol alone was not tested.

(b) Inhalation

Campbell [28] exposed an unstated number of white mice to an atmosphere saturated with cresylic acid vapors either for one 5-hour period or for 1 hour/day for 10 consecutive days. The age and sex of the mice, the concentration of the vapor mixture, and the way the vapors were generated were not specified. The mice were exposed either to a coal tar-derived or to one of five different petroleum-derived cresylic acids. The single 5-hour exposures resulted in no deaths. However, exposures to three of the petroleum-derived cresylic acids and to the coal tar-derived cresylic acid for 1 hour/day for 10 days caused death in a few mice. Irritation of the nose and eyes was a common observation in mice from all of the materials tested.

Inhalation studies of the three cresol isomers were conducted by a commercial laboratory [30] using 18 male albino Charles River rats, averaging 209 g in weight and divided into three groups of six rats each. Each group of rats was placed in a 56-liter inhalation chamber and exposed for a single 1-hour period to a dynamically circulated mixture. Vapor was generated by passing air through undiluted liquid cresol, but it was not clear whether an elevated temperature was needed. The rats were placed in the chamber after the concentration had reached 99% of the theoretical maximum concentration. The concentrations attained were 0.71 mg/liter (710 mg/cu m or 161 ppm) for m- and p-cresol and 1.22 mg/liter (1,220 mg/cu m or

280 ppm) for o-cresol. The rats were observed for signs of toxicity until, at the end of 14 days, they were killed and autopsies were performed. All of the rats survived exposure to the cresol isomers. Evidence of toxicity was observed only in rats exposed to o-cresol. They showed generalized inactivity and lacrimation. No abnormalities were observed grossly at autopsy.

Uzhdavini et al [24] examined the effects of o-cresol inhalation on animals of various species. The authors stated that sufficient o-cresol vapor to produce signs of toxicity after a single exposure could not be generated because of its low vapor pressure. Therefore, animals were exposed to a mixture of o-cresol vapor and aerosol generated under static conditions, possibly by warming the material as stated in a subsequent study [25]. Mice (sex and age not given) were exposed to o-cresol, described as vapor and aerosol, at concentrations that varied in the chamber from 26 to 76 mg/cu m (average, 50 mg/cu m) for 2 hours daily, 6 days/week, for 1 month [24]. Control mice were also used. It was recognized that, in addition to the mice being exposed to o-cresol by inhalation, percutaneous penetration was also possible. Although it was not stated by the authors, apparently the mice were killed after the 1-month exposure, and autopsies were performed.

Irritation, presumably of the mucous membranes of the respiratory tract, was noticed in the mice in the first few minutes of exposure [24]. In 18-20 days, the ends of the tails of some exposed mice fell off. The exposed mice gained weight more slowly than controls, but the organ-to-body weight ratios of unspecified internal organs were unchanged in both the experimental and control groups. Microscopic and gross examinations were

performed on several tissues. The CNS contained excess blood, and degenerative changes had occurred in the nerve cells and glial elements. Hyperemia, edema, and a proliferation of cellular elements were observed in the respiratory tract. There were small hemorrhagic patches in the lungs, and the mucous membranes of the airways were inflamed. Degenerative changes of the myocardial fibers were noted, and there were indications of protein degeneration in the liver and kidney cells.

In another part of this study, rats and guinea pigs (number not given) were exposed to o-cresol vapor for 6 hours/day, 5 days/week, for 2 months, and then for 4 hours/day, 5 days/week, for another 2 months [24]. The results were compared with those from control animals. The mean concentration during the exposure period was 9.0 ± 0.9 mg/cu m. In the experiments with rats, the authors measured what they identified as the elementary conditioned defensive reflex, leukocyte levels in the peripheral blood, and leukoid and erythroid elements in the bone marrow. Bone marrow smears at unspecified intervals were also studied. Hexobarbital narcosis was tested in the rats as an indirect measure of liver function. In the experiments with guinea pigs, the blood elements were analyzed, and results of electrocardiograms (ECG's) were briefly mentioned.

By the end of the 2nd month, all exposed rats had lost the defensive reflex [24]. This reflex was also depressed in control rats, but at a slower rate. At 2 months, 30% of the controls still demonstrated the conditioned reflex, and less than 10% still manifested it by 4.5 months. The exposed male rats had a greater number of leukocytes in the peripheral blood (about 22,000/cu mm) than did the controls (about 14,000/cu mm), especially by the 4th month of exposure. One month after exposure to

cresol had ended, the leukocyte count in the exposed rats had returned to essentially control values. No effects on leukocyte count in female rats were described. After rats were exposed to o-cresol for 4 months, some changes in bone marrow were reported. Exposed rats had a statistically significant decrease in the numbers of elements in the erythroid series compared to controls, which was reflected in a statistically significant difference in the leukoid-to-erythroid ratio (1.3:1 in exposed rats and 2.1:1 in controls). After the 4-month exposure, the duration of hexobarbital narcosis was significantly greater in exposed rats than in controls, 62.0 ± 5.2 minutes versus 37.4 ± 0.7 minutes. The authors attributed this change to the effect of cresol on the liver. A slight decrease in the reactivity of the pituitary-adrenal system of rats exposed to o-cresol was observed, but it was not stated how this was measured.

In guinea pigs, inhalation of o-cresol had no effect on the leukoid-to-erythroid ratio in the bone marrow [24]. Some unspecified changes in the hemoglobin concentration were mentioned. The R wave component of the ECG was slightly decreased in exposed guinea pigs, but it was not indicated when these measurements were taken.

In addition to noting a threshold concentration for irritation of the nasal mucosa in humans (see (b) in Effects on Humans), Uzhdavini et al [24] interpreted respiratory irritation in five cats by measuring secretions from fistulas of the salivary parotoid glands. The threshold concentration was stated to be 5-9 mg/cu m.

This report [24] is difficult to evaluate, because the data presented are incomplete. For example, in the description of exposure conditions, neither the type of chamber employed nor the method used for generating

vapor-aerosols was given. The number of animals employed for various experimental procedures generally was not specified, and control conditions were not detailed adequately. Despite these shortcomings, the agreement of the findings of Uzhdavini et al with those reported by other investigators, such as Deichmann and Witherup [31], suggests that satisfactory test and control procedures were used. Therefore, NIOSH believes that the adverse effects found by Uzhdavini et al [24] are meaningful.

In 1975, Kurlyandskiy et al [35] reported the effects on rats exposed to tricresol vapor. Three groups of six rats each (sex and age unspecified) were exposed to tricresol vapor at concentrations of 2.4, 0.1, and 0.01 mg/cu m for 24 hours. Three other groups of six rats served as controls. No description was given of the exposure method or of the system used to generate the vapor. After the rats had been exposed for 24 hours, the amount of neutral red dye absorbed by the lung tissue was measured. The experimental procedure used in determining the absorption of dye was not described. The authors regarded dye absorption as an indication of protein denaturation, which, they reported, was one of the toxic actions of tricresol. An increase in the absorption of dye or decrease in the excretion of dye would indicate a denaturation of protein. The absorption of the dye, expressed in extinction units, was measured spectrophotometrically. In rats exposed to tricresol at a concentration of 2.4 mg/cu m, absorption was significantly higher than it was in the controls ($P<0.001$). This was also the case at 0.1 mg/cu m ($P<0.05$), but, at 0.01 mg/cu m, the effect was not significant ($P>0.05$). Dye absorption at the 0.01 mg/cu m level was greater than that seen at 0.1 mg/cu m, indicating that there was no direct dose-response relationship. The value

for the control animals used in the group exposed at 2.4 mg/cu m was markedly different from control values for the 0.1 and 0.01 mg/cu m groups; however, the authors offered no explanation for the differences observed.

Kurlyandskiy et al [35] also exposed two groups of rats (unstated number) to tricresol vapor at concentrations of 0.05 and 0.0052 mg/cu m for 3 months. It is unclear how many hours/day the animals were exposed and whether the exposure was daily. A third group of rats served as controls. The variables observed during the experiment were body weight, CNS effects, oxygen and carbon dioxide metabolism, total protein content in the blood, tertiary structure of an unspecified protein molecule, cardiovascular effects, and the activity of an unnamed liver transaminase.

Compared with controls, the rats exposed to tricresol at 0.05 mg/cu m showed less weight gain, increased excitability of the CNS (method of measurement not given), higher oxygen consumption and carbon dioxide excretion, and lower concentrations of the gamma globulins in the blood [35]. The tertiary structure of the globular and aglobular portions of the protein molecule was altered, and an increased absorption of dye in the lungs was noted. The observed changes were reversible after exposure ended. No changes were seen in rats exposed to tricresol at a concentration of 0.0052 mg/cu m, and the authors recommended this value as the mean daily maximum permissible concentration. It is difficult to assess these findings because of some unexplained differences noted in the experimental results, the difficulty in evaluating toxicity from a colorimetric determination of protein denaturation, and unanswered questions concerning the procedures used to measure central nervous system function.

Uzhdavini et al [25], as part of their study of various cresol and xylenol isomers (see also (a) and (c) in Animal Toxicity), reported the effects of inhalation of o-cresol and of five xylenol isomers on mice exposed to a vapor-aerosol formed by warming the compounds. They determined that the LC50 for o-cresol in mice was 0.179 mg/liter (179 mg/cu m), but the duration of exposure was not specified. It was noted that o-cresol precipitated on the walls of the exposure chamber and on the fur of the mice, so there was possible exposure by the dermal and oral routes, as well as by inhalation. Toxic signs of exposure to o-cresol as a heated vapor-aerosol included irritation of the mucous linings, dilation of the vessels of the ears and extremities, excitation, hematuria, and convulsions. No inhalation results for the other materials were given. The authors concluded that the danger of poisoning from cresol exists when vapor-aerosol mixtures are present that may lead to skin penetration.

(c) Other Routes of Administration

In 1944, Deichmann and Witherup [31] published their study comparing the toxicities of phenol and o-, m-, and p-cresol. They exposed rats, rabbits, and cats by various routes of administration to determine the minimum lethal doses of each compound. In one experiment, single subcutaneous injections of phenol or one of the cresol isomers, as 10% solutions in olive oil, were given to one cat in each of 10 dose groups. The doses ranged from 0.024 to 0.94 g/kg. The minimum lethal doses were 0.080, 0.055, 0.180, and 0.080 g/kg for phenol and o-, m-, and p-cresol, respectively. The authors concluded that "o-cresol was slightly more toxic than phenol and p-cresol, and that m-cresol was the least toxic following subcutaneous injection."

Rabbits were also given oral doses of phenol or of each of the cresol isomers as 20% aqueous emulsions [31]. The compounds were given by stomach tube at doses ranging from 0.18 to 2.10 g/kg to one rabbit in each of seven groups. Phenol and p-cresol each appeared to be somewhat more toxic than o-cresol. Again, m-cresol was the least toxic. Minimum lethal doses were 0.42, 0.94, 1.40, and 0.62 g/kg for phenol and o-, m-, and p-cresol, respectively.

Single iv injections of 0.5% aqueous solutions of the compounds were given to rabbits in the marginal ear vein at the rate of 1 ml/minute [31]. The doses, ranging from 0.08 to 0.42 g/kg, were administered to one rabbit in each dose group. Given iv, phenol, o-cresol, and p-cresol were equally toxic, with a minimum lethal dose of 0.18 g/kg. The minimum lethal dose for m-cresol was 0.28 g/kg.

Single oral doses of 10% solutions of phenol or cresol in olive oil were given to rats by stomach tube, and the LD50 of each compound was determined [31]. The LD50 values were 1.35 g/kg for o-cresol, 1.5 g/kg for phenol, 1.8 g/kg for p-cresol, and 2.02 g/kg for m-cresol.

Deichmann and Witherup [31] also reported that the signs of poisoning were quite similar for phenol and for the cresol isomers by all of the routes of administration they tested. One of the first apparent effects was a twitching in the muscles of the eyes, eyelids, and ears, which later occurred in isolated muscles throughout the body. The pupils were contracted in the early stages of poisoning but later became dilated. Labored breathing was marked, and pulse and respiration became slow, irregular, and weak after initial increases. Cats and rabbits convulsed

before they became lethargic and comatose, and rabbits exhibited asphyxial convulsions just before death. Convulsions were generally less severe after cresol exposure than after exposure to phenol, although signs of weakness, collapse, and the depth of coma were greater with cresol.

Oral LD50 values for phenol, cresols, and xylenols were also determined by Uzhdavini et al [25]. The compounds were administered as 10% solutions in oil into the stomachs of mice and rats. The LD50 values are listed in Table III-3.

Oral toxicity determinations on the three cresol isomers were included as part of a commercial laboratory study [30] previously discussed (see (a) and (b) in Animal Toxicity). In one study, male albino rats, weighing approximately 180 g, were each given single oral doses by stomach tube of one isomer in undiluted form. Five animals were used at each dose level for each of the three compounds administered. Signs of intoxication, including mortality, were recorded for 14 days, at which time all survivors were killed. Autopsies were performed on all rats. The LD50 values were 121, 242, and 207 mg/kg for o-, m-, and p-cresol, respectively. Signs of intoxication observed in the rats exposed to any one of the isomers included hypoactivity, tremors, convulsions, salivation, prostration, and death. Dyspnea and cyanosis were also observed in rats given p-cresol. Autopsies on exposed rats that died revealed inflammation or hemorrhage of the gastrointestinal tract and hyperemia of the lungs, liver, and kidneys. The only gross change observed in rats that survived exposure was inflammation of the gastrointestinal tract in those given p-cresol.

TABLE III-3

LD50'S OF PHENOL, CRESOL, AND XYLENOL IN MICE AND RATS

| Substance* | LD50 with Confidence Intervals (mg/kg) | |
|---|---|---|
| | Mice | Rats |
| Phenol | 436 (311-610) | - |
| o-Cresol | 344 (270-436) | 1,470 (1,170-1,830) |
| m-Cresol | 828 (695-985) | 2,010 (1,240-3,200) |
| p-Cresol | 344 (266-443) | 1,460 (1,260-1,670) |
| 2,4-Xylenol | 809 (724-914) | 3,200 (2,780-3,680) |
| 2,5-Xylenol | 1,140 (797-1,530) | 1,270** |
| 2,6-Xylenol | 980 (823-1,166) | 1,750 (1,420-2,150) |
| 3,4-Xylenol | 948 (658-1,365) | 1,620** |
| 3,5-Xylenol | 836 (773-906) | 1,915** |

*Administered in 10% oil solution by stomach tube
**No confidence intervals available

Adapted from reference 25

(d) Metabolism

In 1950, Bray and associates [36] published a study on the metabolism of the cresol isomers in rabbits. They administered each isomer, in sodium bicarbonate solution, by stomach tube to rabbits weighing 2-3 kg each. Doses of 500-600 mg of o- or m-cresol were given, but no more than 200-300 mg of p-cresol could be tolerated unless the rabbits had been fed 1-2 hours

beforehand. Ethereal sulfates, ether glucuronides, and free and total cresol were measured in the urine during the 24 hours after each dose was given. Conjugated compounds accounted for most of the cresol excreted, an average of 87% of the total dose of o-cresol, 70% of that of m-cresol, and 76% of that of p-cresol. Of the amount of cresol excreted as conjugated products, most was the ether glucuronides. The average percentages of o-, m-, and p-cresol excreted as the glucuronides were 72%, 60%, and 61%, respectively. Additional metabolites were detected by paper chromatography. About 7% of p-cresol was excreted as free hydroxybenzoic acid and about 3% as conjugated hydroxybenzoic acid. o-Cresol and m-cresol each yielded about 3% of 2,5-dihydroxytoluene. The urinary metabolites of the three isomers are summarized in Figure XI-1.

Correlation of Exposure and Effect

The ability of cresols to be absorbed through the skin and produce local and systemic effects has been demonstrated in humans [14,16(p 36),17-21]. The skin, considered to be the primary route of occupational exposure, is the site of most of the worker injuries reported from cresols [16(pp 3,28,36)]. Skin contact with cresols has resulted in skin peeling on the hands [18], facial peripheral neuritis [18], severe facial burns [14], and damage to internal organs, including loss of kidney function [17] and necrosis of the liver and kidneys [21]. Cresols have also caused sensitization of the skin [19,20]. Dermatitis developed on the fingers of workers who had been using a solution containing cresol and cresylic acid [19]. Of 30 workers in a synthetic plastics plant, 6 developed dermatitis

on the hands and face resulting from exposure to cresol and phenol [20]. Although the information in these reports was insufficient to allow determination of dose-response relationships, industrial experience indicated that only small quantities of cresols were needed to produce chemical burns of the skin [16(p 3)].

Animal studies have also indicated that cresols can cause local irritation and be absorbed after skin contact [28,30,33]. Discoloration of the skin, convulsions, and death occurred in rats given dermal appplications of 1 ml/kg of various coal tar-derived cresylic acids [28]. In rabbits that had any of the three cresol isomers applied dermally in doses of 1 ml/kg for 24 hours, severe edema, erythema, or subdermal hemorrhaging developed [30]. Other effects included salivation, lacrimation, hypoactivity, tremors, convulsions, sedation, and death [30]. Shelley [33] reported that repeated dermal application of 0.5% p-cresol caused depigmentation of the hair and epidermis and local corrosion of the skin in mice.

Appreciable concentrations of cresol vapors are rarely generated in industry because all three cresol isomers have low vapor pressures [16(pp 21,25)]. However, a hazardous concentration of vapor may be generated at elevated temperatures, and there have been a few reports in the literature [22,24] describing effects from inhalation of cresol vapor. Corcos [22] reported that seven workers exposed to airborne cresol at an unspecified concentration developed headaches and nausea. Some workers also had hypertension, muscular irritability, convulsions, and decreased kidney function [22]. Interviews with workers exposed to cresol and phenol at concentrations of 0.02-10 ppm (0.08-38 mg/cu m) in air did not delineate

effects on the eyes, nose, and throat [23]. The airborne concentration was reported as total phenols, so the actual exposure to cresol was not known. However, Uzhdavini et al [24] found that 8 of 10 subjects experimentally exposed to o-cresol vapor at a concentration of 6 mg/cu m complained of dryness of the respiratory mucosa, nasal constriction, irritation of the throat, and the sensation of an unspecified taste. In spite of the lack of specific details regarding methodology, this is the only reference of human inhalation exposure to a pure cresol and should not be ignored.

Inhalation experiments on mice [24,25,28], rats [24,30,35], and guinea pigs [24] have produced some varying results, especially with regard to the concentrations of cresol necessary to produce irritation of the eyes and respiratory tract and to cause death. No deaths were reported [30] in rats exposed for 1 hour to o-cresol vapor at a concentration of 1.22 mg/liter (1,220 mg/cu m) or to m- or p-cresol vapor at a concentration of 0.71 mg/liter (710 mg/cu m). The only toxic effects seen were inactivity and lacrimation in rats exposed to o-cresol. Uzhdavini et al [25] reported that the LC50 of warmed o-cresol administered for an indeterminate exposure period to mice as a vapor-aerosol was 179 mg/cu m. Mice inhaling coal tar- or petroleum-derived cresylic acid vapors at "saturated" concentrations for a single 5-hour period showed no effects.

Although no reports of effects in humans from long-term exposure to cresols were found, toxic effects have been observed in animals repeatedly exposed by inhalation [24,28,35]. Campbell [28] reported irritation of the nose and eyes and some deaths in mice that inhaled coal tar- or petroleum-derived cresylic acid vapors at "saturated" air concentrations for 1 hour/day on 10 consecutive days. Uzhdavini et al [24] observed some

microscopic changes in mice exposed to o-cresol vapor-aerosol at an average concentration of 50 mg/cu m for 2 hours/day, 6 days/week, for 1 month, and in rats and guinea pigs exposed to o-cresol vapor at a concentration of 9 mg/cu m for 6 hours/day, 5 days/week, for 2 months, and 4 hours/day, 5 days/week, for another 2 months. These authors also reported irritation of the upper respiratory tract in humans exposed to airborne o-cresol at 6 mg/cu m and in cats exposed at 5-9 mg/cu m. They did not comment on whether similar effects were found in rats and guinea pigs. Kurlyandskiy et al [35] found that 0.05 mg/cu m of tricresol vapor was the lowest concentration at which effects, including CNS excitability and protein denaturation, were noted in rats exposed for 3 months.

Several cases of cresol ingestion and its intravaginal application have shown cresol to be corrosive to body tissues and to cause toxic effects on the vascular system, liver, kidneys, and pancreas. Cresol introduced into the uteri of pregnant women has produced abortion [15,26], extensive hemolysis [26], erosion of blood vessels [15], damage to the kidney tubules [26], necrosis of the liver [26], and death [26].

Most cases of cresol ingestion have been the result of attempted [11,12,27] or successful [11,13] suicides. The smallest amount of cresol that produced death was 4 ml of a 25-50% cresol solution in an 11-month-old child [11]. Systemic effects observed after cresol ingestion reflected those observed after its use as an abortifacient and included elevated blood pressure [27], damage to the vascular system [27] and kidneys [11-13,27], and acute pancreatitis [13,27].

Mice [25], rats [25,30], and rabbits [31] that were exposed to cresol by the oral route have shown toxic effects similar to the effects on

humans. Reported effects included labored breathing, cyanosis, inactivity, and convulsions [30,31], inflammation and hemorrhage of the gastrointestinal tract [30], and hyperemia of the lungs, liver, and kidneys [30].

Although no data were found that compared the effects of o-, m-, and p-cresol in humans, several animal studies [25,30,31,36] suggest that their biologic actions are similar. Mortality studies using dermal, oral, subcutaneous, or iv administration have generally shown that o- and p-cresol are about equal in toxicity, but that m-cresol is less toxic. The only inhalation study [30] that compared the three isomers showed no difference in effect between m- and p-cresol at identical concentrations; o-cresol was given at a somewhat higher concentration. The toxic effects other than mortality observed in these studies [25,30,31] were qualitatively similar for the three isomers, and included skin irritation, CNS disturbances, and liver and kidney damage. The urinary metabolites of the three isomers have also been found to be similar [36]. Compounds conjugated at the hydroxyl group accounted for the majority of the metabolites.

In summary, the most frequently observed effects resulting from occupational exposure to cresols are burns of the skin and eyes. In addition to being strong tissue irritants, cresols may cause impairment of kidney and liver function and CNS and cardiovascular disturbances. The effects of exposure to cresols on humans and animals are summarized in Tables III-4 and III-5, respectively.

Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

No investigations of the mutagenic or teratogenic potential of cresol were found in the literature. Boutwell and Bosch [34] presented data on the role of phenol and its derivatives, including cresol, in promoting the formation of both papillomas and carcinomas. They found that each of the cresol isomers promoted DMBA-induced papillomas in mice, but no carcinomas were produced. Administration of several of the tested xylenols resulted in increased numbers of papillomas and carcinomas in mice. In addition, some of the xylenols were found to be weak carcinogens. This report suggests that the cresol and xylenol isomers may promote the action of DMBA resulting in the production of benign tumors.

TABLE III-4

EFFECTS OF EXPOSURE TO CRESOLS IN HUMANS

| Route of Exposure | Subjects | | | Exposure | | Observed Effects | Reference |
|---|---|---|---|---|---|---|---|
| | No. | Age (yr) | Sex | Description | Duration | | |
| Dermal | 1 | 47 | M | Total body immersion in vat of cresylic acid derivative | - | Burns, anuria, high BUN, coma, heart failure, death | 17 |
| " | 1 | <1 | " | 20 ml of 90% cresol poured on head | - | Burns, edema, internal hemorrhage, kidney damage, death | 21 |
| " | 1 | 16 | F | Anesthetic mask soaked in 10% cresol on face | 2 hr | Erythema, blisters, scars | 14 |
| " | 1 | 41 | M | Hands in 6% cresylic acid | 5-6 hr | Skin dry and peeling, erythema, tearing, facial peripheral neuritis | 18 |
| " | - | - | - | - | - | Burns | 11, 16(p 36) |
| " | - | - | - | Work in plastics or cable and rubber plant | - | Eczema | 20 |
| " | 1 | 21 | M | Contact with antimildew solution with cresol and cresylic acid | 8 mon | Dermatitis | 19 |
| Inhalation | 34 | 23-32 | - | Cresol vapor | - | Headache, vomiting, hypertension, tremors, spasms, elevated Ambard's constant, enlarged heart | 22 |
| " | 10 | - | - | o-Cresol at 6 mg/cu m | - | Respiratory tract irritation | 24 |
| " | - | - | - | Degreasers with cresol and phenol at up to 10 ppm | - | None | 23 |

TABLE III-4 (CONTINUED)

EFFECTS OF EXPOSURE TO CRESOLS IN HUMANS

| Route of Exposure | Subjects | | | Exposure | | Observed Effects | Reference |
|---|---|---|---|---|---|---|---|
| | No. | Age (yr) | Sex | Description | Duration | | |
| Ocular | - | - | - | - | - | Eye irritation | 11 |
| Oral | 1 | 49 | F | 250 ml of Lysol (50% cresol) plus 250 ml of ethyl alcohol | - | Unconsciousness, kidney failure, pancreatitis, pneumonia | 27 |
| " | - | - | - | 4-120 ml of Lysol (25-50% cresol) | - | Abdominal pain, vomiting, unconsciousness, death | 11 |
| " | 1 | 24 | F | 25 ml of Lysol | - | Unconsciousness, pneumonia | 12 |
| " | 1 | 31 | " | Unknown amount of Lysol | - | Pancreatitis, fat necrosis, kidney congestion, death | 13 |
| Vaginal | 1 | 26 | " | " | - | Low blood pressure, breathing difficulty, hemolysis, pulmonary oil embolism, blood vessel erosion, death | 15 |
| " | 4 | 18-35 | " | " | - | Vaginal bleeding; elevated temperature, pulse, WBC; hemolysis; pulmonary edema; liver and kidney damage; death | 26 |

TABLE III-5

EFFECTS OF EXPOSURE TO CRESOLS IN ANIMALS

| Route of Exposure | Species | Isomer/ Compound | Exposure: Concentration | Exposure: Duration | Effects | Reference |
|---|---|---|---|---|---|---|
| Dermal | Rat | Coal tar cresylic acid | 1-2 ml/kg | 1-2 hr | Skin discoloration, convulsions, death | 28 |
| " | " | Coal tar cresylic disinfectants | 1-3.5 ml/kg | " | " | 28 |
| " | " | Coal tar cresol | 1.0-1.7 ml/kg | " | Skin discoloration, death | 28 |
| " | " | Petroleum cresylic acid | 1.0 ml/kg | " | Skin irritation, discoloration | 28 |
| " | " | m-Cresol | 1,100 mg/kg | Single dose | LD50 | 25 |
| " | " | p-Cresol | 750 mg/kg | " | " | 25 |
| " | " | o-Cresol | 620 mg/kg | " | " | 25 |
| " | Mouse z | o- or m-Cresol | 0.5% | 6 wk | No effects | 33 |
| " | " | p-Cresol | " | " | Skin corrosion, depigmentation | 33 |
| " | Rabbit | m-Cresol | 1,000-3,160 mg/kg | 24 hr | Skin irritation, convulsions, death, hyperemia | 30 |
| " | " | o-Cresol | 681-2,150 mg/kg | " | Erythema, tremors, death | 30 |
| " | " | p-Cresol | 215-681 mg/kg | " | Skin irritation, tremors, sedation, death, kidney inflammation | 30 |
| Inhalation | Rat | o-Cresol | 1,220 mg/cu m | 1 hr | Inactivity, lacrimation | 30 |
| " | " | m-Cresol | 710 mg/cu m | " | No effects | 30 |
| " | " | p-Cresol | " | " | " | 30 |

TABLE III-5 (CONTINUED)

EFFECTS OF EXPOSURE TO CRESOLS IN ANIMALS

| Route of Exposure | Species | Isomer/ Compound | Exposure: Concentration | Exposure: Duration | Effects | Reference |
|---|---|---|---|---|---|---|
| Inhalation | Rat | o-Cresol | 9.0 mg/cu m | 4 mon | CNS effects, blood changes | 24 |
| " | " | Tricresol | 2.4 mg/cu m | 24 hr | Protein denaturation in lungs | 35 |
| " | " | " | 0.1 mg/cu m | " | " | 35 |
| " | " | " | 0.01 mg/cu m | " | No effects | 35 |
| " | " | " | 0.05 mg/cu m | 3 mon | CNS excitation, protein denaturation in lungs | 35 |
| " | " | " | 0.052 mg/cu m | " | No effects | 35 |
| " | Mouse | Cresylic acid | Saturated air | 10 d | Mucosal irritation, death | 28 |
| " | " | " | " | 5 hr | No effects | 28 |
| " | " | o-Cresol | 26-76 mg/cu m | 1 mon | Vascular congestion, changes in CNS, inflammation of airways | 24 |
| " | Guinea pig | o-Cresol | 9.0 mg/cu m | 4 mon | Changes in ECG | 24 |
| Oral | Rat | m-Cresol | 1,700-2,700 mg/kg | Single dose | Twitching, coma, death | 31 |
| " | " | p-Cresol | 1,300-2,700 mg/kg | " | " | 31 |
| " | " | o-Cresol | 1,000-2,200 mg/kg | " | " | 31 |
| " | " | m-Cresol | 215-464 mg/kg | " | Hypoactivity, convulsions, GI tract inflammation, hyperemia, death | 30 |
| " | " | p-Cresol | 215-316 mg/kg | " | " | 30 |
| " | " | o-Cresol | 100-215 mg/kg | " | " | 30 |

TABLE III-5 (CONTINUED)

EFFECTS OF EXPOSURE TO CRESOLS IN ANIMALS

| Route of Exposure | Species | Isomer/ Compound | Exposure | | Effects | Reference |
|---|---|---|---|---|---|---|
| | | | Concentration | Duration | | |
| Oral | Rat | m-Cresol | 147 mg/kg | Single dose | Hypoactivity, convulsions, GI tract inflammation, hyperemia | 30 |
| " | " | p-Cresol | 100-147 mg/kg | " | " | 30 |
| " | " | o-Cresol | 68 mg/kg | " | " | 30 |
| " | Rabbit | m-Cresol | 1,400-2,100 mg/kg | " | Convulsions, coma, death | 31 |
| " | " | o-Cresol | 940-1,400 mg/kg | " | " | 31 |
| " | " | p-Cresol | 620-1,400 mg/kg | " | " | 31 |
| iv | " | m-Cresol | 280-420 mg/kg | " | " | 31 |
| " | " | o-Cresol | 180-280 mg/kg | " | " | 31 |
| " | " | p-Cresol | " | " | " | 31 |
| " | Mouse | m-Cresol | 2,010 mg/kg | " | LD50 | 25 |
| " | " | o-Cresol | 1,470 mg/kg | " | " | 25 |
| " | " | p-Cresol | 1,460 mg/kg | " | " | 25 |
| Subcutaneous | Cat | m-Cresol | 180-940 mg/kg | " | " | 31 |
| " | " | p-Cresol | 80-940 mg/kg | " | " | 31 |
| " | " | o-Cresol | 55-940 mg/kg | " | " | 31 |