III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Hydroquinone was first synthesized in 1820 by Pelletier and Caventou by the dry distillation of quinic acid [1]. In 1844, Wohler investigated the compound, established its structure, and named it hydroquinone. In the early 20th century, European patents were granted for its production by oxidation of phenol with alkaline permanganate (German) or with hydrogen peroxide (British) [2]. Another German method of preparation involved heating para-chlorophenol with copper sulfate under pressure. Hydroquinone was first used by Alonet in 1880 as a photographic developer [3].

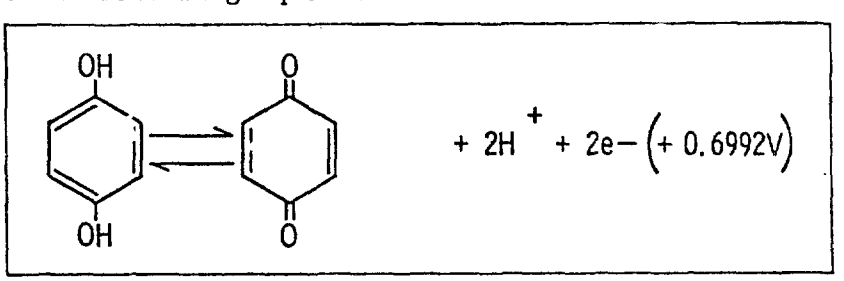
Merck and Company began producing hydroquinone in 1914 [2]. EI du Pont de Nemours and Company was the first to manufacture hydroquinone in commercial quantities after World War I, using a process introduced by a French company, Usines de Rhone [2]. This manufacturing process involved oxidation of aniline with sodium dichromate, reduction of the formed quinone with sulfur dioxide, and extraction of the hydroquinone with ether. In 1924, in an effort to reduce the cost of hydroquinone, Eastman Kodak decided to manufacture its own chemical products and formed a subsidiary, Eastman Chemical Corporation, which began operation in that year [2]. Aniline was oxidized to quinone by manganese dioxide and sulfuric acid, and the formed quinone was reduced with iron dust to hydroquinone.

Besides these methods of synthesis, two other techniques for hydroquinone production from quinone have been patented [2]. In one of these, quinone is distilled under vacuum into a solution of hydroquinone,

at a temperature below 35 C, to form quinhydrone. The quinhydrone is subsequently reduced to hydroquinone. The second method involves the reaction of quinone in a substantially neutral, aqueous solution, in the presence of metallic zinc and a small quantity of potassium or ferric chloride, by heating at 70-75 C. Since hydroquinone can be easily oxidized to quinone and quinone-like products, it has become one of the most widely used organic reducing agents.

Hydroquinone (C6H4(OH)2), formula weight 110.11, is a white solid that can be crystallized from water as hexagonal prisms [1,4]. It has a melting point of 173-74 C and a boiling point of 285 C at 730 mmHg [5]. Hydroquinone is soluble in water to the extent of 73 g/liter at 25 C [4]. It is also highly soluble in alcohol and ether but only slightly soluble in cold benzene (about 0.2 g/liter) and in other nonpolar solvents [1]. Hydroquinone possesses two phenolic hydroxyl groups having dissociation constants of 1.22 x 10*10 and 9.18 x 10*13, respectively, at 30 C (* means "to the negative power of") [1]. The designation "hydroquinone" is given to 1,4-dihydroxybenzene and as a general designation, to 1,2-dihydroxybenzene and 1,3-dihydroxybenzene, which are given the more specific names of catechol and resorcinol, respectively.

Hydroquinone is a reducing agent (standard oxidation potential = 0.6992 volts at 25 C and pH 0) that is reversibly oxidizable to quinone according to the following equation:



The oxidation potential of hydroquinone at 20 C and pH 7.03 is 0.2982 volts [6]. For comparison, the standard oxidation potentials of some biologic substances are given in Table XI-2 [7]. Hydroquinone has a very low vapor pressure (0.000018 mmHg at 25 C) [8], while quinone sublimes at room temperature (0.1 mmHg at 25 C) [9]. Other physical and chemical properties of hydroquinone and quinone are shown in Table XI-3 [1,4,5,8-11]. The most common synonyms used for hydroquinone include p-dihydroxybenzene, 1,4-benzenediol, and 1,4-dihydroxybenzene [1]. A complete list of synonyms and trademarks is given in Table XI-1 [1,4,10,12]. Most of the commercial uses of hydroquinone are related to its chemical property as a reducing agent.

Hydroquinone and quinone form a reversible oxidation-reduction system [13], but the nature of this oxidation-reduction system is somewhat more complex than that shown in the above equation. The formation of a relatively stable semiquinone radical by a single electron transfer to quinone has been reported [13]. This semiquinone radical can undergo reversible dimerization reactions to form peroxides with other compounds or with quinone to form a colored "charge transfer" complex called quinhydrone. Autoxidation of hydroquinone to quinone proceeds in two steps [14]. In the first, a divalent hydroquinone ion loses one electron and yields a semiquinone ion, which gives off an electron to form quinone. The semiquinone ion is formed also by the reaction of a hydroquinone ion with quinone.

Hydroquinone is easily oxidized to quinone by nitric acid, halogens, and persulfates, and, in alkaline solution, by oxygen [4]. This reaction is reversible with a suitable reducing agent [1]. However, in the dry form pure hydroquinone is quite stable, darkening slowly upon prolonged exposure

to air [15]. The oxidation of hydroquinone is very rapid in the presence of alkali, producing a brown solution when the substance is exposed to air [16]. In alkaline solution, hydroquinone is readily oxidized to quinone and hydrogen peroxide by oxygen [17]. The peroxide oxidizes quinone to hydroxyquinone. The oxidation rate of hydroquinone by oxygen is rapid even in slightly alkaline solution, and the reaction is strongly catalyzed by the cupric ion. The oxidation of hydroquinone in slightly alkaline solutions has been summarized by Flaig et al [18], in the flow chart in Figure XI-1. Oxidation products included p-benzosemiquinone, hydroxy-p-benzoquinone, p-benzoquinone, and di-p-benzoquinone. Hydroquinone is also oxidized by Fehling's solution in the absence of air [4]. It may prevent the oxidation of substances, such as aldehydes and sulfite solutions. Silver salts are rapidly reduced by hydroquinone at room temperature. In acidic solution hydroquinone is very resistant to oxidation [19]. The oxidation is slight until the solution becomes more alkaline than pH 7.3-7.8, and then it becomes very rapid. Airborne hydroquinone in the occupational environment may be oxidized to quinone at room temperature in the presence of moisture. However, neither the rate of oxidation nor the equilibrium concentrations at room temperature are known.

Hydroquinone is widely distributed in nature as a component of the glucoside arbutin, from which it can be produced by hydrolysis [1]. Arbutin can be obtained from the leaves of many plants; among the most important are the bearberry (Arctostaphylos uva ursi), the mountain cranberry (Vaccinium vitisidaea), the whortleberry (Vaccinium myrtillus), and the honeyflower (Protea mellifera). Arbutin is a minor constituent of aniseed oil from the fruit of the evergreen Chinese anise (Illicium verum),

and it has been isolated from the bark and buds of the pear tree. Hydroquinone has also been found in cigarette smoke [1].

Hydroquinone can be synthesized by the oxidation of aniline with sodium dichromate and sulfuric acid and subsequent reduction by bisulfite, by the reduction of quinone by nascent hydrogen liberated from a mineral acid by a metal, by persulfate oxidation of phenol, or by the reaction of acetylene with carbon monoxide [16]. The most popular and commercially useful method for production of hydroquinone is the oxidation of aniline by manganese dioxide or sodium dichromate in sulfuric acid to quinone, which is subsequently reduced to hydroquinone with iron dust [1]. Recently, another method has been developed to produce hydroquinone from propylene and benzene [20]. Benzene is alkylated with propylene to p- and m-diisopropylbenzene. The p-diisopropylbenzene is oxidized to the dihydroperoxide and then rearranged to yield hydroquinone and acetone.

Nomiyama et al [21] and Williams [22] reported that one of the metabolic (oxidative) products of benzene is phenol and that phenol is further metabolized to hydroquinone in rabbits and in humans. These metabolites of benzene are excreted mainly in the conjugated forms. In rabbits, ethereal sulfate formation appeared to be more important than glucuronic acid conjugation [22]. Bakke [23] reported that, when rats were fed 10% extra tyrosine in their diet, small amounts of hydroquinone (as much as 1.4-1.7 mg/24 hours for 2 days) were detected in the urine by gas and thin-layer chromatographic analysis.

Gregg and Nelson [24] reported that quinone was formed when hydroquinone was oxidized in the presence of the enzyme laccase, one atom of oxygen being used per molecule of hydroquinone. However, the same

amount of hydroquinone was oxidized by tyrosinase in the presence of catechol, but more than one atom of oxygen per molecule of hydroquinone was consumed. The author concluded that the tyrosinase brought about a different type of oxidation than did the laccase, probably the introduction of a third hydroxyl group on hydroquinone.

In 1974, the United States produced about 22.1 million pounds of technical grade hydroquinone and sold about 17.4 million pounds [25]. In 1975, the annual production capacity for hydroquinone in the United States was about 29.7 million pounds [26]. These are the latest years for which data are available. Hydroquinone is usually packaged and shipped in fiber drums: 100 and 325 pounds net, 108 and 345 pounds gross [1].

Hydroquinone is used in several ways. It is used extensively as a photographic developer [1,4,10]. It is used also as a dye intermediate [4] and as an antioxidant and stabilizing agent [4,27]. For instance, small amounts of hydroquinone greatly retard the autoxidation of furfural, formaldehyde, isopropyl ether, esters of linoleic acid, olefins, and ethylcellulose [1]. Hydroquinone can be used to stabilize such compounds as epinephrine and furan against oxidation in solutions [1,28]. Biologic specimens, such as phospholipid preparations, can be preserved by the addition of 0.5-1.0% hydroquinone. Ferricytochrome c can be reduced rapidly to the ferrous state by hydroquinone [29]. The antioxidant activity of hydroquinone is also seen in its influence on polymerization reactions [1] where hydroquinone often inhibits polymerization by reacting with and destroying free radical intermediates. Similarly, hydroquinone is used to retard gelation of rubber sols and to prevent precipitation of gums from leaded aviation gasoline. The rate of deterioration of cotton fabrics

containing copper naphthenate and exposed to light can be decreased by hydroquinone [1].

As a photographic developer, hydroquinone reduces the exposed silver halide grains in a photographic emulsion at a rate considerably faster than that of the unexposed grains [1]. Sodium sulfite is added to developing solutions to prevent autoxidation of the developer, and quinone is immediately removed from the solution. Compared with other developing agents, eg, p-aminophenol, p-methylaminophenol, pyrocatechol, and p-phenylenediamine, hydroquinone is distinguished by its energetic action, producing high densities of developed silver and images of high contrast. However, the developing action of hydroquinone is sensitive to the concentration of bromide ion in the developing solution.

Many insects synthesize simple quinones, and these substances' high vapor pressure and unpleasant odor and taste serve as a defense against predators [30]. Plants such as tobacco, alfalfa, and wheat contain a variety of more highly substituted quinones and their cyclization products, eg, tocopherols. Cultures of a number of bacteria produce quinones of biological significance, including Coenzyme Q. This coenzyme, also known as ubiquinone, operates as an electron acceptor in the metabolic process of oxidative phosphorylation in the mitochondria of mammalian cells. Naphthoquinones, such as vitamin K_1, are found in several plants, and vitamin K_2 occurs in putrefied fish meal.

Biologically active quinones, eg, plastoquinone and ubiquinone (coenzyme Q), catalyze some biochemical reactions in animals, plants, and microorganisms [30]. These substances appear to be of suitable size, shape, and redox activity to transfer electrons to and from other

coenzymes. Quinones or phosphorylated quinols may play an active role in oxidative phosphorylation and in the respiratory cycle.

Hydroquinone derivatives are also important antioxidants, although many of them are too toxic to be used in biologic systems [31]. A hydroquinone derivative having "lipid properties" and the ability to be metabolized to nontoxic compounds would be a potentially useful antioxidant for edible fats. The antioxidant capacity of hydroquinone is superior to that of alpha-tocopherol [31]. Although hydroxychromans, tocopherols, and 5-hydroxycoumarans belong to the group of phenolic antioxidants, they are also derivatives of hydroquinone and form a separate subgroup [32]. Some of the naturally occurring inhibitors from vegetable oils are similar to or even identical with tocopherols and may replace vitamin E, although the vitamin E-like activity does not parallel the antioxidative potency. At least eight naturally occurring tocopherols with both pregnancy-maintaining and antioxidative activities are known [33].

Kusumoto and Nakajima [34] found that hydroquinone did not produce methemoglobinemia in vivo but had a strong methemoglobin-forming action in vitro. However, quinone acts to form methemoglobin both in vivo and in vitro. Quinone also readily combines with proteins, probably by addition reactions involving free amino and sulfhydryl groups, and this property causes quinone to stain skin and accounts for its use as an agent for tanning leather [35]. Cohen and Hochstein [36] observed the generation of hydrogen peroxide in human erythrocytes after the addition of the hydroquinone-quinone redox system. This finding supports the concept that hydrogen peroxide toxicity plays a major role in hemolysis induced by exposure to hydroquinone.

Hydroquinone is also used to prepare therapeutic bleaching cream. It is used as a 2% cream in a hydrophilic, stabilized, and nongreasy base [37] to bleach and lighten localized areas of darkened skin (severe freckling and skin blemishes).

Several other uses for hydroquinone have been proposed by various investigators. Hydroquinone has shown promise as an antitumor agent on B16 mouse melanoma cells in tissue culture [38] and on melanoma cells in black goldfish [39].

The National Occupational Hazards Survey 1976 (NIOSH unpublished data) reports that about 250,000 workers are potentially exposed to hydroquinone in about 151 occupational categories in the United States. Table XI-4 [40] is a list of major occupations in which workers may be exposed to this substance.

Historical Reports

Gibbs and Hare [41] stated in 1890 that the intravenous (iv) lethal dose of hydroquinone for dogs was 0.08-0.1 g/kg. In 1905, Koll [42] demonstrated that turbidity of the cornea could be produced in rabbits by exposure to the fumes of quinone. Velhagen [43], in 1931, was the first to document the occupational exposure effects of quinone vapor and hydroquinone dust on six workers actively involved in the manufacture of hydroquinone. These people worked in the plant for more than 4 years, and their ages varied from 28 to 55 years. Exposure levels were not reported. All six workers had band-shaped brown pigmentation of the conjunctiva and cornea near the eyelid fissure. Three of them also had decreased visual acuity.

Effects on Humans

Much of the early information about the effects of hydroquinone on humans has come from accidental, suicidal, and attempted suicidal ingestion of hydroquinone alone or of mixtures of photographic developers. Some questions posed by these reports have stimulated occupational and experimental studies involving controlled exposures of humans. No report of acute or chronic toxic effects in humans from inhalation of hydroquinone vapor or dust has been found.

(a) Short-term Effects

Mitchell and Webster [44], in 1919, reported a case of suspected hydroquinone poisoning in a 21-year-old woman. She suddenly became ill and was admitted to a hospital. The amount of hydroquinone ingested was not known, but about 20 grains (1,296 mg) of hydroquinone was recovered from about 4 pints (80 British fluid ounces or about 77 U.S. fluid ounces) of stomach washings. When admitted to the hospital, the patient was unconscious and pallid. Blood-stained foam on the mouth, pale lips, cold and clammy skin, a subnormal temperature, and a fast and feeble pulse were observed. The patient's pupils reacted to light, but the conjunctivae were insensitive to touch. Knee-jerk responses were absent, but the plantar reflex was present. There was no vomiting or diarrhea. The urine was green and positive for albumin. A series of violent convulsions occurred about 10 minutes after hospitalization. Respiration became very shallow but then improved. The patient remained semiconscious until the next day, when she showed some signs of recovery. On the 3rd day, knee-jerk responses were present, and from that day onward she improved steadily.

In 1927, Remond and Colombies [45] described a case of attempted suicide in which a 36-year-old man took about 12 g of hydroquinone. Shortly after ingesting hydroquinone, he experienced tinnitus, a suffocating sensation, a swollen tongue, and difficulty in breathing. Physical examination showed labored and rapid respiration, slightly cyanotic skin, and extreme exhaustion and sleepiness. He also had a fast but fairly strong and regular pulse, and the heart sounds and blood pressure were normal. Digestive and respiratory tracts, various reflexes, and nervous sensitivity were normal. The urine was dark. The patient's condition was markedly improved after 24 hours. His urine became clear after 4 days. A test for phenol in the urine was positive for the first few days; however, albumin was not present. Blood examination showed hypoglycemia and hypercholesterolemia. Thirteen days after the poisoning, all the values were normal except for the serum cholesterol, which was still somewhat high. The patient was released from the hospital at that time.

Halbron and associates [46], in 1931, published a case of fatal poisoning of a 37-year-old man who ingested 10 g of photographic developer containing 5 g of hydroquinone, 4.5 g of pyrocatechol (o-isomer of hydroquinone), 0.5 g of methyl-p-aminophenol sulfate, and a small amount of potassium metabisulfite. Fifteen minutes after ingesting the developer, the patient became unconscious, and he remained physically exhausted after regaining consciousness. He had a slight pain in the right hypochondrium and in the hepatic region. Gastric lavage yielded a black fluid. The urine and stool were dark. The urine contained a trace of bile pigment but no albumin, methemoglobin, or blood. After 4 days, icterus was noticeable,

and it gradually increased. A hematologic examination showed about 50,000 leukocytes, no eosinophils, 1.35 million red blood cells, and numerous nucleated red blood cells. He developed anuria on day 9 and died on the 12th day. The main gross autopsy findings were petechiae of the mucosa of the gastrointestinal tract and a slightly enlarged spleen. Microscopic examination showed significant changes in the liver, a hemorrhagic infiltration of the perilobular regions, and biliary pigmentation of parenchymal cells. The kidneys were hemorrhagic and contained much cellular debris.

In 1939, Busatto [47] reported the suicide of a 29-year-old woman who ingested two powders of 6 g of hydroquinone and 2 g of methyl-p-aminophenol sulfate. The first was taken at about 9:00 p.m. on the 1st day and the second the next morning. During the first 4 days after poisoning, she developed hypotension (90/45 mmHg), a weak pulse, cyanosis, mild jaundice, extreme exhaustion, and general weakness. On the 5th day, icterus increased markedly, and hyperthermia and pains in the urinary bladder developed. Her pulse also became very weak. The patient died on the 6th day. During hospitalization, she excreted urine in normal amounts, but it became brownish-black on standing exposed to air. Hyaline and granular casts as well as tubular epithelial cells appeared in the urine on the 5th day. Gross autopsy findings were icterus, mainly on the face, hands, and sclera, small scattered foci of bronchopneumonia, pulmonary edema in the posterior portions of the lower lobes, discoloration and swelling of the liver and kidney with blurring of the border between the renal medulla and cortex, and reddish-brown urine in the bladder. The gall bladder was filled with thick, dark bile. Microscopic examination showed cloudy

swelling and fatty infiltration with almost complete degeneration of the tubular epithelium in the kidneys, severe fatty vacuolation of hepatocytes (some had pyknotic nuclei and most had palely stained nuclei), moderate myocardial degeneration and acute myocarditis, and small bronchopneumonic areas especially in the edematous portions of the lungs. The lungs also contained emphysematous areas.

Zeidman and Deutl [48], in 1945, documented two fatal cases of poisoning by a developing powder that was a mixture of hydroquinone and monomethyl-p-aminophenol sulfate. The percentages of these compounds in the mixture were not mentioned. Both men (ages unspecified) took about 15 g of developing powder, mistaking it for Epsom salts. Within 5 hours, one developed diffuse abdominal pain, vomiting, and shock; the other developed severe, diffuse abdominal pain with no vomiting or immediate shock. In both patients, cyanosis, tachycardia, black stools (due to altered blood), and hematuria were observed during hospitalization. On the 3rd day of hospitalization, one man showed a reversal of the pupillary response to light. Urinalyses, performed on specimens immediately after urination, showed albumin, numerous erythrocytes, and free hemoglobin. The patients died 73 and 92 hours after ingesting the developing powder. The autopsies performed 12 hours after death and the subsequent microscopic examinations indicated that both patients had developed hemolytic anemia with jaundice. The principal post-mortem findings were marked dilation of the venous sinuses of the splenic red pulp, occasional phagocytosis of erythrocytes by endothelial and monocytic cells in the spleen and Kupffer cells in the liver, marked nephrosis and heavily pigmented casts in the kidney, deposition of bile pigment within the cytoplasm of hepatocytes,

hemoglobinuria, and jaundice. Acute myocarditis, acute passive congestion of lungs, and acute bronchitis were also noticed. Urine from the bladder of one cadaver contained active reducing substances.

In 1969, Grudzinski [49] reported a case of lethal poisoning in an 18-month-old child who had ingested 3-5 g of a photographic developer containing 80% hydroquinone (2.4-4.0 g) and 20% methyl-p-aminophenol sulfate (0.6-1.0 g). Abdominal pains and paleness of the skin and mucous membranes appeared about 12 hours after ingestion of the developer. After 2 days, the urine was brown and then became red, and feces were tarry. The patient was admitted to a hospital, where she developed periodic hand tremors and respiratory disorders and became comatose. The liver was enlarged and painful when palpated. The child was kept at the hospital and developed hemolytic anemia with leukocytosis. The patient had extreme pallor and was delirious and in a serious condition. Periodic convulsions of the limbs (unspecified) and areflexia appeared. When the patient went into a coma, cyanosis intensified and apnea developed. The child died after 2 days of hospitalization. Autopsy disclosed mucous gastritis, acute hemorrhagic enteritis, mucopurulent bronchitis, edema of the brain and lungs, and internal organ congestion. Microscopic examination of the internal organs showed numerous, small, hemorrhagic patches in the white substance of the brain and in the lungs, liver, and kidneys.

In 1974, Larcan et al [3] cited a case history of a 28-year-old photographer who ingested half a glass of photographic developer containing about 0.8 g of hydroquinone, 0.15 g of phenidone (1-phenyl-3-pyrazolidinone, a high-contrast photographic developer), 15 g of sodium carbonate, 10 g of sodium sulfite, and 0.15 g of potassium bromide. Two

hours after ingesting the solution, he had convulsions and was admitted to a hospital emergency room. Examination revealed a slight pulmonary infection and acidosis. Neurologic test results were normal. At first, he showed a methemoglobinemia of 13% and a hemoglobinemia which increased from 473 mg/liter to 515 mg/liter on the 5th day. The hematocrit was 36%, and the blood count showed 17,500 white blood cells and 3,710,000 red blood cells. Other unspecified laboratory tests were normal. Lesions of the posterior pharyngeal wall, the vocal folds, and the palate were found. A week after the ingestion, cystoscopy revealed urethral inflammation and radiologic examination of the gastrointestinal tract revealed inflammation of the duodenal bulb. Gastroscopy found petechial gastritis, mainly localized in the body of the stomach. The patient recovered after 12 days of hospitalization. The authors concluded that, although the patient ingested a small amount of developer, he showed the symptoms of major poisoning, such as convulsions, acidosis, anemia, increased polymorphonuclear cells, hemoglobinemia, methemoglobinemia, and petechiae of the gastric mucosa with erosion.

Since the patients described in all but two of the above reports [3,46-49] ingested other chemicals in addition to hydroquinone, hydroquinone toxicity cannot be accurately evaluated. However, reports by Mitchell and Webster [44] and Remond and Colombies [45] indicated that hydroquinone alone can cause mild to severe systemic effects in humans.

(b) Ocular Effects

Occupational exposures to quinone vapor and hydroquinone dust in industries reportedly have their primary effects on the eye. The ocular involvement presented in a number of reports [17,50-53] was characterized

by mild irritation and staining of conjunctivae and cornea. As the condition of the workers worsened with prolonged exposure in this environment, changes in the thickness and curvature of the cornea, loss of normal corneal luster [50], impaired vision, and decreased visual acuity [50,51,53] were evident.

In 1947, Oglesby et al [54] studied occupational exposure to airborne quinone vapor and hydroquinone dust concentrations. The air samples analyzed for hydroquinone and for quinone were collected from different work areas in the plant, with isopropyl alcohol as the absorbing agent in a midget impinger with all-glass impinger tubes. Samples were analyzed by a colorimetric procedure using phloroglucinol as the reagent and measuring absorbance at about 520 nm. However, this method does not distinguish quinone from hydroquinone. The frequency of air sample collections in these areas was not reported. The stationary air monitoring data were taken from mixing, filter press, oxidation, centrifugation, and packaging operation areas. Quinone concentrations ranged from 0.01 to 3.2 ppm (about 0.044 to 14.1 mg/cu m). Personal monitoring data were not collected.

The concentrations of hydroquinone dust in the packing area in January 1944 were between 20 and 35 mg/cu m. In January 1946, after enclosure and ventilation of the actual packing operation, the concentration of hydroquinone dust in this area fell to a mean of 1.3 mg/cu m (range 0.17-4.8 mg/cu m). The packing area was the only one in which hydroquinone dust was found; the other areas contained quinone vapor only. The precise analytical method used to determine this range was not specified [54], but it may have involved collecting hydroquinone dust on some type of membrane filter, followed by analysis of the collected

material by the same method used for quinone vapor. Emphasis was also placed on good housekeeping as an important factor in preventing eye injury from exposure to quinone and hydroquinone.

Oglesby et al [54] found that the odor of quinone became perceptible at or just above 0.1 ppm (0.4 mg/cu m), became strong at a mean concentration of 0.34 ppm (1.5 mg/cu m), and was marked above 0.15 ppm. The number of subjects was not given. Irritation of the eyes was evident when the concentration rose above 0.60 ppm, or 2.7 mg/cu m (mean concentration for irritation in four subjects was 0.8 ppm, or 3.5 mg/cu m), and became marked at about 3.0 ppm (14.1 mg/cu m). Since no evidence of systemic injury was encountered, the authors concluded that permissible concentration limits for quinone vapor and hydroquinone dust should prevent eye injury and ensure a comfortable working environment. On the basis of these findings, the authors suggested that a value of 0.1 ppm (about 0.44 mg/cu m) should be set tentatively as a maximum permissible working limit for quinone vapor and, pending further study, they arbitrarily selected a value of 2-3 mg/cu m (about 0.44-0.66 ppm) as a practical working limit for hydroquinone dust. They also suggested that hydroquinone dust may remain in contact with the eye longer than does quinone vapor, since the former compound dissolves in aqueous solvents only slightly. The intrinsically more irritating quinone vapor may limit its own adverse effects on orbital structures by inducing lacrimation so that the material in contact with those tissues is diluted and flushed away.

In 1947, Sterner and coworkers [17] described the effects of quinone vapor and hydroquinone dust on exposed workers involved in the manufacture of hydroquinone. Out of 201 workers of unspecified age and sex exposed to

hydroquinone, 94 were found to have eye injuries. Exposure concentrations and durations were discussed, but specific values were not presented. Exposure concentrations are assumed to be the same as those reported by Oglesby and his associates [54] because Sterner et al [17] referred to the paper of Oglesby et al [54] for definition of the conditions of exposure.

The eye injuries involved both the conjunctiva and the cornea, with those of the cornea being considered to be of greater importance because they could interfere with vision [17]. The conjunctival lesions consisted of a pigmentation varying from a slight, diffuse, brownish tinge to a dense, brownish-black stain in the interpalpebral fissure (between the eyelids). The dense stains on the conjunctivae were associated frequently with infiltration by grayish-white opacities. The pigment deposition occurred in the form of spheres, some of which were quite large; they were most marked in older workers and were observed in those areas of the conjunctiva that normally contain fat. A second, rarer conjunctival lesion consisted of the superficially embedded, small, white, irregular flecks mentioned above being associated with dense pigmentation which is distinct from the brown granules. The corneal injuries were of two types: a diffuse, greenish-brown stain, mainly in the superficial layers of the cornea, and grayish-white opacities of varying size and shape. These corneal lesions also tended to be restricted to the interpalpebral area. Signs of continued eye irritation, conjunctivitis, photophobia, moderate lacrimation, a burning sensation, and even impaired vision were occasionally observed.

The authors [17] concluded that the severity of eye injury increased with the length of employment. Severe corneal injury was not found in

workers with less than 5 years of general plant exposure. However, one or two workers with relatively short exposure (1 or 2 years) showed slight conjunctival staining. Removal of the workers from the exposure areas considerably reduced the conjunctival staining, but there was little or no abatement of the corneal opacities. No relationship between the workers' jobs and eye injuries could be determined, because the workers circulated through all the operations in the plant. However, those workers who spent the most time near the filter press unit developed the highest degree of injury.

Anderson [51], in 1947, studied the ocular lesions that developed in 44 persons engaged in the manufacture of hydroquinone. These people had worked in the plant for from 6 months to more than 15 years, their ages ranging between 22 and 55 years. Exposure concentrations were not reported. The author discussed three cases in detail. One man, who showed the most severe corneal damage, had worked with hydroquinone for 13 years. Six months before he was examined, he was transferred to another worksite because of visual difficulties. Examination with a slit lamp showed no gross conjunctival staining, but fine, discrete, brownish granules were observed with high magnification. In the superficial layers of the cornea, many fine, grayish, translucent, highly refractile dots and many fine wrinkles in vertical distribution were observed. In this case, hypesthesia (hypoesthesia) was also present.

In a second affected employee, who had worked with hydroquinone for 11 years, staining of the conjunctivae had been present for 8 years and low visual acuity had been present for 4 years [51]. The lesions in both eyes

were identical. Examination of the eyes with the slit lamp at low power showed pigmentation of the conjunctivae and the cornea.

A third affected man, who had worked with hydroquinone for 9 years, showed staining of both the conjunctivae and cornea in the interpalpebral fissures [51]. The patient's eyes were reexamined about 22 months after the first examination. The diffuse staining of the conjunctivae and cornea was less marked, but the dark brown globules had increased in size and number and the left eye showed conjunctival pigmentation without corneal changes.

Anderson [51] concluded that the duration of exposure was the most "constant factor" in determining the degree of injury. Severe ocular lesions had developed in some persons exposed to hydroquinone for 5 years or longer. The author also suggested that prolonged exposure to this compound had produced corneal dystrophy and dyskeratosis.

In 1954, Miller [53] reported cases of ocular discoloration in workers exposed to hydroquinone and quinone. Five cases of ocular discoloration were observed among seven workers exposed principally to hydroquinone powder in a hydroquinone manufacturing plant. These workers had worked in the plant as mixers or sifters for from 1 to 20 years, their ages falling between 21 and 66 years. Exposure levels were not reported. One worker's vision was seriously affected. His visual acuity was less than 6/60 for the right eye and 6/36 for the left eye. This worker, who was 52 years old and had worked in the plant for 20 years, also had both conjunctival and corneal pigmentation. Three other workers also had decreased visual acuity. Two showed conjunctival staining, and the third had corneal pigmentation. These three workers were 48-65 years old and had

worked in the plant for 14-20 years. Three other workers, who were 21-44 years old and had worked 1-5 years in the plant, showed little or no abnormality of the conjunctivae or cornea or loss of visual acuity. The author suggested that the length of exposure to hydroquinone was the main determining factor in producing eye damage and that the older workers were more prone to ocular complications than the younger ones.

Anderson and Oglesby [50], in 1958, delineated the ocular hazards of hydroquinone for workers manufacturing this compound. In 1955, 201 workers were screened. Almost all employees, including some executive and clerical personnel, were exposed to unknown amounts of hydroquinone. Their eyes were examined with a slit lamp. Effects from exposure to hydroquinone were observed in 105 people employed in a hydroquinone manufacturing area for 1-26 years. They were subdivided into four major groups: group A consisted of workers retired because of marked visual loss; group B contained workers transferred from their jobs because of severely impaired vision; group C included workers having moderate ocular involvement, including conjunctival and corneal staining; and group D contained workers with little or no staining of conjunctivae or cornea. The number of workers in each group was not stated. In 1956, the authors reexamined all members of groups A and B (seven workers from each) and certain members of group C who had been noted previously to have potentially serious eye lesions (24). No workers in groups A and B had been exposed to hydroquinone within the last 3 years, and all conjunctival staining had disappeared. The members of these two groups had worked in the manufacture of hydroquinone for a mean of 11.3 years (range 1-21 years) but had been away from such employment for a mean of 5.6 years (range 3-11 years).

In groups A and B, only 2 of the 14 severely affected workers developed pterygia (triangular patches of mucous membrane attached to the conjunctiva and cornea, usually on the nasal side of the eye) [50]. However, pterygia were found in 8 of 24 workers in group C. According to the authors, the significance of this observation was unclear. Ten of 14 workers in groups A and B developed bilaterally conspicuous dark brown lines (Hudson-Stahli lines). These lines lie horizontally in the cornea and are most prominent just below the lower border of the undilated pupil. They are relatively well-defined, sinuous streaks consisting of greenish-brown granular material. These lines were also equally conspicuous in 14 of 24 workers in group C. The authors suggested that the development of these lines was the most frequent, and perhaps the earliest, sign of corneal change seen in these patients and that the lines are probably associated with the corneal changes that produced astigmatism. Vertical striae were also observed in 7 of 14 workers in groups A and B and in 2 of 24 workers in group C. These striae were widely dispersed and resembled glass rods in a somewhat sinuous and uneven pattern.

The visual acuity (Snellen) in group A was a mean of 20/150 for both eyes. Full correction could be achieved in none of these eyes. In group B, the mean visual acuity of the right eyes was 20/69 and that of the left eyes was 20/42. Full correction was achieved for 5 of the 14 eyes in this group. Severe astigmatic errors developed in 8 of 14 workers in groups A and B; however, severe astigmatism was not seen in group C. The mean visual acuities in this last group were 20/20 for the right eyes and 20/19 for the left eyes. The authors occasionally observed increased eye sensitivity (hyperesthesia), conspicuous, possibly enlarged, corneal

terminal nerve filaments, loss of normal corneal luster, and dryness and scarring of the conjunctivae and cornea.

Anderson and Oglesby [50] concluded that quinone vapor or hydroquinone dust directly affected only the most superficial layers of the cornea, the epithelium and Bowman's membrane. They postulated that the tension generated in the deeper parenchyma by the stretching or contracture of these superficial structures produced the deeper striae. These striae represented the second and more advanced stage in a process that led to a flattening or double angulation of the cornea, which, in turn, caused astigmatism and could possibly cause keratoconus, ie, a conical protrusion of the cornea.

In 1966, Naumann [52] studied the microscopic changes in three corneal specimens obtained when keratoplasty (corneal grafting) was done on three workers who had been exposed to hydroquinone for 9, 9, and 11 years, respectively. The exposure concentrations were not reported. The corneal grafts were performed to restore sight 7, 7, and 20 years after the three workers' exposures ended. The results of the microscopic examinations were very similar for all three corneal samples. Two types of pigment were present. One, which was found in the epithelial layer, was iron-positive (diffuse brown pigment) and was described by the author as the type seen in the corneas of many elderly persons. The other was located in the most damaged part of the corneal stroma and, like the oxidation products of hydroquinone, was argyrophilic. The corneal stroma had degenerated, had lost its fibrillar structure and birefringence with polarized light, and contained deposits of acid mucopolysacharides. Bowman's membrane was either irregularly thickened or absent in places. Naumann thought that the

loss of keratocytes and the marked damage of the cornea might be responsible for the astigmatism of the workers exposed to hydroquinone for long periods.

No studies are available which document serious eye injuries caused by exposure to pure airborne hydroquinone. All studies were related to the mixed exposure to quinone vapor and hydroquinone dust.

(c) Dermal Effects

In 1939, Oliver and associates [55] reported occupational leukoderma (depigmentation) at several industrial operations among workers who wore a certain brand of rubber gloves. Patch tests with the chemical components of the gloves performed on the affected workers (numbers not reported) showed that an antioxidant caused positive inflammatory reactions on all subjects' hands and forearms. The antioxidant was known by the trade name of Agerite Alba, which was the monobenzyl ether of hydroquinone and was said to contain less than 1% free hydroquinone. A definite depigmentation, diagnosed as leukoderma, occurred at the site of reaction, but there was no scar formation. Examinations showed not only that all affected workers had depigmentation on the hands and forearms but also that several of them were affected on the covered parts of the body. The authors noted that the skin slowly became repigmented when the workers wore gloves made without using the antioxidant.

Lapin [56], in 1942, described contact dermatitis in 6 infants under 3 months of age and on 1 of 30 newborn infants to whom "antiseptic baby oil" was applied. The name of the antiseptic baby oil was not given; however, it contained hydroquinone (as an antioxidant), hydroxyquinoline, and chlorobutanol in unstated concentrations. The faces of the first six

children were cleansed with the baby oil alone for about 3 months. The infants showed a patchy, erythematous, and vesicular dermatitis with occasional papules. The dermatitis was almost entirely limited to the cheeks and forehead. When bland ointments were used instead of the baby oil, the lesions disappeared in a few days. In a patch test, the antiseptic baby oil was applied to an unspecified area, and patches soaked in olive oil and liquid petrolatum were used as controls. After 48 hours, the patches were removed, and the areas in contact with the antiseptic baby oil had erythematous and vesicular lesions, while the control areas were completely unaffected in all six infants.

The author [56] used the same patch tests on 30 newborn children from 2 to 9 days old, with "salad oil" (mainly cottonseed oil) and liquid petrolatum serving as control substances. One child showed the typical erythematous and vesicular response to the antiseptic baby oil. Lapin concluded that the hydroquinone in the baby oil caused seven children in his two studies to develop contact dermatitis.

In 1952, Denton et al [57] applied continuous patch tests of 10% and 30% hydroquinone in yellow petrolatum to the backs of seven young adults for 30 days. Five of the subjects were black and two were white with freckles. Three black subjects developed depigmentation from both concentrations of hydroquinone. The higher concentration of hydroquinone produced the greatest depigmentation. Dermatitis was also observed in two black subjects, and the authors concluded that it was caused by hydroquinone.

Spencer [58], in 1961, studied the bleaching effect of hydroquinone and two of its derivatives on pigmented skin in simulated use tests with a

group of 53 white and 45 black men who were middle-aged or older. Five percent hydroquinone was initially used as a bleaching agent in a vanishing cream base. The cream was applied twice daily, 7 days a week, for 4 months, but the concentrations were reduced to 1.5% and 2% after 3 weeks because redness, burning, and contact dermatitis occurred in 33 subjects. This inflammatory reaction subsided when the concentrations were decreased, and no cases of contact dermatitis developed after the concentration of hydroquinone in the bleaching cream was decreased. The incidence of depigmentation was higher in the white (31%) than in the black (14%) subjects. An inflammatory reaction did not always precede depigmentation. When it did occur, it seemed to enhance the bleaching effect by increasing the degree and rate of depigmentation.

In 1965, Spencer [59] studied the depigmentation effects of 2, 3, and 5% stabilized hydroquinone ointments on 94 middle-aged and older white men with various pigmentation abnormalities and on 43 normal black men in the same age group. The hydroquinone ointment was applied to the back of one hand twice daily for 3 months. The ointment base was applied to a similar area on the other hand, and this site served as a control.

Of the subjects who used 2 or 3% hydroquinone ointment, 50-76% showed depigmentatory effects from hydroquinone [59]. Of subjects who received applications of 5% hydroquinone ointment, 10 and 75% of blacks and whites, respectively, showed depigmentatory effects. No white men treated with 2 or 3% hydroquinone ointment showed sensitization, but two who used 5% hydroquinone ointment developed severe sensitization. The treatment was stopped for these two men. Patch tests performed with 5% hydroquinone ointment produced a strong positive reaction in them. Samples of skin were

removed from both hands of 19 white men before and after treatment. The microscopic findings in hydroquinone-treated skin sections were a greater dispersion of melanin, less melanin in the nuclear caps, an unspecified alteration in the melanin granules, with clumping into globules, a normal number of melanocytes with fewer melanin granules, and a 50% drop in the concentration of melanin present when compared with that in control skin sections. No microscopic changes were seen in blacks. The author suggested that the depigmentatory effect of hydroquinone was primarily a cellular reaction; however, the total destruction of melanocytes did not occur when 2 or 3% concentrations of hydroquinone were used.

Arndt and Fitzpatrick [60], in 1965, reported the effects of the topical use of hydroquinone as a depigmentatory agent on 56 hyperpigmented patients. Hydroquinone, as a 2 or 5% cream, was applied by all patients twice daily. Sex and age were not stated. Seven of the patients were black and the rest white. For most patients, only portions of an area were treated, ie, half of the face or only one extremity. In this way, each patient served as his or her own control. All patients were examined monthly. If no effect was observed by the 3rd month, treatment was stopped.

The 5% hydroquinone cream produced a high incidence of primary-irritant reactions [60]. While the 2% hydroquinone cream appeared to be equally effective for lessening hyperpigmentation, it produced less severe irritant reactions. The depigmentatory effect was usually observed after 4 weeks of treatment; however, the onset of initial (primary irritant) changes varied from 3 weeks to 3 months. Of the 56 patients, 44 (78.6%) showed a response to hydroquinone cream, but this cream did not completely

cure their pathologic hypermelanosis. Thirty-two percent of the patients using 5% hydroquinone cream had erythema and a tingling sensation at the site of application; only 8% of the patients using 2% hydroquinone cream had mild reactions. Only one patient who used 5% hydroquinone cream experienced a possible allergic sensitization. Patch tests on this patient with both the 2% and the 5% hydroquinone creams showed a positive reaction after 48 hours, and generalized eczematous eruptions were observed also. The authors suggested that hydroquinone was a moderately effective depigmentatory agent in about 78.6% of the cases. When it was used in 2% concentration, the incidence of irritation or sensitization was negligible. These findings were confirmed by Albert and Goldberg [61] in 1966 and Garza Toba [62] in 1968.

In 1975, Findlay et al [63] reported the effects on skin of the repeated use of strong hydroquinone bleaching creams (5% hydroquinone or more). From 1969 to 1974, they examined 35 adult South African Bantu women who had used creams containing high unspecified concentrations of hydroquinone for up to 8 years and who had slowly developed dermatosis over a period of 6 months to 3 years or longer. The maximum incidence occurred in women 30-39 years of age. The most frequent gross change was the occurrence of colloid milia, which consisted of clustered or confluent tense papules and micropapules.

Bentley-Phillips and Bayles [64], in 1975, assessed the safety of hydroquinone in cosmetic skin-lightening products to determine the optimal concentration of hydroquinone. The 778 volunteers who took part in the study were selected from several racial groups, and their skin varied from very fair to very dark. These subjects were blacks (Zulu), Asians

(Indian), and "coloureds" (a mixture of black and white). They were tested by open-patch tests and standard 48-hour closed-patch tests.

In the open-patch tests, 200 Indian factory workers (170 men and 30 women) were tested with 5, 6, and 7% hydroquinone in soft paraffin [64]. The preparations were applied to the sides of the neck and behind the ears, and they were rubbed in for 30 seconds. The test areas were examined after 24 hours, and the preparations were reapplied as before. A second examination was made after 72 hours. Six of the 200 subjects showed a positive irritant reaction with all 3 tested concentrations after 24- and 72-hour examinations. Mild erythema was found in each case; erythema became more marked at 72 hours than it had been at 24 hours.

In standard 48-hour closed-patch tests, 578 volunteers selected from the different racial groups (170 male and 30 female Asians, 60 male and 256 female blacks, and 62 female "coloureds") had closed patches applied to their backs for 48 hours [64]. The test areas were examined after 48 hours and 1, 2, and 4 weeks. Preparations of skin-lightening lotions, creams, and ointments were used at concentrations of 1, 2.5, 3.5, 5, and 7% hydroquinone. All other constituents of the cosmetic preparations were similarly tested. A blank patch was applied as a control.

Little or no irritant reaction was observed in the closed patch tests at concentrations of 1, 2.5, and 3.5% of hydroquinone after any observation period [64]. However, 0.0-83.6% of the subjects in different racial groups had adverse reactions of the skin at concentrations of 5 and 7% hydroquinone after 2-, 7-, and 30-day observation periods. Blacks and "coloureds" had much higher percentages of reactions than did Indians. The authors suggested that the large differences in response at higher doses

were probably caused by their using people of various races. The blacks and "coloureds" were thought possibly to have become sensitized to hydroquinone by prior use of bleaching preparations for lightening the colors of their skins, whereas the Indians were considered to be usually content with the colors of their skins. The 3.5 and 5% creams produced considerably more reactions than lotions of the same strength. No significant differences were seen between creams and lotions containing 1 and 2.5% hydroquinone. The authors concluded that high concentrations of hydroquinone should be avoided and that the 3% concentration was reasonably safe and effective for all pigmented skin, although about 5 or 6% of black females reacted to patches containing 1 or 2.5% hydroquinone.

A test was started with 52 female black volunteers and 10 black nurses who were to apply a 7.5% hydroquinone cream to skin on one side of the body for a period of time. This test was abandoned because of uncertain performance of the applications and of gradual dropping out of nearly 56% of the volunteers. No data were presented from the test.

(d) Long-term Systemic Effects

The following studies of experimental subjects [65] or workers exposed [17] to hydroquinone for longer periods indicate that exposures cause few or no adverse systemic effects and that they are not similar to those acute findings described previously [44,45].

In 1953, Carlson and Brewer [65] studied the toxicity of hydroquinone on 19 men and women. Two men ingested 500 mg of hydroquinone daily for 5 months, and 17 subjects, both men and women, ingested 300 mg/day for 3-5 months. The compound was taken with meals in three divided doses. While the experiment was in progress, red blood cell and white blood cell

differential counts were made and the concentration of hemoglobin in the blood, sedimentation rate, platelet count, coagulation time, and icteric index were determined separately for all subjects. Urinalyses were also performed, including albumin, reducing sugars, counts of white and red blood cells and of casts, and urobilinogen. The subjects served as their own controls, with a control period of 1 month. Analyses of the blood and urine of all 19 subjects that ingested 300-500 mg of hydroquinone daily for 3-5 months showed no abnormal findings. The authors suggested that, because the compound was taken in three divided doses at mealtime, the rate of absorption might have been diminished under these circumstances; the dosage did not produce toxic effects in the subjects.

Sterner et al [17] studied workers (age and sex unspecified) with eye injuries produced by exposure to quinone and hydroquinone for evidence of systemic absorption and intoxication. Physical examinations and laboratory tests were performed (hemoglobin, red blood cell, total white cell, and differential counts, hematocrit, sedimentation rate, and icteric index), including the ratio of inorganic sulfate to total sulfate in the urine. Two groups of employees were selected for study in each of the two years, 1943 and 1945. One group included 47 employees with some degree of eye injuries and workers with perhaps the greatest exposures to quinone and hydroquinone. The second group included all the employees involved in the manufacture of hydroquinone (100 persons in 1943 and 101 in 1945). The control group consisted of 1,018 employees in the same plant who had no exposure to harmful materials or who gave no evidence of untoward effects from potentially toxic substances. Exposure concentrations and duration were discussed, but specific values were not presented. It is stated that

exposure concentrations were those reported by Oglesby and his associates [54].

No significant differences were found between the control values and the findings for employees with eye injury or for those engaged in the manufacture of hydroquinone [17]. The most nearly significant differences from the control values were in the percent of lymphocytes in the blood for all exposed employees and those with eye injuries in 1943, in the icterus index of the employees with eye injuries in 1945, and in the percent of basophils in the blood of exposed employees in 1943. There were no significant differences between measurements made on the people with eye injuries and those of the entire exposed population of employees.

Physical examinations and laboratory tests did not discover any evidence of systemic absorption and systemic toxic effects [17]. The authors concluded that the exposure to quinone and hydroquinone was sufficient to produce the eye injuries but that it did not produce systemic toxic effects that were measurable by physical examinations and laboratory tests.

Woodard [15], in 1951, studied absorption and excretion of hydroquinone in a human volunteer (age not reported). Hydroquinone was administered orally at a dose of 200 mg (3 mg/kg) and a 24-hour urine sample was collected. A 200-ml urine sample was analyzed after ether extraction for the recovery of free hydroquinone. Similar samples were analyzed after acid hydrolysis to determine conjugated hydroquinone.

No free hydroquinone was found in the urine [15]. Excretion of the conjugated forms accounted for 10% of the 200-mg dose. Hydroquinone was excreted partly as the ethereal sulfate and partly as the glucuronide. The

author postulated that the failure to recover hydroquinone in the urine may have been caused by the low dosage level (200 mg) or by the failure to hydrolyze hydroquinone vigorously enough to obtain complete hydrolysis.

Epidemiologic Studies

No epidemiologic studies of populations exposed to hydroquinone were found in the published literature.

Animal Toxicity

The following animal experiments present effects that are representative of hydroquinone administration. Studies are included which illustrate the mode of toxicity of hydroquinone and other effects that have not been demonstrated or confirmed in humans.

(a) Short-term Effects

There is abundant documentation showing that experimental (oral, intraperitoneal, intravenous, and subcutaneous) administration of hydroquinone has produced short-term toxic effects in animals. No report of short-term toxic effects in experimental animals from inhalation of hydroquinone vapor or dust has been found.

Oettel [66], in 1936, described hydroquinone poisoning in 11 cats (1.8-5.0 kg). Signs of intoxication and the times of death were recorded for all animals, but their sex, age, and breed were not stated. Administration by gavage of 20, 40, or 50 mg of hydroquinone/kg/day over 12 days produced an increased sensitivity to physiologic stimuli, choreiform movements, subsequent partial paralysis, loss of muscle tone, hypothermia,

labored breathing, and edema of buccal mucosa, lips, and conjunctivae. Seven cats died within 16 days. Leukocytosis, reticulocytosis, and increased fragility of the red blood cells were found in all treated animals after 24 hours. The author never found methemoglobin in the blood of living cats, but it was observed in blood samples from dead animals. However, the action of hydroquinone on hemoglobin is not clear from this study.

In 1940, Busatto [67] reported the effects of subcutaneously injected hydroquinone in white mice. The sex and age of the mice were not reported. The behavior of 40 animals weighing 15-25 g was observed after they had received single injections of up to 0.5 mg of hydroquinone/g of body weight. The author saw three separate stages of poisoning. The initial stage, which lasted about 40 minutes, was characterized by markedly increased motor activity, hyperactive reflexes, sensitivity to light and sound, labored breathing, and cyanosis. The second stage lasted for 1 hour and was characterized by clonic convulsions, which increased in frequency and intensity. The third stage, which lasted about 6 hours, was characterized by complete motor exhaustion, paralysis, a nearly complete loss of sensitivity and reflexes, semicoma, and death. The author reported that the minimal lethal dose of hydroquinone for mice was 0.16-0.17 mg/g. Larger doses diminished the duration of each stage, a dose about twice the minimal lethal dose producing death immediately after the second stage.

Woodard [15] published a report about the single-dose toxicity of hydroquinone in several species in 1951. The author used equal numbers of male and female Osborne-Mendel rats (in groups of 10 or more) and adult Swiss mice (in groups of 10) weighing 18-30g, 24 mongrel dogs weighing 5-12

kg, 10 rabbits, 20 guinea pigs, 10 cats, and 7 pigeons. Other information on the age, sex, and strain of the animals was not reported. Unfasted animals and animals fasted for 18 hours were given hydroquinone by the routes mentioned below and then were given access to Purina Laboratory Chow and water ad libitum.

After 30-90 minutes, rats, guinea pigs, pigeons, and cats receiving single oral doses of a 2 or 3% aqueous solution of hydroquinone salivated and developed tremors and convulsions; the pigeons and cats also vomited [15]. Death occurred from respiratory failure and depression of the CNS within a few hours. Dogs receiving hydroquinone by stomach tube or in gelatin capsules and rats administered hydroquinone iv or ip reacted similarly. The oral LD50's for these animals, reported in mg/kg, were: rats, 302; mice, 390; rabbits, 540; guinea pigs, 550; pigeons, 500; cats, 50; and dogs, 200. The approximate LD50's for rats injected iv and ip were 115 and 160 mg/kg, respectively. Cats were found to be the species most sensitive to intoxicaton by hydroquinone. Woodard suggested that food in the gastrointestinal tract reduced the toxicity of hydroquinone, perhaps by affecting both the rate and the extent of absorption of the compound.

Fassett and Roudabush [68], in 1952, reported the results of a short-term toxicity study of hydroquinone in rats. The strain and sex of the rats were not reported. Rats weighing about 275 g were given ip injections, 5 days/week, for about 3 weeks. The selected doses were fractions of a predetermined ip LD50 (200 mg/kg), starting with one-half of this value and reducing the dose by some equal log interval. Only one or two rats were used for each dose. Control rats were injected with only the solvent (water or propylene glycol) in a dose equal in volume to that of

the largest dose of the compound tested. The doses were adjusted for body weight at weekly intervals. The rats were observed for weight changes, food intake, behavior, appearance, and death. Pathologic examinations were also performed, including liver and kidney weights, hematologic studies, and occasional excretion studies. Hydroquinone produced little or no cumulative effect at a dose of 100 mg/kg/day. Alterations of anatomic and histologic details and white blood cell counts were not observed. The authors reported an acute oral LD50 of 400 mg/kg for hydroquinone in rats; however, experimental details were not given.

In 1953, Carlson and Brewer [65] published a study of the short-term toxicity of hydroquinone for rats, dogs, and cats. The ages and sexes of these animals were not reported. In LD50 studies, hydroquinone was dissolved in glycerine, propylene glycol, or water and administered in different (unspecified) doses by stomach tube to unfasted and fasted (for at least 18 hours) Sprague-Dawley and Wistar rats. In each experiment, 6 groups of 10-40 rats were used to determine the LD50. Twenty-eight dogs and 10 cats also were given unspecified doses of hydroquinone in sugar-coated tablets with a small amount of meat. The LD50's of hydroquinone in both strains of unfasted rats were 731-1,295 mg/kg (mean, 1,050 mg/kg). However, in fasted rats the LD50 averaged 310 mg/kg, which represents a 2- to 3-fold increase in toxicity. The oral LD50 of hydroquinone for dogs was 299 mg/kg, and for cats it was between 42 and 86 mg/kg.

Delcambre et al [69], in 1962, studied the short-term effects of hydroquinone on rats and rabbits. Seventy Wistar rats weighing 200-300 g were injected ip with hydroquinone. The sex of the rats and the exact amounts in the different doses of hydroquinone were not stated. Rabbits

were injected iv with hydroquinone. The number, age, sex, and strain of the rabbits were not mentioned. The ip LD50 of hydroquinone for rats was 194 mg/kg; 50 mg/kg produced "tremors-hypotonia," and 10 mg/kg produced ketonuria in fasting rats. In rabbits, an iv injection of hydroquinone at a dose of 150 mg/kg produced death; 100 mg/kg produced "tremors-hypotonia" followed by death, and 10-20 mg/kg produced hypertension and hyperkalemia.

In 1966, Mozhayev and associates [70] examined the short-term toxic effect of hydroquinone in albino rats and mice. Hydroquinone in 6% solutions, either freshly prepared or oxidized (unspecified), was injected iv into 230 albino rats and 70 albino mice. The ages and sexes of the rats and the mice were not given. The iv LD50's of hydroquinone were 340 mg/kg for mice and 720 mg/kg for rats. The authors also reported that the toxicity of the oxidized solution of hydroquinone did not differ significantly from that of the freshly prepared solution of hydroquinone. The administration of hydroquinone in divided doses significantly reduced its toxicity.

Nomiyama and associates [21], in 1967, determined the median lethal doses of benzene metabolites, including hydroquinone, in mice by subcutaneous administration. An aqueous solution of hydroquinone was injected into 4-week-old male mice of the ICR-JCL strain weighing about 20 g. The animals were supplied with commercial pelleted food and water ad libitum. Fifty-two mice in 9 dose groups were injected with hydroquinone solution in the dose range of 0.08-0.24 g/kg, with 4 to 7 mice in each dose group. The LD50 was calculated from the mortalities during the 6 days after the injections. The subcutaneous LD50 of hydroquinone was 0.19 g/kg in mice. Most mice had convulsions and died within 24 hours.

In 1976, Christian et al [71] reported the short-term toxic effects of hydroquinone in 116 young adult rats. Male and female rats, 8-10 weeks old, from Carworth Farms were given a 5% aqueous solution of hydroquinone by intubation, either freshly prepared or 1 week old. Doses ranged between 180 and 2,100 mg/kg. Signs of sickness and the number of dead animals were recorded daily for 3 weeks.

Within 2-10 minutes after administration of hydroquinone, the rats became hyperactive, hypersensitive to auditory and tactile stimuli, increasingly tremorous, moderately convulsive (clonic), and severely spastic [71]. When the dose was sufficiently large, death occurred during a severe tonic spasm within 2 hours after ingestion of hydroquinone. When the dose was sublethal, recovery was complete within 3 days. The authors did not find any difference between the mortality produced by oxidized (prepared 1 week earlier and darkened by aging) and that produced by freshly prepared solutions of hydroquinone. The oral LD50's of hydroquinone in the freshly prepared solution for the males and females were 743 and 627 mg/kg, respectively, and the overall average for both sexes was 680 mg/kg with 95% confidence limits of 457-1,016 mg/kg.

(b) Ocular Effects

Hughes [72], in 1948, published the results of a study of the tolerance of rabbits' corneas for various chemical substances, including hydroquinone. The age, sex, and strain of the rabbits used were not reported, and no control group was mentioned. Three rabbits were injected intracorneally with 0.1 ml of hydroquinone solution having a concentration between 0.05 and 0.012 molar. The effects of hydroquinone on the rabbits' corneas were observed during 7-14 days. Secondary infection was uncommon.

Accidental injection of air with hydroquinone solution into the cornea did not increase the severity of the reaction produced by hydroquinone. The occurrence of severe lesions produced by hydroquinone in the cornea of rabbits' eyes was about 5% (mild reaction).

(c) Dermal Effects

In 1952, Denton and coworkers [57] reported the effects of oral and parenteral administration of hydroquinone and other p-hydroxyphenyl compounds on pigmented guinea pigs and mice. In one experiment, five adult male guinea pigs (average weight 564 g) were given capsules containing hydroquinone in doses increasing from 22 to 88 mg/kg/day (total dose 2.38 g) for 76 days. A similar group was used as the control. Hydroquinone did not produce any toxic effect in guinea pigs up to the highest dose tested. After 4 weeks of treatment, questionable depigmentation was seen in one animal. No control animals showed depigmentation.

In another experiment, Denton et al [57] used four adult black C-57 male mice weighing about 20 g. They were given 0.05 ml of aqueous hydroquinone solution (about 0.88%) subcutaneously at a daily dose of 22 mg/kg/day for 76 days. Another group of four mice was given hydroquinone in drinking water in doses increasing from 37 to 262 mg/kg/day for 76 days. All mice were observed for 76 days for pigmentary changes in their hair. All hydroquinone-injected mice showed marked depigmentation at the site of injection, whereas the mice that received hydroquinone in their drinking water had only a questionable pigmentary change. However, when the authors repeated this experiment with 7-week-old male C-57 black mice, two of the four mice given hydroquinone in drinking water had some general depigmentation. Two of the four adults and all four young mice receiving

hydroquinone in the drinking water developed alopecia (loss of hair) on the back of the neck. The authors concluded that high concentrations of injected hydroquinone produced depigmentation at the injection site; when hydroquinone was given orally to mice, some unknown factor associated with the age of the mouse determined the result.

Bleehen and associates [73], in 1968, discussed the depigmentatory potencies of 33 compounds, including hydroquinone, in guinea pigs. Hydroquinone was applied to wax-epilated (hair removed by application of molten wax and forceful removal of the solidified wax) skin of the back and unepilated skin of the ear of eight black guinea pigs in concentrations of 1, 3, 5, 7, and 10% in three vanishing creams. The number of animals used at each concentration was not stated. The mixtures were applied once daily, 5 times/week, for 1 month. The vanishing creams without hydroquinone were similarly applied to six black guinea pigs that served as controls. The back of each guinea pig was epilated weekly. The animals were observed for the degree of depigmentation and of skin irritation. Mild to moderate depigmenting potency was found in all areas to which creams containing 1-10% hydroquinone were applied. However, hydroquinone in the creams was irritating only at and above the 5% concentration. There was no depigmentation or irritation in the controls.

In 1974, Jimbow et al [74] reported depigmentation in the skin and hair of 24 black guinea pigs receiving topical applications or subcutaneous injections of hydroquinone. In the first experiment, hydroquinone was topically applied to the epilated backs of adult male and female guinea pigs weighing 600-1,000 g. Creams containing 2 or 5% hydroquinone in an oil-water emulsion base were applied daily, 6 days/week, for 3 weeks.

Specimens of the skin were taken from five animals at 1-, 2-, and 3-week intervals for histochemical evaluation and electron microscopic examination. Specimens were taken from the epilated skin of five control animals that received either no application or an emulsion-base cream with all ingredients except hydroquinone. The remaining 19 experimental animals were used to evaluate depigmentation. In the second experiment, the depigmentatory effects on the melanocytes in the hair were evaluated after subcutaneous injection of hydroquinone solution. Two milliliters of 1% hydroquinone in normal saline was injected subcutaneously daily for 8 days around both epilated and nonepilated areas. Specimens of skin were taken 4, 8, and 15 days after the first injection. Specimens taken from the epilated and nonepilated hair follicles, with or without the injection of 2 ml of saline solution, served as controls. Each specimen of skin removed for biopsy was divided into two parts for histochemical studies of the 3,4-dihydroxyphenylalanine (DOPA) reaction of epilated and nonepilated skin and for electron microscopic studies of skin and hair follicles.

Jimbow and coworkers [74] observed that the topical application of 2 or 5% hydroquinone creams to guinea pigs' skin caused depigmentation, inflammatory changes, and thickening of the epidermis. Depigmentation was first seen within 8-10 days and was greatest between 14 and 20 days. Total depigmentation of the skin was rarely found. Cream containing 5% hydroquinone produced more marked depigmentation and scaling than cream containing 2% hydroquinone. A mild inflammation produced by the topical application of hydroquinone was characterized by the migration of dermal cells into the epidermis. These cells were mainly histiocytic, but some lymphocytes and polymorphonuclear leukocytes were also observed. Skin

treated with hydroquinone also had a markedly thickened epidermis, mostly in the granular layer. Desquamation of the epidermis was prominent and was often observed within a week after hydroquinone application.

After incubating the epidermal sheets in DOPA solution (which defines the location of melanin), Jimbow and associates [74] found decreases in the relative numbers of DOPA-positive melanocytes proportional to the duration of hydroquinone application. Both 2 and 5% hydroquinone caused a marked decrease in the concentration of melanocytes. When hydroquinone was applied topically for 3 weeks, it produced a marked decrease in the numbers of melanotic melanosomes in the cells and of actively functioning melanocytes. The authors suggested that some melanocytes were directly affected by hydroquinone and were destroyed and removed from the skin with the exfoliating scales.

Subcutaneous injections of 2 ml of 1% hydroquinone produced depigmentation of the hair in the epilated or nonepilated skin [74]. The new-growing hair shaft was distinctly less pigmented 10-12 days after hydroquinone injection than the normal hair. The newly emerged hair shaft rarely showed total loss of color. Hydroquinone also affected the follicular (hair root) melanocytes directly, either through destruction and decreased formation of melanosomes or through the formation of abnormal melanosomes. These effects were very similar to those produced by a topical application of hydroquinone to the skin. The authors suggested that hydroquinone not only affected the formation, melanization, and degradation of melanosomes but also produced abnormal membranous structures of melanocytes and finally caused necrosis of whole melanocytes.

In 1971, Chavin [75] published an account of studies of the reaction of melanocytes and melanophores to depigmentatory agents by monitoring the distribution and turnover of 14C-radioactive hydroquinone in 4-week-old black goldfish (Carassius auratus). In the experiment, 48-60 black goldfish were subcutaneously injected with radioactive hydroquinone at a depigmentatory dose of 30 mg/kg (radionuclide dosage of 0.071 microcuries/g). In each group, 4-5 fish were killed at 12 intervals, ranging from 30 minutes to 96 hours after hydroquinone injection, and body tissues were examined. The distribution and turnover within the fish of the labeled hydroquinone were rapid. The maximum concentrations occurred at the earliest time interval in all the tissues examined except the liver and the gall bladder. The maximum amount of radioactive hydroquinone in fish skin was 6.1% of the injected dose 30 minutes postinjection, and its concentration was 1.83 μg/g of wet skin. The radioactive hydroquinone was excreted primarily through the liver into the bile.

In another experiment, Chavin [75] studied the melanin-synthesizing activity and lifespan of cells by injecting 4-week-old black goldfish with hydroquinone and uniformly labeled 14C-tyrosine. The fish were injected intramuscularly (im) with hydroquinone at a dose of 40 mg/kg, 3 times/week, for 10 injections. Forty-eight hours after the last dose of hydroquinone, 14C-tyrosine was injected im at a dose of 1 microcurie/g. The fish were killed at 22 intervals from 3 hours to 900 days after 14C-tyrosine injection. Fifteen normal, black goldfish were similarly injected with 14C-tyrosine only and killed at 12, 24, and 72 hours. Melanin was extracted from the skin and eye tissues.

Chavin [75] found that developing melanocytes and melanophores converted 14C-tyrosine into melanin granules. The incorporation of 14C from tyrosine into melanin granules after 12 hours in the fish dosed with hydroquinone was about 50 times that in the controls. He concluded that the developing new pigment cells synthesized melanin more actively than the mature, established pigment cells of the untreated fish. The biologic half-life of the radio-melanin was 319 days. Radio-labeled melanin granules were lost slowly, the rate of loss indicating that the average lifespan of the melanophore was longer than 639 days. However, the pigmented cells of the retinas of fish given hydroquinone showed a conversion of radio-labeled tyrosine to melanin only 5.3 times that in controls. The peak uptake of 14C-tyrosine was also slower (about 3 days) in the retina than in the integumental cells. The retinal pigment cells required 1,441 days (calculated) to completely lose radio-melanin. The author suggested that, compared to integumental cells, retinal pigment cells were less active in regard to both hydroquinone effects and pigment synthesis.

(d) Long-term Systemic Effects

Vollmer [76] conducted a significant study on systemic effects from repeated doses of hydroquinone in 1932. He demonstrated an increased toxicity with repeated subcutaneous injections of hydroquinone at doses below the single "lethal dose" of 0.22-0.25 mg/g of body weight in two experiments. In the first experiment, 12 white mice (sex not specified; weight range, 14.0-20.5 g) were injected on six different occasions at 5-day intervals with hydroquinone at doses of 0.05 mg/g of body weight. Five mice of the same weight, handled and fed in the same manner as the

experimental mice, served as controls and displayed only slight "restlessness" during the experiment. Similar signs were noted in the experimental mice after the first injection. After the third injection, all mice displayed signs of trembling, and after the fourth injection clonic spasms were observed in 9 of the 12 mice. Four deaths were reported after both the fifth and sixth injections. The total dose for six injections was 0.3 mg/g of body weight.

For the second experiment, 33 white mice of the same weight range as above were used. Six hydroquinone doses each of 0.12 mg/g of body weight were injected into 17 of these mice at 5-day intervals, the remaining 16 mice being used as controls during the first two injections. At the third injection, five of the controls were given their first of four injections. Seven of the remaining 11 controls were included in the group of injected animals for the fourth injection, and the remaining 4 for the fifth and sixth injections. Trembling and clonic spasms were noted in the 17 originally treated mice following the first two injections, these effects being of longer duration after the second dose (45 minutes as compared with 15-25 minutes after the first). Two deaths occurred following the second injection. Clonic spasms of about 60 minutes' duration, followed by weakness and paralysis, were evident in all mice after the third injection. Five of these mice died. Two deaths were recorded after the fourth injection, four after the fifth, and three after the sixth, with one survivor. Controls entering the treatment sequence at various stages followed the same pattern as the first 17 mice, ie, they became sensitive to repeated small doses of hydroquinone.

These results were interpreted to mean that repeated small (non-lethal) doses of hydroquinone stimulated metabolic oxidative processes so that subsequent small doses of the compound were rapidly converted to more toxic substances. Hence, non-toxic doses could become toxic under such conditions.

In 1951, Woodard [15] studied the long-term toxicity of hydroquinone in several species. In the first experiment, two male and two female young mongrel dogs weighing 6.1-8.4 kg were administered hydroquinone as a 2% aqueous solution by stomach tube at a single dose of 100 mg/kg. After this initial dose, the animals received gelatin capsules containing hydroquinone at doses of 25 or 50 mg/kg, 6 days/week, for 809 days. The two dose groups each consisted of one male and one female, and two untreated dogs served as controls. All animals were given Purina Laboratory Chow and water ad libitum. Weight was monitored, and blood counts were performed on days 0, 3, 31, 120, 230, 400, 650, and 664 of the experiment. Hydroquinone administration was suspended on days 20-73 for one dog (25 mg/kg) because of weight loss and on days 238-309 for all animals to study the effects of administration on body weight. The six dogs were killed at the end of the experiment for gross and microscopic examinations of their internal organs.

After the 100 mg/kg dose, the tissues around the dogs' eyes were moderately to severely swollen and abnormal in appearance [15]. Occasional profuse salivation, slight diarrhea, and emesis were observed at this time, but these subsided during the daily dose period. The weights of two animals also initially decreased. However, in general, the weights of all animals increased, with fluctuations from time to time. Blood counts were essentially unchanged throughout the experiment, but microscopic

examination at the termination of the experiment showed hyperplasia of the bone marrow and excessive pigment deposits in the spleens of all dogs.

In another experiment, Woodard [15] administered 2% hydroquinone solution orally to six cats, one rabbit, and three guinea pigs. The age, sex, strain, and diet of the animals were not reported. Cats received 0, 30, or 70 mg/kg/day for 1-8 days, the rabbit was administered 100 mg/kg/day for 26 days, and the guinea pigs received 50 mg/kg/day for 20-27 days. Red blood cell, white blood cell, and differential counts were performed periodically on all animals. The author found that neutrophils had increased from about 70 to 98% in the cats by the end of the study. The values were generally unchanged for the other animals.

Continuing these studies, Woodard [15] examined the development of tolerance to hydroquinone in rats and dogs. In one experiment, six groups of six adult Osborne-Mendel rats (sex unspecified) weighing 154-173 g were fed ground Purina Laboratory Chow containing 0.0, 0.25, 0.5, 2.0, 4.0, or 8.0% hydroquinone for 2 or 3 days. The rats were caged separately, and, 24 hours after each daily feeding, the remaining food was removed and weighed. Individual and average food consumption figures were calculated.

On the 1st day, the average food intakes were 11.8, 13.3, 9.0, 4.3, 2.3, and 2.7 g for rats receiving hydroquinone at 0.0, 0.25, 0.5, 2.0, 4.0, and 8.0%, respectively, in the diet [15]. Thus, reduction of food consumption was noticeable for rats receiving 0.5% or more hydroquinone. However, on the 2nd and 3rd days, rats given hydroquinone ate as much as or more than they had on the 1st day, while controls ate somewhat less.

In another experiment, Woodard [15] administered hydroquinone orally in a single 100 mg/kg dose to two groups of dogs, each containing two male

and two female mongrels weighing 6.3-13.9 kg. The first group had received daily doses of 25 or 50 mg/kg of hydroquinone for 694 days in a concurrent study, while the second group had never before received hydroquinone or any other xenobiotic material. The health of all animals was monitored for an unspecified period.

The dogs previously given hydroquinone had no adverse effects from the oral dose of hydroquinone, except for salivation in one animal [15]. Three of the four dogs in the second group had emesis, and two had swollen periorbital tissues. Woodard [15] concluded that rats and dogs developed an apparent, partial tolerance to hydroquinone from previous administration.

Woodard [15] reported the comparative toxicities of quinone and hydroquinone in experiments with rats. He mentioned that quinone was much more irritating and toxic than hydroquinone. However, in contrast to hydroquinone, quinone did not produce tremors or convulsions when administered either orally or iv. Quinone did not stimulate the CNS but did produce severe depression. Death in rats occurred as long as 2 to 5 days after administration of quinone, whereas, after administration of hydroquinone, death occurred within a few hours.

The author [15] also stated that "the oil-water distribution ratio for hydroquinone is very unfavorable for its penetration through cell walls and particularly its penetration into nervous tissues. Yet its site of action appears to be the central nervous system. On the other hand, quinone is very soluble in oil and should easily penetrate cell membranes." He concluded that symptoms of quinone poisoning were not observed following either short-term or long-term hydroquinone administration in the animals.

Actually, Woodard's determination of the water-oil distribution ratio was 12.3 at 37 C. This indicates an appreciable, but small, solubility of hydroquinone in oil, which may permit moderately rapid transport of the material across the largely lipid cell membranes. The present knowledge of the structure of cell membranes indicates that they are mosaic structures with occasional protein blocks embedded in a predominantly lipoidal matrix, so that even materials that are exclusively water soluble would have some ability to cross cell membranes.

In a 104-week toxicity study of hydroquinone published in 1953, Carlson and Brewer [65] used Sprague-Dawley rats, initially 23-24 days old. In one experiment, 4 groups, each containing 10 rats of each sex, were fed a basic diet containing 0.0, 0.1, 0.5, or 1.0% hydroquinone. In a second experiment, hydroquinone was heated with the lard component of the diet at 190 C for 30 minutes and then incorporated into the basic diet at concentrations of 0.0, 0.1, 0.25, or 0.5%. There were 8 groups of rats with 16-23 rats/group. In a third experiment, 8 groups of 20 rats, including separate groups of males and females, were fed the basic diet containing 0.0, 0.1, 0.5, or 1.0% hydroquinone plus 0.1% citric acid. Some males and females (numbers not reported) in each experiment were also mated after 6 months of study to produce two successive litters. The specific groups in which matings were carried out were not stated. In addition, 14 adult rats (sex not reported) were given the basic diet containing 5% hydroquinone for 9 weeks. An equal number of control rats were fed only the basic diet. The weights of the animals were recorded periodically. All animals were killed at the end of 104 weeks. Sections were prepared from various internal organs and examined microscopically.

During the 1st month, hydroquinone decreased the growth rate of rats in the first experiment receiving the diet containing 0.5 or 1.0% hydroquinone [65]. On the average, control male and female rats gained 27 and 22 g/week, respectively, while the rats fed a diet containing 1.0% hydroquinone gained only 16 g/week. This effect was not seen in the second experiment, in which hydroquinone was heated with lard before being mixed into the basic diet.

In general, the final body weights of the experimental rats after 104 weeks on diets containing up to 1.0% of hydroquinone were not significantly different from those of the controls in the first experiment [65]. In the second experiment, final body weights of females that received 0.5% hydroquinone were significantly ($P<0.05$) lower than those of the control females. A similar reduction of the final body weight was found in the males that received 0.1 or 1.0% hydroquinone in the third (citric acid) experiment. Red blood cell counts, percent hemoglobin, and total and differential white blood cell counts did not show any significant variation from the control values. Microscopic examinations showed that the liver, kidneys, spleen, heart, lungs, bone marrow, stomach wall, pancreas, adrenals, omentum, and "subperitoneal and intramuscular abdominal fat" were normal. There was no difference between the average numbers of offspring of experimental and control female rats in two successive litters. These offspring, fed diets containing 0.0, 0.1, 0.25, or 0.5% hydroquinone previously heated with lard, developed at a normal rate. Adult rats maintained on the basic diet containing 5% hydroquinone lost 46% of their body weight in 9 weeks and developed aplastic anemia. Microscopic examination of the bone marrow of these rats showed a marked atrophy of the

hematopoietic elements. Pathologic studies also showed "atrophy of liver cord cells, lymphoid tissue of the spleen, adipose tissue, and striated muscle together with superficial ulceration and hemorrhage of the stomach mucosa."

Carlson and Brewer [65] also administered hydroquinone to three mongrel dogs, initially 4 months of age, for 80 weeks. One dog was fed 16 mg of hydroquinone/kg/day for 80 weeks. Two dogs were each fed 1.6 mg of hydroquinone/kg/day for 31 weeks. Both dogs then received 40 mg/kg/day for the next 49 weeks. Two dogs served as controls. The sex distribution in treated and control dogs was not given. In addition, five adult male dogs ingested hydroquinone at a dose of 100 mg/kg/day for 26 weeks. The compound was administered in sugar-coated tablets mixed with the food. Routine blood and urine analyses (unspecified tests) were performed periodically, and weight gain was monitored. At the end of each experiment, the dogs were killed and autopsied. Dogs that received 16 mg/kg/day for 80 weeks or 1.6 mg/kg/day hydroquinone for 31 weeks and then 40 mg/kg/day for 49 weeks grew normally. Adult dogs fed 100 mg/kg/day for 26 weeks maintained their body weights. The gross and microscopic findings, urinalyses, and hematologic analyses showed no marked differences between experimental and control animals.

In cumulative toxicity studies, Carlson and Brewer [65] used six groups of rats with 20-48 animals in each group. The sex and strain of these rats were not reported, and no control group was mentioned. Groups received 500, 750, 1,000, 1,250, 1,500, or 1,750 mg of hydroquinone/kg 9 times in 12 days by stomach tube. Sixteen rats were also given doses of 500 mg/kg 101 times during 151 days. Deaths were recorded during the

experimental period, and, at the end of the study, all the surviving animals were killed and autopsied.

In the groups scheduled to receive 500-1,750 mg/kg of hydroquinone 9 times in 12 days, 71% of the total mortality occurred within 24 hours after the first dose [65]. The actual number of deaths was not stated. During the remaining 11 days, in which eight more doses were administered, the mortality averaged less than 5%/day. Survivors that received 500 mg/kg of hydroquinone 101 times during 151 days grew at the same rate as controls. The autopsy findings were generally negative, although more than half of the rats died after the first 2 months of hydroquinone feeding. The authors concluded that there was no cumulative toxicity from hydroquinone, at least when given by stomach tube.

In two subchronic toxicity studies, Delcambre et al [69] administered hydroquinone by gastric intubation to rats. Freshly prepared solutions of hydroquinone were given to male Wistar rats (age unspecified). In the first experiment, 2 groups of 25 animals each were administered hydroquinone at a dose of 7.5 or 15 mg/kg, 6 days/week, for 40 days. Twenty rats given a 5% glucose solution by gastric intubation served as controls. At each dose, two rats were killed on days 8, 15, 26, and 36, and seven rats were killed for blood examination on day 40 of the experiment.

The red blood cell, white blood cell, and differential counts of the experimental animals did not differ from those of the control animals at the end of the 1st and 2nd weeks, but, during the 4th week, one rat given hydroquinone at a dose of 7.5 mg/kg developed anisocytosis (a difference in the size of erythrocytes) with polychromatophilia (the presence of

erythrocytes with unusual staining characteristics in the blood) [69]. However, these abnormalities were not seen in the animals administered 15 mg/kg of hydroquinone. Rats killed on day 36 did not show any abnormalities at the 7.5-mg/kg dose, but one rat given hydroquinone at 15 mg/kg developed slight anemia with decreased neutrophils, anisocytosis, severe polychromatophilia, and numerous erythroblasts. When the rats were killed on day 40 and their blood samples were examined, one animal in the control group showed anisocytosis and erythroblastosis; one rat in the group given 7.5 mg/kg/day also had erythroblastosis. In the group given 15 mg/kg/day, four animals had anisocytosis, five had definite polychromatophilia, and four had erythroblasts in the peripheral blood.

In the second experiment [69], 2 groups of 15 animals each were administered an aqueous solution of hydroquinone intragastrically at a dose of 5 or 10 mg/kg, 6 days/week, for 4 months. Fifteen rats given a 5% glucose solution served as controls. At the end of the experiment, three rats from each group were killed for blood examination. Nine rats died during the experiment, one each from the control and the 5 mg/kg groups and seven from the 10 mg/kg group. Three of these seven deaths occurred during a scabies epidemic. The rats receiving 5 mg/kg of hydroquinone, with the exception of the one that died, did not show any ill effects; however, in the 10 mg/kg dose group some body weight loss was seen at the 3rd month when the mortality was greatest. In general, the body weight gain in this group was comparable with that in the other two groups. Differential blood counts were normal in each group at the end of the study.

In 1966, Mozhayev et al [70] studied the subchronic toxic effects of hydroquinone on albino rats. Hydroquinone was added to the drinking water

at concentrations designed to provide doses of 0.025, 0.05, 0.25, 0.5, 5, 50, or 100 mg/kg/day for 6 months. The control rats were fed a basic diet and water. The number, age, and sex of rats were not reported. Body weight, hemoglobin concentration, erythrocyte and leukocyte counts, and motor chronaxies of the antagonistic muscles were monitored at the end of 2 and 6 months of the experiment. At the end of the experiment, rats were killed, and the liver, spleen, kidneys, small intestine, and brain were sectioned, stained, and examined.

Rats which received hydroquinone for 6 months at doses of 0.025-50 mg/kg showed no significant weight changes when compared with controls ($P>0.1$) [70]. However, the rats receiving 100 mg/kg of hydroquinone gained weight at a significantly slower rate than did control animals ($P<0.05$). A slight decrease in hemoglobin ($P<0.1$), a decrease in the number of erythrocytes ($P<0.01$), and an increase in the number of leukocytes ($P<0.05$) were also observed in the blood of rats that received hydroquinone at doses of 50 mg/kg or more when compared with controls. Hydroquinone administered at doses of 50 or 100 mg/kg caused dystrophic changes in the small intestine, liver, kidneys, and myocardium. Changes in the functional state of the central and peripheral nervous systems were mild in hydroquinone-administered rats, even at a dose of 50 or 100 mg/kg, as judged by chronaxies of extensor and flexor muscles.

Christian and associates [71], in 1976, reported the cumulative toxic effects of hydroquinone in adult rats. Males and females 8-10 weeks old from Carworth Farms were fed Purina Chow pellets ad libitum. Hydroquinone was added to drinking water at concentrations of about 2,500, 5,000, or 10,000 ppm. At each concentration, six male and six female rats were

maintained for 8 weeks. Six males and six females kept on a normal diet and water served as controls. Body weights were measured weekly, and blood examinations, including hemoglobin, hematocrit, and total and differential leukocyte counts, were made at 5 weeks. Changes in the microsomal enzymes in the liver were evaluated indirectly at 6 weeks by measuring the length of the period of sleep produced in the rats by an ip injection of 125 mg/kg of sodium hexobarbital. The interval between loss and recovery of the righting reflex was taken as the sleep time. Rats were killed at the end of 8 weeks, and gross and light microscopic examinations of the liver, heart, lungs, kidneys, spleen, brain, gonads, pituitary, and adrenals were performed.

All rats survived, and none showed signs of toxicity during the experimental period; however, growth was poor in all rats of the highest dose group, and some depression of growth was also seen in the females receiving 5,000 ppm [71]. Hematologic examination did not show any adverse effects. The hexobarbital sleep time decreased consistently in male rats with higher concentrations of hydroquinone, but this decrease was not found in the female rats. In rats of both sexes, the weights of the liver and kidneys relative to the body weight increased with the concentration of hydroquinone in the drinking water. These increases were statistically significant for males at a hydroquinone concentration of 5,000 ppm and for both sexes at 10,000 ppm. Other organs did not show any noticeable change in relative weights when compared with those of the controls. Microscopic examination of the different organs showed no pathologic changes.

In a similar experiment, Christian et al [71] studied the cumulative toxic effects of hydroquinone in male and female weanling rats maintained

on Purina Chow pellets. Hydroquinone was given in the drinking water at concentrations of about 0, 1,000, 2,000, or 4,000 ppm for 15 weeks. Each group consisted of 20 male and 20 female Carworth Farms weanlings at each concentration. Body weights were measured weekly for all rats. Blood examinations, including hemoglobin, hematocrit, and total and differential leukocyte counts, were made only on male rats at 5, 10, and 14 weeks. Hexobarbital sleep times were determined at 14 weeks. The animals were killed after 15 weeks, and gross and microscopic examinations of the same tissues listed in the 8-week study were performed.

All rats survived and none showed signs of toxicity throughout the experiment; however, the growth rate was significantly less in males receiving 4,000 ppm hydroquinone than in controls ($P<0.001$) [71]. The hematocrits and the hemoglobin concentrations of the blood were slightly reduced in rats given 2,000 or 4,000 ppm of hydroquinone for 5 and 10 weeks, but all values were normal at 14 weeks. There were no changes in the concentration of leukocytes in the blood or in the differential count in the treated rats. The sleeping time with hexobarbital was not affected by ingestion of hydroquinone at these concentrations in either sex. Except for the females' kidney weight at 1,000 ppm, which had no significant weight increase relative to body weight, both sexes showed statistically significant ($P<0.01$) increases in liver and kidney weights relative to body weight at all concentrations of hydroquinone. The weights of the other organs examined were not noticeably affected in either sex. Microscopic examination of the different organs showed no pathologic changes.

Vollmer [76], in 1932, also reported an increase of hydroquinone toxicity following repeated injections of ethyl alcohol. Ethyl alcohol was

administered subcutaneously to 32 white mice (weight range 16.6-22.7 g) at a dose of 4.73 mg/g of body weight on 7 different occasions at 5- or 6-day intervals. On the 6th day following the last alcohol injection, hydroquinone at a dose of 0.2 mg/g of body weight was subcutaneously injected into all 32 mice. Within 184 minutes 21 died. Of the survivors, six exhibited paralysis and five had clonic spasms. Another group of 32 white mice of similar weight was handled and tested in a similar manner, except that no ethyl alcohol injections were given. Following the injection of 0.2 mg/g hydroquinone, six of these mice died after an average of 14 hours. Of the surviving mice, 5 suffered from paralysis, 19 from clonic spasms, and 2 from trembling. The author suggested that the generation of hypersensitivity to hydroquinone (and other compounds) could be the result of a stimulating effect of repeated small doses of alcohol on metabolic oxidative processes, which in turn could convert hydroquinone rapidly to more toxic products.

Woodard [15], in 1951, reported absorption and excretion of hydroquinone in a dog weighing 12.8 kg. The age and sex of the dog were not reported. Hydroquinone was administered to the dog orally at a dose of 640 mg (50 mg/kg), and a 24-hour urine sample was collected. A 100-ml sample of the urine was analyzed after ether extraction for the recovery of free hydroquinone. Similar samples were analyzed after acid hydrolysis to determine conjugated hydroquinone.

Only 0.34% of the dog's dose was found as free hydroquinone [15]. Excretion of the conjugated forms accounted for about 30% of the dose. Hydroquinone was excreted partly as the ethereal sulfate and partly as the glucuronide, as determined by qualitative tests on the urine.

In another experiment, Woodard [15] found that a single oral dose of 300 mg/kg of hydroquinone produced signs of poisoning (tremors) and 6 deaths among 20 mice tested. The sex, age, and strain of the mice were not given. However, when this dose was divided into 3 doses of 100 mg/kg given at 2-hour intervals, no signs of poisoning were noticed in 20 mice. When repeated doses of 200 mg/kg were given to 20 mice, cumulative toxicity was observed, as judged by the presence of tremors following each dose. The author concluded that hydroquinone was rapidly absorbed from the gastrointestinal tract and eliminated from the body or detoxified at nearly the same rate.

Deichmann and Thomas [77], in 1943, reported the effect of hydroquinone on the excretion of organic sulfates and glucuronic acid in three rabbits. Hydroquinone was given orally at a single dose of 90 mg/kg (about half the lethal dose). The urine was collected for analysis on the three days following hydroquinone administration. Hydroquinone increased the excretion of organic sulfates, but had no effect on that of glucuronic acid.

In 1971, Temple et al [78] reported the diuretic effects of hydroquinone and its elimination in groups of four female Wistar strain rats weighing an average of 225 g. Rats were fasted for 15 hours before the experiment, but drinking water was available ad libitum. A fluid overload of normal saline solution (25 ml/kg) was administered to each animal. Hydroquinone was given orally at a single dose of 200 mg/kg in a 2.5% syrup suspension. Four control rats were given isotonic saline only. The urine of all animals was collected every hour for 8 hours and then at 24 hours. The daily urinary flow was 18 ml/kg in control rats and 35 ml/kg

in the rats administered hydroquinone, an increase of 94%. The diuretic action of hydroquinone lasted for a long, otherwise unspecified, period. Hydroquinone was normally eliminated in urine as the glucuronic acid conjugate.

Miller et al [79], in 1976, reported the metabolic fate of hydroquinone in cats at a sublethal iv dose of 20 mg/kg. Intravenous injections of a solution of 14C-hydroquinone (1-5 millicuries/mmol) were administered to two anesthetized cats, one male and one female, which had been previously fasted for 24 hours. The common bile ducts and ureters of these cats were cannulated after ligation of the gall bladders. Urine samples were collected at hourly intervals for 6 hours. The radioactivity of the urine samples was determined with a liquid scintillation spectrometer. Radioactive areas were also detected on paper chromatograms by scanning, and the relative radioactivity of each spot was determined from the record of the scanner. To confirm these findings, urine samples were acidified, extracted with ether, and analyzed by paper and gas chromatography.

During 6 hours, 89-93% of the iv dose of radioactive carbon was excreted in the urine [79]. About 10% of the radioactivity excreted in the urine was in unchanged hydroquinone. The main metabolite, accounting for 87% of the urinary radioactivity, was hydroquinone sulfate. A second metabolite, containing about 3% of the urinary radioactivity, gave a positive naphthoresorcinol reaction for glucuronic acid but was not identified further. The authors concluded that, because about 10% of the injected hydroquinone was excreted unchanged, the ability of cats to form a sulfate conjugate of hydroquinone is limited.

A study of the metabolism of hydroquinone [79] indicated that hydroquinone was excreted from the body in conjugated forms (about 90%) as ethereal sulfate and glucuronide, and as unchanged hydroquinone (about 10%) but that it might not be converted to the more toxic quinone in the body.

In 1933, Ciaranfi [80] studied the effect of hydroquinone on hemopoiesis in guinea pigs. Two guinea pigs were injected subcutaneously daily with 0.04 g of hydroquinone in aqueous solution. The age, sex, weight, and strain of the guinea pigs were not reported, no control group was mentioned, and other experimental details were not given. The author observed a decrease in the red blood cell count and an increase in the amount of hemoglobin per cell. The number of reticulocytes and basophilic cells increased. The author concluded that hydroquinone had an inhibiting effect on hemopoiesis in guinea pigs which was similar to that produced by an ultrafiltrate of serum from patients with pernicious anemia. However, this conclusion is based on results observed in only two animals.

Tarasova and Troitskii [81], in 1968, reported the effects of hydroquinone on rabbit blood proteins and the development of dietary hypercholesterolemia and atherosclerosis of the aorta. The animals, weighing 2.5-3.0 kg, were fed 0.3 g/kg of cholesterol (as 10% solution in an unspecified oil) daily for 3 months. Ten such rabbits were injected subcutaneously with 1 ml of a 6% hydroquinone solution every other day. Hydroquinone was also given orally to five cholesterol-fed rabbits at a dose of 0.5 g daily for 3 months. A control group of 15 rabbits was fed cholesterol only. The sex and strain of the rabbits were not reported. After the experiment was completed, the total serum proteins were determined by refractometry and by the biuret method. The serum proteins

were fractionated by salting out with ammonium sulfate and were then analyzed by the biuret method and electrophoresis. The concentrations of cholesterol in the serum and cholesterol in the individual protein fractions were also determined. Atherosclerotic damage to the aorta was estimated by an arbitrary scoring system that gave points for presence of plaques throughout the aorta.

The authors [81] found no significant difference between the concentration of proteins in the sera of the experimental and the control groups. The sums of the alpha and beta globulin fractions was 1.83 ± 0.3% in controls and 1.95 ± 0.1 and 1.96 ± 0.2% in animals receiving hydroquinone (orally or subcutaneously) plus cholesterol. When rabbits were fed cholesterol and injected with hydroquinone subcutaneously, the relative concentration of beta globulin increased and exceeded that of the alpha globulin by a factor of 2-4. When animals received both cholesterol and hydroquinone orally, the relative concentration of alpha globulin was significantly increased, on the average to 26.8% of the total protein, while that of beta globulin remained within normal limits.

Tarasova and Troitskii [81] also observed that the administration of hydroquinone reduced the degree of cholesterolemia. After rabbits had received hydroquinone for 2 months (orally or subcutaneously), the cholesterol levels were 50-70% of the control level. However, at the end of the experiment (3 months), the concentrations of cholesterol in the blood of these two groups of animals did not differ significantly and the degree of cholesterolemia was decreased by 35%. These rabbits were killed after 3 months, and atherosclerotic changes in the aorta were examined. One of the 15 rabbits showed moderate atherosclerotic changes in the aorta.

In 5 of the 15 animals, the aorta did not show any change, and 7 rabbits had only a single plaque each. Hydroquinone injected subcutaneously or given orally reduced the degree of aortic damage by more than 71 and 84%, respectively. The authors concluded that, regardless of the route of administration, hydroquinone had an antisclerotic effect.

In 1968, Guillerm et al [82] reported the effects of hydroquinone and quinone on the ciliary activity of the rats' tracheal mucous membrane in vitro. Rats were killed, and their tracheas were removed and cut into small rings. Pure hydroquinone and quinone were dissolved in Tyrode's solution at pH 7.4-7.8. Hydroquinone concentrations were 10, 50, 100, and 150 μg/ml, while those of quinone were 25, 50, 75, and 100 μg/ml. Tracheal rings were kept in hanging drop suspension in the various solutions, and control tracheal rings were kept in Tyrode's solution. Ciliary activity was examined with the microscope at 5-, 10-, 20-, 30-, 40-, and 60-minute intervals. Hydroquinone at 10 and 50 μg/ml did not produce ciliostatic effects during 60 minutes of observation. However, hydroquinone at 100 μg/ml produced a mild effect after 30 minutes, and, at 150 μg/ml, had a severe effect on ciliary activity after 5 minutes of exposure. By contrast, 75 μg/ml of quinone greatly retarded ciliary activity in 20 minutes and stopped it by 50 minutes.

(e) Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

There are no papers in the available literature that show that hydroquinone is teratogenic. No evidence was found that inhalation of hydroquinone influenced the incidence of tumors in animals. Further studies of this nature, using other routes of exposure, are desirable.

Boyland and coworkers [83], in 1964, reported studies of the carcinogenic activity of hydroquinone in mice. Stock mice bred in the Chester Beatty Research Institute were used, but their original number, age, and sex were not reported. Cholesterol pellets containing hydroquinone were implanted in the bladder. The amount of hydroquinone used in the preparation of these pellets was not given, but Boyland (written communication, June 1977) stated that the concentration of hydroquinone was 20% in 10-mg cholesterol pellets, so that the total dose was 2 mg. A control group was implanted with pellets containing only cholesterol. The mice were observed for the development of bladder tumors. The termination time of the experiment was not stated. However, Boyland (written communication, June 1977) stated that the animals with tumors were killed between 25 and 40 weeks after the implantation of the pellets. The probability that tumors in survivors occurred by chance was calculated by the Chi-square test.

Twenty-five weeks after implantation, 77 and 19 mice survived in the control and hydroquinone-implanted groups, respectively [83]. In the control group, four mice (5.2% of the survivors) developed adenomas or papillomas and five (6.5% of the survivors) developed carcinomas, yielding a total incidence of tumors of 11.7% in the control group. In the hydroquinone-implanted group, six mice (32% of the survivors, P=0.03) developed carcinomas, but none had adenomas or papillomas. The authors concluded that the incidence of tumors (carcinomas) was significantly high enough to confirm the carcinogenic activity of hydroquinone, although they stated that 30-40 mice/group are required for statistical accuracy. The

findings of this study were inconclusive because there were too few mice in the hydroquinone-implanted group.

In 1955, Roe and Salaman [84] reported the results of a study of the carcinogenicity of hydroquinone in mice. Twenty-four albino "S" strain male mice 7-9 weeks old were used. A 6.7% solution of hydroquinone was prepared in acetone, and 0.3 ml (20 mg) of this solution was applied evenly on the clipped back of each mouse. These mice also received 18 applications of croton oil, starting 3 weeks after the hydroquinone application. Mice were observed for 18 weeks. A group of 20 mice, receiving weekly applications of 0.3 ml of 0.5% croton oil in acetone for 18 weeks, served as controls. All surviving mice of both groups were killed 1 week after the end of the experiment and examined grossly and microscopically for the incidence of tumors and other abnormalities (unspecified).

A skin tumor was observed in 1 of the 22 surviving mice in the experimental group [84]. However, 1 of the 20 surviving mice in the control group had 3 skin tumors.

Carlson and Brewer [65] reported a study of chronic toxicity performed on somewhere between 368 and 424 young male and female Sprague-Dawley rats. The animals were fed batches of the basic diet to which had been added 0.0, 0.1, 0.5, or 1.0% hydroquinone for 104 weeks. None of these rats developed tumors, which is evidence against the carcinogenicity of hydroquinone, at least after ingestion of the listed concentrations in the diet and under the experimental conditions used.

In 1948, Parmentier and Dustin [85] reported the effects of hydroquinone on the cells of the small intestine in mice. The number, age,

sex, and strain of the mice were not stated, and no control group was mentioned. Hydroquinone solution was injected ip or subcutaneously at single doses of 0.150 or 0.175 mg/g, and the mice were killed at intervals after hydroquinone administration. Intestinal tissues were fixed in Carnoy's solution, stained with iron-hematoxylin, and examined microscopically for abnormal chromosomes.

During the first 2 hours after hydroquinone injection, there was a progressive accumulation of arrested metaphases before a pyknotic effect occurred [85]. The percentage of metaphases became as high as 92%, while normal anaphases and telophases tended to disappear. Some metaphases showed an irregular distribution of chromosomes, which were short, thick, and clumped together in the middle of the cell. In most of the cells in metaphase, a peculiar appearance was noted; small groups of chromosomes were found near the poles in addition to those collected in the equatorial plate (later called three-group metaphase). Signs of chromosomal stickiness were seen from 1 hour onwards after hydroquinone injection. The central mass of chromosomes became increasingly clumped together, and chromosomal bridges were observed between central and polar chromosomes.

Parmentier [86], in 1953, reported the effects of hydroquinone on the bone marrow of golden hamsters. Hydroquinone was injected ip in a single dose varying from 0.150 to 0.200 mg/g body weight. The number, age, sex, and strain of the hamsters were not mentioned, and a control group was not described. Tissue was prepared by the Feulgen-squash method at intervals after hydroquinone injection and examined microscopically. In the first 6 hours after hydroquinone administration, arrested mitoses in groups of three were observed in most cell divisions in the bone marrow cells of

hamsters at all doses. The mitoses were characterized by a normally formed metaphase plate and abnormal "chromatic" bodies, which appeared mostly in the cells of the granular series. The erythroblast divisions remained unaffected. After 6 hours, when the destructive action was greatest, some "three-group metaphases" underwent condensation of chromatin and produced an image termed the "three-group pyknosis." At the same time, pyknotic nuclei became more numerous, and the number of white cell mitoses gradually decreased. After 24 hours, mature polynuclears were relatively more abundant, and "three-group metaphases" were not visible.

In 1953, Rosin and Doljanski [87] reported the effects produced by hydroquinone in vitro on chick fibroblasts. Chick fibroblast cultures were immersed in a solution of 1 in 10*6 (* means "to the negative power of") hydroquinone in Ringer's solution and incubated for 1 hour, or immersed in a solution of 1 in 10*7 and incubated for 2 hours. The whole cultures were then fixed and stained with Giemsa's stain. The stained cultures were examined microscopically for abnormal chromosomes. A control group was not reported. The mitotic action of hydroquinone was observed 1 hour after fibroblast immersion. There was a definite increase in the number of three group metaphases. These findings agreed with those discussed by Parmentier and Dustin in 1948 [85].

In another experiment, Rosin and Doljanski [87] injected hydroquinone ip into rats in a single dose of 0.150 or 0.175 mg/g. The number, age, sex, and strain of the rats were not mentioned, and no control group was reported. The rats were killed at different intervals after hydroquinone injections. Tissues taken from the liver, bone marrow, and cornea were stained and examined microscopically for abnormal chromosomes. Two hours

after hydroquinone administration, the authors observed liver cell mitoses that had the same characteristic features described by Parmentier and Dustin [85]. In the bone marrow, the "three-group metaphases" were observed only in the white cell precursors, whereas the precursors of erythrocytes often showed very marked karyorrhexis (fragmentation of the nucleus). In general, mitoses were not numerous in the bone marrow of rats given hydroquinone. In the corneas of rats, the same effect was observed 2 hours after instillation of one drop of a 5% solution of hydroquinone into the conjunctival sac or after ip injection of hydroquinone in the doses mentioned above. The authors [87] suggested that hydroquinone had a general effect on mitosis in various tissues (liver, bone marrow, and cornea) which was manifested by changes in the morphologic aspect of mitosis and that it acted directly on the cell.

Mozhayev et al [70], in 1966, reported the effect of hydroquinone on the mitotic activity of the bone marrow of albino rats. Hydroquinone was given daily in the drinking water at concentrations designed to provide daily doses of 0.05, 0.5, or 5 mg/kg for 6 months. The number, age, and sex of the rats were not stated. Rats kept on a basic diet and water served as controls. Rats were killed at the end of the experiment, and the mitotic activity of the bone marrow cells was measured by the mitotic index (number of dividing cells/1,000 cells examined).

Hydroquinone decreased the mitotic activity of bone marrow cells [70]. The mitotic indices of the bone marrow cells were 20, 22.2, 17.5, and 15.6/1,000 cells examined in rats receiving 0.0, 0.05, 0.5, and 5 mg/kg of hydroquinone, respectively. However, only the mitotic index in the rats

receiving 5 mg/kg of hydroquinone differed significantly from that of the controls ($P<0.02$).

In 1971, Zhirnova [88] examined the diurnal changes in the reaction of the corneal epithelium to hydroquinone. Ten albino mice aged 1.5-2 months (sex not reported) were used in this experiment. At 8 am, physiologic saline solution was applied to the left corneas, which served as controls, and 5% hydroquinone solution was applied to the right corneas of five mice. Five other mice received similar applications at 6 pm. Mitotic activity was graded by the number of dividing cells found in a constant area of the cornea by a microscopic examination. Hydroquinone applied during the morning increased mitotic activity in the corneal epithelium to 252, compared to 175.8 in controls. This increase was caused mainly by delayed division of the epithelial cells in the metaphase stage. An increased number of metaphases was seen in epithelial cells of corneas to which hydroquinone had been applied. However, the percentages of anaphases and telophases were reduced by 40-73% ($P=0.003$). The mitotic activity of the corneal epithelium was low in the mice that had hydroquinone applied to their eyes in the evening, and was not significantly changed by hydroquinone ($P=0.5$) when compared with that of the controls. During the evening, the percentage of cells in the corneal epithelium in metaphase was nearly 5 times that in the controls, as indicated by decreases in the percentages of cells in anaphase and in telophase of 82% and 84%, respectively. Abnormal mitoses were very rare in the corneal epithelia of the controls' eyes. However, abnormalities of the cornea were more common in eyes exposed to hydroquinone and were especially frequent in the mice treated in the evening (33.3%, $P=0.02$).

A few studies have suggested that hydroquinone produced abnormalities in cell division of plants [89], whereas two studies in vitro [90,91] have indicated that hydroquinone did not induce mutations in bacteria and yeasts. An in vitro study with chick fibroblasts [87] and in vivo studies with mice [85,88], rats [70,87], and golden hamsters [86] have indicated that hydroquinone produces abnormal cell division, but they have not demonstrated that this compound causes specifically mutagenic actions. Meaningful studies which would test the mutagenic potential of this compound in mammals are needed.

Racz et al [92], in 1958, reported the effect of hydroquinone on the sexual cycle of albino rats. Ten mature female rats were orally given 200 mg/kg/day of hydroquinone solution for 2 weeks. Fresh hydroquinone solution was prepared daily in physiologic saline. A control group of 10 female rats received 5 ml of physiologic saline solution orally. When three rats died during the experiment, the doses were reduced to 100 or 50 mg/kg/day, but the number of animals used was not stated. Daily vaginal smears from the rats were stained with methylene blue and examined.

All female rats were in diestrus at the beginning of the study [92]. The period of diestrus was prolonged in some rats at the 50 and 100 mg/kg/day doses, while in other rats the diestrus period was similar to that of the control animals. At the 200 mg/kg/day dose, all animals remained in diestrus during the 14 days of the study. The Fallopian tubes of the dead rats contained an excess amount of blood. Maturing follicles were present in the ovaries, but no fully mature Graafian follicles were observed.

In 1964, Skalka [93] studied the influence of hydroquinone on the fertility of male rats. Sixteen male rats were injected subcutaneously with hydroquinone at a dose of 100 mg/kg/day for 51 days. Seventeen male rats served as controls. The age and strain of the animals and the vehicle used to prepare the hydroquinone solution were not stated.

At the end of the injection period, seven injected and seven control rats were killed and their testes, epididymides, seminal vesicles, and suprarenal glands were weighed and fixed. The weight of each organ was expressed as g/100 g of body weight. Sections of the testes and epididymides were stained, and the content of deoxyribonucleic acid (DNA) in sperm heads in the epididymides was examined.

The remaining 9 injected and 10 control rats were mated, 1 male to 2 females. After 5 days the males were separated from the females. The females were killed 7 days later and their uteri were examined for fetuses.

Seventeen days after the injections ended, six previously injected male rats with lowered fertility rates were mated with 2 normal female rats each and then killed. The sperm were expressed from the epididymides into Tyrode's solution at 37 C, and the mobility was observed by phase contrast. After an additional 7 days the females were killed and examined for the presence of fetuses in their uteri.

The average weights of the testes, epididymides, seminal vesicles, and suprarenal glands were decreased by 26.1, 21.4, 41.2, and 21.2%, respectively, in the experimental rats compared with those of the control animals [93]. Histologic changes in the testes of the hydroquinone animals indicated that spermiogenesis had been disrupted. The decline in the

biologic quality of the sperm in 66% of the experimental rats was apparently related to the diminished content of DNA in sperm heads.

Normal females mated with the hydroquinone-treated males had an average of 10.4 fetuses/two females; 39% had no pregnancies. Normal females mated with control males had an average of 15.4 fetuses/two females; 20% had no pregnancies. Compared with the controls, male fertility was decreased by 32.5% and the pregnancies in mated females were reduced by nearly 24% in the experimental group.

The fertility rate of the experimental males, which had already been reduced, began to decline further as soon as injections of hydroquinone stopped. Females mated with nine males at the end of the injection period had an average of 7.3 fetuses/two females; 58% had no pregnancies. When six of these males were mated with another 12 females 17 days after injections were stopped, the females had an average of 6.3 fetuses/two females; 58% were not pregnant. In the males killed after this mating, the sperm extracted from the epididymides into the Tyrode's solution were motile.

In 1962, Telford and associates [94] reported the effects of hydroquinone on fetal resorption in rats. Rats of Walter Reed-Carworth Farms strain in their first gestation and weighing about 200 g at the time of breeding were used. After positive matings, the females were randomly divided into experimental and control groups. Experimental females were given a total of 0.5 g of hydroquinone in their diet during pregnancy. On day 22 of pregnancy, the rats were killed and young were delivered by Caesarian section. A close macroscopic examination was performed on both uterine horns for resorption sites. In 126 normal, untreated, pregnant

rats, 40.8% had one or more resorption sites and 10.6% of the total implantations terminated in resorptions. Ten females fed hydroquinone-containing diets had 105 implantations from which 77 normal fetuses were produced and 26.7% terminated in resorptions. All the pregnant rats had one or more resorption sites. The authors concluded that the administration of hydroquinone to pregnant rats increased the fetal resorption rate.

Ames and coworkers [95], in 1956, reported the effect of hydroquinone on the reproductive process of pregnant rats. The weight, age, and strain of the rats were not mentioned. Hydroquinone was added to the stock diet of female rats at 0.003% and 0.3% concentrations (30 and 3,000 ppm), and the rats were fed these mixtures for 10 days before mating. Although this was not mentioned by the authors, it is assumed that the rats were fed these mixtures throughout their pregnancies. Ten female rats were used at each concentration. Seventeen females, maintained on a stock diet, served as a negative control. All pregnant rats were observed for their reproductive performance. Fertility index, litter efficiency, mortality index, mean length of gestation, mean litter size, viability index, and lactation index did not differ in controls and hydroquinone-administered groups at either concentration.

These studies by Telford and associates [94] and by Ames and associates [95] were considered to furnish negative indications of teratogenesis by hydroquinone in rats, even though they were not directed specifically toward this subject.

Correlation of Exposure and Effect

In the occupational incidents [17,50,52,53,55], direct ocular contact with airborne quinone vapor or hydroquinone dust [17,50,52,53] and dermal contact with hydroquinone [55] have been the primary routes of exposure, but the possible contribution of inhalation of dust or vapor has not been ruled out. Although ingestion has been the predominant route of entry into the body for hydroquinone used alone [44,45] or in mixtures [3,46-49] in attempted suicides and accidental poisonings, it is a minor route for occupational exposure when proper sanitary practices are observed.

The most immediate and noticeable effects of acute, high-dose, oral ongestion of hydroquinone are on the CNS. Two cases of acute hydroquinone poisoning in humans were reported [44,45]. Mitchell and Webster [44] described a case of suspected hydroquinone poisoning in a young woman who ingested an unknown amount of hydroquinone. About 20 grains (1,296 mg) of hydroquinone was recovered from 4 pints (80 British fluid ounces or about 77 U.S. fluid ounces) of stomach washings. She had a subnormal temperature, a fast and feeble pulse, and a series of violent convulsions and was semiconscious. She recovered slowly after 3 days of hospitalization. The patient studied by Remond and Colombies [45] ingested about 12 g of hydroquinone and quickly experienced tinnitus, a suffocating sensation, cyanosis, and extreme sleepiness, but he recovered after receiving symptomatic treatment for 13 days.

A dose of about 1.30 g of hydroquinone can cause mild to moderate toxic effects in humans [44], but even much larger doses (about 12 g) may not be fatal [45]. Since several patients ingested mixtures of

hydroquinone with other chemicals, the toxic dose of hydroquinone can not be accurately evaluated [3,46-49]

Many reported effects of acute exposure to hydroquinone in humans have been confirmed in animals. Vomiting occurred in pigeons and dogs [15], labored breathing in mice [67] and cats [66], cyanosis in mice [67], and hypothermia in cats [66]. Coma and convulsions followed by death were reported in rats [15,71], mice [21,67], guinea pigs [15], cats [15,66], and dogs [15].

It is evident that acute, high-dose, parenteral exposure to hydroquinone produces noticeable effects on the CNS in humans [44,45] and in animals [15,21,66,67,71], but these effects have not been seen in workers who were exposed to lower concentrations of hydroquinone in actual industrial situations [17,50-53].

Carlson and Brewer [65] studied the long-term systemic effects of hydroquinone in humans and did not find noticeable signs of toxicity in subjects who ingested 300-500 mg of hydroquinone/day for 3-5 months.

A few long-term toxicity studies have suggested that, in the experimental administration of hydroquinone, systemic effects are produced in rats [66,69-71], cats [15], and dogs [15] and that, in mice, they may be intensified if repeated doses of alcohol have been given prior to hydroquinone [76]. The systemic toxic effects of hydroquinone in these species were dose-dependent and cumulative only at higher doses. Woodard [15] has reported that rats and dogs developed an apparent partial tolerance to hydroquinone after prior oral administration. However, contradictory evidence was provided by Vollmer [76], who demonstrated an

increase in hydroquinone toxicity after repeated subcutaneous injections into white mice.

Woodard [15] reported that, when hydroquinone was administered orally in doses of 200 mg to a man and of 640 mg to a dog, it was rapidly absorbed from the gastrointestinal tract and eliminated from the body or detoxified at almost the same rate. None of the dose given to the man and only 0.34% of the dose administered to the dog was found as free hydroquinone. Excretion of conjugated forms in the urine accounted for 10 and 29% of the administered doses after 24 hours in man and the dog, respectively. No conjecture as to the fate of the remaining portions was made.

Temple et al [78] found that, when hydroquinone at a single dose of 200 mg/kg was given orally to rats, it was normally eliminated through the urine as the glucuronide. However, Miller and coworkers [79], studying the metabolic fate of radiolabeled (14C) hydroquinone in cats, found that 87% of the label excreted in the urine during a 6-hour period was in the form of hydroquinone sulfate and that 3% was in an unidentified metabolite conjugated with glucuronic acid. The remaining 10% was unchanged hydroquinone. This study of the metabolic fate of hydroquinone [79] in cats indicated also that it may not be converted to the more toxic quinone in the cat, at least during the first 6 hours of its sojourn there. The small amount of conjugation of hydroquinone and its metabolites with glucuronic acid in the cat agrees with the finding [96] that this species has little, if any, glucuronyl-transferase.

Airborne hydroquinone may be oxidized to quinone at room temperature in the presence of moisture, but the rate of the oxidation and equilibrium concentrations at room temperature are not known. The colorimetric method

used by most investigators to estimate airborne hydroquinone concentrations does not distinguish between quinone and hydroquinone.

Epidemiologic studies and reports of effects from inhalation exposures to hydroquinone are not available in the published literature.

Lapin [56] reported contact dermatitis in seven infants under 3 months of age that had been caused by the application of an "antiseptic baby oil" containing an unspecified concentration of hydroquinone as an antioxidant.

Although the dermal depigmentation effects of topically applied hydroquinone have been well documented [57-60,63], the exact exposure time required for these effects to appear has not. The reported times for visible bleaching of the skin varied from 3 weeks to about 4 months. Not all treated subjects were affected and none were completely depigmented. The highest concentrations of hydroquinone used (30%) produced the greatest depigmentation [57]. Bentley-Phillips and Bayles [64] suggested that high concentrations of hydroquinone should be avoided, that about 3% is the optimal concentration for use in creams, lotions, and ointments, and that the 3% concentration is safe for all pigmented skin. Arndt and Fitzpatrick [60] reported, however, that 8% of their patients who used a cream containing 2% hydroquinone had mild erythema at the site of application.

Repeated skin contact with strong hydroquinone bleaching creams (5% or more hydroquinone) produced skin irritation [60,64], allergic sensitization [59,60], dermatitis [57,58,63], and depigmentation [55,57-60,63,64]. However, repeated skin contact with cream containing 2% or less hydroquinone produced little or no irritation or sensitization [58,60,64].

Depigmentation effects of hydroquinone have been confirmed by dermal applications or subcutaneous injections of hydroquinone in guinea pigs [57,73,74], mice [57], and goldfish [75].

Eye lesions produced by quinone vapor or hydroquinone dust in workers manufacturing hydroquinone have been described [17,50,52,53]. Acute exposures to quinone vapor, as in cleaning the filter press used to separate hydroquinone from its mother liquor, have caused slight and transient eye irritation, conjunctivitis, photophobia, moderate lacrimation, and a burning sensation [17]. Injury of the corneal epithelium, pigmentation of conjunctivae and cornea, and a severe decrease in visual acuity were observed in workers exposed to 20-35 mg/cu m of hydroquinone dust [17]. Staining of the conjunctivae and cornea [50,51,53], pterygia, changes in thickness and curvature of the cornea, loss of normal corneal luster [50], impaired vision, and decreased visual acuity [50,51,53] were seen in workers exposed to the concentrations of quinone vapor or hydroquinone dust in the general atmosphere of the plant for 5 or more years. Occasionally, employees with only 1 or 2 years' exposure showed slight staining of the conjunctivae. Prolonged exposure (10-21 years) to quinone vapor or hydroquinone dust also produced corneal dystrophy and dyskeratosis [51]. The severity of the eye injury was proportional to the length of exposure and to the atmospheric concentration of quinone vapor or hydroquinone dust [17,50,51,53]. Sterner et al [17] pointed out that even the correlation between eye injury and the length of time employed was not perfect, citing as examples two employees who had only slight conjunctival staining despite having worked for 13 and 15 years in situations with exposures apparently as great as those experienced by

the employees who developed definite eye injury. Corneal grafts were required in three patients to restore vision [52]. Miller [53] also reported that older workers were more prone to ocular lesions than younger ones.

Sterner and associates [17] distinguished two types of ocular injury. The first was characterized by various degrees of pigmentation of the interpalpebral portions of the cornea and conjunctiva and by corneal changes. The corneal changes might be caused, in part, by the irritative action of hydroquinone dust but were more likely to be the result of hydroquinone penetration into the cornea. The second type of injury was characterized by pitting and erosion of the corneal surface, thinning of the cornea, and development of stained areas.

Oglesby and associates [54] reported that, when hydroquinone dust levels were controlled to 1-4 mg/cu m in the packaging area of a manufacturing plant, eye injuries were mild and reversible in most exposed workers. Since no evidence of systemic injury was found, the authors proposed that the permissible concentration limit for hydroquinone dust should prevent eye injuries and ensure a comfortable working environment. On the basis of their findings, the authors selected a value of 2-3 mg/cu m as a practical working limit for hydroquinone dust.

Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

One investigation [83] has found that pellets of cholesterol containing hydroquinone (2 mg/pellet) implanted in the bladders of mice caused an excessive number of carcinomas of the bladder when compared with

that in mice implanted with pellets of cholesterol alone. In the control group, four mice (5.2% of the survivors) developed adenomas or papillomas and five (6.5%) developed carcinomas. However, in the hydroquinone-implanted group, six mice (32% of the survivors in this group) developed carcinomas while none had adenomas or papillomas. Although the difference between the incidences of tumors of the bladder in the control group and in the group implanted with pellets containing hydroquinone was significant (P=0.03), this study is not considered to yield a valid estimate of the comparative carcinogenicity of hydroquinone because of the small number of mice that survived for the duration of the study (25 weeks).

Another study [84] reported an unspecified skin tumor in 1 of 22 surviving mice painted with a single application of 0.3 ml of a 6.7% solution of hydroquinone in acetone (20 mg hydroquinone) 3 weeks before the first of 18 weekly applications of croton oil. One of 20 mice that received 18 weekly applications of croton oil without pretreatment with any other compound developed 3 tumors. Hydroquinone was not considered, therefore, to have any tumor initiating activity.

No reports of carcinogenicity from the inhalation of hydroquinone dust have been found.

A few investigators have shown that hydroquinone produced abnormal cell divisions (abnormal metaphase, abnormal mitosis, and pyknosis) in chromosomes of plants [89], mice [85,88], rats [70,87], golden hamsters [86], and chick fibroblasts [87]. Two studies [90,91] have indicated that hydroquinone did not induce mutations in bacteria and yeasts.

Abnormal mitosis, termed "three-group metaphase," was observed by Parmentier [86] in the bone marrow of golden hamsters when hydroquinone was

injected ip in single doses of from 0.15 to 0.20zmg/g. Progressive accumulation of arrested metaphases before the pyknotic change was reported [85] in the cells of the small intestine in mice when hydroquinone was injected ip or subcutaneously at single doses of 0.150 or 0.175 mg/g. In most cells in metaphase, a distinctive finding of a peculiar migration of small groups of chromosomes towards the poles was seen. Similar findings were made by Rosin and Doljanski [87] in the liver, bone marrow, and corneas of rats.

Klein [97] studied the responses of mouse liver and duodenal cells following subcutaneous injections of hydroquinone. Details on the strain, age, and sex of the mice were not given.

The principal effect of hydroquinone on the liver and the duodenal-lining cells was centered in the nucleus [97]. The onset of the effect was rapid. Thirty minutes after a subcutaneous dose of 0.2 mg/g was injected into a mouse, the liver cells became enlarged and had cytoplasm more granular than usual with numerous small vacuoles; the nuclei of these cells stained more lightly than those of normal cells and contained coarsely granular chromatin interspersed with acidophilic granules. After 2.5 hours the cytoplasmic vacuoles had disappeared, the cells were crowded into abnormal shapes, and the nuclei were granular and acidophilic (eosinophilic). There was an increased number of binucleated cells, but no mitotic figures were present. Some nuclei were hardly visible, being shrunken and apparently devoid of chromatin. Five hours after dosing, the nuclei had become more dense, and some of them had unusual and bizarre shapes. Some of the cells were disintegrating and apparently contained

white or red blood cells. After 10 hours, mitotic figures were present. After 24 hours, numerous normal mitoses were visible.

Five to 15 minutes after subcutaneous doses of hydroquinone of 0.25 to 0.175 mg/g were administered to the mouse, the nuclei of the basal epithelial cells of the duodenal mucosa had become swollen and contained acidophilic "balls" [97]. There was no increase in mitotic figures. After 2.5 hours, the Paneth cells in the fundi of the crypts contained unusually large dense granules, and nuclei of all types of cells were disintegrating. Debris of degenerated cells and nuclei was evident in the crypts. At 10 hours, the degeneration was regressing. Mitotic figures were present, and, by 24 hours, the epithelial cells had returned almost to the normal state.

The author [97] emphasized the rapid onset of, and recovery from, the toxic action of hydroquinone on the nucleus compared with those pertaining to the other nucleotoxins tested. In addition, the acidophilic "ball" formation, ie, the pyknomitosis of the nuclear substance caused by hydroquinone, was unlike the arrested mitoses that characterize the effect of such other nucleotoxins as colchicine and urethane.

One reproductive study reported by Racz et al [92] has indicated that hydroquinone given orally at 200 mg/kg/day for 14 days disturbed the sexual cycle of female rats; all 10 hydroquinone-treated rats remained in diestrus during the 14 days of the study. The diestrus period was prolonged in some animals at the 100 and 50 mg/kg/day doses, while in other rats the diestrus period was similar to those of the controls. Maturing follicles were present in the ovaries, but no mature Graafian follicles were seen.

A study reported by Skalka [93] has shown that hydroquinone affected the fertility of male rats when 16 rats were injected subcutaneously with

hydroquinone at a dose of 100 mg/kg/day for 51 days. Male fertility was decreased by 32.5%, and the pregnancies in mated females were reduced by nearly 24% in the experimental rats compared with the corresponding values for the controls. The histologic changes in the testes of the hydroquinone-injected rats showed evidence of disruptions of spermiogenesis. The decline in the biologic quality of the sperm in 66% of the experimental rats seemed to be related to the diminished content of DNA in the sperm heads.

One study [94] with rats suggested that a total of 0.5 g of hydroquinone given to females in their diets during pregnancy produced fetal resorption. Uteri from 10 female rats given hydroquinone contained 105 implantations from which 77 normal fetuses were produced. The other 26.7% of the embryos were resorbed. However, in 126 normal, untreated, pregnant rats, 10.6% of the total implantations terminated in resorption. Another study [95] has indicated that hydroquinone added at concentrations of 0.003 or 0.3% to the stock diet of rats for 10 days before insemination and probably thereafter throughout pregnancy did not affect reproductive success. There are no reports which suggest that hydroquinone produced either gross, visceral, or skeletal deformities in newborn animals.

The lack of information in the general area of carcinogenicity, mutagenicity, teratogenicity, and effects on reproduction by hydroquinone indicates that these areas need further study.

Summary Tables of Exposure and Effect

The effects of short- and long-term exposures to hydroquinone on humans and animals that were presented in Chapter III are summarized in Tables III-1, III-2, and III-3. Human data appear in Tables III-1 and III-2 and general animal toxicity data in Table III-3.

TABLE III-1

SUMMARY OF EFFECTS OF EXPOSURE TO HYDROQUINONE ON HUMANS

Route of Exposure*	Number, Sex, and Age of Workers	Amount or Concentration	Length of Exposure	Effects	Reference
Ocular	105	-	1-26 yr	Conjunctival and corneal staining, astigmatism, impaired vision	50
"	3 M	-	9-13 yr	Corneal and conjunctival lesions, visual failure	51
"	1 M	-	11 yr	Deep corneal scars	52
"	2 M 47 and 53 yr	-	9 yr	Staining of conjunctiva and cornea	52
"	201	-	>1 yr	Corneal and conjunctival lesions	17
Dermal	1 F 6 M	10 and 30%	30 d	Dermatitis, depigmentation	57
"	30 F 170 M	5, 6, and 7%	1/d x 2 d	Erythema	64
"	348 F 230 M	1, 2.5, 3.5, 5, or 7%	48 hr	Irritation, mild erythema	64
"	137 M middle aged	2-5% in ointment	2/d x 3 mon	Skin sensitization, depigmentation	59
"	98 M	5% in cream	2/d x 3 wk	Dermatitis	58
		then 1.5 and 2% in cream	2/d x 14 wk	Dermatitis subsided, depigmentation	
"	56	2 or 5% in cream	2/d <3 mon	Depigmentation, erythema, sensitization	60

TABLE III-1 (CONTINUED)

SUMMARY OF EFFECTS OF EXPOSURE TO HYDROQUINONE ON HUMANS

Route of Exposure	Number, Sex, and Age of Workers	Amount or Concentration	Length of Exposure	Effects	Reference
Dermal	36 2 d-3 mon	Hydroquinone in "antiseptic baby oil"	48 hr	Inflammation	56
"	35 F 30-39 yr	"Strong" hydroquinone cream	<8 yr	Dermatosis	63
Oral	1 F 21 yr	>20 grains (1,296 mg) in stomach aspirent	-	Loss of consciousness, violent convulsions	44
"	1 M	Approximately 12 g	-	Tinnitus, semi-coma, cyanosis	45
"	19 M&F	0.3-0.5 g/d	3-5 mon	No toxic effects	65

*No reports of exposure by inhalation were found.

TABLE III-2

SUMMARY OF EFFECTS OF INGESTION OF PHOTOGRAPHIC DEVELOPER ON HUMANS

Number and Sex	Age	Amount Ingested	Effects	Reference
2 M	-	15 g	Vomiting, tachycardia, hematuria, death	48
1 M	37	10 g	Unconsciousness, convulsions, death	46
1 M	1.5	3-5 g	Abdominal pain, coma, hemolytic anemia, convulsions, death	49
1 F	29	-	Spastic bladder pain, death	47
1 M	28	-	Convulsions, coma, anemia, methemoglobinemia, hemoglobinemia	3

TABLE III-3

SUMMARY OF EFFECTS OF EXPOSURE TO HYDROQUINONE ON ANIMALS

Route of Exposure*	Species	Number, Sex, and Age	Concentration	Length of Exposure	Effects	Reference
Dermal	Guinea pigs	-	7 and 10%	1/d x 1 mon	Skin irritation	73
"	"	24 Adult	2 and 5%	1/d x 3 wk	Depigmentation, skin irritation	74
Subcutaneous	Mice	52 M 4 wk	80-240 mg/kg	-	LD50, 190 mg/kg	21
"	"	-	Up to 500 mg/kg	-	LD50, 160-170 mg/kg	67
Oral	Rats	156 M&F	1,000-10,000 ppm	8-15 wk	Growth rate decreased	71
"	"	58 M 58 F Adult	180-2,100 mg/kg	-	LD50, 743 mg/kg for males, 627 mg/kg for females	71
"	"	180 M&F	158.5-501.2 mg/kg	-	LD50, 302 mg/kg	15
"	"	16 Young	500 mg/kg	101 x in 151 d	More than 1/2 died	65
"	"	-	50-100 mg/kg	1/d x 6 mon	Weight loss, increased leukocytes	70
"	"	6 Adult	0.25-8.0% in diet	3 d	No toxic effects	15
"	"	50 M	7.5-15 mg/kg	1/d x 40 d	Decreased neutrophils, anisocytosis, polychromatophilia	69
"	"	30	5-10 mg/kg	1/d x 17 wk	Weight loss, decreased blood cells, no toxic effects	69
"	"	14 Adult	5%	9 wk	Weight loss, aplastic anemia	65
"	Mice	M&F	158-631 mg/kg	-	LD50, 390 mg/kg	15
"	Mice (black)	8 M Young	37-262 mg/kg total, 247 mg	1/d x 76 d	Alopecia, depigmentation	57
"	Rabbits	10	300-700 mg/kg	-	LD50, 540 mg/kg	15
"	"	1	100 mg/kg	1/d x 26 d	No change in blood	15

TABLE III-3 (CONTINUED)

SUMMARY OF EFFECTS OF EXPOSURE TO HYDROQUINONE ON ANIMALS

Route of Exposure	Species	Number, Sex, and Age	Concentration	Length of Exposure	Effects	Reference
Oral	Guinea pigs	20	500 or 794 mg/kg	-	LD50, 550 mg/kg	15
"	"	5 M Adult	22-88 mg/kg total, 2.38 g	1/d x 76 d	No toxic effects	57
"	"	3	50 mg/kg	1/d x 23 d	No change in blood	15
"	Dogs	2 M 2 F	100 mg/kg plus 25 or 50 mg/kg	Once 1/d x 20 - 809 d	Swollen tissues around eyes, weight loss, hyperplasia of bone marrow, excess pigment in spleen	15
"	"	5 M Adult	100 mg/kg	1/d x 26 wk	No toxic effects	65
"	Dogs	4 M&F	100 mg/kg	1/d -	Vomiting, swollen tissues	15
"	"	3 4 mon	1.6-40 mg/kg	1/d x 80 wk	No toxic effects	65
"	Cats	16	30-70 mg/kg	1/d	LD50, 50 mg/kg	15
"	Pigeons	7	100 -2,000 mg/kg	-	LD50, 500 mg/kg	15
iv	Rabbits	-	100-150 mg/kg	-	Tremors, death	69
"	"	-	10-20 mg/kg	-	Hypertension	69
ip	Rats	-	100 mg/kg	1/d x 3 wk	No effect on growth	68
im	Goldfish	- 4 wk	140 mg/kg	3 wk 10 doses	Depigmentation	75

*No reports of exposure by inhalation were found.