VI. DEVELOPMENT OF STANDARD

Basis for Previous Standards

In 1955, the first environmental limit for hydroquinone was introduced in the United States by the American Conference of Governmental Industrial Hygienists (ACGIH) as a tentative Threshold Limit Value (TLV) of 2 mg of hydroquinone/cu m of air [120]. The value was established as a maximum average atmospheric concentration of hydroquinone to which workers could be exposed for an 8-hour working day without injury to health. Although no justification for the environmental limit was given at the time of publication, the information used to derive the value was provided in the 1962 edition of Documentation of Threshold Limit Values [121]. The tentative TLV of 2 mg/cu m was adopted as the recommended value by the ACGIH in 1956 [122] and has remained basically unchanged since then, except that a tentative Short Term Exposure Limit (STEL) for a 15-minute exposure of 4 mg/cu m was introduced by the ACGIH in 1976 [123]. The STEL should be considered a maximal allowable concentration, or absolute ceiling, not to be exceeded at any time during the 15-minute excursion period [123].

According to the first Documentation of Threshold Limit Values [121], the ACGIH TLV of 2 mg/cu m of hydroquinone was based on the study of Sterner et al [17], who reported that quinone vapor and hydroquinone dust arising from the manufacture of hydroquinone were injurious to the eyes of workers. The injuries developed gradually over a period of years, with no serious damage appearing from exposures of less than 5 years. No injured workers were reported to have associated systemic effects.

"Quinone vapor is the probable major factor in the production of lesions although the effect of hydroquinone dust cannot be eliminated as a contributing agent" [17]. This document stated further that a large number of clinical and environmental studies of workers in plants where these two substances were manufactured confirmed the finding of the previous report that no systemic effects arose at a concentration of 2 mg/cu m of hydroquinone dust. It was also stated that animal experimentation performed at the Eastman Kodak Laboratory had confirmed the relative lack of systemic toxicity of hydroquinone.

The 1971 (third) edition of Documentation of the Threshold Limit Values for Substances in Workroom Air [124] by the ACGIH presented the same TLV and bases for this TLV of hydroquinone that were given in the 1962 Documentation [121] with a few minor changes and the addition of the following citations. A study by Anderson and Oglesby [50] indicated that hydroquinone produced abnormal curvature of the cornea, which caused astigmatism long after exposure (10-21 years) and after the stain and pigment had disappeared. Zeidman and Deutl [48] reported two fatalities from ingestion of about 15 g of hydroquinone and methyl-p-aminophenol sulfate. Symptoms of severe poisoning, such as tinnitus, dizziness, increased respiration, muscular twitching, and delirium, were also reported.

According to a joint report, Permissible Levels of Toxic Substances in the Working Environment, of the International Labour Office and the World Health Organization (ILO/WHO) [125], maximal allowable concentration (MAC) limits for hydroquinone exposure have been established in four states within the United States. Mississippi (1958), Florida (1960), Pennsylvania

(1966), and California (1970) reported values which are the same as the TLV of 2 mg/cu m established by the federal government. The bases for these standards were not reported.

Finland (1962), the Federal Republic of Germany (1966), Poland (1967), Rumania (1966), and Yugoslavia (1964) have set 2 mg/cu m as the MAC value for hydroquinone [125]. The only justification given by ILO/WHO [125] for any of these foreign standards was that the MAC value for the Federal Republic of Germany was based on the 1966 ACGIH TLV [126].

The present (1976) federal standard for hydroquinone, 2 mg/cu m of air (about 0.44 ppm) as an 8-hour TWA concentration (29 CFR 1910.1000), is based on the 1968 ACGIH TLV [127].

Basis for the Recommended Standard

(a) Permissible Exposure Limits

Studies of human intoxication from hydroquinone have indicated that direct ocular [17,50,52,53] and dermal [55] contacts with airborne hydroquinone have been the primary routes of occupational exposure to this chemical without, however, ruling out the possible contribution of inhalation of dust or vapor. In cases of attempted suicide and accidental poisoning, ingestion has been the route of entry in two cases of human poisoning by hydroquinone [44,45] and by photographic developing mixtures containing hydroquinone as a major constituent [3,46-49]. Ingestion is a secondary route in occupational exposure, however.

Carlson and Brewer [65] studied the systemic effects of hydroquinone on 19 humans and found no significant signs of toxicity in experimental

subjects who ingested 300-500 mg of hydroquinone/day for 3-5 months. Attempted suicidal [45] and accidental [44] poisonings have indicated that ingestion by humans of hydroquinone in an amount of 12 g and in an unknown amount above 1.3 g has produced acute systemic effects.

A few long-term toxicity studies suggested that experimental administration of hydroquinone produced systemic toxic effects in rats [15,65,69-71], cats [66], and dogs [15,65]. The systemic toxic effects of hydroquinone in these animals were dose-dependent and cumulative only at higher doses. However, Woodard's experiment [15] suggests that rats and dogs developed a tolerance for hydroquinone from previous administration of that chemical.

The CNS effects produced by hydroquinone at higher doses in humans [45,44] and in animals [15,21,66,67,71] are not seen in workers exposed to lower concentrations of hydroquinone in industries [17,50-53].

Temple et al [78] have indicated that, when hydroquinone was given orally to rats in a single dose at 200 mg/kg, it was normally eliminated in the urine as the glucuronic acid conjugate. Miller et al [79] studied the metabolic fate of hydroquinone in cats by injecting ^{14}C-hydroquinone iv at a sublethal dose of 20 mg/kg. They found that 87% of the urinary radioactivity was excreted as hydroquinone sulfate and 3% as an unidentified metabolite conjugated with glucuronic acid; the remaining 10% was unchanged hydroquinone. These investigators found no evidence that hydroquinone was converted to quinone in the body.

Woodard [15] reported that when hydroquinone was administered orally at a dose of 200 mg to a man and 640 mg to a dog it was rapidly absorbed and eliminated from the body or detoxified. None of the hydroquinone given

to the man and only 0.34% of that given to the dog was found as free hydroquinone in the urine, and the urinary excretions during 24 hours of the conjugated forms of hydroquinone by these two species accounted for 10 and 30%, respectively, of the doses given. Of the hydroquinone administered, 90% was unaccounted for in the human and 70% in the dog.

No epidemiologic studies of populations occupationally exposed to hydroquinone have been published, and no studies are available which document the effects of inhaling hydroquinone in either dust or aerosolized solutions.

Carcinogenic, mutagenic, and cell division studies are inconclusive, and further investigation is needed. One investigation [83] has indicated that pellets of cholesterol containing hydroquinone (2 mg/pellet) implanted in the bladders of mice are carcinogenic. Another paper [84] reported the production of an unspecified skin tumor in 1 of the 22 surviving mice painted with 0.3 ml of a 6.7% hydroquinone solution in acetone (20 mg hydroquinone) followed 3 weeks later by a series of croton oil applications. No reports of carcinogenicity from the inhalation of hydroquinone dust have been found.

A few investigators have found 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], and two studies [90,91] have indicated that hydroquinone did not induce mutations in bacteria and yeast.

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 given these doses the diestrus period was similar to those of the controls. Maturing follicles were present in the ovaries, but no mature Graafian follicles were seen.

Another 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 nearly 32.5%, and the number of pregnancies in mated females was reduced by nearly 24% in the experimental rats compared with that in the controls. Histologic study of the testes of the hydroquinone-injected rats found evidence of disruption of spermiogenesis. The decline in the biologic quality of the sperm in 66% of the experimental rats was thought to be caused by diminished content of DNA.

One study [94] concluded that a total of 0.5 g of hydroquinone given to female rats in their diets during pregnancy produced fetal resorptions. However, another study [95] has indicated that hydroquinone added at concentrations of 0.003 or 0.3% to the stock diet of female rats for 10 days before they were inseminated and thereafter during gestation did not affect reproductive success, even though these animals probably ingested about twice as much hydroquinone during their pregrancies as did those of Telford et al [94]. Further research is needed to ascertain the effect of hydroquinone on reproductive success in laboratory animals. No data have been uncovered in the literature to suggest that hydroquinone produced gross, visceral, or skeletal abnormalities in newborn animals.

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].

Lapin [56] reported contact dermatitis in seven infants under 3 months of age that was caused by the application of an "antiseptic baby oil" probably containing an unspecified concentration of hydroquinone as an antioxidant in the oil. Dermal depigmentation by topical applications or subcutaneous injections of hydroquinone was found in guinea pigs [57,73,74], mice [57], and goldfish [75].

Oglesby et al [54] described the correlation between airborne quinone vapor and hydroquinone dust concentrations and occupational exposures. Stationary air monitoring data were taken from the mixing, filter press, oxidation, centrifugation, and packaging operation areas, and mixed vapor and dust concentrations ranged from 0.01 to 3.2 ppm (about 0.04 to 12.8 mg/cu m). No information was presented to correlate personal monitoring data with the incidence of eye injuries. The authors indicated that a correlation exists between eye injuries and concentrations of airborne quinone obtained from stationary site data in the plant. The odor of quinone became perceptible at or just above 0.10 ppm and was definite above 0.15 ppm. Signs of irritation were noted above 0.50 ppm (2 mg/cu m) and were marked at 3.0 ppm (12 mg/cu m). The initiation of greater ventilation and the use of an exhaust cabinet in which the drum was placed to receive hydroquinone (the final product) reduced the high concentration of hydroquinone dust (20-35 mg/cu m) to 1-4 mg/cu m. This reduced

concentration was accepted as satisfactory. The authors did not find any correlation between the degree of eye irritation and the concentration of hydroquinone dust in the air.

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

The clinical characteristics of eye lesions produced by quinone vapor or hydroquinone dust in workers manufacturing hydroquinone have been described [17,50-53]. Immediate eye irritation, conjunctivitis, photophobia, moderate lacrimation, a burning sensation, injury of the corneal epithelium, and even loss of vision were observed in workers exposed to quinone vapor or hydroquinone dust at high concentrations [17]. Staining of the conjunctivae and cornea [50,51,53], pterygia, astigmatic error, loss of normal corneal luster [50], and impaired vision or decreased visual acuity [50,51,53] were seen in workers exposed to quinone vapor or hydroquinone dust for 5 years or more. 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 roughly proportional to the length of exposure and to the atmospheric concentration of quinone vapor or hydroquinone dust [17,50,51,53]. Miller [53] also stated that the older workers were more prone to ocular lesions than were the younger ones. However, no available studies show that exposure to pure airborne hydroquinone produced serious eye injuries.

Long-term medical and industrial hygiene observations by Anderson and Oglesby [50], Oglesby and his associates [54], and Sterner et al [17] in one major hydroquinone-manufacturing plant indicated that if hydroquinone dust concentrations average 2 mg/cu m of air, eye lesions either do not occur or are mild and reversible. The authors [54] selected an MAC of 2-3 mg/cu m of air as a practical working concentration for hydroquinone dust and one of 0.4 mg/cu m for quinone.

Both quinone vapor and hydroquinone dust may occur in workplaces, hydroquinone being readily oxidizable to quinone in the presence of a slightly alkaline medium [4]. Therefore, NIOSH believes that the occupational exposure concentration of hydroquinone should be no higher than 2.0 mg/cu m as a ceiling concentration determined on a 15-minute air sample. If this sample is collected at a rate of 1.5 liters/min, as specified in Appendix I, it should yield a concentration of hydroquinone in the aqueous acetic acid of 1.8 μg/ml at the recommended occupational exposure limit. The recommended standard is based on presently available data which indicate that hydroquinone dust and quinone vapor produced eye injuries. Hydroquinone at higher doses has also caused dermatitis and CNS damage.

NIOSH recommends that all the provisions of the recommended standard be complied with in any work situation where exposure to hydroquinone has been known to reach or exceed the recommended 15-minute ceiling of 2 mg/cu m and in those occupational situations where exposure might be expected to reach or exceed this ceiling concentration. Many workers handle small amounts of hydroquinone or work in situations where, regardless of the amount used, there is only negligible contact with this substance. For

example, in the course of photographic development, once the powdered hydroquinone is in solution, usually at a concentration far below 5% by weight (RL Raleigh, written communication, November 1977) the potential for contact with hydroquinone is exceedingly low. The mixing and diluting of developing solutions containing hydroquinone is generally done on a weekly or even monthly basis, thus further limiting the extent of exposure. Under such conditions, it should not be necessary to comply with the provisions of this recommended standard, which has been prepared primarily to protect workers' health under more hazardous circumstances. Even so, personnel in contact with hydroquinone under such circumstances should exercise care to avoid excessive contact of the chemical with their skin, eyes, and respiratory and gastrointestinal systems. Reasonable attention to cleanliness, should be sufficient to protect the health of workers in these facilities. Turnover of the air in such a facility every 10-15 minutes, along with reasonable attention to cleanliness, should be sufficient to protect the health of everyone working there.

(b) Sampling and Analysis

The technology is currently available to collect and analyze air samples containing hydroquinone at half the recommended environmental limit and to institute appropriate engineering controls to keep air concentrations below this limit. A portable pump with a mixed cellulose ester membrane filter of effective pore diameter of 0.8 μm (discussed further in Appendix I) is recommended for personal breathing-zone sampling of airborne hydroquinone aerosol [100]. The analytical technique commonly used to determine hydroquinone in the industrial environment is a colorimetric determination with alkaline phloroglucinol [54]. Colorimetric

determination is a simple method for analyzing airborne hydroquinone, but it cannot distinguish hydroquinone from quinone. The use of a high-pressure liquid chromatograph equipped with a detector capable of UV detection at 290 nm, discussed in Appendix I, is the preferred analytical method for airborne hydroquinone aerosol [100]. This analytical method is capable of distinguishing hydroquinone from quinone.

(c) Medical Surveillance and Recordkeeping

Several human [17,44,45,50,52,53,55-60,63,64] and animal [15,57,65,66, 69,70,73,74] studies reported that ocular exposure to airborne hydroquinone produced eye injuries, and that dermal exposure caused skin irritation, allergic sensitization, dermatitis, and depigmentation. Ingestion of large doses has resulted in severe gastrointestinal disturbances, followed by hypotension, loss of reflexes, unconsciousness, convulsions, hemolytic anemia, jaundice, toxic nephrosis, anuria, and death. A medical surveillance program should therefore include preplacement and periodic medical examinations that give particular attention to the eyes and skin. Medical attention should be provided to workers accidentally overexposed to hydroquinone as described in Chapter I (Section 2).

Personnel occupationally exposed to hydroquinone should be advised of the adverse effects of a single accidental overexposure and long term exposure and should be informed of the symptoms and of their possibly delayed onset. If eye contact occurs, the affected eye should be immediately flushed with water and examined by a physician. In case of occupational exposure to hydroquinone, workers' eyes should be examined at least annually by medical, paramedical, or other properly trained

personnel. Employees exposed to hydroquinone at any level should receive annual eye examinations from properly trained personnel with a slit lamp (biomicroscope) or with any better technique. If staining of the cornea is present, workers should be sent to an ophthalmologist. Workers should be informed of the importance of these examinations.

Because hydroquinone produces delayed eye injuries [17,50,53], all medical and other pertinent records for workers exposed to hydroquinone should be kept for at least 30 years after termination of employment. These procedures will facilitate the detection of chronic systemic and eye injuries from hydroquinone which may be related to the employee's known occupational exposure.

(d) Personal Protective Equipment and Clothing

Because ocular [17,50,53] and dermal [55-58,60,63,64] contact with hydroquinone has induced eye injuries, skin irritation, dermatitis, and depigmentation in humans and animals, care must be exercised to ensure adequate protection against contact with hydroquinone. Work clothing should be available which can prevent hydroquinone dusts from reaching the skin. Face shields for protecting the eyes and skin of the face should be worn and supplemented with protective goggles when there is the possibility that hydroquinone may be aerosolized. Water resistant clothing should be available where large volumes of hydroquinone solutions are handled. Respiratory protective equipment should be worn when the concentration of airborne hydroquinone may exceed the permissible level, eg, in emergencies. Work practices that prevent generation of airborne particles or droplets of hydroquinone-containing materials should be followed. Showers and eyewash

fountains should be available for immediate use if accidental contamination of eyes or skin occurs.

(e) Informing Employees of Hazards

Continuing education is important in a preventive hygiene program for employees exposed to such hazardous materials as hydroquinone. Workers should be periodically informed by properly trained persons of the possible sources of hydroquinone exposure as well as of the conversion of hydroquinone to the more toxic quinone. They should also be apprised of the adverse health effects associated with excessive and long-term exposure to hydroquinone, the engineering and work practice controls used and those being planned to limit exposure to acceptable concentrations, personal hygiene and good housekeeping programs used, and the procedures for environmental and medical monitoring to assess the health status of employees. The types and functions of monitoring equipment, such as personal samplers, should be explained so that employees understand their own role in monitoring their personal exposure.

(f) Work Practices

Because hydroquinone can produce intoxication from ingestion [44,45], it is recommended that food storage, handling, dispensing, and eating be prohibited in hydroquinone work areas, regardless of the air concentrations. In addition, employees who work in a hydroquinone area should thoroughly wash their hands before smoking, eating, or using toilet facilities.

(g) Engineering Controls

Engineering controls should be used when needed to keep concentrations of the airborne hydroquinone within the recommended ceiling

value. Where hydroquinone is present, a closed system of control should be used if feasible. During the time required to install adequate controls and equipment, make process changes, perform routine maintenance and operations, or make repairs, overexposure to hydroquinone can be prevented by the use of respirators and protective clothing and in some cases by administrative controls. However, respirators should not be used as a substitute for proper engineering controls in normal operations.

Spills and leaks of hydroquinone must be cleaned up immediately to prevent overexposure of personnel caused by dispersal of the material in the work atmosphere. All personnel involved in cleanup operations must be provided with suitable protective equipment and clothing.

(h) Monitoring and Recordkeeping Requirements

To ensure that workers are not exposed to hydroquinone at concentrations which exceed the recommended environmental limit, concentrations in the workplace should be monitored at least annually and, if found to be necessary by an industrial hygiene survey, quarterly. If changes in production or processes are likely to increase air concentrations, the workplace should be monitored within 10 days after these changes. If the air concentration in work areas exceeds 2 mg/cu m, corrective measures must be taken and monitoring performed weekly until two consecutive samples contain less than 2 mg/cu m of air.

Records of sampling and analysis of both personal and area air samples for hydroquinone should be preserved for at least 30 years so that workplaces can be evaluated and possible correlations between air levels of hydroquinone in the workplace and delayed actions on workers' health can be detected.

VII. RESEARCH NEEDS

Available information on the pharmacokinetics of hydroquinone is inadequate to determine whether the toxicity of hydroquinone is caused by the parent compound or by its metabolite or metabolites. The half-life of hydroquinone in blood, plasma, and various tissues, as well as fecal and urinary excretion rates, should be investigated.

Airborne hydroquinone may be oxidized to quinone at room temperatures in the presence of moisture. However, the rate of the oxidation and the equilibrium concentrations at room temperatures are not known. Therefore, there is a need to develop a sensitive, practical, and economical method of determining the rate of oxidation in air of hydroquinone to quinone under various environmental conditions of humidity, temperature, and pH. This information will indicate the concentration of hydroquinone that is permissible at a workplace before toxic concentrations of quinone become present.

Direct ocular contact with airborne hydroquinone is a major cause of eye injuries in workers exposed to this compound. There are many incidents of occupational exposure [17,50-53] in which direct impingement of airborne hydroquinone dust or quinone vapor upon the eye has produced injuries, but animal data regarding this route of exposure are meager.

No studies of the toxicity from inhalation of airborne hydroquinone for humans or animals have been found to date. Good quantitative studies of this sort are sorely needed.

No epidemiologic report on hydroquinone has been found in the literature. Such studies are needed to provide information on the long-term effects of occupational exposures to hydroquinone and to determine the relationship between air concentrations and observed effects.

The toxicity in animals of hydroquinone administered by direct ocular and inhalation routes should be investigated, since this chemical exists as a dust or vapor in the industrial work environment. Such studies should involve investigation of both short- and long-term effects. Studies on the mechanism of action causing eye injuries in humans are also needed.

In addition, no human or animal studies have been found on the possible teratogenic effect of hydroquinone, and research efforts should be initiated. Only two studies of carcinogenesis in mice [83,84], a few studies indicating abnormal cell divisions in plants [89], mice [85,88], rats [70,87], golden hamsters [86], and chick fibroblasts [87], two mutagenic studies [90,91] in bacteria and yeast, and a few reproductive studies [92-95] in rats have been reported. Since most of these studies are inconclusive, further investigation should be initiated.

Although effects of hydroquinone on the CNS are suggested by the results of human [44,45] and animal [15,21,66,67,71] studies, the extent and reversibility of the changes after short-term exposures and the possibility of structural damage after prolonged, low concentration exposures are not clear at this time. Further research in this area is especially important because of the significant number of persons who are in contact with hydroquinone in fairly dilute solutions in darkrooms during photographic development. Unless elementary cleanliness and care are

exercised in the manipulation of photographic films and papers in the tanks and trays of developer solution, the darkroom may become generally contaminated with hydroquinone and its spontaneously produced, and more hazardous product, quinone. Toxicologic information on other physiologic systems, eg, cardiovascular and pulmonary, is lacking. The effects of hydroquinone on these organ systems in animals need to be studied.

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