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CHAPTER 93

Vinyl Chloride and Polyvinyl Chloride

Henry Falk and N. Kyle Steenland

The announcement by the B.F. Goodrich Company in early 1974 of several cases of hepatic angiosarcoma (HAS) among its polyvinyl chloride (PVC) polymerization workers set off a rapid chain of events that had a dramatic impact on the field of occupational health. First, vinyl chloride monomer (VCM: H_2c = CHCL), the starting material in the production of PVC resins, to which tens of thousands of workers had been exposed in recent decades, was transformed from a relatively innocuous industrial substance to a carcinogen that produces a fatal malignancy. Second, human epidemiologic data and animal experimental evidence for the carcinogenicity of VCM appeared almost simultaneously, providing definitive results that quickly brought about sharply lower occupational standards and changed industrial and environmental practices in many countries. Third, because of the many consumer uses of VCM and vinyl plastics, concern spread beyond the traditional confines of occupational health to the general public.

Several excellent review articles and conference proceedings highlight the multifaceted research stimulated by the first report of HAS induced by VCM (1–6). More recent reviews have focused on the toxicologic and occupational mortality data (7,8). In recent years there has been rapidly expanding knowledge on the mechanisms of carcinogenicity of VCM. This chapter focuses principally on the medical and epidemiologic findings.

H. Falk: Division of Environmental Hazards and Health Effects, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia 30341-3724.

N.K. Steenland: National Institute for Occupational Safety and Health, Cincinnati, Ohio 45226.

PVC POLYMERIZATION

Worldwide demand and production capacity for PVC continues to grow; 1996 global demand was estimated at about 44 billion pounds per year, and production capacity is increasing at a rate of close to 4% per year. Growth is most rapid in Asia, particularly China (9). PVC has been used principally in building and construction (particularly PVC pipe, electrical wire and cable, and flooring), home furnishings, recreational products (e.g., records and toys), packaging (e.g., film sheet, bottles), apparel, and transportation materials (e.g., automobile tops, upholstery, mats), besides a variety of other products, including medical tubing (3,7).

The PVC industry, begun in the United States in the early 1940s, consists of three separate processes. The first step is vinyl chloride monomer production, usually by direct chlorination or oxychlorination of ethylene. This is done in a closed system, although leaks or breaks in the process may lead to high levels for brief periods. In the United States, ten companies (15 plants) were engaged in this process in 1976 (slightly fewer in 1988); several thousand U.S. workers have been employed in this phase of the industry (3,7). The second step is polyvinyl chloride polymerization, in which gaseous VCM (boiling point −13.5°C) is liquefied under pressure in large polymerization reactors or vessels and chemically reacts to form PVC polymer (2). The polymerization reaction can be carried out in several different ways—suspension, emulsion, bulk, or solution polymerization—to produce polymer or copolymer particles of different size and quality (3). In 1976 there were 22 companies (39 plants) that polymerized PVC in the United States; tens of thousands of U.S. workers have been employed in this phase of the indus-

try. The highest exposures to VCM occurred in these plants, particularly because of the need to open and clean reactor vessels between reactions, a process that allows residual unreacted monomer to escape from the vessel. At one time workers were lowered into reaction vessels to clean them manually, and undoubtedly they were exposed to peak VCM exposure levels of several thousand parts per million (ppm). That practice was phased out in the late 1960s and 1970s, after the identification of acroosteolysis (AOL) in these VCM-exposed workers. The third step, PVC compounding and fabricating, involves compounding PVC resins with a variety of substances, such as pigments, plasticizers, fillers, antistatic agents, and stabilizers, and then making them into the various products. Many more fabricating workers are employed than polymerization workers, but VCM exposures have been considerably lower, arising principally from retained unreacted monomer (levels of which have been considerably reduced in recent years). Emissions and effluents from VCM and PVC production plants are the main sources of VCM released into the environment, although multiple smaller sources exist (7).

HEALTH EFFECTS

Two very uncommon diseases, AOL and hepatic angiosarcoma (HAS), are clearly linked to work in PVC polymerization plants. HAS actually represents the end stage of a hepatic fibrotic precursor lesion (described in detail below). The earliest references in the literature to liver disease or findings suggestive of AOL in VCM-exposed workers date from 1949 and have been summarized (4,5,10). The liver findings in these early reports were described as hepatitis-like changes, hepatomegaly, and abnormalities on liver function tests. Detailed descriptions of AOL appeared in 1966 and 1967, and during the early 1970s the characteristic liver disease and its pathogenesis were described by Lange and co-workers and by Marsteller and associates in Germany, as well as by Creech and co-workers and Popper and Thomas in the United States (22,27–31).

Acroosteolysis

In 1967 Harris and Adams (11) described two cases of AOL in Britain. The main findings included symptoms of Raynaud's phenomenon, osteolysis in the terminal phalanges of some of the fingers, and thickening of the skin or raised nodules on the hands and forearms. One case that included puffiness of the face was initially interpreted as scleroderma. The lytic lesions of the terminal phalanges of the fingers gave the appearance of clubbing (pseudoclubbing); additional findings suggestive of a systemic effect included lytic lesions of the feet, cortical erosion in the patella, and widening and marginal sclerosis of the sacroiliac joint.

In 1967 Wilson and colleagues (12) described 31 cases of AOL (fewer than 3% of the polymerization workers) in a U.S. company. They observed the same primary triad of Raynaud's phenomenon, sclerodermatoid lesions on hands and forearms, and lytic lesions of the terminal phalanges of the fingers; systemic manifestations, such as radiographic abnormalities in the feet, were not seen. AOL was subdivided into a mild stage (loss of cortex of one or more tufts of the distal phalanges), an advanced stage (more severe lytic destruction with complete loss of the tuft and a portion of the shaft of the distal phalanx), and a healing stage (fragmentation of the tuft or shaft and subsequent bony or fibrous union; Fig. 1). AOL was observed to occur primarily in workers who cleaned reactors, leading to restriction of manual activity of some workers, although in others the process improved spontaneously.

An epidemiologic study of 5,011 U.S. employees reported in 1971 identified 25 definite and 16 possible cases of AOL (13). Of the 25 patients, 24 had Raynaud's phenomenon and all 25 patients had cleaned reactors at some point, leading to the conclusion that manual cleaning of reactors was important in causation (14).

Other reports also pointed to some systemic changes in skin, bones, and sacroiliac joints (2,15–19). Rats dosed orally with VCM for 2 years were shown to develop thickening of the skin, with evidence of increased collagen synthesis (20); this provides some further support for the systemic nature of the skin findings. Vascular changes in the digital arteries of the hand associated with AOL, including narrowing of the lumen and partial or total occlusion, have been demonstrated by arteriography (21,22). In immunologic studies of workers with vinyl chloride disease, some of whom had evidence of Raynaud's phenomenon or AOL, Ward and colleagues (23) identified a number of abnormalities, including evidence of circulating immune complexes and their deposition in vessels. The hypothesis that these immune changes may be related to the pathogenesis of AOL and to other aspects of VCM-induced disease needs further study. The relationship of AOL to other environmentally induced sclerodermatoid disorders has been reviewed (24).

A puzzling aspect is that AOL was not described in detail until the 1960s. Unlike HAS, which has a latency period of approximately 20 years, AOL can have a very short latency period of 1 to 2 years and thus should have occurred in the 1940s and 1950s. Either the disease was missed during those years or it did not occur because of unidentified factors that are yet to be explained. One author suggested that AOL first occurred after the introduction of vinyl chloride–vinyl acetate copolymers (3). Unfortunately, such exposure information is lacking in virtually all published reports of AOL.

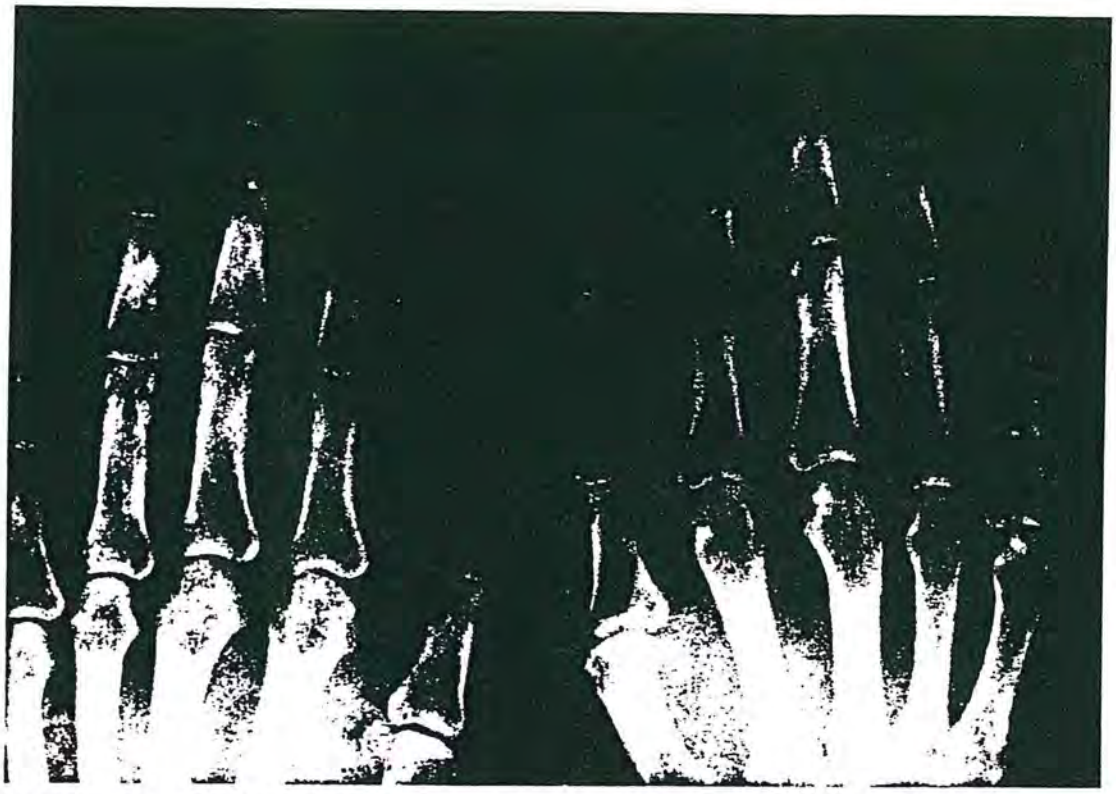

FIG. 1. Radiograph of long-term polyvinyl chloride polymerization worker's hand shows marked acroosteolysis, November 1964. (Courtesy of Dr. John Creech, B. F. Goodrich Company, Louisville, Kentucky.)

With the reduction of exposures that have occurred in this industry over the last two decades, case reports of AOL are now rare.

Liver Disease

Studies carried out during the 1960s in Romania reported hepatomegaly in vinyl chloride workers (reversible in some after cessation of VCM exposure), which was often associated with abnormalities of liver function tests (25). The spectrum of VCM-induced liver disease began to emerge from studies of PVC polymerization workers in Germany, starting in 1972. Lange and co-workers (22) described workers with hepatic fibrosis, splenomegaly, and thrombocytopenia—all findings suggestive of portal hypertension—in the absence of significant hepatic parenchymal damage. In a subsequent report, 81% of 70 workers studied were noted to have thrombocytopenia, 67% had increased Bromsulphalein (BSP) sodium retention, and 57% had splenomegaly; 14% had increased serum enzyme levels, indicating hepatic damage (25). Histologic studies demonstrated activation of hepatic sinusoidal cells and hepatic (particularly perisinusoidal) fibrosis, with less extreme changes in hepatocytes (26); fibrosis of the liver capsule was clearly visualized at laparoscopy (27).

In 1974 Creech and Johnson (28) first reported hepatic angiosarcoma following VCM exposure when they described three cases among PVC polymerization workers at the B. F. Goodrich plant in Louisville, Kentucky. Subsequent detailed studies at that plant identified additional cases of HAS and cases of nonmalignant hepatic disease, consisting principally of hepatic fibrosis, portal hypertension, and splenomegaly (29). Study of pathology specimens from VCM-exposed workers at various stages of liver disease and of serial biopsies in a number of workers who ultimately developed HAS enabled Popper and colleagues (30–32) to establish the morphologic progression and pathogenesis of HAS, which are similar to those seen in HAS from other causes known and unknown.

The earliest findings in the precursor stage are areas of combined hyperplasia of hepatocytes and sinusoidal cells associated with an excess of reticulin and with sinusoidal dilatation. These changes can progress to hepatic fibrosis, portal hypertension (33), and occasionally peliosis hepatitis or hepatocellular carcinoma (34,35); the hyperplastic sinusoidal cells become increasingly atypical and eventually undergo malignant transformation in the development of HAS (Fig. 2). Hepatocellular injury is not a feature of the early stages of this sequence, although it does appear in the later ones. Therefore, the hepatic dis-

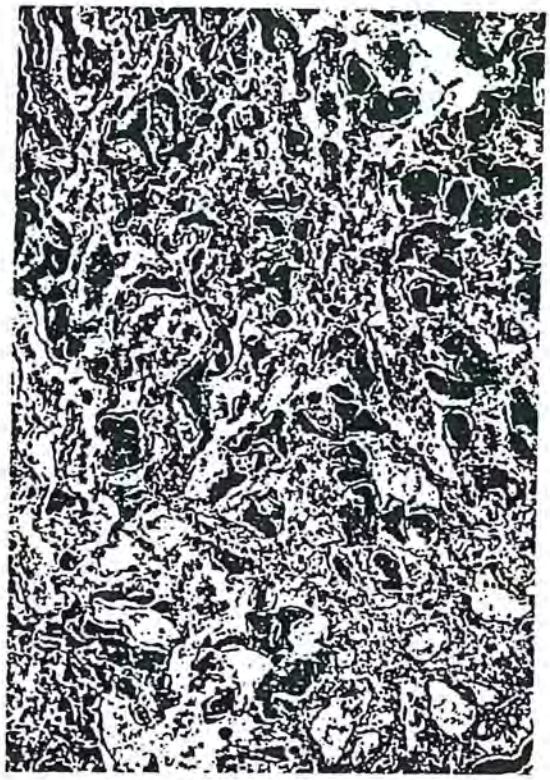

FIG. 2. Trabecular angiosarcoma in a VCM worker. Note cords of hyperplastic hepatocytes, sometimes surrounding bile plugs. These cords are surrounded by layers of angiosarcoma cells. The sinusoidal spaces are dilated (hematoxylin eosin stain, ×60). (Courtesy of Dr. Hans Popper, Mt. Sinai School of Medicine, New York.)

ease caused by VCM is quite distinct from that caused by most previously identified hepatotoxins (36).

An increased frequency of abnormalities of standard liver function tests, particularly in VCM-exposed workers whose clinical findings are compatible with VCM-related hepatic disease, has been reported in a number of studies (25,37). Liver function abnormalities, however, are a relatively late finding (38), and a number of cross-sectional studies of actively employed PVC polymerization workers have not detected gradual decrements in function (39–41). Nevertheless, when incorporated into ongoing medical surveillance, standard liver function tests have been valuable in identifying VCM-induced hepatic disease, particularly when multiple abnormalities or prolonged abnormalities on repeated examination have been observed (42,43). As a result, periodic screening with standard liver function tests was included in the National Institute for Occupational Safety and Health (NIOSH) recommendations and U.S. regulations (44).

There is a generally perceived need for the development of reliable screening tests for the early stages of VCM-induced hepatic disease. Proposed measures have included sensitive clearance tests to detect very early loss of hepatic function (45–48) or of increased liver endothelial cell activity (49), scintigraphy and other means of detecting altered hepatic architecture (50–53), and capillary microscopy in vivo (54). The degree of reversibility of the hepatic fibrotic precursor lesion has not been determined (55), but withdrawal from exposure is prudent, in the hope of preventing progression. Survival of patients with untreated HAS continues to be very poor and has been estimated to average 6 months or less. Dannaher and co-workers (56) reported on the use of chemotherapy in cases of VCM-associated HAS to improve the duration and quality of survival.

Pulmonary Effects

Lilis and colleagues (10) reported a decrease in pulmonary function in PVC polymerization workers exposed to VCM and PVC dust. Gamble and associates (57) found no evidence of such a decrease, but they did demonstrate a temporary loss of pulmonary function during the course of a single work shift. A report from England described some deterioration of lung function, slight abnormalities of the chest radiograph, and complaints of slight dyspnea associated with exposure to PVC dust (58). Baser and co-workers (59) reported pulmonary function abnormalities and increased respiratory tract symptoms in PVC fabrication workers (59). Reports of respiratory function decreases in PVC fabrication workers continue to occur, most recently from Asia and Africa (60–62).

Cases of pneumoconiosis induced by PVC resin also have been reported, and a report from Italy described 20 cases of PVC pneumoconiosis in workers exposed to PVC dust (63–65). Ultrastructural evaluation of lung biopsy material demonstrated apparent PVC particles in pulmonary macrophages and giant cells (63,65). The respective roles of retained VCM, PVC dust, and PVC additives such as plasticizers in the development of these pulmonary changes need to be clarified.

CYTOGENETIC STUDIES

Particularly during the late 1970s there were a number of reports of increased frequencies of chromosome aberrations in cytogenetic studies of peripheral lymphocytes from VCM-exposed workers. Subsequent studies reported apparently conflicting results and difficulties in reconciling these findings, although the various methods, particularly of measuring VCM exposure and of choosing of control groups, were not always comparable. Giri (66) has recently reviewed the genetic toxicology literature, and concluded that VCM, particularly following metabolic activation or directly from its active metabolites, has significant mutagenic activity and can directly interact with DNA, leading to chromosomal aberrations and sister-chromatid exchanges. The bulk of the literature supports this conclusion, and Giri interprets the smaller

number of negative studies as being limited by small sample size, inadequate exposure, or presence of confounding factors. The positive studies have been in workers with relatively long periods of exposure to VCM, and often to the high levels seen before 1975. Several reports have demonstrated the disappearance of cytogenetic abnormalities in groups of workers followed periodically after cessation of exposure (67). Fucic and co-workers (68,69) have explored the localization of chromosome breaks in human lymphocytes and the potential relation to oncogenic activation. In any event, it is uncertain how to interpret these cytogenetic findings in terms of health risk to individual workers. Also, potential confounding factors in the industrial setting demand consideration in greater detail.

REPRODUCTIVE EFFECTS

As part of a cross-sectional medical screening of PVC polymerization workers, Infante and colleagues (70) noted increased reporting of fetal loss by wives of VCM-exposed workers. A number of methodologic issues have been raised concerning that report, and, clearly, data on spontaneous abortions obtained directly from the workers' wives would have been preferable (71). High rates of congenital anomalies of the central nervous system have been reported in communities with PVC polymerization plants (72,73); subsequent case-control studies have not been able to confirm that the excess of defects is related to VCM exposure (73,74). Nevertheless, the ever-expanding literature on the mutagenic effects of VCM in microbial and mammalian test systems raises concern about possible genetic or reproductive effects, although teratogenicity (production of major congenital anomalies) has not been identified in animal systems (5).

OTHER EFFECTS

A number of other findings, including hypertensive changes and symptoms such as headaches and fatigue (possibly related to the anesthetic effect of large doses), have been reported (22,25,37,39,40). Peripheral neuropathy was reported in a group of workers in Italy (75); a variety of neurologic findings were reported from a plant in Poland (76).

CANCER

Hepatic Angiosarcoma Registry

Two initial reports from NIOSH, in 1975 and 1978, summarized the worldwide distribution of, as it was then known as, VCM-related cases of HAS (77,78). The great majority of those cases occurred in PVC polymerization workers; 64 had been identified to NIOSH as of October 1977. At that time, 23 cases had been identified in the United States, 10 in Canada, nine in the Federal Republic of Germany, eight in France, and most of the remainder from nine European countries. For those 64 cases, the latency period (interval from first exposure to diagnosis) ranged from 9 to 38 years (median 21); the length of exposure ranged from 4 to 31 years (median 18); and the age at diagnosis ranged from 37 to 71 years (median 49). The majority of cases were diagnosed after 1973.

A world register of HAS due to VCM has been maintained since 1974 on behalf of the Association of Plastic Manufacturers in Europe (79). In 1985, Forman and co-workers (80) published an interim analysis of data in the registry. Through 1984, 118 cases had been reported. The number of deaths appeared to have peaked in the 1975 to 1979 period (9.2 per year). Mean age at diagnosis was 52 years. Twelve countries had reported at least one case. Most came from the United States, 35 cases; West Germany, 26; France, 18; Canada, 10; and the United Kingdom, 9.

The most recent tabulation from the register shows 173 deaths through October 1993 (81). The period of peak occurrence is still 1975 to 1979, and has been diminishing since then (approximately 5 cases/year from 1990 to 1993). Western Europe has reported 106 cases; North America, 57; and the remainder of the world, 10.

Cases of HAS have been reported in persons exposed to lesser concentrations of VCM than PVC polymerization workers, for example, PVC fabricating workers and residents near PVC plants (77,82,83), but, because of the relatively large numbers of persons potentially exposed to lower levels, additional epidemiologic studies are needed to evaluate the associations. In a study of Thorotrast-induced HAS, the initially reported cases involved exposure to large doses and relatively short latency periods, while a larger number of cases that appeared later were associated with smaller doses and longer latency periods (84). Thus, it is important to follow trends of VCM-related cases of HAS in the future, to observe shifts in epidemiologic patterns. In nationwide reviews of HAS in the United States (1964 to 1974) and the United Kingdom (1963 to 1977), some 6% to 7% of pathologically confirmed cases occurred among PVC polymerization workers (12 of 168 in the United States; two of 35 in the United Kingdom) (81,85).

Occupational Cohort Studies

Studies on animals exposed to VCM have identified a multiplicity of tumors, in addition to HAS, (see below). As a result, a series of cohort mortality studies, principally of PVC polymerization workers, have evaluated the risk for all malignant neoplasms in these groups. Some of the primary difficulties in conducting and interpreting these studies (particularly the early cohort studies reported in the 1970s) included the relative youth of the

PVC industry (most of the workers in the various cohort studies had not passed through the age of peak cancer incidence), the relatively few deaths among workers who had been long exposed and quite some time earlier in some of the studies, and the difficulty of precisely quantifying past exposure to VCM, PVC, and other chemicals used in the polymerization processes such as other monomers used to produce copolymers (8). Doll (8) provided a comprehensive overview of the cohort mortality studies in 1988. His analysis combined data from the largest and most recent studies in four countries (United States, United Kingdom, Canada, Italy), each of which fulfilled the criteria of providing substantial numbers of observations more than 25 years after first exposure and covering a period long enough for more than 10% of the workers to have been expected to die. Doll's conclusion was that only HAS can be definitively related to VCM exposure in these cohorts. The increases previously noted for three other sites (brain, lung, and lymphatic and hematopoietic tissue) are in his analysis either insignificant or only weakly suggestive of a small effect.

Most epidemiologic data published since the 1988 Doll (8) review have tended to confirm the view that the only cancer outcome caused by exposure to vinyl chloride is liver cancer, particularly angiosarcoma. Two large studies were done, one in the United States and one in Europe. Wu et al. (86) studied 4,835 workers at a single VC/PVC manufacturing plant, 3,635 (75%) of whom had been exposed to VC, and 1,181 (24%) of whom had died (86). This study was an update of an earlier study of Waxweiler et al. (87). Among those exposed to VC, the lung, brain, liver, and hematopoietic cancer standardized mortality ratios (SMRs) were 1.15 (0.95–1.39), 1.45 (0.79–2.48), 3.33 (2.02–5.21), and 0.78 (0.48–1.21) based on 80, 10, 14, and 15 deaths, respectively. Nested case-control studies of lung, brain, and liver cancer within the entire cohort, using estimated rankings of cumulative exposure, showed that only liver cancer was associated with increased exposure to VC. Furthermore, when liver cancers were categorized by angiosarcomas and other liver cancers, based on the death certificate and medical records, only angiosarcoma showed a positive dose-response. The nested case-control studies showed no risk for exposure to PVC dust.

Simonato et al. (88) conducted a mortality study 14,351 subjects (1,438 dead) in 19 plants manufacturing VC or PVC in England, Sweden, Norway, and Italy. These plants included some that had been studied previously but that were updated. Lung cancer, brain cancer, liver cancer, and hematopoietic cancer had SMRs of 0.97 (0.82–1.14), 1.07 (0.59–1.80), 2.86 (1.83–4.25), and 0.89 (0.60–1.29), respectively, based on 144, 14, 24, and 29 deaths. A nested case-control study for liver cancer showed a significant positive dose-response with estimated cumulative VC exposure. A second nested case-control study of angiosarcomas showed an even steeper does-response.

Three other smaller studies have been published since the 1988 Doll (8) review. Laplanche et al. (89) updated earlier work in a 7-year follow-up for 1,100 VC-exposed subjects and 1,100 nonexposed subjects for morbidity and mortality. These workers were aged 40 to 55 and exposed at time of baseline in 1980. There were only 82 deaths in this group; three angiosarcomas occurred in the exposed and none in the nonexposed. Morbidity data indicated an excess of Raynaud's disease in the exposed versus nonexposed (14 versus 1 case), and an excess of cardiovascular disease, which was primarily due to more hypertension in the exposed (55 versus 34 cases). The excess hypertension, while apparently associated with higher exposures, did not lead to a significant excess of myocardial infarction in exposed versus the nonexposed (21 versus 16 cases). Smulevich et al. (90) studied 3,232 workers producing VC and PVC between 1939 and 1977. They found 288 deaths, with a significant four- to five-fold excess of both leukemia and other hematopoietic cancers, each based on five deaths. However, there were no deaths from liver cancer, which might have been expected. Furthermore, considering the literature as a whole, there appears little support for excesses of hematopoietic cancers or lymphomas among VC-exposed workers. Finally, Hagmar et al. (91) studied 2,031 workers in a PVC processing plant with low exposures to VC (1–10 ppm). Among the 149 deaths, no angiosarcomas were observed. Using morbidity data, lung cancer (rate ratio 1.86, 0.99–3.18) and brain cancer (rate ratio 2.29, 0.84–4.98) were elevated.

Although one cannot completely exclude a causal role for VC exposure and other cancers, the epidemiologic data suggest the risk is limited to angiosarcoma. These data suggest that the risk of angiosarcoma is concentrated among workers with higher exposures, e.g., at least 1 year above 50 ppm, although one cannot exclude some increase in risk for workers with lower exposures. As current exposures for workers are generally below 1 ppm, one can anticipate minimal risk for currently exposed workers.

Several reports suggest the occurrence of cases of primary liver cancer or hepatocellular carcinoma (92,93), which might be expected based on animal studies, but the number of cases is very small. It should be noted that for individual plants actual historical exposures to VCM, PVC, and other copolymers and additives are not certain, and that unique or unusual exposures may have occurred at some of the plants. Such information could be lost in a large meta-analysis.

Experimental Studies

In 1971 Viola and co-workers (94) first demonstrated the carcinogenicity of VCM in rats exposed to 30,000 ppm for 12 months. Hepatocarcinogenicity, particularly HAS, was reported later in a series of experiments by

Maltoni (95,96) and reproduced in other laboratories (5,7). VCM has been reported to produce HAS at doses as low as 25 ppm in rats, and a variety of tumors, including Zymbal gland carcinomas, nephroblastomas, nonhepatic angiosarcomas, and skin, brain, lung, and mammary tumors, have been produced in multiple species (including rats, mice, and hamsters) (7,95). Hepatocellular carcinomas also have been observed after exposure of newborns to VCM. The carcinogenicity data for animals has been reviewed in the Agency for Toxic Substances and Disease Registry (ATSDR) toxicologic profile for vinyl chloride (7).

A metabolite of vinyl chloride, rather than VCM itself, is the ultimate carcinogenic substance (97). In bacterial and other test systems, the mutagenicity of VCM is much increased by the addition of a metabolizing system (e.g., rat liver microsome), and an evaluation of animal carcinogenicity data suggested a closer link between HAS formation and the amount of VCM metabolized than the VCM exposure concentration (98). Although a number of mutagenic metabolites are formed, the reactive epoxide (chloroethylene oxide) formed during oxidative metabolism of the VCM double bond appears of greatest concern. Recent studies have demonstrated the formation of DNA adducts by the reactive metabolites of VCM (99–107), and such data have been used in the development of models to predict cancer risk (108,109). The short-lived active metabolites are formed in the hepatocytes but are carcinogenic in the adjacent sinusoidal cells, which, unlike the hepatocytes, appear to have limited ability for detoxification (110).

The most exciting developments in recent years are those that begin to explain how DNA damage may initiate the carcinogenic process. Several possibilities have been suggested, including (a) mutations in *ras* oncogenes and expression of their encoded p21 proteins, (b) mutation of the p53 tumor suppressor gene, and (c) detection of Kaposi's sarcoma-associated herpesvirus-like DNA sequences in angiosarcoma (111–115). There is also the possibility that mutant p21 or p53 in serum could serve as a biomarker for detection of disease.

The evidence for the carcinogenicity of vinyl chloride raised considerable concern about the safety of a number of structurally related halogenated hydrocarbons (116,117). Studies on animals indicate some evidence for carcinogenicity of vinylidene chloride (118), vinyl bromide (116), and trichloroethylene and tetrachloroethylene. Green (119) has summarized the differences between VCM and these structurally related chemicals: in short, he states that VCM produces more tumors, in more species, more consistently, and at lower doses, and by a direct genotoxic mechanism, and therefore has more marked carcinogenic properties. For some of these related compounds, however, only limited data are available on potential human carcinogenicity (119).

OCCUPATIONAL STANDARDS

In the United States, the Occupational Safety and Health Administration (OSHA) requires that a worker's exposure to VCM not exceed 1 ppm (8-hour time-weighted average) [permissible exposure limit (PEL) TWA]. The ceiling concentration limit for 15 minutes or less is 5 ppm [short-term exposure limit (STEL) 15 minutes] (44). In general, except in the Scandinavian countries, European VCM exposure standards are somewhat higher than in the United States (5).

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