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VC health info

49. Vinyl Chloride and Polyvinyl Chloride

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The notification made by the B. F. Goodrich Company in early 1974 of the occurrence of several cases of hepatic angiosarcoma 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), the starting material in the production of PVC resins, to which tens of thousands of workers had been exposed in recent decades, was transferred from a relatively innocuous industrial substance to a carcinogen producing 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 discuss the multiple facets of disease induced by vinyl chloride [5, 26, 48, 57, 67, 74]. This chapter focuses primarily on the medical and epidemiologic findings.

PVC POLYMERIZATION

About 2.5 billion kg/yr of VCM ($H_2C=CHCl$) is produced in the United States, most of it for production of PVC resins. PVC is used primarily 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, and bottles), apparel, and transportation materials (e.g., automobile tops, upholstery, and mats), besides a variety of other products, including medical tubing [48].

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 transiently high exposure levels. In the United States, ten companies (15 plants) were engaged in this process in 1976; several thousand

Trade names are used in this chapter for identification only; this use does not constitute endorsement by the Public Health Service or by the U.S. Department of Health and Human Services.

U.S. workers have been employed in this phase of the industry. 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 (of capacities ranging from several thousand gallons to as much as 35,000 gallons) and chemically reacts to form PVC polymer [26]. The polymerization reaction can be carried out in several different ways—suspension, emulsion, bulk, or solution polymerization—to produce polymer or copolymer particles of differing size and quality [48]. In 1976 there were 22 companies (39 plants) that polymerized PVC in the United States; [illegible] of thousands of U.S. workers have been employed in this phase of the industry. The highest exposures to VCM occur 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 ppm—a practice that was phased out in the late 1960s and 1970s after the identification of acroosteolysis in 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).

VCM-INDUCED HEALTH EFFECTS

Two very uncommon diseases, acroosteolysis (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 [40, 57, 67]. The liver findings in these early reports were escribed 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 et al. and by Marsteller et al. in Germany as well as by Creech and co-workers and Popper and Thomas in the United States.

Acroosteolysis. In 1967 Harris and Adams described two cases of AOL in Britain [32]. 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 forearm. One case included puffiness of the face and was initially interpreted as scleroderma. The lytic lesions of the terminal phalanges of the fingers led to an appearance of pseudoclubbing; additional findings suggestive of a systemic effect included lytic lesions of the phalanges of the feet, cortical erosion in the patella, and widening and marginal sclerosis of the sacroiliac joint.

In 1967 Wilson et al, described 31 cases of AOL (less than 3 percent of the polymerization workers) in a U.S. company [78]. They observed the same primary triad of Raynaud's phenomenon, scleroderma-like 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) (Figs. 1 and 2). AOL was observed to occur primarily in workers who cleaned reactors, leading to restriction of manual activity of some workers, although the process also spontaneously improved in others.

An epidemiologic study of 5,011 U.S. employees reported in 1971 identified 25 definite and 16 possible cases of AOL [16]. 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 [13].

Recent reports have continued to point to some systemic changes in skin, bones, and sacroiliac joint [17, 25, 30, 37, 45]. 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 [38]. In immunologic studies of workers with vinyl chloride disease, some of whom had evidence of Raynaud's phenomenon or AOL,

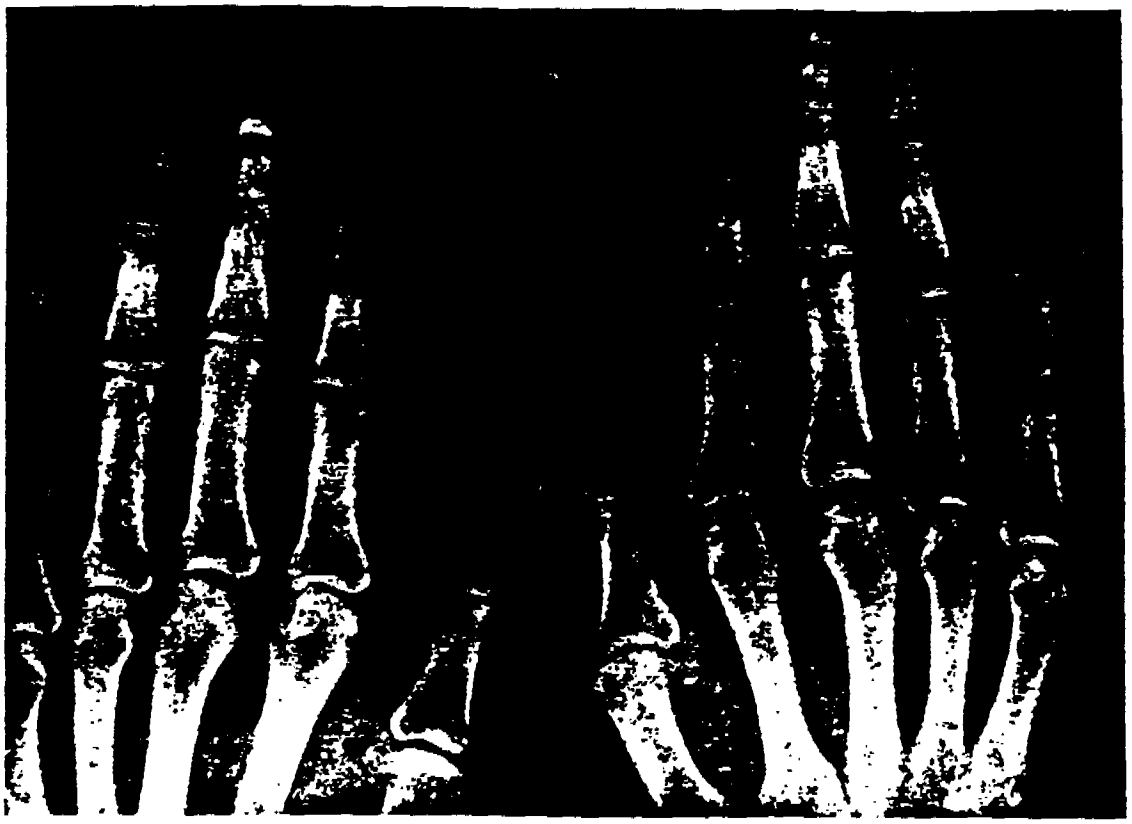

FIGURE 49-1. Hand x-ray of long-term polyvinyl chloride polymerization worker with marked acro-osteolysis, November 1964. (Courtesy of Dr. John Creech, B. F. Goodrich Company, Louisville, Kentucky.)

Ward et al. identified a number of abnormalities, including evidence of circulating immune complexes and their deposition in vessels [70]. The hypothesis that these immunologic changes may be related to the pathogenesis of AOL and to other aspects of VCM-induced disease needs further study.

A puzzling aspect is that AOL was not described in detail until the 1960s. Unlike HAS, which has a prolonged 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 [48]. Unfortunately, such exposure information is lacking in virtually all published reports of AOL).

Liver Disease. In studies carried out during the 1960s in Rumania, Suciu et al. described hepatomegaly in vinyl chloride workers (reversible in some after cessation of VCM exposure), which was often associated with abnormalities of liver function tests [60]. The spectrum of VCM-induced liver disease began to emerge from studies of PVC polymerization workers in Germany, starting in 1972. Lange et al. described workers with hepatic fibrosis, splenomegaly, and thrombocytopenia—all suggestive of portal hypertension—in the absence of significant hepatic parenchymal damage [38]. In a subsequent report, 81 percent of 70 workers studied were noted to have thrombocytopenia, 67 percent had increased Bromsulphalein (BSP) retention, and 57 percent had splenomegaly; 14 percent had increased serum enzyme levels, indicating hepatic damage [66]. Pathology studies demonstrated activation of hepatic sinusoidal cells and hepatic (particularly perisinusoidal) fibrosis, with lesser changes in hepatocytes

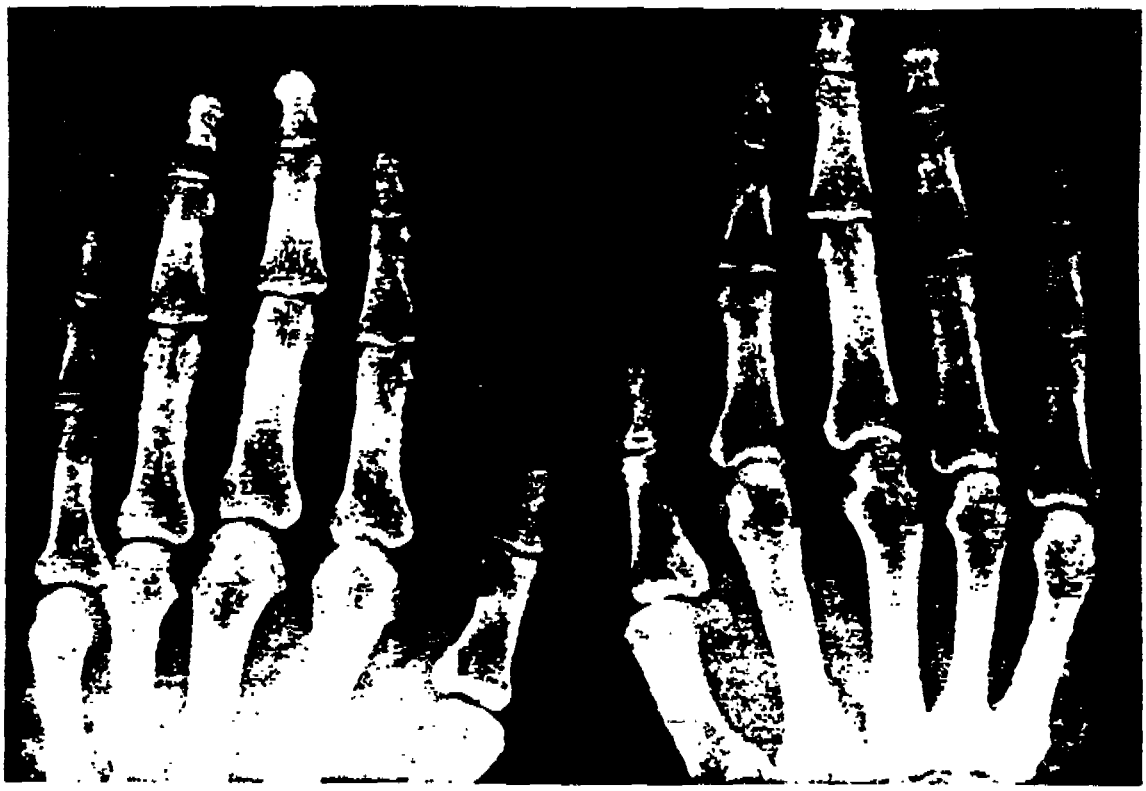

FIGURE 49-2. Follow-up hand x-ray of same worker as in Figure 49-1 almost 10 years after cessation of polymerization work, April 1974. (Courtesy of Dr. John Creech, B. F. Goodrich Company, Louisville, Kentucky.)

[27]; fibrosis of the liver capsule was clearly visualized at laparoscopy [46].

In 1974 Creech and Johnson 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 [14]. Subsequent detailed studies at that plant identified additional cases of HAS and cases of nonmalignant hepatic disease, consisting primarily of hepatic fibrosis, portal hypertension, and splenomegaly [20]. 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 et al. to establish the morphologic progression and pathogenesis of HAS, which are similar to those seen in idiopathic HAS and HAS resulting from other causative agents [54, 55, 64].

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 dilation. The latter changes can progress to hepatic fibrosis, portal hypertension [6], and occasionally peliosis hepatis; the hyperplastic sinusoidal cells become increasingly atypical and eventually undergo malignant transformation in the development of HAS (Figs. 3 and 4). Hepatocellular injury is not a feature of the early stages of this sequence, although it does appear in the later stages. Therefore, the hepatic disease caused by VCM is quite distinct from that caused by most previously identified hepatotoxins [53].

An increased frequency of abnormalities of standard liver function tests, particularly in VCM-exposed workers with clinical findings compatible with VCM-related hepatic disease, has been reported in a number of studies [40, 60, 66]. As can be seen from the above discussion, however, liver function abnormalities are a relatively late finding, and a number of cross-sectional studies of actively employed PVC polymerization workers

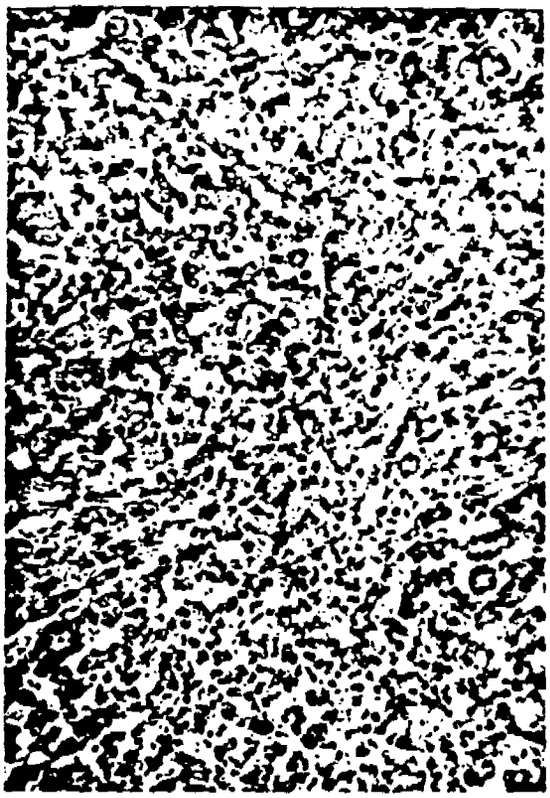

FIGURE 49-3. Circumscribed nodule, showing hyperplasia and hypertrophy of hepatocytes and sinusoidal cells, in a vinyl chloride worker. Hematoxylin eosin, 100×. (Courtesy of Dr. Hans Popper, Mount Sinai School of Medicine of the City University of New York.)

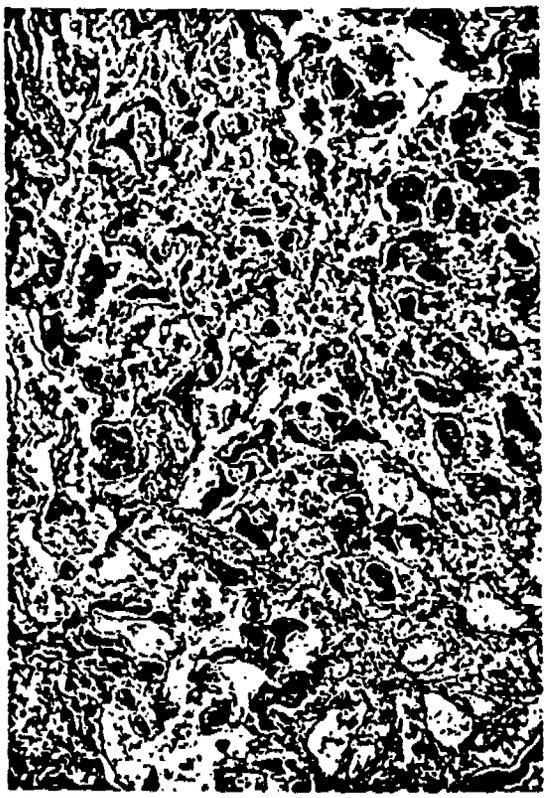

FIGURE 49-4. Trabecular angiosarcoma in a vinyl chloride worker. Note cords of hyperplastic hepatocytes, sometimes surrounding bile plugs. These cords are surrounded by layers of angiosarcoma cells. The sinusoidal spaces are dilated. Hematoxylin eosin, 60×. (Courtesy of Dr. Hans Popper, Mount Sinai School of Medicine of the City University of New York.)

have not detected increased abnormalities [72, 79]. 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]. As a result, periodic screening with standard liver function tests has been included in NIOSH recommendations and U.S. regulations [65].

There is a generally perceived need for the development of reliable screening tests for the early stages of VCM-induced hepatic disease. Tamburro et al. utilized hepatic clearance of indocyanine green as a sensitive indicator of liver function and noted the value of radioisotopic liver scans in detecting early anatomic lesions [62, 76]. Other tests under evaluation include gray-scale ultrasonography and *in vivo* capillary microscopy [44, 77]. The degree of reversibility of the hepatic fibrotic precursor lesion has not been determined [4], but withdrawal from exposure is prudent, in the hope of preventing progression. Survival after HAS is diagnosed has been estimated to average only several months. Dannaher et al. recently reported on the use of chemotherapy in cases of VCM-associated HAS to improve the duration and quality of survival [15].

Pulmonary Effects. Lilis et al, reported a chronic decrease in pulmonary function in PVC polymerization workers exposed to VCM and PVC dust [39]. Gamble et al. found no evidence of a chronic decrease, but they did demonstrate acute loss of pulmonary function during the course of a single workshift [25]. A recent report from England de-

scribes some deterioration of lung function, slight abnormalities of the chest radiograph, and complaints of slight dyspnea associated with exposure to PVC dust [58].

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 [2, 47]. By ultrastructural evaluation of lung biopsy material, Arnaud et al. demonstrated PVC particles in pulmonary macrophages and giant cells [2]. 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.

An increased risk of lung cancer in PVC polymerization workers has also been reported (see below).

CYTOGENETIC STUDIES

Since 1975 there have been a number of reports of increased frequencies of chromosomal aberrations in cytogenetic studies of peripheral lymphocytes from VCM-exposed workers. Subsequent negative reports have presented apparently conflicting results and difficulties in reconciling these findings, although the various methodologies, particularly with regard to level of VCM exposure and choice of control groups, have not always been comparable [23, 52]. It has been suggested that positive results are related primarily to the elevated VCM exposures occurring before 1975; two reports have demonstrated the disappearance of cytogenetic abnormalities in groups of workers followed periodically since 1975 [1, 31]. 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 et al. noted increased reporting of fetal loss by wives of VCM-exposed workers [35]. 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. High rates of congenital anomalies of the central nervous system have been reported in communities with PVC polymerization plants [33]; subsequent case control studies have not been able to confirm that the excess defects are related to VCM exposure [18]. Nevertheless, an 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 [67].

OTHER EFFECTS

A number of other findings, including hypertensive changes and symptoms such as headaches and fatigue (possibly related to the anesthetic effect of high dose exposures), have been reported [38, 40, 60, 72].

EPIDEMIOLOGY OF HEPATIC ANGIOSARCOMA

Two reports from NIOSH, in 1975 and 1978, summarized the worldwide distribution of known VCM-related cases of HAS [41, 59]. The great majority of such cases have occurred in PVC polymerization workers; 64 such cases had been identified to NIOSH as of October 1977. At that time, 23 cases had been identified in the United States, 10 in Canada, 9 in the Federal Republic of Germany, 8 in France, and the remainder from Belgium, Czechoslovakia, Great Britain, Italy, Japan, Norway, Sweden, and Yugoslavia. For those 64 cases, the latency period (i.e., the time from first exposure to diagnosis) ranged from 9 to 38 years, with a median of 21 years; the length of exposure ranged from 4 to 31 years, with a median of 18 years; and the age at diagnosis ranged from 37 to 71 years, with a median of 49 years. The majority of cases were diagnosed after 1973.

The most recent tabulation of cases worldwide documents 98 cases of VCM-related HAS, predominantly in PVC polymerization workers (personal communication, John Stafford, ICI Petrochemicals and Plastics Division, Welwyn Garden City, England). The years of peak occurrence were 1975 through 1978 (9–11 cases per year), although the reporting may not be complete for the most recent years. The patient with the most recent date of first exposure began work in 1966.

Cases of HAS have been reported in individuals exposed to lesser concentrations of VCM than PVC polymerization workers—for example, PVC fabricating workers or individuals residing near PVC plants [3, 9, 19, 41]—but, because of the relatively large numbers of individuals potentially

exposed at these lower levels, additional epidemiologic studies are needed to evaluate these associations. In a study of Thorotrast-induced HAS, the initially reported cases had high-dose exposures and relatively short latency periods, while a larger number of cases that appeared later had exposures associated with lower doses but prolonged latency periods [22]. Thus it is important to follow trends of VCM-related cases of HAS in the future for any shifts in epidemiologic patterns.

In nationwide reviews of HAS in the United States (1964–1974) and the United Kingdom (1963–1977), from 6 to 7 percent of pathologically confirmed cases occurred among PVC polymerization workers (12 of 168 in the United States; 2 of 35 in the United Kingdom) [3, 21].

OCCUPATIONAL MORTALITY STUDIES

Studies on animals have identified a multiplicity of tumors, in addition to HAS, following exposure to VCM (see below). As a result, a series of cohort mortality studies, primarily of PVC polymerization workers, have evaluated the risk for all malignant neoplasms in these groups [10, 12, 24, 49, 50, 61, 63, 75]. Some of the primary difficulties in conducting and interpreting these studies included the relative youth of the PVC industry (so that most of the workers in the various cohort studies have not passed through the age of peak cancer occurrence), the relatively small numbers of deaths among workers with prolonged exposure and latency in some of the studies, and the difficulty in precisely quantifying past exposure to VCM, PVC, and other chemicals used in the polymerization processes, such as other monomers used in the production of copolymers.

An increased risk of HAS was seen in the majority of studies [12, 24, 49, 61, 63, 75]. Waxweiler et al. noted an increased risk of respiratory cancer [74]. Detailed follow-up investigation demonstrated that the excess lung cancer risk was primarily in the large-cell undifferentiated histologic subtype (not previously related to either smoking or chemical exposure) and was related most closely to PVC dust exposure rather than to VCM exposure [74]. An increased risk of respiratory cancer was seen also by Buffler et al. at a VCM production plant, where exposure would have been to VCM rather than to PVC resin [10]. Increases in brain cancer and lymphatic tumors have been noted [75]. Therefore, it is imperative to continue follow-up of the already identified and studied cohorts and to distinguish between exposures to VCM and PVC in the analyses, to discover whether the trends of excess cancer risk noted above continue and are confirmed.

EXPERIMENTAL STUDIES

In 1971 Viola et al. first demonstrated the carcinogenicity of VCM in rats exposed to 30,000 ppm for 12 months [69]. Hepatocarcinogenicity, particularly HAS, was reported later in a series of experiments by Maltoni [43] and reproduced in other laboratories [67]. 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) [43]. Hepatocellular carcinomas also have been observed after exposure of newborns to VCM. Maltoni's data suggest an increase in mammary tumors at doses as low as one ppm [43].

It appears that a metabolite of vinyl chloride, rather than VCM itself, is the ultimate carcinogenic substance. In bacterial and other test systems, the mutagenicity of VCM is greatly increased by the addition of a metabolizing system (e.g., rat liver microsomes), and an evaluation of animal carcinogenicity data suggested a closer link of HAS formation with amount of VCM metabolized than with VCM exposure concentration [7, 28]. Although a number of mutagenic metabolites are formed, the reactive epoxide (chloroethylene oxide) formed during the oxidative metabolism of the VCM double bond appears of greatest concern. 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 [51, 56]. The reactive metabolite(s) are thought to initiate the carcinogenic process by covalent bonding to hepatic macromolecules, including DNA [71].

The evidence for the carcinogenicity of vinyl chloride has raised considerable concern about the safety of a number of structurally related halogenated hydrocarbons [11]. Studies on animals indicate the probable hepatocarcinogenicity of vinylidene chloride [68] and vinyl bromide [8], and epidemiologic studies on humans (although of questionable quality) have raised concern about the carcinogenicity of chloroprene [36]. Reviewing

the available data on the carcinogenicity of selected halogenated hydrocarbons, Infante and Marlow have stressed the paucity of available epidemiologic data to evaluate this question in humans, in spite of the demonstrated animal carcinogenicity for a number of these compounds [34].

OCCUPATIONAL STANDARDS

In the United States, the Occupational Safety and Health Administration (OSHA) requires that a worker's exposure to VCM not exceed one ppm (8-hour time-weighted average). The ceiling concentration limit for 15 minutes or less is 5 ppm [65]. In general, European VCM exposure standards, except those of the Scandinavian countries, are set somewhat higher than in the United States [29, 67].

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