III. BIOLOGIC EFFECTS OF EXPOSURE

Vinyl halides are of growing industrial importance, especially in the plastics industry. The vinyl halides, vinyl chloride, vinylidene chloride, vinyl bromide, vinyl fluoride, and vinylidene fluoride, are easily polymerized or copolymerized with various compounds, such as acrylonitrile, vinyl acetate, and styrene, to form pliable, lightweight plastics or thermoplastic resins. Whereas there are many reports of epidemiologic, carcinogenic, mutagenic, and metabolic studies of vinyl chloride, there are few reports of studies of the biologic effects of any of the other vinyl halides. Because of the paucity of information on these latter compounds, NIOSH has undertaken evaluations of the structure-activity relationships, based on chemical and physical properties, of the compounds and has used these relationships, along with data from the vinyl chloride literature, as a basis for extrapolation from actual to potential hazards for substances about which direct information is inadequate. Pertinent physical and chemical properties of these vinyl halides are presented in Table XVII-1, and a list of some of the synonyms for these compounds is presented in Table XVII-2.

The vinyl halides undergo metabolic conversions, presumably initiated by enzymatic oxidation, to the corresponding oxiranes (epoxides) [1-4]. Subsequently, the oxiranes are presumed to either bind covalently to cellular macromolecules or be spontaneously rearranged to the aldehyde or acyl halide, hydrolyzed to the diol, conjugated with glutathione, or reduced back to the parent compound. The major adverse biologic effects of the vinyl halides or their metabolites may include carcinogenesis, mutagenesis, teratogenesis, and damage to the liver. Such effects may be associated with electrophilic reactions (alkylation) with essential cellular components, whereas the rearrangements and other reactions (reduction, hydrolysis, conjugation) have often been considered to be detoxification mechanisms. It is realized that the rates of these possible reactions may vary and that the risk of adverse effects would be a function of the relative rates leading to, and corresponding half-lives of, each metabolic intermediate. Therefore, toxicity of a different order of magnitude may be elicited by each of these compounds. Indeed, not all of these effects have been associated with each of the vinyl halides.

The absorption and subsequent metabolism of vinyl chloride have been described as concentration-dependent; a saturable enzyme system, predominantly responsible for its metabolism at low concentrations, and a secondary oxidative system, predominant at higher concentrations, have been postulated [4-6]. The authors of these reports have further postulated that the oxirane is formed predominantly at the higher concentrations, ie, through the secondary oxidative pathway. The halogenated acetaldehyde is common to both pathways, however. Thus, even if the oxirane is not formed at low concentrations, the potential for macromolecular alkylation exists through the aldehyde and subsequent intermediates.

The covalent reactions of the vinyl halides and/or their metabolites with biologic materials may alter the chemical behavior and physical characteristics of the cellular constituents so as to prevent the altered molecules from functioning normally in physiologic processes. The formation of stable reaction products may account, in part, for the subsequent harmful effects observed in biologic systems exposed to the vinyl halides. The alkylation of the biologic materials controlling cellular metabolism by the vinyl halides and/or their metabolites is the most plausible basis for the induction of genetic and neoplastic alterations in cell populations exposed to these chemicals. Because of the long latent period before adverse effects such as neoplasia become manifest, measurable effects may not be observable until many years after exposure at low concentrations.

Extent of Exposure

NIOSH has estimated that approximately 2.5 million US workers may be occupationally exposed to vinyl halide monomers. A more precise estimate is difficult to make because of the lack of information on exposure to monomer released in manufacturing processes involving the polymers or copolymers. Some of occupations that involve exposure to the vinyl halides are listed in Table XVII-3.

(a) Vinyl Chloride

Vinyl chloride has the chemical formula $CH_2=CHCl$. At room temperature, it is a gas with a sweet, pleasant odor, and it has a boiling point of -13.9 C and a solubility in water of 0.11 g/100 ml at 24 C (Table XVII-1). It is easily liquified and is stored and used industrially in the liquid form [7,8]. Vinyl chloride was first prepared by Regnault in 1835 by reacting dichloroethane with alcoholic potash [7]. An effective industrial method for preparing vinyl chloride was established in 1913 by Griesheim-Elektron, using hydrochlorination of acetylene, with mercuric chloride as a catalyst, as described by Klatte and Rollett in 1911. It was not until World War II, however, that production of vinyl chloride for use in synthetic rubber was established on a large scale in the United States. Vinyl chloride is currently produced commercially by the oxychlorination of ethylene, by the liquid or gaseous reaction of acetylene with hydrochloric acid, and by the pyrolysis of ethylene dichloride [8].

Production of vinyl chloride in 1975 in the United States amounted to about 4,063 million pounds [9], and the annual growth rate in the vinyl chloride industry is expected to be about 6% up to 1980 [10]. Vinyl chloride is used principally to produce polyvinyl chloride and other resins, which are used in a wide variety of end products. It has also been used as a chemical intermediate, solvent, aerosol propellant, and refrigerant [7]. In 1974 NIOSH estimated that 2.2 million workers in the United States were potentially exposed to vinyl chloride.

(b) Vinylidene Chloride

Vinylidene chloride has the chemical formula $CH_2=CCl_2$. At room temperature, it is a clear, colorless liquid with a pleasant, sweet odor; its boiling point is 31.56 C and its solubility in water is 0.25 g/100 ml at 25 C (Table XVII-1). It was first prepared and described by Regnault, who obtained it by reacting 1,1,2-trichloroethane with alcoholic potash [11]. It is still prepared commercially by reacting 1,1,2-trichloroethane with lime or caustic, most often aqueous calcium hydroxide, at 90 C [12]. Other syntheses involve bromochloroethane, trichloroethyl acetate, tetrachloroethane, or catalytic cracking of trichloroethane [12].

The US production of vinylidene chloride in 1974 was about 170 million pounds [13]. It is primarily used in the production of plastics, including copolymerization with vinyl chloride or acrylonitrile to form various thermoplastic resins [8]. In 1974 NIOSH estimated that 57,000 workers in the United States were potentially exposed to vinylidene chloride.

(c) Vinyl Bromide

Vinyl bromide, $CH_2=CHBr$, is a colorless gas at room temperature and has a boiling point of 15.85 C and a solubility in water of 0.565 g/100 ml at 25 C (Table XVII-1). It was first prepared and described by Regnault, who obtained it by reacting dibromoethane with alcoholic potash [11]. In 1872, Reboul reported the preparation of vinyl bromide after reacting acetylene with hydrogen bromide. The major commercial method for producing vinyl bromide is the reaction of ethylene dibromide with sodium hydroxide [14].

Production of vinyl bromide in the United States amounted to over 5 million pounds in 1976 [14]. Currently, vinyl bromide is used primarily as a flame-retarding agent for acrylic fibers [8]. In 1974 NIOSH estimated that 26,000 workers in the United States were potentially exposed to vinyl bromide.

(d) Vinyl Fluoride

Vinyl fluoride, $CH_2=CHF$, is a colorless gas at room temperature; it has a boiling point of -72.0 C and is essentially insoluble in water (Table XVII-1). It was first prepared and described in 1901 by Swarts, who obtained it by reacting 1-fluoro-1,2-dibromoethane with zinc dust in the presence of alcohol [11]. It is currently made by reacting acetylene with hydrogen fluoride [15].

Although the amount of vinyl fluoride used each year has not been reported, an average of 0.6 pound of acetylene is required to produce 1 pound of vinyl fluoride by the current method. Each year about 2 million pounds of acetylene are used in the United States for producing vinyl fluoride, which is used for making various copolymers that are used in end products such as insulation for electrical wires and in protective paints and coatings [13], indicating that some 3.3 million pounds of vinyl fluoride are produced

annually. The number of workers potentially exposed to vinyl fluoride has not been estimated by NIOSH.

(e) Vinylidene Fluoride

Vinylidene fluoride, $CH_2=CF_2$, is a colorless gas at room temperature with a faint, ethereal odor; it has a boiling point of -85.7 C and its solubility in water is 0.018 g/100 ml at 25 C (Table XVII-1). It was first prepared by Swarts by reacting 2,2-difluoro-1-bromoethane with sodium amylate [11]. Vinylidene fluoride is used in making polymers and copolymers that are found in such end products as insulation for high-temperature wire, protective paints and coatings, and chemical tanks and tubing [8]. In 1974 NIOSH estimated that 32,000 workers in the United States were potentially exposed to vinylidene fluoride.

Historical Reports

The vinyl compounds assumed economic importance with the increased demand for synthetic rubber and the advent of the plastics industry. The first study [16] of the toxicity of vinyl chloride was conducted after its potential industrial importance became apparent.

Patty et al [16], in 1930, exposed guinea pigs to vinyl chloride at concentrations of 0.5-40% (5,000-400,000 ppm; 12.8-1,024 g/cu m) in air. Unsteadiness, staggering, and ataxia appeared within 2-5 minutes and lasted 50-90 minutes at concentrations of 2.5 and 5%. After 90 minutes of exposure at these concentrations, the animals fell on their sides and remained in a state of narcosis until death or termination of exposure. Within 1-2 minutes of exposure at 10-25%, respiration became jerky and rapid, and the animals lapsed into a state of deep narcosis accompanied by convulsions and involuntary movements that terminated in death. At 40%, the same signs occurred within 15 seconds. Examination of the animals that died during exposure showed congestion and edema of the lungs and hyperemia of the kidneys and liver. On the basis of these findings and comparisons with other experiments, the authors concluded that vinyl chloride was less harmful than benzene, gasoline, carbon tetrachloride, or chloroform. They further suggested that the comparatively low toxicity and the narcotic action of vinyl chloride might make it useful as a surgical anesthestic.

The first two vinyl chloride-related occupational deaths were reported in 1960 by Danziger [17]. The first case involved a 21-year-old worker who cleaned polymerization tanks. The man had entered a tank wearing an air-supplied mask after explosiometer tests had shown that the concentration of vinyl chloride in the tank was below the explosive limit (30,000 ppm; 76.8 g/cu m). Ten minutes after he had last spoken to the worker, the foreman saw the man lying on the bottom of the tank. After an unspecified delay to get rescue equipment, the man was removed from the tank. He was not breathing, and he did not respond to artificial respiration. The rescue workers stated

and he did not respond to artificial respiration. The rescue workers stated that they did not detect any odor of vinyl chloride in the tank or on the worker. At the post-mortem examination, no "remarkable" changes in the internal organs were observed that could have caused the sudden death. The heart was enlarged, the blood failed to clot, and the spleen, kidneys, and liver were congested. Cyanosis of the fingernails and toenails was also observed. At the inquest, the presiding physician stated that the man died of asphyxia from an undetermined cause. The information suggests, however, that the death may have been due to respiratory depression caused by vinyl chloride.

The second case involved a 39-year-old worker who was bleeding condensed water out of a vinyl chloride storage tank [17]. The worker had to turn a valve that was located in a 7-foot-deep pit immediately adjacent to the tank. Another worker found the man lying unconscious in the pit about 20 minutes after he had entered it, and the second worker climbed in to get him out. This worker reported that he shut the open valve but then began to feel "giddy" and saw "circles" in front of his eyes. He went for assistance. After help was obtained, the first worker was removed from the pit, whereupon artifical respiration was attempted unsuccessfully. Autopsy revealed cyanotic fingernails, brown discolorations of the conjunctivae, acute hyperemia of the lungs, trachea, and bronchi, and failure of the blood to clot. Other findings were not remarkable, even though congestion of the kidneys was again observed. Asphyxiation was again indicated as cause of death; however, in this case, it seems to have been more clearly attributable to exposure to vinyl chloride.

Information on the biologic effects of the other vinyl halides has begun to be published only recently. This information is discussed in the relevant sections in this chapter.

Effects on Humans

Prior to 1970, few industrial exposure studies had been conducted on vinyl compounds other than vinyl chloride. Two factors worked in conjunction to delay recognition of the potential health hazards from exposure to vinyl compounds. First, early acute exposure studies on volunteers [18] had indicated that the symptoms of exposure were relatively mild and that they were observed only at concentrations well above the odor thresholds, so that adequate warning of potential danger was assumed to be present. Second, these compounds had been of economic importance for a relatively short time, and the correlation between adverse systemic effects and occupational exposure was not readily apparent. There are still comparatively few reports of effects on humans or epidemiologic studies of populations of workers handling vinyl compounds, and only those persons working with vinyl chloride and vinylidene chloride have been examined for chronic effects from exposure to these compounds. No reports of effects on workers from exposure to vinyl bromide, vinyl fluoride, or vinylidene fluoride have been located in the literature.

(a) Vinyl Chloride

Lester et al [18], during 1961 and 1962, exposed six volunteers, three men (26, 35, 50 years of age; 86, 78, 73 kg, respectively) and three women (25, 40, 55 years of age; 64, 52, 61 kg, respectively), to vinyl chloride gas at concentrations of 0.0, 0.4, 0.8, 1.2, 1.6, or 2.0% (0, 4,000, 8,000, 12,000, 16,000, or 20,000 ppm; 0-51.2 g/cu m). Exposures were for 5 minutes twice each day, separated by a 6-hour interval, on 3 successive days. Each subject was exposed at these six concentrations in a different order over the 3 days. Either the gas mixture or plain air was administered through a mask, at a flowrate of 50 liters/minute, with the subject seated in a chair. When the mask was removed, the subject was asked to report his or her feelings in comparison with those just before putting on the mask.

When only air was presented, no differences were reported, except by subject 3, who felt "slightly dizzy" [18]. At a concentration of 0.4% vinyl chloride, no differences were reported by any subject. Similar results were obtained at 0.8%, except that subject 3 felt "slightly heady." At 1.2%, subjects 2 and 6 became dizzy, while the others reported no difference. At 1.6%, subject 5 reported no effect, but the others reported various degrees of dizziness, nausea, lightheadedness, and dulling of vision and hearing. These symptoms disappeared rapidly when the exposure ended. At 2.0% vinyl chloride, all subjects reported symptoms more intense than those at 1.6%, and subject 1 reported a headache that persisted for 30 minutes.

The authors concluded that the maximum concentration of vinyl chloride causing no acute effects on humans after exposure for 5 minutes was between 0.8 and 1.2% [18]. The authors also stated that "vinyl chloride causes clear-cut intoxicating symptoms which can serve as adequate warning signs of its presence." While these conclusions were valid for the acute irritant and psychomotor effects caused by the 5-minute exposures to vinyl chloride, the possibility of adverse effects of vinyl chloride at concentrations lower than those necessary to produce these symptoms was not discussed.

Suciu et al [19] described clinical manifestations of vinyl chloride poisoning in 168 workers at two vinyl chloride manufacturing plants in Rumania. Although workplace concentrations of vinyl chloride were given for each year from 1962 to 1972 (Table III-1), methods for these determinations were not reported.

The authors compared the workers' reports of symptoms indicative of effects on the nervous system in 1962 with those reported in 1966 [19]. For these 2 years, the percentages of workers (n=168) reporting dizziness were 47 and 10.2, drowsiness, 45 and 16.6, headache, 36.6 and 6.9, loss of memory, 13 and 8, euphoria, 11 and 1.2, and nervousness, 9 and 0.6. These data indicate that the central nervous system (CNS) effects observed were concentration-dependent.

TABLE III-1

WORKPLACE CONCENTRATIONS OF VINYL CHLORIDE

Year	mg/cu m	ppm*
1962	2,298	898.5
1963	675	263.9
1964	286	111.8
1965	126	49.3
1966	98	38.3
1967	100	39.1
1968	108	42.4
1969	111	43.4
1970	111	43.4
1971	119	46.5
1972	146	57.1

*Calculated from authors' data

Adapted from reference 19

Other signs and symptoms of exposure to toxic materials were also reported including increased blood pressure, loss of appetite, hepatomegaly, Raynaud's syndrome, coughing and sneezing, bronchial rales, emphysema, pulmonary fibrosis, decreased respiratory function, abnormal liver function, abnormal serum enzyme activities and anemias [19]. The frequency of these manifestations generally decreased with decreasing workplace concentration of vinyl chloride. The exception to this was the incidence of contact dermatitis which increased from 4.4% in 1962 to 7.4% in 1966, indicating that contact dermatitis was not primarily dependent on the concentration of airborne vinyl chloride.

The authors stated that the frequency of adverse effects had diminished between 1962 and 1972 because of the institution of exposure-control and therapeutic measures [19]. These measures included reduction of workplace concentrations of vinyl chloride, flushing vinyl chloride from the reactors before cleaning, wearing gloves (unspecified type) during manual cleaning operations, reduction of the workshift to 6 hours, semiannual medical examinations coupled with transfer to another workplace if poisoning was suspected, interdiction of smoking (presumably only at the workplace), administration of vitamin C, vitamin B complex, and iron for 10 days a month, and supplying ointments with cortisone to prevent skin lesions. The authors stated that these measures "reduced all symptoms by two-thirds."

The importance of this paper [19] lies in its characterization of the wide range of adverse effects observed in a worker population exposed to vinyl chloride; however, which exposures and which workers were associated with particular effects is often unclear. The authors did not state in all cases whether or not the workers examined in 1965 and in subsequent years were the same ones that were examined in 1962. The changes induced by the vitamin therapy and the changes caused by different engineering and administrative controls and work practices are also impossible to evaluate independently.

Veltman et al [20] studied the effects of exposure to vinyl chloride in 70 polyvinyl chloride workers who had been employed for from 6 months to 21.8 years (average 7.7 years) in cleaning autoclaves and centrifuges, in drying and sifting processes, and in wrapping polyvinyl chloride as a dry end product. Exposure concentrations were not reported.

The workers complained of headache (12.9%), pain in the calves (12.9%) and joints (24.3%), potency problems (18.6%), increased perspiration (27.1%), sensation of cold in fingers or hands (25.7%), numbness or tingling in fingers or toes (31.4%), frequent dizziness (37.1%), fatigue (38.6%), and upper abdominal distress (60.0%) [20]. On physical examination, 6 of the 70 (8.6%) had acroosteolysis, a softening or destruction of the distal phalanges of the hands or feet. Other abnormalities in the workers included Raynaud's syndrome (8.6%), scleroderma-like skin changes on the hands and forearms (11.4%), varices in the esophagus or stomach (11.4%), increased serum enzyme activities (14.3%), reticulocytosis (41.0%), increased sulfobromophthalein (BSP) retention (67.2%), leukopenia (7.1%), slight to severe thrombocytopenia (81.0%), and splenomegaly (57.4%).

Arteries in the fingers were narrowed, and microscopic changes, notably fragmentation of elastic fibers, were found in the fingers of all workers with skin abnormalities and in 6 of 28 workers with apparently unchanged skin [20]. Thrombocytopenia was associated with enlargement of the spleen, but it was also found in patients whose spleens were not enlarged. Only 6 of 29 patients with thrombocytopenia showed improvement in their platelet counts 1-1.5 years after having left their jobs; 20 had even lower platelet counts than those seen initially, and 3 showed no change. None of the most seriously affected

workers showed improvement in their platelet counts. All of the phalangeal lesions healed within 2 years after the workers left polyvinyl chloride production work, however.

The authors [20] stated that this study was significant because it showed that acroosteolysis was associated with employment in polyvinyl chloride production, it demonstrated that a vinyl chloride disease existed, and it indicated that vinyl chloride disease might be detected by external signs (changes in fingers or skin) or blood tests (thrombocytopenia). The authors also stated that thrombocytopenia was the earliest manifestation of vinyl chloride toxicity and that platelet counts should be required of vinyl chloride workers. However, only 8.6% had club-like changes of the fingertips and only 11.4% had skin changes. Although 81% of the workers had thrombocytopenia, which in some cases persisted or worsened after exposure to vinyl chloride ended, the nonspecific nature of thrombocytopenia and the possibility that it might signal damage that is already irreversible casts doubt on the usefulness of this clinical sign for the early detection and diagnosis of vinyl chloride disease. It is apparent that the vinyl chloride syndrome is complex, involving changes in the skin, bones, blood and blood vessels, liver, spleen, and possibly the nervous system. Until the disease process is better understood, a decision on which changes are true constituents of a syndrome and which are independent events, coincidentally discovered by the same examination, is impractical. Frequent dizziness in 26 of the 70 patients (37.1%) in this study [20] supports the findings of Suciu et al [19] and suggests that the CNS may be affected by exposure to vinyl chloride, possibly indirectly by a vascular mechanism. Interference with CNS function might increase the risk of accidental injury to vinyl chloride workers.

Moulin and coworkers [21] observed four cases of scleroderma accompanying vinyl chloride-induced acroosteolysis in workers. Three of the four workers had scleroderma of the face, and each had shortening of the fingers, thickening of the skin of the fingers with adhesion to the deep layers, palmar erythema and hyperhydrosis, difficulty in extending the fingers completely, and thickened skin on the palmar surface of the wrist and forearm with hard projecting nodules that were most prominent over the flexor tendons. Raynaud's syndrome had been experienced by two workers, one of whom whose feet, face, and hands had slightly edematous, scleroderma-like lesions.

One individual's condition was studied in detail and followed for 4 years [21]. The worker, aged 33 years, had for 4 years cleaned autoclaves used in vinyl chloride polymerization. There was no suggestion of a predisposition toward the development of acroosteolysis in the medical history of either the individual or his family. The worker had a history of consuming 2 liters of wine a day. He was hospitalized for malaise and was found to have slurred speech, paralysis of the right arm and right side of the face, and loss of skin sensations on the same side of the abdomen. Results of neurologic, roentgenographic, and electroencephalographic examinations showed mild deviations from normal. While the worker was hospitalized, marked

abnormalities of his fingers were noted. The last phalanx of each finger seemed shortened and enlarged, with the nail clubbed and wider than it was long. The patient had all the skin changes described previously as accompanying scleroderma. Microscopic examination of two nodules from his forearm showed a normal epidermis and a thickened, fibrous dermis with edema separating fragmented collagen fibers, but no signs of inflammation. Elastic fibers were few and segmented. No significant abnormalities of the blood vessels were reported. Roentgenograms of both hands showed osteolysis of the last phalanx of each finger of both hands, the distal three-fourths of each phalanx having disappeared. A complete roentgenographic examination of the skeleton showed beginning sacroiliac arthritis, but normal phalanges in the toes. Arteriography showed normal circulation through the arm, but decreased circulation in the wrist and hand caused by extreme hypertonia of the blood vessels of the fingers.

Three years after assignment to other work, the individual showed regression of the scleroderma, the fibrous nodules, and the circulatory disturbances [21]. The fingers remained hypothermic compared with the thumb, and painful paresthesia still affected the fingertips. Bone repair was seen in most of the phalanges.

Moulin and coworkers [21] concluded that the incidence of acroosteolysis in vinyl chloride polymerization workers could be considerably reduced by introduction of control measures to reduce exposure to vinyl chloride. They believed that the distal vasoconstriction they observed in these workers was not a true arteritis, although it was severe, and that the acroosteolysis and sclerodermatous changes in the skin were secondary complications of the peripheral vascular hypertonia. Because of the similarity of this disease to acrosclerotic scleroderma, the authors suggested that dermatologists obtain an occupational history from any patient presenting the signs and symptoms described in their paper.

Several other authors have reported CNS effects [22], acroosteolysis [23-25], and Raynaud's syndrome or scleroderma accompanying acroosteolysis [26-29] in workers exposed to vinyl chloride during its manufacture or polymerization. The information concerning signs and symptoms of vinyl chloride exposure in these reports is substantially the same as that in the reports previously discussed [19-21].

Other studies have identified adverse liver effects on workers exposed to vinyl chloride. Marsteller et al [30] reported on 50 workers in a vinyl chloride polymerization plant, 45 of whom underwent peritoneoscopy and 48 of whom had samples of liver taken for biopsy. All 50 underwent intravenous (iv) cholecystography and radiography of the upper gastrointestinal tract. Scintography of the liver and spleen was performed for 48, using ^{197}Hg. The liver was found by palpation to be enlarged in 31 cases and the spleen in 37 by scintography. The hepatic surface showed conspicuously augmented vascularization and stellate, reticular, or nodular fibrosis and scarring of the capsule. The spleen was not well visualized by peritoneoscopy except when

it was markedly enlarged; then the crenate margin was sharply indented and showed capsular fibrosis and subcapsular hemorrhages. Early signs of portal hypertension were noted, including ascites and dilatation and tortuosity of gastric and peritoneal veins.

Muller et al [31] described microscopic changes observed in liver specimens taken for biopsy from 50 polyvinyl chloride production workers. Liver cells showed focal hydropic swelling, single-cell necrosis, focal granular disintegration of the cytoplasm, hyperplasia with enlargement and polymorphism of cell nuclei, and often the presence of several nucleoli. Periportal and centrilobular fibroses were described, without accompanying cellular activity or involvement of the portal vessels, and about one-half of the specimens of liver contained fatty degeneration. Changes in the cells lining the liver sinusoids were described as "most impressive," and had begun to develop in the first few years of exposure. Proliferation of sinusal cells was the first change observed, and, after 6-10 years of exposure, sinusal cell nuclei had become markedly atypical. Three cases of hemangioendothelial sarcoma of the liver were discovered. The authors reported that the regions around the sarcomas gave the impression that there was a transformation of atypical sinusal cells to tumor cells and that the cytologic atypias of sinusal cells might be of prospective importance.

Thiess and Frentzel-Beyme [32] made a retrospective survey of diseases reported to be associated with industrial exposure to vinyl chloride in the Federal Republic of Germany. Insurance records listed 180 cases of "vinyl chloride disease," among then current employees of which 57 were recognized by the Occupational Medical Officer as being cases of true occupational illness. Signs associated with vinyl chloride disease in the original 180 cases, in order of decreasing occurrence, were: thrombocytopenia (78), liver damage (67), splenic abnormalities (47), Raynaud's syndrome (27), circulatory disturbances (22), lung function disturbances (21), scleroderma (18), acroosteolysis (16), and esophageal varices (13).

There were five cases of "haemangioendotheliosarcoma" in workers who had been employed in vinyl chloride or polyvinyl chloride production areas for 11-17 years; four of the workers, aged 38-44 years, had died. Only 46% of the workers exposed to vinyl chloride at one particular plant were still working in a polyvinyl chloride plant or were otherwise traceable; the rest were lost to the statistical survey. The authors noted that there were many difficulties in retrospective surveys for occupational health hazards. They stated that although mortality data were necessary in identifying a new disease, morbidity data were even more important, because death certificates were not always accurate. They also stated that prospective investigations were preferable to retrospective ones, although the latter approach had received priority due to considerations of the time required in relations to the yield of information. Physicians representing the government, universities, and the vinyl chloride and polyvinyl chloride industries in the Federal Republic of Germany were said to be cooperating in further epidemiologic studies. The authors pointed out that more data on vinyl

chloride concentrations in the workplace, periods of worker exposure, and control measures were needed before an association between exposure to vinyl chloride and the development of angiosarcoma and other disorders could be proven.

The authors stated that, with regard to the cause of death among employees at this plant, "a relatively large proportion of deaths occurring at an early age, are due to unnatural causes of death i.e. accident at the work place or road accidents" [32]. This may suggest that the worker exposed to vinyl chloride could himself become an occupational and social health hazard because of behavior-modifying effects of the material, and may therefore support the inferences drawn from the work of Veltman et al [20] and Suciu et al [19] discussed previously.

Lange et al [33], in 1975, analyzed the medical and work histories of 15 workers employed in the polyvinyl chloride processing industry in the Federal Republic of Germany for an average of 5 years (range 1.5-13 years). Seven of the workers (47%) complained of sensations of pressure or pain in the upper abdomen, three (20%) of frequent dizziness, two (13%) of cold hands and feet, and one (7%) of increasing weakness in his legs. Medical investigations conducted on the workers consisted of a dermatologic examination and several laboratory tests. A BSP retention test was performed on 9 of the workers, a reticulocyte count on 10, roentgenograms of the chest, hands, and feet on 12, and a liver-spleen scintigram, using 99 mTc-sulfur colloid on 11. Four of the workers also underwent laparoscopy and liver biopsy.

Dermatologic examination revealed no clinical signs of scleroderma or Raynaud's syndrome [33]. The results of the laboratory tests, however, showed slight to moderate thrombocytopenia (63,000-139,000 cells/μl) in seven workers (47%); increased BSP retention (5.2-15.1% at 45 minutes) in seven workers (47%); reticulocytosis of 1.7-4.4% in six workers (40%); and leukopenia (3,250 cells/μl) in one worker (7%); more than one abnormality was found in some of the workers. One of the workers examined by liver-spleen scintigram had slight splenomegaly and one of the workers who underwent laparoscopy and liver biopsy showed changes, although less distinct, "of the kind observed in PVC-production workers." The authors concluded that, despite the small sample size, thrombocytopenia, increased BSP retention, reticulocytosis, splenomegaly, and leukopenia were characteristic of vinyl chloride disease.

Lange et al [33] also presented case studies of two workers from the same polyvinyl chloride plant who had died of malignant tumors. The first case was that of a 38-year-old autoclave cleaner who was employed for 12 years in the plant. Physical examination in 1968 showed a large tumor in the upper abdomen in the area of the liver and spleen. Chest roentgenograms showed destruction of the fourth rib, on the left side of the back. Laboratory findings included increased erythrocyte sedimentation rate (22-67 mm/hour), considerable anemia, reticulocytosis of 6%, a reduction of serum iron (25μg/100 ml), an increased serum gamma-globulin (25 relative percent), an "increased" alkaline phosphatase level (65 units/ml), and an increased SGOT level (24 units/ml),

all indicative of liver damage. The liver-spleen scintigram showed splenomegaly, hepatomegaly, and reduced storage in the liver reticuloendothelial system. The patient then underwent a laparotomy, which revealed a generally enlarged liver with many palpable nodes on the surface. Microscopic examination of two of the liver biopsy specimens showed hemangioendothelial sarcomas. After the laparotomy, the patient was given cytostatic treatment, but his condition continued to deteriorate and he died within a year after the initial diagnosis of the tumor.

The second case was that of a 39-year-old man who had worked for some portion of 11 years as an autoclave cleaner in the plant and for 2 years in a machine-producing factory [33]. He had felt pain in the lower right quadrant of his thorax for some months and had experienced a painful hardening in the upper right portion of his abdomen several weeks before his medical examination. Physical examination disclosed a tumor the size of an apple on the epigastric angle. Laboratory tests showed these values, which the authors considered abnormal: erythrocyte sedimentation rate (44-73 mm/hour), and the "lactic" dehydrogenase (296 units/ml), and alkaline phosphatase (80 units/ml) activities in the serum. Normal differentiated blood counts and platelet counts were found. Laparotomy, performed twice on this worker, showed a fist-sized whitish-yellow tumor on the lower part of the left lobe of the liver that extended to the posterior portion of the right lobe. Numerous other nodules were palpable in the liver. A small degree of congestive spleen enlargement (not further defined) was also found. Microscopic examination of several biopsy specimens led to the diagnosis of hemangioendothelial sarcoma of the liver. Although postoperative radiotherapy was given, the patient died about a year after the initial diagnosis.

Makk et al [34], in 1974, reported that one of the authors, having noticed a diagnosis of angiosarcoma of the liver on a death certificate, recalled having performed a liver biopsy 3 years earlier that led to the same diagnosis. An investigation showed that both of these patients had worked in a polyvinyl chloride plant in Kentucky, and a search of plant and area hospital records showed autopsy reports of three other cases over a 10-year period; two additional cases were diagnosed by biopsy. A systematic program was therefore undertaken for detection of liver abnormalities in workers in a chemical plant producing polyvinyl chloride and synthetic rubber, using automated 12- or 18-factor blood analyses.

Screening profiles from the 12- or 18-factor analyses were obtained for 1,183 employees, of whom 75 (6.3%) had either 2 liver-related abnormalities on the initial screening or 1 such abnormality that persisted [34]. As a result of further testing including exploratory laparotomy of these 75 workers, 2 unsuspected cases of angiosarcoma and 3 cases of portal fibrosis were discovered. A biopsy of the liver was performed on two other workers who requested it, but both samples proved to be normal. Abnormal test results were reported for serum alkaline phospbatase in 35/72 (48.6%), SGPT in 13/73 (17.8%), SGOT in 19/68 (27.9%), serum lactic dehydrogenase (LDH) in 8/72 (11.1%), serum bilirubin in 19/72 (26.4%), serum isocitrate dehydrogenase in

9/59 (15.3%), and serum gamma-glutamyl transpeptidase in 31/70 (44.3%). The authors stated that, of the liver function tests, gamma-glutamyl transpeptidase seemed to have been the most useful for detecting abnormalities and reflecting the extent of liver damage. Fetoglobulin and carcinoembryonic antigen tests gave results in the normal range.

The results of this study [34] have helped to provide a basis for identifying clinical manifestations of vinyl chloride-induced liver damage. No single test was found to be pathognomonic for this disease, and both false positives and false negatives were common. Sometimes the clue to the presence of angiosarcoma of the liver was not the magnitude of elevation of an enzyme activity, eg, LDH, but the persistence of that elevation. Curiously, the percentage of workers with abnormal 12-factor test results was lower in polyvinyl chloride production workers (21.5%) than in either synthetic-rubber production workers (28.6%) or all other workers (26.7%). However, abnormal results serious enough to warrant comprehensive examinations were present in 9.8% of the polyvinyl chloride production workers, while only 6.9% of the synthetic-rubber workers and 4.9% of all other workers had such seriously abnormal results.

In a 1975 report, Creech and Makk [35] amplified this early report of screening test results [34]. Specimens of the liver for biopsy were obtained from 16 employees of that same plant, 3 of whom had normal results on clinical screening tests [35]. The results of these three biopsies were normal, as were the results from two other biopsies taken from employees with minor abnormalities on the screening examinations. Two cases of angiosarcoma were detected, both with accompanying fibrosis. Periportal fibrosis was the most common biopsy diagnosis occurring in polyvinyl chloride workers and in two workers from other production areas. Two polyvinyl chloride production workers also had enlarged spleens, splenic vein thrombosis, and esophageal varices. Only one of seven workers with acroosteolysis had an abnormal battery of screening tests, and the test results returned to normal within 3 weeks after the employee stopped drinking alcoholic beverages. Results of the clinical tests were essentially the same as had been previously reported [34]. The percentages of abnormal test results among 274 polyvinyl chloride production workers, compared with those of 411 other production workers, were: total bilirubin, 35.6 vs 29.6; alkaline phosphatase; 47.5 vs 50.9; LDH, 3.4 vs 8.3; and SGOT, 33.9 vs 28.8. A further battery of liver function tests on 59 polyvinyl chloride production workers and 132 other production workers who had exhibited serious abnormalities in the first screening tests showed the following percentages of abnormalities: SGOT, 46.9 vs 46.2; gamma-glutamyl transpeptidase, 50.0 vs 33.3; SGPT, 34.4 vs 20.5; alkaline phosphatase, 59.4 vs 61.5; LDH, 9.4 vs 28.2; and total bilirubin, 43.8 vs 41.0. As a result of the screening program, 59 employees were transferred to areas of minimal exposure to hepatic toxins.

Creech and Makk [35] concluded that no individual test was adequate to detect angiosarcoma or fibrosis, although the persistent 20-second "tumor blush" on angiography was useful for diagnosing angiosarcoma and venous

pressure studies were useful for diagnosing fibrosis. Blood tests did not predict the results on liver scans, and scans did not always detect fibrosis. The authors stated that a combination of blood tests, liver scans, venous pressure studies, angiography, and biopsies would be necessary for the diagnosis of fibrosis and angiosarcoma. This study, like the earlier one [34], concentrated on attempting to assemble a diagnostic test profile and did not report workplace vinyl chloride concentrations or attempt to correlate examination results with extent or duration of exposure.

In 1974, Creech et al [36] reported on four cases of angiosarcoma of the liver diagnosed in employees in one chemical plant between 1967 and 1973, that have been previously discussed [34]. The four workers, with a mean age of 44.5 years (36, 41, 43, and 58), had each worked at least 4 continuous years in the vinyl chloride polymerization section of the plant prior to the onset of the disease and had been exposed to vinyl chloride for an average of 18 years (14, 14, 17, and 27) [36]. Extensive, nonalcoholic-type cirrhosis, in addition to the angiosarcoma, was found in all four workers. Gastrointestinal bleeding was found in two of the four; other effects observed in one or more workers included portal hypertension, enlarged livers and spleens, weight loss, jaundice, an epigastric mass, and thrombocytopenia. None of the workers had a history of prolonged use of alcohol or exposure to hepatotoxins known to produce angiosarcoma, eg, thorium dioxide or arsenic, either at work or elsewhere.

Falk et al [37], in conjunction with NIOSH, conducted an investigation at a vinyl chloride polymerization plant in Kentucky where seven cases of angiosarcoma of the liver had been discovered, including the four which had previously been reported by Makk et al [34] and Creech et al [36]. These seven cases were compared with four cases of portal fibrosis found in the same worker population. Factors in the comparison were: age at diagnosis, initial symptoms, physical examination findings, liver function studies, biopsy or autopsy findings, and work performed and overall duration of employment. The 11 patients were white males and were between the ages of 28 and 58 at the time of diagnosis.

The seven men with tumors had been employed at the plant for an average of 18.0 years; one had no complaints, but the authors reported fatigue, abdominal pain, chest pain, weight loss, black stools, bloody vomit, and weakness [37]. The four men with nonmalignant liver disease (portal fibrosis) had been employed an average of 20.6 years; one reported chest pain and weight loss, one reported having had black stools on two occasions, one had been noted to be jaundiced when hospitalized for hernia repair, and one had been hospitalized for gallstones.

The physical examinations of these 11 men [37] disclosed enlarged livers or spleens in 4 of the 7 with angiosarcoma and in 3 of the 4 with portal fibrosis. In addition, one of the tumorous patients had upper-right-quadrant tenderness. Two patients with angiosarcoma and 1 with portal fibrosis had no detectable abnormalities. Results of liver function studies on the men of the

two groups were similar. In both groups there were elevations of the concentrations of total bilirubin and the activities of alkaline phosphatase, SGOT, and LDH in serum, but no consistent pattern matched to the clinical manifestations emerged. Of the seven workers with angiosarcoma, five had elevated SGOT activities, four had elevated activities of alkaline phosphatase or increased concentrations of total bilirubin, three had heightened activities of LDH, and one had a decreased platelet count. Liver-spleen scans showed defects or other abnormalities in five. In the four workers with portal fibrosis, the concentration of total bilirubin and the activity of SGOT were each elevated in three, the activity of alkaline phosphatase was elevated in two, the activity of LDH was increased in one, and two had abnormal liver-spleen scans. Platelet counts were not reported for this group. Twelve samples of liver for biopsy were obtained by opening the abdomen and only three by puncturing the abdominal wall and the liver with a Manghini needle. In the seven men found to have angiosarcoma, liver biopsy findings included angiosarcoma in four, hepatitis in two, fibrosis in two, and cirrhosis in one. The biopsy sample from the four men without angiosarcoma revealed fibrosis of the liver; two of them had portal and subcapsular fibrosis, one had portal fibrosis, and one had chronic hepatitis with focal fibrosis. All five of the patients who died of angiosarcoma had had biopsies, but angiosarcoma had been diagnosed in only two. Angiosarcoma had been diagnosed previously by biopsy in the two surviving patients, and fibrosis had been diagnosed previously by biopsy in the four without angiosarcoma.

Falk et al [37] stated that the development of angiosarcoma was related to exposure to vinyl chloride and that it was more closely related to the type of work performed than to the overall duration of employment. They suggested that a higher risk was associated with longer duration of employment as a helper (reaction vessel cleaners) than with work in which the monomer was handled in a closed system or in which only polymerized material was handled. The data presented, however, do not completely support this suggestion since several workers without angiosarcoma had actually had longer durations of exposure as chemical helpers than those workers with angiosarcoma. Since conditions of exposure undoubtedly do not correlate exactly with job classifications, exposure concentrations and durations must be determined to permit assigning relative risk factors.

Whelan et al [38] described the angiographic characteristics typical of hepatic angiosarcomas found in the vinyl chloride workers previously discussed [34-37]. Liver scans were performed on all of the 1,180 workers at the vinyl chloride polymerization plant [38], using radioisotopes of gold, iodine, or most often technetium. On 50 of the workers, hepatic venograms, hepatic and celiac angiograms, and pressures in the right atrium, the inferior vena cava, and both free and wedged hepatic vein positions were recorded. Specimens of liver for biopsy were obtained also. Vinyl chloride concentrations in the workplace were not reported.

Four employees had angiosarcoma of the liver; their average age was 43 years (range 37-49 years) and they had been employed in polymerization of

vinyl chloride for 15 years (range 12-20 years) [38]. Although several tumors were found in some livers, no tumors of the spleen were found although splenomegaly was present in some cases. No outstanding pathologic condition was found in either the venous or the arterial systems of the liver, but the centers of the tumors appeared to be less vascular than normal liver tissue.

Because the wedged venous pressure measurements resulted in hepatic infarction in three patients, these tests were discontinued as part of the routine screening procedure [38]. The area of infarction that resulted from measurement of wedged venous pressure caused one worker to appear erroneously to have angiosarcoma when he was examined angiographically. Spleen enlargement occurred with and without portal hypertension; about 10% of the 1,180 employees had enlarged spleens without any evidence of tumor.

Whelan et al [38] concluded that isotopic liver scans were the most useful procedures for detecting angiosarcoma. They also concluded that a peripheral tumor stain, puddling of the contrast agent from the midarterial phase up to 34 seconds, and hypovascularity of the central portions of the tumor were characteristic angiographic features of this tumor. Because hepatic infarcts following measurements of wedged venous pressures may give a similar angiographic picture, the authors recommended that wedged venous pressure studies, when necessary, be done after angiography.

Popper and Thomas [39] studied surgical and autopsy samples from the livers of 11 vinyl chloride and polyvinyl chloride workers, in six of whom angiosarcoma of the liver had been diagnosed and five of whom had hepatic fibrosis. Two cases of primary hepatic carcinoma, one in a worker who had laminated polyvinyl chloride sheets for 17 years and the other in the 8-year-old daughter of a vinyl chloride polymerization worker, were described also, but no information on the concentrations and durations of exposure of these two persons was supplied.

In addition to angiosarcoma of the liver, typical lesions found in the livers of the 11 patients included subcapsular, portal, and perisinusoidal fibrosis, increased numbers of fibroblasts, formation of connective tissue septa, sinusoidal dilatation (without signs of passive congestion, such as compression of hepatocytes), increased size and number of sinusoidal lining cells, and enlarged hepatocytes with hyperchromatic nuclei accompanied by bile stasis [39]. These lesions were usually more prominent in the group with angiosarcoma than in that with hepatic fibrosis.

Five patients (two with angiosarcoma and three with precursor signs) had enlarged spleens with "grossly visible and conspicuously enlarged Malpighian follicles separated by a meaty-appearing homogeneous red pulp" [39]. The follicles had large germinal centers with phagocytic cells. The periarteriolar lymphatic sheaths were markedly enlarged. Cells lining splenic sinusoids were enlarged but did not show phagocytosis; their elongated cuboidal shape made them resemble glandular cells. Perifollicular hemorrhages were noted, and in one case the presence of Gamna-Gandy bodies suggested old hemorrhages.

Popper and Thomas proposed that hepatic fibrosis and hepatic and splenic cellular proliferation were precursor stages in the development of angiosarcoma [39]. Their evidence was insufficient, however, to prove that these changes were irreversible or progressive. Portal fibrosis was not found to be predictive of the development of angiosarcoma, and the focal intralobular fibrosis in these subjects was similar to that in many elderly patients, particularly diabetics. Hepatic focal subcapsular fibrosis was characteristic of angiosarcoma, however, and could be seen by peritoneoscopy or during surgery. The authors noted that there were similarities between the development of portal fibrosis in workers exposed to vinyl chloride and diseases in European vineyard workers exposed to arsenical pesticides, patients in India with "idiopathic portal hypertension" (Banti's syndrome), and patients with psoriasis who were treated for prolonged periods with Fowler's solution (potassium arsenite). This report is valuable for its comprehensive description of vinyl chloride-induced visceral lesions and its comparison of these with other fibrotic lesions.

Thomas et al [40] extended the previous microscopic studies [39] of the livers and spleens of workers engaged in vinyl chloride polymerization. Among the 15 cases of angiosarcoma of the liver that they studied, the tumor had metastasized to the duodenum in one case, to the lung in a second, and to the lung, heart, kidney, and lymph nodes in a third. Specimens from 20 patients were reviewed microscopically.

These authors [40] again postulated that their observations might have illustrated a developmental continuum in which fibrosis precedes the development of angiosarcoma of the liver. They also noted that a specimen of liver obtained for biopsy from one patient 2 years after his last exposure to vinyl chloride showed that both hepatocytes and sinusoidal lining cells had returned to normal, but the fibrous scars persisted.

The case for development of angiosarcoma of the liver from a fibrotic precursor stage would be compelling if the specimens presented were obtained in a real-time sequence from an individual patient [40]. The authors' arrangement of specimens from 20 different patients is plausible, however, because fibrotic changes are seen throughout angiosarcomatous livers and the same changes in the spleen accompany both fibrosis and angiosarcoma of the liver. The disappearance of abnormal hepatocytes and sinusoidal lining cells from biopsy materials within 2 years after the worker was removed from exposure to vinyl chloride is additional evidence that this exposure caused the hepatic abnormalities.

Zimmermann and Eck [41] reported a case of angiosarcoma of the liver in a 38-year-old chemical laboratory assistant in Germany who was exposed to vinyl chloride at an unspecified concentration for 3 years and 5 months (1960-1963). He was exposed for 3-4 hours two or three times a week and wore no protective mask. The worker was hospitalized with marked abdominal distress about a year before his death in 1974. Tumors of the liver were suspected after

laparoscopy but could not be confirmed by microscopic examination of liver specimens at that time. An open-abdomen surgical sampling of the liver 6 months later produced evidence of occlusion of the portal vein, necrosis, and interstitial fibrosis. The changes were originally attributed to tertiary syphilis, but serologic examinations were negative, and the patient's work history showed exposure to vinyl chloride. The patient lived for another 6 months and died from massive hemorrhage from esophageal varices. Post-mortem examination showed a metastasizing multilocular angiosarcoma of the liver with liver fibrosis. The tumor had spread to the diaphragm, the pleura, and the lymph nodes around the pancreas. Hepatomegaly, with icterus and fibrosis, and splenomegaly were also confirmed, and the heart showed flaccid dilatation. Bronchitis was also indicated.

Microscopic examination showed tumor cells bearing filaments and an abundance of connective tissue between atrophic liver-cell plates [41]. Liver structure was abnormal; lobular centers were often completely fibrotic, and branches of the portal vein were blocked by filamentary connective tissue and the diaphragm was bound to the liver by fibrous tissue. There were localized areas of recent necrosis. The spleen contained blood-forming centers for both red and white cell lines and had localized hemorrhages. The pancreas contained areas of fibrosis and of medium-grade lipomatosis. The testes showed a reduction of spermiogenesis and slight fibrosis. Purulent myocarditis was found. In the brain, there was localized atrophy of cerebellar Purkinje cells and necrosis of the frontoparietal cerebral cortex.

Zimmermann and Eck [41] attributed the development of angiosarcoma in the patient to his prior exposure to vinyl chloride, noting that primary angiosarcoma of the liver is extremely infrequent. In addition to vinyl chloride, the patient had been exposed to methylene chloride, styrene, acrylonitrile, and other substances.

This paper [41] showed some of the problems encountered in determining whether angiosarcoma of the liver was induced by vinyl chloride. The short duration of work involving exposure to vinyl chloride (less than 3.5 years), the long interval (10 years) before the onset of symptoms, the mixed exposures, and the infrequent occurrence of this tumor made the diagnosis and determination of cause difficult.

Christine et al [42], in 1974, noted six microscopically confirmed cases of hepatic angiosarcoma of the liver in Connecticut, five of the cases having been diagnosed after 1966. Two of the patients had apparently been occupationally exposed to polyvinyl chloride. A 47-year-old man had worked for the previous 10 years as an accountant in a factory producing vinyl sheets and processing polyvinyl chloride resins and had frequently visited the plant's production areas. Another patient, a 61-year-old man, had spent 25 years in an electrical plant operating a machine that applied polyvinyl chloride-containing plastic to wires. Two other patients, a 73-year-old man with a history of chronic intake of alcohol and an 83-year-old woman, had had no known occupational exposure to polyvinyl chloride, but both had lived 35

years or longer within 2 miles of the electric wire plant or within 0.5 mile of the vinyl products plant mentioned above. The other two patients, a housewife and an alcoholic man, had neither occupational nor probable residential exposure to vinyl chloride. None of the six patients had a history of hepatitis or exposure to hepatotoxic drugs, medications, or agents other than alcohol.

Many other reports are available in which cases of angiosarcoma in vinyl chloride workers are discussed [43-51]. Several other papers contain reports of scintigraphic investigations [52], histopathologic studies [39,53-56], and clinical aspects [57-60] of liver damage in workers exposed to vinyl chloride. The information contained in these papers is substantially the same as that which has been presented in this section and these reports often discuss the same cases.

NIOSH has compiled a listing as of August 1977 of the cases reported of angiosarcoma of the liver in vinyl chloride workers throughout the world [61]. These data are presented in Table XVII-4; they show that 64 cases of angiosarcoma of the liver had been reported and that 50 of these had been confirmed microscopically. Two workers were still alive at the time of the communication, and no details were available for seven others. Calculations from these data indicate that the latent period from first exposure to vinyl chloride to death averaged 20.5 ±6.0 years with a range of 9-38 years. The average duration of exposure was 17.3 ±6.3 years with a range of 4-30 years. The first death was recorded in 1955. During the period 1955-1968, only 12 of the 57 deaths occurred. During the period 1974-1977, 27 (47%) of the deaths occurred, the largest number (11) occurring in 1975.

Because of the prolonged latent period calculated from these data and the unavailability of complete information on exposure conditions or numbers of workers exposed in the worldwide production of vinyl chloride, any estimate of expected future cases of angiosarcoma in the workforce would be unreliable.

An estimation of risk was performed by Kuzmack and McGaughy [62] in 1975. They projected an incidence rate, using a linear dose-response model, of angiosarcoma as 0.0052/person/year of exposure in highly exposed workers (350 ppm or 896 mg/cu m, 7 hours/day, 5 days/week) from incidence rates in rats. Using data from epidemiologic studies of vinyl chloride workers and data on the exposure durations for the 14 US occupational cases of angiosarcoma that were known as of 1974, a projected incidence rate for angiosarcoma of 0.0031/person/year was calculated. The authors concluded from their calculations that 7.5% of all highly exposed vinyl chloride workers would be expected to develop angiosarcoma and that 15% would develop primary cancers at some site during their lifetimes. They also estimated that, as of 1974, only 38% of the predicted number of angiosarcoma caused by vinyl chloride had been diagnosed.

The authors [62] pointed out several possible sources of error in their estimates. These involved uncertainties in the numerical estimates of the

functions and conceptual inadequacies in the assumptions of the models. For example, the accuracy of the assumed exposure concentration of 350 ppm and the assumed duration of 7 hours/day, 5 days/week, was uncertain. Also, biologic latency was not directly observable, and the time of initiation of some unknown irreversible damage might not have been accurately represented by the duration of total exposure for the known cases. The predictions are based on the assumption that the set of stochastic variables, such as genetic compositions, previous medical histories, diets, etc, that might influence tumor formation is homogeneous. It is further assumed that the then current exposures will be continued with no major change. These two assumptions cannot be supported since homogeneity in worker populations from various geographic areas is highly unlikely and since exposures have been decreasing in recent years.

Two maps prepared by Falk [63] describe the geographic distribution of deaths from angiosarcoma of the liver in vinyl chloride polymerization workers (Figure XVII-1) and in people not engaged in work with vinyl chloride (Figure XVII-2). A comparison of these figures shows that there is no reason to believe that some unknown geographic or demographic feature would account for the clustering of angiosarcomas of the liver in the vinyl chloride worker population.

Casterline et al [64], in 1977, reported a unique case of squamous-cell carcinoma of the buccal mucosa associated with chronic oral exposure to polyvinyl chloride. The patient was a 22-year-old white male who had habitually chewed plastic insulation from wires and other plastic materials since he was 8 years old. He denied using any form of tobacco, alcoholic beverages, or illegal drugs. A pinhead-sized papule was found on the right anterior labial buccal sulcus after an episode of aphthous stomatitis that lasted less than a week. In 3 months, the papule grew to about 1 centimeter in size and was excised by a dentist. Microscopic examination of the tissue resulted in a diagnosis of invasive squamous cell carcinoma. A wider resection showed that the tissue margins appeared free of tumor. No recurrence was noted in the next 6 months. The patient's oral hygiene appeared excellent, but his teeth were grooved as a result of his habit of stripping wire with them. He reported keeping plastic material in his mouth for 6-8 hours at a time. No abnormalities other than the buccal lesion were found, although a complete examination was made specifically to search for signs of vinyl chloride-induced functional aberrations.

Casterline et al [64] believed that the development of this cancer in an area of the mouth where the individual frequently stored polyvinyl chloride materials was more than coincidental. They cited as further support for their belief the high incidence of cancers of the buccal cavity and pharynx found by Tabershaw and Gaffey [65] to be associated with exposure to vinyl chloride. Casterline and coworkers urged that electronics workers be informed of the hazard of repeatedly holding plastic-covered materials in the mouth. If the authors' conclusion is correct, a little-suspected but significant route of exposure to vinyl chloride may exist. The possibility of coincidence, however, may be greater than the authors were willing to concede.

(b) Vinylidene Chloride

McBirney [66], in 1954, reported on a case of fatal poisoning in a worker exposed to the vapor from dichlorethylene (identified as vinylidene chloride [67]) stabilized with 1% of a sodium hydroxide solution. The worker was 35 years old and had worked 8 hours/day, 5 days/week, for a "short" time extracting oil from fish livers using this mixture.

The worker first complained that the odor and vapors from the extraction kettles made him nauseous [66]. A day or two before he was suddenly taken ill, the worker had acted "strangely" and his coworkers at first had thought that he was drunk. He was hospitalized and died within 2 days. At autopsy, the brain, heart, lungs, spleen, liver, and kidneys were observed to be congested. The cause of death was listed as bronchopneumonia.

Lack of exposure information in this report [66], the possibility of a preexisting condition, and the possibility that the vapor described as dichloroethylene may have been 1,2-dichloroethylene (a substance known to have been used in extracting fish oil [68]) does not allow any conclusions to be drawn.

Liver function tests and scans were performed on a group of 46 workers at a New Jersey plant in which the concentration of vinylidene chloride in the air ranged from below the analytic limit of detection (0.00 mg) to 1.45 ppm (about 5.6 mg/cu m) [69]. Previous company experience had established a typical range of 0-5 ppm (0-19.85 mg/cu m), with occasional peaks of 300 ppm (1,191 mg/cu m) associated with accidental spills or leaks and with removal of samples of product from the reactor. This plant used nearly 200 chemicals, including several known hepatotoxins, so that exposure to a single agent was not claimed. The tests included measurements of SGOT, SGPT, and serum gamma-glutamyl transpeptidase, LDH, and alkaline phosphatase activities, total bilirubin, and indocyanine green clearance. None of the 46 employees was found to have total bilirubin counts outside of normal limits, but 39% had abnormal LDH activity, 30% had abnormal gamma-glutamyl transpeptidase activity, 28% had abnormal SGOT activity, 21% had abnormal SGPT activity, and 13% had abnormal alkaline phosphatase activity. Fourteen men had abnormal liver scans, but only five showed what the author defined as "definite hepatomegaly." Six employees (13%) had severe impairment of indocyanine green excretion (less than 10% clearance), 25 (56%) had moderate impairment (10-17% clearance), and 14 (30%) were found to be normal (greater than 17% clearance). Fifteen workers were retested for dye clearance; two had returned to normal, four had deteriorated, and the rest remained unchanged. On the basis of these tests, biopsy studies of the liver were recommended for 10 workers, but only 5 agreed to undergo this kind of study.

All five employees on whom biopsy studies of the liver were performed exhibited abnormal clearances of indocyanine green [69]. Two had borderline or mild portal fibrosis on biopsy, one had mild nonspecific activation of

hepatocytic nuclei and a borderline increase in fat, one had mild steatosis, and one had moderately severe steatosis with stellate fibrosis that suggested an alcoholic liver injury. Two of the five had enlarged livers. None of the microscopic changes was attributed by the pathologist to the effects of industrial toxins.

In a followup study undertaken by NIOSH upon invitation by the company, 256 employees were surveyed for serum total bilirubin, and alkaline phosphatase, GOT, GPT, and gamma-glutamyl transpeptidase activity [69]. Two criteria of abnormality were used. Criterion A was a deviation greater than two standard deviations from the normal population mean of the laboratory performing the analysis; criterion B was the occurrence of a value outside the normal range used by the laboratory performing the analysis. An abnormally high result by either criterion on any test was regarded as indicative of liver impairment. Duration of employment, work history, exposure conditions, use of alcoholic beverages, current symptoms, history of liver disease, and demographics were also recorded. Of these, the only significant variable ($P<0.001$) related to abnormality, according to the more stringent criterion B, was duration of exposure at the site: 5.11 years for "cases" and 3.64 years for "noncases."

A total of 75 employees (29%) at the plant were classified as abnormal by criterion B on the basis of enzyme activity tests [69]. On the individual tests, NIOSH found 46 employees (19%) with abnormal elevations of SGPT activity, 42 (16%) with abnormal serum gamma-glutamyl transpeptidase activity, 31 (12%) with abnormal SGOT activity, and 5 (2%) with abnormally elevated serum alkaline phosphatase activity. Only one employee (0.4%) had an elevated serum total bilirubin value. Every area of the plant had at least one employee who was judged abnormal by one of the two criteria stated. The incidence of abnormal alkaline phosphatase and bilirubin values in this study was lower than that reported previously [34] at a vinyl chloride plant.

The company had tested only a group of workers involved in the polymerization of vinylidene chloride, who were exposed to this monomer at relatively high levels [69]. Whereas NIOSH had studied almost 88% of the employees, nearly 5.6 times as many as the company had studied. The incidence of abnormal results on any test would be expected to be lower in NIOSH's study, therefore, as was the actual case. The substances or the relative concentrations responsible for producing adverse effects where exposures are mixed cannot be identified conclusively. The case for the existence of actual liver damage from exposure to vinylidene chloride rests on the company's correlation of microscopic and dye-clearance data with the liver enzyme studies.

In 1970, Henschler et al [70] and Broser et al [71] each reported on the same two cases of poisoning from occupational exposure to vinylidene chloride copolymers that had occurred in Germany in 1965. In both cases the workers had been transporting an aqueous suspension of vinylidene chloride copolymerized with another unspecified vinyl compound. The authors stated

that the suspension contained about 0.4% of low molecular weight halogenated hydrocarbons, of which vinylidene chloride comprised about one-half. Both workers developed symptoms of poisoning while manually cleaning the transport tank.

The first worker was 33 years old [71]. About 6 hours after he had worked in the tank for a "short," but indefinite time, he experienced fatigue, weakness, lack of appetite, and an "abnormal sense of taste." Nineteen hours after the initial exposure, he again entered the tank and remained for 45 minutes. Five hours later, he experienced nausea, headache, dizziness, and eventually vomiting of blood. A "furry" feeling in the mouth and lips which he had noticed earlier now became more noticeable. He was admitted to a medical clinic 27-28 hours after his first exposure. Conjunctivitis, inflammation of the epipharnyx, herpes labialis, pains in the epigastrium, perception disorders of the face, and deflection of the tongue to the right were observed. Liver and kidney function tests were initially abnormal (low urine specific gravity, 3-6 leukocytes in the urine sediment, SGOT 20 mU, 8% BSP retention, 60% prothrombin time, and what was described as decreased water excretion of 570 ml); however, all findings except the sensory effects returned to normal after 3 weeks.

An extensive neurologic examination performed 3 months later revealed analgesia and hypoesthesia in the total trigeminal area, including the nose and oral mucosa [71]. In addition, hypoesthesia and hypalgesia in the region of both ear muscles and under the angle of the jaw and absence of the corneal reflexes were noted. Other findings were normal except for labile hypertension (blood pressure 170/90 mmHg). Followup examinations conducted 2 and 4 years later showed the same types of findings, and the worker complained of the same symptoms.

The second worker, 53 years old, was exposed in the same way, but for a shorter time than the first [71]. His initial symptoms were essentially the same as those of the other worker. On admission to the medical clinic, 5 days after exposure, herpes labialis, hypertonic fundus, high blood pressure (170/115 mmHg), mild diabetes mellitus, and polycythemia (5.34 million erythrocytes, hemoglobin 17.2 g, color index 32.4, hematocrit 48%) were observed. Kidney and liver functions were not abnormal. Perception disorders in the face and in the fingertips of both hands, paresis of the muscles of the cheeks and tongue, and bilateral double vision were also noted.

After 4 months, the subject complained of loss of the sense of taste, deficient saliva flow, and difficulties in opening his mouth, chewing, and eating [71]. Findings of a medical examination included hyposmia and hypogeusia and analgesia, thermoanesthesia, and hypoesthesia in the area of the trigeminal nerve, the skin of the face, the oral mucosa, the top of the head, the tragus, the ear muscles, beneath the angle of the jaw, base of the tongue, throat, and the external auditory passages. Corneal, nasal, and vomiting reflexes were all absent. Followup examinations 2 and 4 years later revealed no improvement.

The authors [70,71] attempted to find mono- and dichloroacetylene in the aqueous mixture, because of the close resemblance between the signs and symptoms of intoxication with vinyl derivatives and with acetylene dichloride, but were unsuccessful; however, they postulated that the toxic effects observed in these workers could have been caused by mono- or dichloroacetylene. They suggested that caution be exercised where the potential existed for exposure to the intermediate products of polyvinylidene chloride.

Krieger et al [72], in a 1971 report, discussed similar effects on a 32-year-old worker exposed to off-gas from an aqueous dispersion of a vinylidene chloride copolymer. Several hours after receiving a jet of the gas in his face after opening a valve too soon and after manually cleaning a tank used to transport the copolymer, a job that lasted about 2 hours, the worker developed pains in the upper lip, nose, and eyes, a frontal headache, and visual problems. Later he was bothered by a lack of sensation in his face and buccal mucous membranes, somnolence, anorexia, nausea, and difficulty in speaking and eating. Fourteen days after the incident, an examining physician noted bilateral facial anesthesia, corneal anesthesia, and hypoesthesia. The worker had neuralgia involving the anterior two-thirds of his tongue, but no trigeminal motor involvement or facial motor disorders. Krieger et al concluded that, because the clinical picture was similar to that described in previously published reports on the toxic effects of exposure to chlorinated acetylenes, these compounds probably were the toxic agents in this case.

Although none of these authors [70-72] suggested that vinylidene chloride itself was the cause of the "cranial polyneuritis" observed, each suggested that there is a potential hazard to workers exposed to intermediates or impurities of vinylidene chloride copolymerization processes.

(c) Vinyl Bromide, Vinyl Fluoride, and Vinylidene Fluoride

No reports of toxic effects on humans from exposure to vinyl bromide, vinyl fluoride, or vinylidene fluoride have been located.

(d) Summary

The human studies reported in this section do not permit comparisons of the modes of action of the various vinyl compounds. Only for vinyl chloride have reports of a full range of tests on a large population of workers been published. The adverse effects observed on humans exposed to vinyl chloride, eg, the serum enzyme aberrations, CNS effects, vascular abnormalities, and tumors, indicate that such exposure is a serious hazard in the occupational environment. The other vinyl halides are also suspect because of their chemical similarity to vinyl chloride. The paucity of human data for the other vinyls should not be construed as an indication that they are innocuous; the potential hazard from occupational exposure to these compounds was only

recently postulated. The hazards presented by these compounds may vary only quantitatively rather than qualitatively, and the variations may be and are likely to be based on their relative bioreactivities.

Epidemiologic Studies

Although more than 30 epidemiologic studies of populations subject to occupational and environmental exposure to vinyl chloride have been published since 1971, only one epidemiologic study of workers exposed to vinylidene chloride [73] has been located, and no epidemiologic reports on the other vinyl halides were found.

(a) Vinyl Chloride

(1) Acroosteolysis

Two studies [74,75] of workers involved in various phases of the manufacture of vinyl chloride and polyvinyl chloride were published in 1971. Dinman et al [74] investigated the incidence of acroosteolysis and Raynaud's syndrome in employees potentially exposed to vinyl chloride at 32 plants in the United States and Canada. Cook et al [75] conducted industrial hygiene surveys at these same plants in an attempt to correlate the observed differences in health status with differences in work practices among the plants.

In the first study [74], the experimental population consisted of 5,011 workers (96.4% male, 95.7% white, mean age 35.8 years). The control population was the adult male population of Tecumseh, Michigan: 2,407 men over the age of 18. Criteria for selection of the control population were not presented, and analyses comparing vinyl chloride workers with controls were not given. In assessing health status, Dinman et al had each worker complete a questionnaire designed to probe for signs or symptoms related to Raynaud's syndrome or peripheral vascular insufficiency and related hand injuries. Roentgenograms of both hands of each worker were made and were reviewed independently by two radiologists for signs of acroosteolysis. Medical and occupational histories were also obtained from each employee.

Twenty-five clear-cut cases of acroosteolysis were found in the worker population [74]. These cases met the following diagnostic criteria: defects along the shaft margin, sclerosis with recalcification, and shortening of the phalanges, or, marginal defects with residual fragments, transverse defects with or without distal fragmentation, and total resorption of the distal portion of the phalanx. Twenty-two of the 25 workers with abnormalities diagnosed by roentgenographic examination also indicated on the medical questionnaire that they had had symptoms characteristic of Raynaud's syndrome.

In only 7 of the 32 plants investigated were cases of acroosteolysis diagnosed definitively by roentgenographic examination [74,75]. Three other

plants had cases of possible acroosteolysis, ie, cases that did not fully meet the authors' confirmation criteria. A comparison of plant populations showed that the 25 cases of acroosteolysis were from a population of 1,673 workers. Each of the workers with acroosteolysis had served as a reactor cleaner, although one of them had only cleaned a bench-scale reactor in a laboratory. Of the 5,011 workers surveyed, 1,047 (21%) had had reactor cleaning experience. The authors stated that in a few plants the concentrations of airborne vinyl chloride had been measured inside the reactors during scraping operations, and that the vinyl chloride concentrations had been generally below 100 ppm (256 mg/cu m) and usually about 50 ppm (128 mg/cu m). Air samples taken close to the hands of the scrapers had contained concentrations of vinyl chloride ranging between 600 and 1,000 ppm [75]; however, the authors did not present details or identify the plants where these measurements had been made.

Dinman and coworkers [74] and Cook et al [75] concluded that work practices rather than any one specific substance or combination of materials used in the manufacturing process were determinant of whether or not acroosteolysis would occur. They considered acroosteolysis to be a manifestation of a systemic intoxication rather than of local effects by a toxic material, so that prevention of transpulmonary, percutaneous, and gastrointestinal absorptions of materials scraped off the walls of the reactors was seen as the first line of defense of the health of the reactor cleaners, the group of employees in which the greatest incidence of this disease was found. Bagger-packers also had a high incidence of acroosteolysis and were required to have protection against absoprtion of material from the polymerized product from the reactors.

The authors [74,75] stated that, while gloves (unspecified type) were provided for reactor cleaners, the use of gloves was "inconsistent" at those plants having workers with acroosteolysis. They also stated that the procedure for airing out reactors before cleaning was frequently "short-cut" in these plants. They pointed out that the complexity of the manufacturing processes, which involved at least 227 different materials, including monomers, catalysts, ketones, and chlorinated hydrocarbon solvents, made conclusions about the hazard of any single ingredient difficult. They also proposed that "idiosyncratic sensitization or susceptibility" be considered as a possible determinant of the development of acroosteolysis. The authors also stated that there were several problems with the consistency of the diagnostic procedures, eg, the radiologists seldom agreed on a specific diagnosis, and with the accuracy of the survey techniques. The authors' investigation of differences in the plants' work practices did not provide an explanation as to why there were definitive cases of acroosteolysis in only 7 of the 32 plants [74,75]. However, they did report that acroosteolysis was rare in plants using high-pressure water lances for cleaning the reactors and also in those that reduced the pressure within the reactor below the atmospheric pressure to the greatest extent and for the longest time before opening the reactor for cleaning. The authors' suggestion that work practices and engineering controls might not be followed in those plants having cases of acroosteolysis

was not documented. The fact that all cases of acroosteolysis were diagnosed in workers who had been employed at sometime as reactor cleaners, although only 21% of the total worker population had been employed in this category, indicates that employees performing this task were at greater risk of developing acroosteolysis. Since this task also has been found to have the potential for the highest exposure to vinyl chloride, it is reasonable to assume that exposure to this substance contributes to the induction of acroosteolysis.

(2) Clinical Tests

In 1972, Kramer and Mutchler [76] described a study in which environmental measurements were compared with clinical test results and medical histories for 98 men who were occupationally exposed to vinyl chloride and to "small amounts" of vinylidene chloride in a polymerization facility.

Medical surveys and physical examinations had been conducted on 66 of these men during 1965 and 1966, and the results were compared with results from a control group of 605 employees in other departments (not identified) who were examined during the same period [76]. Ninety-five separate items were compared for the two groups by a test for differences between means assuming normal distributions. The only significant differences ($P<0.05$) between the medical histories of the vinyl chloride group and the control group were in the prevalences of asthma (10.8 vs 2.6%), stomach, liver, and intestinal disturbances (6.2 vs 18.0%), kidney stones and bloody urine (9.2 vs 3.0%), nervous disturbances of any sort (4.6 vs 13.4%), and, from occupational histories, work with radioactive substances (1.5 vs 15.5%). The number of significantly different items, 5, is about what would be expected by chance out of any 95 statistical tests.

Six of 20 clinical variables showed significant correlations ($P<0.05$) with the cumulative TWA concentration and the cumulative dose of vinyl chloride when allowance was made for the effects of age and obesity [76]. Systolic blood pressure, diastolic blood pressure, BSP retention, icteric index, and serum beta-globulin concentration increased with increasing TWA exposure concentration and total exposure dose (TWA concentration multiplied by time on the job), while hemoglobin concentration decreased with increasing exposure. Although the authors did not present complete information on exposure concentrations, they stated that the mean TWA exposure concentration was 155 ppm (397 mg/cu m) in 1950 and 30 ppm (77 mg/cu m) in 1965. The authors noted that recent (not further defined) measurements of the workplace concentrations of vinyl chloride had shown them to average about 10 ppm (25.6 mg/cu m) with vinylidene chloride present in "trace" amounts, virtually always less than 5 ppm (19.8 mg/cu m). The authors also mentioned that data concerning exposures for each year since 1950 were available, but they did not present these data.

Kramer and Mutchler [76] also calculated the expected clinical values for these tests as functions of career TWA exposure concentrations, using the regression coefficients from estimated exposures for the study population.

Because blood pressure and the concentration of hemoglobin in the blood did not move outside the normal range of values and the significance of change in the concentration of beta protein was not known, Kramer and Mutchler considered that the only dependent variables significantly linked to possible injury induced by prolonged exposure to vinyl chloride with trace amounts of vinylidene chloride were BSP retention and the icteric index. These measures indicate some interference with the normal liver function. The two persons with the greatest increases in BSP retention were reexamined in 1968, having been removed from further exposure in 1965. One individual, who had a history of hepatitis before exposure to vinyl chloride, retained high values of BSP retention and icteric index; the other individual had essentially normal laboratory findings.

In 1975, Wyatt et al [77] published an epidemiologic study of the results of selected blood screening tests and medical histories of workers in a chemical plant in Kentucky where polyvinyl chloride was made. Since angiosarcoma had been diagnosed in seven workers in the unit where polyvinyl chloride was manufactured (unit 62) in this plant, results from workers in this unit were compared with other workers in the chemical plant who had never worked in unit 62. There were 413 employees with at least 1 month of experience in unit 62; they had means of 14 and 7 years of experience at the plant and in unit 62, respectively. They were compared with 469 employees who had never worked in unit 62 and who had a mean of 12 years of experience at the plant. All employees in the study were male, and less than 10% in each group were nonwhite. The average age was 40 in the unit-62 workers and 41 in the other group. Height and weight were similar in the two groups.

Blood tests were performed for several months, beginning in January 1974 [77]. Blood was drawn in the early morning after an overnight fast and the serum was analyzed for total protein, albumin, calcium, inorganic phosphate, creatinine, uric acid, total bilirubin, alkaline phosphatase, LDH, GOT, CPK, creatinine phosphate, and cholesterol. Normal values for each test were based on the experience of the clinical laboratory performing the tests. Intergroup differences were determined for the means of each test, and significance was tested by calculation of chi-square. The effects of age were analyzed by regression analysis of the mean values of each test plotted by 5-year age groups.

The mean values of each test were not significantly different for the two populations [77]. However, when the results of each test were classified as normal, above normal, or below normal, albumin, alkaline phosphatase, and GOT in the blood serum were found to differ significantly ($P<0.05$) with regard to percentages in each range. Multiple regression analyses showed significant differences ($P<0.03$) in the albumin and cholesterol tests for the two populations. A comparison of the two populations by history of previous illness revealed significant differences ($P<0.05$) in the incidences of genitourinary disease, which was lower in the unit-62 workers, and "allergic" and "liver-spleen" illness, which were higher in the unit-62 workers.

Wyatt et al [77] made no attempt to assess such factors as length of employment, selective criteria for employment, age, or behavioral differences between the groups. They pointed out that many individuals in both groups had abnormal test results, but they stated that this must be "interpreted cautiously," particularly in the absence of a true control group. This study provides no information on exposure to potential chemical hazards for either of the groups. Without this information, the observations of differences between the groups are of limited value.

In 1977, Waxweiler et al [78] described a cross-sectional medical survey designed to compare the prevalence of liver abnormalities and liver disease in vinyl chloride-exposed workers and appropriate controls at a chemical plant in Pennsylvania and to identify the tests best suited to detect these and other illnesses in vinyl chloride workers. Four groups of workers, each representing a different estimated exposure to vinyl chloride, were used in this study. The groups consisted of 134 rubber workers with "no" vinyl chloride exposure, 80 plastics workers with "light" vinyl chloride exposure, 126 chemical workers designated as vinyl chloride "exposed," and 71 former chemical workers who had had "past" vinyl chloride exposure. Information concerning exposure concentrations was not presented. Subjects were classified in one of the first three groups on the basis of their jobs at the time of the health survey. Basic blood screening tests and pulmonary function examinations were performed, and medical histories were obtained. All test results were adjusted for age and the results of the pulmonary function tests and reports of respiratory symptoms were also adjusted for smoking. Alcohol consumption was analyzed, but no basis was found for adjustment of the data.

Of the total study population, there were 21% abnormal SGOT, 5% abnormal total bilirubin, 13% abnormal alkaline phosphatase, and 4% abnormal LDH [78]. The prevalence of these abnormalities was similar in all four groups, except that abnormal LDH values were present in 11.8% of the former chemical workers. The age-adjusted prevalence of hepatomegaly as diagnosed by palpation in current chemical workers (13.2%) was almost twice that in rubber workers (7.1%) and plastics workers (7.3%). A similar gradient was noted when diagnosis was by percussion alone or by percussion and palpation together. One former and three current chemical workers had both abnormal values for two or more of the four liver function tests and hepatomegaly as diagnosed by both percussion and palpation. Liver scintigraphs, after injection of 99 Tc sulfur colloid, were made for 123 workers exposed to vinyl chloride and were read by three specialists in nuclear medicine. In no case did all three specialists agree on whether any single film was abnormal; of the 29 films read as abnormal, only 4 were read as abnormal by 2 reviewers.

No significant differences between the groups were reported for symptoms of Raynaud's syndrome [78]. Twenty-two of 207 roentgenograms of the hand were read as abnormal for some state of acroosteolysis by one of two radiologists. Severe, persistent headaches were reported more frequently by the chemical (13.7%) and plastics (12.7%) workers than by rubber (8.6%) and former chemical (6.4%) workers, and loss of consciousness on the job was more common in

chemical (6.3%), plastic (5.2%), and former chemical (5.8%) workers than in the rubber (2.1%) workers. Neurologic examination revealed "slightly" diminished reflexes in the chemical workers' group. The prevalence of angina pectoris, as measured by the Rose Questionnaire for cardiovascular symptoms, was not noticeably different in the four groups. However, a much higher prevalence of systolic hypertension (>140 mmHg) was noted in the former chemical workers. A significantly higher ($P<0.05$) prevalence of diastolic hypertention (>90 mmHg) was seen in all three vinyl chloride-exposed groups compared with that in the group of rubber workers (39.4-41.0% vs 24.3%).

No differences between the four groups were found in the prevalence of respiratory volume impairment (adjusted for smoking) or of respiratory flow impairment; volume impairment did not differ between smoking and nonsmoking workers, although pulmonary function tests made before and after the workshift showed results related to smoking rather than to job category [78]. Sputum cytologic and chest roentgenographic examinations revealed only "minor" intergroup differences. On the health questionnaire, the plastics workers and former chemical workers reported prevalences of chronic respiratory symptoms "substantially" higher than those in the rubber workers, while the current chemical workers reported prevalences only "slightly" higher than those in rubber workers.

Waxweiler et al [78] concluded that the striking increase in LDH abnormalities in the former chemical workers (12% vs 2-4% for the other three groups) might have been a function of self-selection out of the chemical area because of symptoms of associated abnormalities. They also stated that the "most impressive" difference between the groups was the prevalence and degree of hepatomegaly, which showed a "weak" dose-response relationship with vinyl chloride exposure as estimated from job categories. Finally, the authors pointed out that, because of differences between plants in work practices, production techniques, composition of the workforce, the presence or absence of various associated toxins, and other factors, general conclusions about the hazards of vinyl chloride exposure should not be drawn from the results of this single study.

The types of data most valuable in comparisons of epidemiologic reports, such as daily exposures and total accumulated doses, were not available to these authors [78]. Exposures considered "light" in this plant might have been classified differently in another plant. The bias introduced by preselection for work and self-selection out of a hazardous environment is not quantifiable at present. The impact of these and other considerations, such as the latency of adverse effects on the estimation of the hazard of exposure to vinyl chloride remains to be determined. Waxweiler and coworkers did, however, draw some tentative conclusions that merit further evaluation. The suggestion of a dose-response gradient for hepatomegaly, the significant increase in the incidence of diastolic hypertension in the vinyl chloride-exposed workers, and the severe headaches and loss of consciousness indicate vinyl chloride-induced health hazards that should be closely monitored.

(3) Mortality and Morbidity Studies

In 1977, Fox and Collier [79] reported on the mortality of over 7,000 men exposed to vinyl chloride at some time between 1940 and 1974 at 8 polyvinyl chloride plants in Great Britain. TWA exposure concentrations were estimated by the companies (presumably on the basis of job description and area sampling data) and classified as high (>200 ppm or 512 mg/cu m), medium (25-200 ppm or 64-512 mg/cu m), or low (<25 ppm or 64 mg/cu m), and as constant (most of the time) or intermittent (occasional).

The study included a total population of 7,409 workers, 23% of whom had 10 or more years of exposure to vinyl chloride [79]. The Standard Mortality Ratio (SMR), 100 times the ratio of the number of observed deaths in the population at risk and the number expected to occur from the same cause in a standard population of the same size on the basis of actual mortality figures, for this population was 75.4, using the sex- and age-standardized death rates for England and Wales for comparison. SMR's for all causes of death computed for eight factories revealed that at three of them there were significantly fewer deaths than expected, and that all had overall SMR's below 100. The SMR for cancer deaths was "marginally" higher than expected (101.4) in one plant. Four deaths from cancers of the liver were found, compared with 1.64 expected, for an SMR of 243.9. Two of these cancers were confirmed by microscopic examination as angiosarcoma, and two were confirmed as carcinomas rather than angiosarcoma. The two workers who died of angiosarcoma had had high constant exposures for 8 and 20 years. The two workers with carcinomas had had low, intermittent and medium, intermittent exposures for 6 and 18 years, respectively. Three of the deaths from cancer of the liver occurred in one factory after 1966. One of these was an angiosarcoma. This was significantly in excess of the 0.13 deaths expected in this factory ($P<0.01$).

Analysis of mortality by year of entry into the industry showed that longer employment was associated with higher SMR's for cancer and circulatory disease [79]. Data on cancer of the liver suggested a dose-response relationship, since both cases of angiosarcoma of the liver occurred in members of the highest exposure group. There was a general tendency for the age-adjusted SMR for all causes for those men alive 15 years after they began employment to increase with increasing time on the job, from 100.6 (for men employed 4 years or less) to 104.7 (5-9 years) and to 113.3 (10-14 years).

Approximately 75% of the 7,409 workers had been employed for less than 10 years, and more than half of those ever employed were still employed at the time of the study [79]. Since only about one-fourth of the workers had been exposed to vinyl chloride at high concentrations for a long time, and since most of them who had completed 20 years of service had done so only recently, Fox and Collier suggested that there had not been a sufficient followup period during which to evaluate the carcinogenic effect of vinyl chloride. They also pointed out the complicating factors of the "healthy worker effect" and the "survivor effect" in analyzing these data. The healthy worker effect means

that most people accepted for employment are healthy, and, as a result, the workplace population tends to be in better health than the general population. The survivor effect stipulates that people experiencing adverse effects at the workplace tend to leave their jobs of their own volition; therefore, the remaining work population is composed of a larger percentage of people who are more resistant to the adverse effects of the industry than the population of all people hired. The authors concluded that vinyl chloride was probably a carcinogen causing cancer of the liver in exposed workers; they noted however, that the cases of angiosarcoma observed were associated with exposure at "very high" concentrations. They added that no evidence was found that vinyl chloride caused cancers other than those of the liver, and that although the SMR for cancers as a group was consistently higher than that for all deaths, this was difficult to evaluate because of population selection factors.

These authors' conclusions [79] are necessarily biased by the choice of a general population as the control group, and this fact is pointed out by the authors in their discussion of preselection and survivor effects. Thus, the relation of observed effects in the worker population to expected effects on the general population may give a less than objective analysis of the potential hazard.

In another report, Fox and Collier [80] examined the effects of selection for work and survival in the industry on mortality in industrial cohorts. They used the previously described worker population and data for these comparisons [79]; however, they compared the employees working at the time of their deaths with those who had left the industry [80]. For all causes of death, the SMR for employees alive after 15 years in the industry was 74.0, while for former employees alive after 15 years, the SMR was 108.4. A comparison of SMR's for cancer of the lung between the two groups was particularly striking, 50 for current workers and 156 for former workers. Results of comparisons for other causes of death by 10-year age groups revealed similar differences in SMR's.

Observed and expected deaths categorized by cause of death and length of employment demonstrated increasing SMR's with increasing length of time on the job [80]. The SMR for all causes of death for all workers progressed from 37.4 (for those employed for 0-4 years) to 62.9 (for those employed for 5-9 years) to 75.1 (for those employed for 10-14 years) and to 94.2 (for those employed for more than 15 years).

The authors [80] concluded that the results of the analyses showed clearly that death rates for employees in the polyvinyl chloride industry depended on preselection for employment, their continuing employment in the industry, and length of the time during which the workers continued to work in the industry, and the length of time during which the cohort was studied. They suggested that mathematical models taking these factors into consideration might be productive alternative methods for analyzing mortality studies.

These studies [79,80] indicate the potential pitfalls of assessing an industrial hazard on the basis of comparisons with the general population. The influences of preselection and survival factors are demonstrated by the findings that SMR's are lower both for workers with less experience and for current workers than for former workers. If these factors actually affect the results of an epidemiologic analysis, the assessment of hazard may be lower than is correct.

In 1974, the results of a retrospective study on 8,384 men with at least 1 year of occupational exposure to vinyl chloride before December 31, 1972, were published by Tabershaw and Gaffey [65] and submitted as a report to the Manufacturing Chemists Association by Tabershaw/Cooper Associates Inc [81]. The study compared the mortality experience of the vinyl chloride workers with that of the general population and with that of other employee groups. The vinyl chloride workers were separated into subgroups on the basis of intensity and duration of exposure and of combinations of these two factors. These subgroups were compared on the basis of the SMR's for various causes of death.

Thirty-five plants in the United States that either produced vinyl chloride or used it in the production of polyvinyl chloride gave information from their employment records [81]. Quantitative exposure data were not available for each job, but relative exposures were estimated by plant industrial hygiene and safety personnel. Actual concentrations were not estimated. The authors calculated an exposure index (EI) for each worker on the basis of an average monthly exposure score ranging from 1 (low exposure) to 3 (high exposure).

The median birth year of the 7,128 workers traced successfully was 1931, the median duration of exposure was 80 months (6.7 years), the median EI was 1.44, and the median year in which exposure began was 1962 [81]. With the age-specific death rates as the standard of comparison, SMR's were calculated for approximately 30 causes of death. No SMR for any cause of death was significantly greater than 100, and SMR's for several causes of death were significantly below 100. For example, the SMR for "all causes" was 75 (352 observed deaths vs 467 expected) and that for cardiovascular and renal diseases was 80.

When the workers with vinyl chloride were subdivided according to EI (more or less than 1.5) and duration of exposure (above and below 5 years), no remarkable findings emerged from these tabulations [81]. No SMR's were significantly above 100, although several were significantly below 100. Several trends were apparent, however, from the cross tabulations. SMR's for all malignant neoplasms increased with increasing EI and duration, reaching an SMR of 141 for an employment duration of 5 or more years and an EI of 1.5 or greater. Cardiovascular and renal diseases showed a similar trend, although the SMR's generally remained below 100 for all causes of death except hypertensive disease other than cardiac. There were slight, nonsignificant excesses of observed deaths from respiratory system, digestive organ and

peritoneum, and "other" cancers that increased in relation to increased duration of employment and estimated exposure. Cancers of the buccal cavity and pharynx also appeared in excess but had their highest rate of occurrence in the low, short-exposure group.

The authors [81] stated that the lower than expected overall mortality of the vinyl chloride workers was not a surprising finding because of the 'healthy worker effect," even though vinyl chloride poses a significant risk of death from a particular cause, ie, angiosarcoma of the liver. Deaths from cancers of the digestive organs and peritoneum were further examined to study the role of angiosarcoma in overall mortality. Of the 19 deaths from cancers of the digestive organs and peritoneum, 7 were due to cancers of the liver, 2 of which were identified on the death certificates as angiosarcoma. However, according to the authors, other investigators using the same study population identified four other deaths from angiosarcoma; the death certificates stated the causes of death in three of these as cancer of the liver and in one as cirrhosis of the liver. Laennec's cirrhosis was given as an alternative cause of death on one death certificate identifying cancer of the liver as the primary cause. If there had been no cases of angiosarcoma, the difference from the expected number of cancers of the digestive organs would have been insignificant.

The authors [81] concluded that the "consistent pattern of increase" for particular causes of death with increasing exposure "appears" to relate mortality from cancer of the digestive system or respiratory system, cancer of other unspecified sites, and lymphosarcoma to vinyl chloride exposure. They pointed out areas of possible bias in the study. The use of the US male population as a comparison group may have caused a slight overestimate of the SMR's, since the study population was from the eastern half of the United States, where expected mortality is higher; also, 15% of the workers could not be traced and the assumption that their mortality distribution was similar to that of those traced may have been incorrect. The data obtained on workers who could not be traced showed that, on the average, they were born 10 years earlier than the study group and had much shorter exposures and slightly higher EI's. The effect that these differences may have had on mortality is uncertain. Also, 1,500 workers whose exposures had occurred up to 35 years earlier were located too late to be evaluated in the study. Information about workers exposed for an extended period many years before might have more clearly elucidated the effects of occupational exposure and been especially valuable because of the apparently long latent period for vinyl chloride-induced disorders. Although the authors did not demonstrate a statistically significantly increased risk from exposure to vinyl chloride in this worker population, the observation that the SMR's for various cancers increased with increasing duration ofzemployment and increasing estimated exposure suggests that exposure to vinyl chloride indeed contributes to increased cancer mortality risk.

A followup study [82] reported by Tabershaw/Cooper Associates Inc, in 1975, extended the earlier investigation [81] by tracing through Social

Security records those workers who were lost to followup and by including data on eligible workers not previously included. The additions to the study group, which now totaled 8,714 workers, created only minor changes in the SMR's of observed death rates to those expected based on the US male population. None of these differences changed the major conclusions of the prior study. One more death from angiosarcoma of the liver was discovered.

A final report [83], which included the data from the above studies [81,82], was prepared by Equitable Environmental Health Inc in 1978. This report [83] increased the total worker group available for study to 10,173 from 37 plants. Although the successive additions to the study population resulted in changes in the SMR's, these changes were not significant or compound-related and did not cause any change from the conclusions reported in previous studies.

Monson et al published two nearly identical reports in 1974 [84] and 1975 [85]. They evaluated the mortality of the active and pensioned workers at two plants in Kentucky, one of which was the polymerization plant where the first cases of angiosarcoma were seen, the other of which produced the vinyl chloride used by the former. One hundred and sixty-one death records were analyzed for this study. Causes of death were taken from company abstracts of the death certificates, and the number of observed deaths from each cause, stratified into 5-year age- and time-specific groups, was compared with the number expected on the basis of age-, time-, and cause-specific proportional mortality ratios for US white males.

A 50% excess of deaths from cancer (41 observed vs 27.9 expected) was reported for the exposed populations ($P<0.02$) [84,85]. These cancers included angiosarcoma of the liver and cancers of the brain, lung, gallbladder, bile duct, thyroid, and nasopharynx. The trend was for the ratio of observed to expected deaths from cancer to increase with recency of death (before 1965, 1.1; 1965-1969, 1.4; 1970 and after, 2.1). A 90% excess of deaths from suicide (10 vs 5.3) was also reported.

Monson et al [84,85] stated that it "appeared" that the relative frequency of deaths from all cancers was increasing with time and suggested that additional excess cancer among vinyl chloride workers "would seem likely." They pointed out that an analysis using proportional mortality ratios does not take into account the absolute risk of death in the population studied, and that a high ratio of observed to expected deaths might result from "an excess of one cause of death or a deficit of another cause of death."

While the comparison did introduce an obvious bias in the statistical treatment of results, the authors [84,85] adequately pointed this out in their discussion. The trend in the ratios of observed to expected deaths from all cancers is a particular cause for concern since it indicated that the proportion of deaths caused by cancer was on the increase in this workforce. It must be remembered, however, that this was a study of workers at only two plants, and that the trend may not have been related to the vinyl chloride exposures alone.

Ott et al [86] examined the mortality during 1942-1973 of 594 employees exposed to vinyl chloride between 1942 and 1960. Several methods of sampling and analysis of airborne vinyl chloride had been used since 1950. Samples showed vinyl chloride concentrations before 1959 to have been generally "well below" 500 ppm (1,280 mg/cu m), with occasional excursions to 4,000 ppm (10,240 mg/cu m). In 1959, the company established a guideline of 50 ppm, (128 mg/cu m) as an 8-hour TWA exposure limit, and subsequent exposures were "generally found" to be below this concentration. Occupational histories were obtained from plant records, and exposures in the two largest units, which accounted for 466 of the workers, were classified as low (<25 ppm; <64 mg/cu m), intermediate (25-200 ppm; 64-512 mg/cu m), or high >200 ppm; >512 mg/cu m), and each worker was assigned to one of these exposure groups on the basis of the highest estimated concentration at which he had been exposed for longer than 1 month. The 128 workers from the three smaller production units, for which industrial hygiene data were not adequate to characterize exposures, were classified as having unmeasured exposures, which company industrial hygienists estimated were primarily in the low to intermediate range. For purposes of analysis, each exposure group was subdivided according to exposure at that concentration for less than 1 year or for 1 year or more. Exposures of workers to vinyl chloride at lower concentrations than their assigned category were not considered; for example, worker exposure at concentrations between 25 and 200 ppm for 6 months, and less than 25 ppm for 10 years, would be classified as intermediate exposure for less than 1 year.

All but one of the employees were traced through 1973 [86]. Causes of death were obtained from death certificates for all deceased workers except one who had been employed in a low-exposure job for less than 1 year. Expected numbers of deaths for each exposure classification were calculated from US death data for white males by determining the number of person-years in each exposure group over 5-year periods by 10-year age groups.

The total number of deaths in the study population was 89, compared with 100.1 expected deaths [86]. Malignancies accounted for 20 deaths vs 17.9 expected, and none of these were cancers of the liver. There were three deaths from cirrhosis of the liver (3.1 expected), all in workers exposed to vinyl chloride for less than 1 year. Seventy-two of the vinyl chloride workers had also been employed in an arsenicals production facility where workers previously had an increased cancer mortality risk, and these workers were therefore not included in the population used for the vinyl chloride study.

With arsenicals workers excluded, total deaths in the population of 522 vinyl chloride workers numbered 79, 91% of the US death rate for white males, and the number of deaths due to malignancies was 13, compared with 16.0 expected deaths [86]. When the mortality data were stratified according to exposure concentration, 9 of these deaths from cancer were found to have occurred in the 163 workers with high exposure, compared with 5.1 expected, and 6 of these were in workers exposed at high concentrations for longer than 1 year (2.9 expected). Statistical comparison of the ratio of observed to

expected deaths from cancer in the high-exposure group with that of all other groups combined, assuming a Poisson distribution for small sample sizes, showed a significant difference ($P<0.025$). When only deaths occurring 15 years or more after the employee's initial exposure to vinyl chloride were included, eight of nine deaths from malignancies were in the high-exposure group ($P<0.01$). A survey of case histories of the 13 vinyl chloride workers who died from cancer showed that 2 had also had substantial exposure to benzene, 1 had a family history of malignancies that included 4 deaths in his immediate family, and at least 3 of the 5 who died from lung cancer were smokers.

Ott et al [86] concluded that, although the number of deaths was small, the distribution of malignant neoplasms with respect to exposure categories suggested a possible dose-response relationship. No associations were noted for malignant effects in the lower-exposure categories where the estimated TWA exposure concentration ranged from 10 to 100 ppm.

In 1974, Nicholson et al [87] published a retrospective study of the mortality of a cohort of workers involved in the production of polyvinyl chloride at a plant in New York. From company and union records, 257 men were identified who had begun employment between 1946 and 1963 and who had worked for at least 5 years in the plant. The current health status of 255 workers was determined. More than half of the employees had worked primarily in polyvinyl chloride production, where reactor cleaning was routinely performed without respiratory protection, causing exposure to vinyl chloride. Approximately 25% of the workers had been employed in maintenance, where exposures to vinyl chloride could be significant during repair work, and the remaining workers had been employed mainly in the shipping department and the laboratory. No records were kept of the vinyl chloride concentrations at which the workers were exposed. The only measurements made of environmental concentrations of vinyl chloride were those necessary to ensure that the explosive limit of 30,000 ppm (76.8 g/cu m) was not exceeded. The authors estimated that peak concentrations might often have exceeded 1,000 ppm (2,560 mg/cu m) and may occasionally have reached 10,000 ppm (25.6 g/cu m). This estimate was based on the results of medical examinations conducted in March 1974 on a group of active and past workers, more than 50% of whom reported symptoms of dizziness, headache, or euphoria, and 4% of whom had lost consciousness on the job in comparison with the known development of these symptoms at high concentrations. The median age of the workers on the 10th anniversary of their employment was approximately 37 years, with 16% under 30.

Of the 255 traceable workers, 82 had retired or were working elsewhere, 24 had died, and 149 were still employed at the same plant [87]. Mortality among the workers was higher than expected based on death rates for New York State, excluding New York City, for deaths due to all causes and all cancers in groups exposed 10-15, 15-20, and 20-25 years, but not in the one exposed for 25 or more years. These increases were not statistically significant, however. There were 10 deaths from all causes vs 6.1 expected in the group exposed 10-15 years, 7 vs 6.6 in the group exposed 15-20 years, 7.0 vs 5.0 in

the group exposed 20-25 years, and 0 vs 1.3 in the group exposed 25 years or more. The observed vs expected numbers of deaths from all cancers in these groups were 3 vs 1.2, 3 vs 1.4, 3 vs 1.1, and 0 vs 0.3, respectively. There were three deaths caused by angiosarcoma of the liver and three deaths from other cancers (glioblastoma, reticulum cell sarcoma, and lymphosarcoma) that the authors suggested might have been related to exposure to vinyl chloride.

The authors [87] reported that the three cases of angiosarcoma occurred in workers who had been exposed for the first time before 1951. They suggested that, as the time from first exposure increased, additional cases of occupational cancer might occur in this group of workers. The authors concluded that these data demonstrated the need to prevent exposure to vinyl chloride and to monitor, screen, and further study workers previously exposed to vinyl chloride.

In 1977, Chiazze et al [88] published a study of 4,341 deaths that occurred during 1964-1973 in a population of polyvinyl chloride production plant workers who had had exposure to vinyl chloride. A total of 55 plants of 17 companies supplied mortality data on employees who had died either while actively employed, after retiring from the company with retirement benefits, or after terminating employment but while still covered by a company-sponsored insurance program. A frequency distribution based on hospital and area was calculated for subjects whose cause of death was listed as cancer or liver disease. When one hospital or several hospitals in the same area appeared on several of these death certificates, a Registered Records Administrator visited these hospitals and reviewed all of their pathology records to determine whether any cases of angiosarcoma of the liver had been diagnosed. Five cases of angiosarcoma were found in this manner, but none of these persons had ever been employed at any of the plants in the study.

Over the 10-year study period, the size of many of the plants changed drastically [88]. The number of employees at all plants under study was estimated to have been between 65,000 and 70,000. However, the population at risk could not be accurately determined. Results were therefore reported in terms of proportional mortality ratios, rather than standardized mortality ratios, using race- and sex-specific US mortality figures for comparison purposes.

The total number of deaths from cancer among males was 666 vs 562 expected, for a PMR of 1.19 [88]. Among females, 181 deaths from cancer occurred vs 138 expected, a PMR of 1.31. Approximately 31% of all deaths from cancer were due to cancers of the digestive system (PMR's of 1.29 for men and 1.50 for women). Cancer of the liver was the cause of death for 6 men vs 4.2 expected, for a PMR of 1.43. No deaths of women were attributed to cancer of the liver. PMR's also exceeded 1.0 for all other cancer categories except cancers of the buccal cavity and pharnyx and the genital organs. The authors stated that "due to the nature of the data, formal significance tests and interpretation in probabilistic terms are deemed inappropriate."

Chiazze et al [88] concluded that there "appeared" to be excesses in cancer mortality for both men and women in this study and that these excesses "appeared" to be concentrated in cancers of the digestive system. They listed several factors that made definitive interpretation of the data "difficult." The use of PMR's, they pointed out, does not take into account the absolute risk of death in a population. Also, the overall favorable mortality of working populations, which has been found in numerous investigations, was not considered in this study. The authors did state, however, that their results "appeared to be consistent" with previously published studies [65,84], and that these results suggested a need for continued investigation. Definitive interpretation is difficult because special efforts were made to get supplementary hospital data for all deaths attributed to liver disease, malignant or not. The authors do not state whether this resulted in changing any death certificate causes from nonmalignant to malignant liver disease, with consequent problems of comparability with US published data. The absence of cancer of the liver in women is not surprising, since the population was relatively small (601).

In 1976, Waxweiler et al [89] reported the results of a NIOSH retrospective mortality study of a cohort from four vinyl chloride polymerization plants. In 1974, these plants had employed 250, 75, 250, and 250 workers and had been in the business of polymerizing vinyl chloride for 28, 20, 24, and 31 years, respectively. Only workers with at least 5 years of exposure to vinyl chloride and for whom 10 years had elapsed since the initial exposure were included in the cohort group of 1,294 workers (1,151 alive, 136 deceased, and 7 lost to followup). The total person-years at risk was 12,720. The authors compared death rates among these workers to those among US white males, adjusted for age, calendar year, and cause, but not for smoking history. Mortality among the exposed workers was higher than expected for nonmalignant respiratory disease (6 observed vs 3.4 expected) and for all malignant neoplasms (35 observed vs 23.5 expected), and lower than expected for cirrhosis of the liver and violent deaths. The number of deaths from all malignant neoplasms differed significantly ($P<0.05$) from that expected. Significant increases ($P<0.01$) were reported only for deaths from cancer of the biliary system and liver among the workers for whom more than 10 years had elapsed since initial exposure. For the workers with more than 15 years since the initial exposure, significant increases were reported for cancer of the brain, CNS, and respiratory system ($P<0.05$), and biliary system and liver ($P<0.01$).

In each cancer mortality category, the calculated SMR was higher for the 15-year group than for the 10-year group [89]. The authors stated that this demonstrated the importance of considering latency when looking for occupationally induced malignant neoplasms. They suggested that restricting the study to at least 10 years after initial worker exposure had minimized the "healthy worker effect," thereby eliminating the overall deficit of deaths in workers exposed to vinyl chloride often reported by other investigators. A

similar pattern of latency had been reported previously by Nicholson et al [87]. These results demonstrate an increased risk of cancer for vinyl chloride workers and show the essentiality of taking latency into account.

In 1975, Duck et al [90] reported on the mortality experience of workers exposed to vinyl chloride in a plant in Great Britian. A total of 2,120 male workers who had been exposed to vinyl chloride at some time since 1948 was identified from company records. Information from death certificates was compiled for these workers, and the mortality was compared with that of men in England and Wales. Workers who died at more than 74 years of age or before 1955 were excluded from consideration in both populations.

SMR's were computed on the basis of cause of death, job description, duration of exposure, and year of first exposure [90]. No significant excess mortality was found for the workers in any of the comparison categories. No cases of angiosarcoma of the liver were identified in either population within the study period (1955-1975); however, the authors stated that one such death occurred after the end of the study and before the paper was published.

The authors [90] pointed out that their comparisons did not allow for the selective effects of employment. They also noted that their findings conflicted with those of Monson et al [84]. The significance of these observations is difficult to determine, since the authors did not supply exposure information in this report. It is possible that, because of unique work practices and engineering and administrative controls, the mortality of workers from this plant may not be representative of workers from other plants or from the industry as a whole.

(4) Chromosomal Studies

Two studies from the United States [91,92] and one from West Germany [93] found no observed increases in lymphocytic chromosomal aberrations in vinyl chloride workers. Other reports [94-99] indicate that vinyl chloride may increase the incidence of lymphocytic chromosomal aberrations in exposed workers; however, the latter reports are based on results from relatively few workers.

In a preliminary report, Kilian et al [91] examined 2,291 lymphocytes from 75 applicants for employment and 6,050 lymphocytes from 121 workers exposed to vinyl chloride and small concentrations of vinylidene chloride. The authors pointed out that the group of applicants contained only 2 persons over 50 years old, whereas the exposed group included 30 persons over 50. During the previous 5 years, vinyl chloride concentrations in the workplace had been approximately 5 ppm (12.8 mg/cu m); 1 year prior to the study, concentrations of 1-2 ppm (2.56-5.12 mg/cu m) had been common; and 3 months before the study, vinyl chloride concentrations had been measured at less than 1 ppm (2.56 mg/cu m). The following results were obtained for the applicants and the exposed workers, respectively: chromatid breaks, 6.72 and 2.94%; chromosome breaks, 1.48 and 1.37%; dicentrics, 0.17 and 0.46%; rings, 0.00 and 0.02%; exchanges, 0.17 and 0.08%; and abnormal cells, 6.07 and 4.26%.

Picciano et al [92] recently reviewed data from 209 workers in a plant manufacturing vinyl chloride, with an average length of employment of 48.3 months (range 1-332 months); these were compared with data from preemployment tests on 295 individuals. The average age of the workers was 39.5 years, and that of the applicants was 25.1 years. The proportion of lymphocytes with chromatid breaks, chromosome breaks, rings, dicentics, and exchange figures did not differ significantly between the two groups (exposed 3.7% vs controls 4.5%), nor did the occurrence of any single aberration. The authors also related the extent of vinyl chloride exposure to the number of chromatid and chromosomal aberrations. Workers were classified into estimated exposure categories of less than 1 ppm (<2.56 mg/cu m), 1-5 ppm (2.56-12.8 mg/cu m), or greater than 5 ppm (>12.8 mg/cu m) on the basis of job classification. In none of the groups was the percentage of aberrations found in workers significantly different from that found in controls. The authors stated that the difference in mean age between the exposed and preemployment groups was not considered to be a "confounding" factor in their analyses, since the cytogenetic change most often associated with aging was chromosomal loss rather than chromosomal breakage. The authors concluded that adverse cytogenetic effects could be avoided in "controlled, minimal-exposure environments," but they did not suggest a quantitative exposure limit.

Fleig and Thiess [93] tested 10 vinyl chloride-exposed chemists and technicians for lymphocyte chromosomal aberrations. The 10 workers were exposed to vinyl chloride at concentrations of 1-25 ppm (2.56-64 mg/cu m) at the time of the study but had previously been exposed at concentrations as high as 3,000 ppm (7,680 mg/cu m) for an average total of 13 years (range 4-34 years). Four control subjects had frequencies of chromosomal aberrations in the range of 0-5%. The 10 exposed workers also had frequencies of aberrations in the range of 0-5%. The authors concluded that exposures in the plant had not increased the rate of chromosomal abnormalities, but they also mentioned that the study group was small and that a realistic final conclusion could not be drawn until all exposed workers had been tested.

Leonard et al [94] also examined vinyl chloride workers for lymphocytic chromosomal aberrations. Eleven polymerization workers, 7 vinyl chloride laboratory workers, and 10 controls selected from outside the factory environment were included in the study. Although vinyl chloride concentrations in the plant were not recorded, the authors assumed that the concentrations must have exceeded 500 ppm (1,280 mg/cu m) several years prior to the time of the study and had been reduced to less than 10 ppm (25.6 mg/cu m) by 1976, when the study was made. They also assumed that laboratory concentrations of vinyl chloride were negligible. The laboratory workers had been employed an average of 9.3 years (range 2-15 years) and the polymerization workers an average of 6.5 years (range 1-17 years). Two hundred cells from each subject were examined. In controls, 2.6% of the cells had structural aberrations, in laboratory workers, 1.9%, and in polymerization workers, 2.8%. The incidences of chromatid gaps and breaks and chromosomal gaps did not differ significantly between the three groups. The authors

stated that polymerization workers had chromosomal fragments, translocations, rings, and dicentrics, whereas the control group did not; however, the authors noted that the vinyl chloride workers had had several roentgenographic examinations, which might have been responsible for the chromosomal aberrations.

In 1976, Szentesi et al [99] reported the occurrence of chromosomal aberrations in the lymphocytes from 45 polyvinyl chloride workers, 44 industrial controls (workers not exposed to polyvinyl chloride), and 49 persons with no occupational exposure to chemicals. The mean ages of these groups were 27.3 years for the polyvinyl chloride workers, 43.9 for the industrial controls, and 29.1 for the nonexposed persons.

Aberrations of chromatids were observed in 165/1,600 cells (10.31%) from the polyvinyl chloride workers, in 199/2,988 cells (6.66%) from the industry controls, and in 149/2,523 cells (5.90%) from the nonexposed persons [99]. The frequency of these aberrations was significantly higher ($P<0.001$) in the lymphocytes from polyvinyl chloride workers than in those from either control group. Unstable chromosomal aberrations were also significantly higher ($P<0.001$) in the polyvinyl chloride workers (25/1,600 cells; 1.56%) than in the industry controls (17/2,988 cells; 0.56%) or in the nonexposed persons (9/2,523 cells; 0.35%). Data for each worker were scored individually and plotted against years of exposure to vinyl chloride. Seven polyvinyl chloride workers had values outside the confidence limit for the nonexposed control group. One of these workers had been exposed to vinyl chloride for 6-7 years, one for 10-11 years, and the other five for 12 or more years. These data may indicate that increasing duration of exposure to vinyl chloride increases the risk of lymphocytic chromosomal aberrations. The effect of age was not considered in this analysis, however.

In 1977, Heath et al [95] reported the results of cytogenetic analyses on the peripheral lymphocytes from 35 men employed for 10 years or longer in a large chemical/rubber plant and from 4 male controls who worked for the Center for Disease Control (CDC). Of the chemical/rubber plant employees, 14 worked in polyvinyl chloride polymerization (presumed high exposure to vinyl chloride), 4 in polyvinyl chloride processing (presumed low exposure to vinyl chloride), and 17 in rubber tire manufacture (industry controls with presumed negligible exposure to vinyl chloride). The average group ages were 49.4 years for the high exposure group, 52.5 for the low exposure group, 48.5 for the industry controls, and 44.3 for the CDC controls.

Chromosome breakage was scored for each group [95]. The high exposure group had 6.7% breakage (74/1,105), the low exposure group had 7.8% breakage (14/180), the industry controls had 5.9% breakage (77/1,306), and the CDC controls had 3.6% breakage (21/586). The frequency of breakage was significantly higher ($P<0.05$) in all three of the industry groups than in the CDC controls, but there were no significant differences between the industry groups. The majority (86%) of the aberrations observed in each group were chromatid gaps. Chromatid breaks and isochromatid gaps and breaks were also observed.

The authors [95] also attempted to relate frequencies of breakage to duration of employment. No significant gradient was reported for the high and low exposure groups, but a signficant gradient ($P<0.01$) was observed for the industry controls (100-199 months, 0% breaks, 2 subjects; 200-299 months, 1.3% breaks, 2 subjects; 300-399 months, 6.7% breaks, 13 subjects). The authors stated that the interpretation of this gradient was "uncertain" because of the small number of employees, and because the mean age increased with employment duration (31.0, 44.5, and 51.8 years, respectively).

The authors [95] noted that their observations were not inconsistent with previous studies suggesting a twofold increase in chromosome breakage frequency with occupational exposure to vinyl chloride; however, they concluded that the finding that the overall frequency of breakage did not differ significantly among high, low, and negligibly exposed industrial groups indicated that other agents in the chemical/rubber plant were capable of inducing the breaks, making it impossible to relate a particular agent to the abnormal effects observed. This difficulty does not diminish the concern warranted by the increased frequency of chromosome damage seen in chemical industry workers compared with that in workers outside the chemical industry.

Ducatman et al [96] compared the lymphocytic chromosomal aberrations in 11 polyvinyl chloride workers (4-28 years of exposure, average 15 years) with those seen in 10 control subjects. Although no data were available on ambient concentrations of vinyl chloride, it was assumed, on the basis of reports of odor detection, dizziness, and headaches, that they must have exceeded 500 ppm (1,280 mg/cu m) at times. Fifty metaphases from lymphocyte cultures were examined for each individual. The results indicated a slightly higher incidence of chromosomal aberrations in the exposed workers. The mean numbers of aberrant cells and the standard deviations determined for exposed and control subjects were: breaks and gaps, 5.64 ±1.91 vs 4.40 ±0.97 ($0.1>P>0.05$); unstable changes (fragments, dicentrics, and rings), 1.55 ±1.29 vs 0.30 ±0.48 ($P<0.01$); and stable changes (monosomy, trisomy, deletions, and exchanges), 3.36 ±1.63 vs 2.90 ±2.18 ($0.6>P>0.5$).

Funes-Cravioto et al [97] compared chromosomal aberrations in cultured lymphocytes from seven male employees who had worked for 9-29 years in a vinyl chloride polymerization shop with those from three nonexposed workers. Exposure data were not given, but the authors estimated that the vinyl chloride concentrations in the polymerization department were 20-30 ppm (51-77 mg/cu m). The exposed workers, none of whom had clinical signs of disturbed liver function, acroosteolysis, or abnormal hematologic changes, had an average of 9.52% abnormal cells (138/1,450) compared with 1.94% (11/566) for the three control workers. The difference was statistically significant ($P<0.001$); however, the frequency of abnormal cells was highest in the employees who had been exposed to vinyl chloride for the shortest period.

Purchase et al [98] examined 100 lymphocytes from each of 56 polyvinyl chloride workers and 24 workers with no exposure to vinyl chloride. Workers who had been exposed to X-rays, prolonged drug treatment, or recent viral

infections were excluded from the study. Exposed workers had 6.3% of cells with breaks and gaps, 1.45% of cells with unstable changes, and 0.38% of cells with stable changes. Nonexposed workers had 3.63%, 0.46%, and 0.09% of cells in these respective categories. The authors stated that all group differences were statistically significant ($P<0.05$).

A secondary analysis was conducted by Dresch and Norwood [100] on the data from a number of studies of human lymphocytic chromosomal aberrations [94-99]. This analysis [100] made use of a binomial model, assuming a homogeneous group, and the Cochran model, a model with provision for differences among clusters. The authors stated that the secondary analysis of each paper agreed with the authors' analysis, and that the cumulative data from all papers combined showed a statistically significant increase in the frequency of chromosomal aberrations with increasing exposure to vinyl chloride or polyvinyl chloride. They pointed out, however, that the frequencies of aberrations were small. only a "fraction" of background, and that, in view of the inconsistency between laboratories, the positive statistical evidence should be "treated with caution."

(5) Reproduction Studies

Infante et al [101], in 1976, reported on a study of pregnancy outcome in wives of workers exposed to vinyl chloride. Interviews were conducted with 95 vinyl chloride polymerization workers and a control group of 158 rubber and polyvinyl chloride workers who were known to have had little or no exposure to vinyl chloride monomer. Paternal age, pregnancy outcome, and estimates of the date of conception for all pregnancies were obtained. Wives of the workers were not interviewed and maternal age and health status were not determined.

The fetal death rates in the families of the exposed workers were age-matched, for paternal age, with the control group, and the two groups were compared before and after exposure, ie, to vinyl chloride monomer for the exposed group and to rubber and polyvinyl chloride fabrication emissions for controls [101]. Prior to exposure, there was no significant difference in fetal death rates between the offspring of vinyl chloride workers and those of the controls (6.1% and 6.9%). After exposure, however, this rate was significantly higher ($P<0.05$) for offspring of vinyl chloride monomer workers (15.8% vs 8.8%). To determine the effect on the overall rate of fetal deaths of the data from women who chronically experienced abortions, workers' wives who had had more than two abortions were excluded from the calculations. The results showed that prior to exposure the offspring of the controls had a higher fetal death rate than those of vinyl chloride workers (6.9% vs 3.1%), but that after exposure of the fathers the rate for the offspring of the vinyl chloride workers was the higher (10.8% vs 6.8%).

Infante et al [101] postulated that germ-cell damage in the father was the leading possibility as the cause of fetal death. Unfortunately, this study

relied on indirect knowledge of the key variable, fetal deaths, by interviewing only the fathers. Therefore, the reliability of this information must be considered questionable.

Infante [102] also compared the incidence of malformations among children born to residents of communities around polyvinyl chloride polymerization plants in Ohio. He compared the rates of production of malformed children born in three cities with polyvinyl chloride plants with those in cities without such plants and with that of malformations in the entire state from 1970-1973. Infante found a significant excess incidence ($P<0.001$) of malformations in the three cities with polyvinyl chloride facilities above that in 10 cities without polyvinyl chloride plants. Although the congenital malformation rate in the cities with polyvinyl chloride plants was greater than the rate for the state, two cities without polyvinyl chloride plants had even greater rates. Moreover, anomalies were not restricted to the cities with polyvinyl chloride exposures; for example, one city without a plant had a higher rate than two cities with plants. Infante concluded that these preliminary findings did not link polyvinyl chloride production with an increased occurrence of birth anomalies.

Edmonds et al [103] evaluated CNS birth defects recorded in Kanawha County, West Virginia, during 1970-1974 in an attempt to determine whether they were related to occupational or residential exposure of the parents to vinyl chloride from a local polyvinyl chloride plant. Kanawha was one of two counties, out of seven US counties with polyvinyl chloride production plants, where CNS birth defects were significantly higher than the national rate for this 5-year period. Infants born with CNS defects and whose parents were Kanawha County residents were identified from the register of the Center for Disease Control's Birth Defects Monitoring Program (BDMP) and records of the West Virginia Department of Vital Statistics. Infants without malformations born immediately before and after those born with CNS birth defects were used as controls. Families of 41 affected infants and of 1 of the 2 controls for each, selected randomly, were interviewed to obtain histories of previous pregnancies and residential and occupational histories of the parents for the 5 years before the birth of the child.

BDMP and State records showed that the rate of CNS defects/10,000 births was higher in Kanawha County than in the United States as a whole for 1970, 1971, and 1972 [103]. The Kanawha County rates for these years were 37.5, 39.7, and 34.9, respectively, compared with US rates of 21.8, 22.1, and 21.6. In 1973, however, the rate of CNS birth defects in Kanawha County declined to below the national average, and in 1974 the rate was only 3.0, compared with a national rate of 18.4. The Kanawha County rates differed significantly ($P<0.05$) from the national rates for 1970, 1971, and 1974.

The CNS birth defect cases for the 5-year period were closely matched with controls for race, paternal education, maternal age, and socioeconomic status [103] as indicated by the Hollingshead Index. The groups did not differ

significantly in maternal education or paternal age. All of the malformed infants were white and the majority were female (25:16). No seasonal variation in the rate of CNS birth defects was noted.

The reproductive histories of mothers in both groups were similar in the number of previous pregnancies and the percentage of live births and of other children with congenital anomalies [103]. However, a family history of birth defects was reported by 11 of the 41 families in the case group but by only 4 of the 41 families in the control group. A family history of CNS birth defects was reported in 5 of the case families but in none of the control families. Occupational histories showed that two fathers in each group had been employed in the local polyvinyl chloride plant at the time their infants were conceived, and that none of the mothers had ever worked in the polyvinyl chloride plant.

In evaluating the distance from the polyvinyl chloride plant to both the place of work and the place of residence of the parents, Edmonds et al [103] found no significant differences between the birth defect and the control groups. However, multivariate analysis showed that, in families living within 3 miles of the plant, CNS birth defect cases were concentrated in the area northeast of the plant ($P<0.02$). The authors attempted to determine whether this clustering was related to atmospheric vinyl chloride concentrations, but concluded that existing data on plant emissions and meteorologic conditions were insufficient to reconstruct vinyl chloride concentrations at the time of conception. Edmonds and his associates concluded that there was no evidence that the high rate of CNS birth defects in Kanawha County for 1970-1974 was related to vinyl chloride exposure.

(6) Summary

Although the results of the various vinyl chloride epidemiologic studies are sometimes contradictory, there is substantial evidence that workers in vinyl chloride plants may have an increased incidence of atypical liver function [76,78], increases in cancers of the liver, brain, and respiratory systems [79,81,84-89], and increases in somatic chromosomal abnormalities [95,97-99]. One study [101] that suggested an increased fetal mortality due to exposure of the fathers to vinyl chloride has also been published; however, the method of data acquisition for this study was of questionable validity. Two reports [102,103] seem to indicate that birth defects and anomalies in offspring of parents living in the vicinities of vinyl chloride polymerization plants probably are not related to exposure to vinyl chloride.

Each of these studies has similar deficiencies, eg, the lack of exposure information for most cohorts, the relatively few workers for whom significant time has elapsed since first exposure, ie, >15 years, and the difficulties of assessing the "healthy worker" and "survivor" effects. Without this information, it is impossible to quantitate the hazards from exposure to vinyl

chloride. Although the results and conclusions of individual studies can be questioned on scientific grounds, they justify an increased concern about the hazard from increased exposure to vinyl chloride.

(b) Vinylidene Chloride

Ott et al [73] reported the mortality statistics and health examination findings on 138 workers exposed to vinylidene chloride containing small amounts (0.2%) of vinyl chloride. Estimations of exposure were made on the basis of job descriptions and industrial hygiene data. Estimated career doses were then calculated based on duration of exposure and monthly average exposure concentrations. Mortality data for the cohort were compared with those for US white males. Health examination data for the cohort were compared with data from controls paired as closely as possible for age, smoking history, date of employment, and date of participation in the plant health inventory program. Individuals in the control population were exposed to a variety of chemicals other than vinyl chloride used at the plant and therefore represented a background experience for chemical workers.

Comparison of the results of mortality experience of the total cohort, cohort with 15+ years of experience, and cohort with a total calculated dose exceeding 500 ppm-months (1,985 mg/cu m-months) showed no significant increase for any cause of death [73]. Comparison of the results of 17 clinical laboratory parameters showed no significant differences between the matched pairs of exposed and control workers. Regressions of the individual pair differences on estimated cumulative dose and duration of exposure showed no positive correlations at the 0.05 level.

The authors [73] concluded that there were no findings "statistically related or individually attributable to vinylidene chloride exposure" in the cohort studied. The study included few workers, however, and they were all from a single plant. The authors recommended that additional epidemiologic studies be conducted to develop information on chronic exposure to vinylidene chloride. This study does not indicate that there is an occupational hazard from exposure to vinylidene chloride.

(c) Vinyl Bromide, Vinyl Fluoride, and Vinylidene Fluoride

No epidemiologic studies on workers exposed to vinyl bromide, vinyl fluoride, or vinylidene fluoride have been located.

Animal Toxicity

The results of experiments involving exposure of laboratory animals to vinyl halides show that some of these compounds can induce the same toxic effects on rodents as on humans, including the characteristic angiosarcoma of the liver. No lifetime animal experiments have been located that demonstrate a no-observable-adverse-effect concentration for any of the vinyl halides.