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OCCUPATIONAL EXPOSURE TO VINYL HALIDES

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
Center for Disease Control
National Institute for Occupational Safety and Health

April 1979

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PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and provide for the safety of workers occupationally exposed to an ever-increasing number of potential hazards. The National Institute for Occupational Safety and Health (NIOSH) evaluates all available research data and criteria and recommends standards for occupational exposure. The Secretary of Labor will weigh these recommendations along with other considerations, such as feasibility and means of implementation, in promulgating regulatory standards.

NIOSH will periodically review the recommended standards to ensure continuing protection of workers and will make successive reports as new research and epidemiologic studies are completed and as sampling and analytical methods are developed.

A permanent Federal standard exists for worker exposure to vinyl chloride. This current standard was promulgated on October 4, 1974 (Federal Register 39:35896), became effective January 1, 1975, and was included in the Code of Federal Regulations (29 CFR 1910.1017) in January 1976. As part of NIOSH's efforts to ensure continuing protection of workers by periodically reviewing criteria and standards, this criteria document presents recently completed research and epidemiologic studies as well as revised sampling and analytical methods for vinyl chloride. In addition, this document presents complete criteria and a recommended standard for four additional vinyl halides.

The contributions to this document on vinyl halides by NIOSH staff, other Federal agencies or departments, the review consultants, the reviewers selected by the American Academy of Occupational Medicine, the American Academy of Industrial Hygiene, and the Society of the Plastics Industry, and Robert B. O'Connor, M.D., NIOSH consultant in occupational medicine, are gratefully acknowledged.

The views expressed and conclusions reached in this document, together with the recommendations for a standard, are those of NIOSH. They are not necessarily those of the consultants, the reviewers selected by professional societies, or other Federal agencies. However, all comments, whether or not incorporated, were considered carefully and were sent with the criteria document to the Occupational Safety and Health Administration for consideration in setting the standard. The review consultants and the Federal agencies which received the document for review appear on pages vi and vii.

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The Division of Criteria Documentation and Standards Development, National Institute for Occupational Safety and Health, had primary responsibility for the development of the criteria and recommended standard for vinyl halides. Alfred N. Milbert, Ph.D., of this Division served as criteria manager. SRI International developed the basic information for consideration by NIOSH staff and consultants under contract CDC-99-74-31.

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I. RECOMMENDATIONS FOR A VINYL HALIDES STANDARD

NIOSH recommends that employee exposure to vinyl halides in the workplace be controlled by adherence to the provisions for vinyl chloride in 29 CFR 1910.1017, the contents of which are provided as Appendix I of this document, with the exception that the respirator provisions in 29 CFR 1910-1017 (g)(1)(i-iv) and also 29 CFR 1910 (g)(6)(ii) shall be replaced with those given below. All provisions shall be adhered to for each of the vinyl halides as defined below. The recommended occupational exposure limits are measurable by techniques that are valid, reproducible, and available to industry and government agencies. Sufficient technology exists to permit compliance with the recommended standard. Employers should make every effort to limit employee exposure to the vinyl halides to concentrations that are as low as possible, with an eventual goal of zero exposure. Employee exposures shall be kept at or below the limits prescribed in 29 CFR 1910.1017. The criteria and standard will be subject to review and revision as necessary.

These criteria and the recommended standard apply to workplace exposure of employees to the monomers vinyl chloride ($CH_2=CHCl$), vinylidene chloride ($CH_2=CCl_2$), vinyl bromide ($CH_2=CHBr$), vinyl fluoride ($CH_2=CHF$), and vinylidene fluoride ($CH_2=CF_2$), including any unreacted monomer that may remain in polymers of these halides. As used in this document, "vinyls" and "vinyl halides" refer only to these five compounds unless the terms are otherwise qualified.

The biologic effects of exposure to the vinyl halides may include changes in behavior, cardiovascular abnormalities, degenerative changes in the liver and bones, and the induction of malignant neoplasms, especially angiosarcomas of the liver. A great deal of information is available concerning the effects of exposure of humans and animals to vinyl chloride, much of this is relatively new information having been developed since October 1974, when 29 CFR 1910.1017 was promulgated. As part of its effort to provide worker protection, NIOSH has extensively reviewed the newly completed studies as well as the older literature on vinyl chloride and has considered this information in its evaluation of the other vinyl halides. The data that are available from studies of carcinogenicity, mutagenicity, and metabolism, and predictions of biologic reactivity on the basis of physical and chemical properties of the vinyl halides suggest that the other vinyl halides have carcinogenic potentials similar to that of vinyl chloride. There is strong evidence from animal studies of carcinogenicity on the part of vinylidene chloride and vinyl bromide. Although there is a lack of toxicity data on vinyl fluoride and vinylidene fluoride, until some animal toxicity and/or metabolism data are available, there appears to be no reason to treat these two compounds differently from the other vinyl haldies in considerations of worker protection.

Procedures for the collection and analysis of workroom air samples for compliance with this standard shall be as provided in Appendices II-VI or by any methods shown to be at least equivalent in precision, sensitivity, and accuracy to the methods specified for vinyl chloride in 29 CFR 1910.1017 (d)(4).

Continuous monitoring equipment with alarm capability has been developed for vinyl chloride and vinylidene chloride and should be used as specified for vinyl chloride in 29 CFR 1910.1017 (g)(6)(ii).

TABLE I-1

RESPIRATOR SELECTION GUIDE FOR VINYL HALIDES

Concentration	Respirator Type Approved under Provisions of 30 CFR 11
Less than or equal to 10 ppm	Chemical cartridge respirator with end-of-service-life indicator, if approved, for the specific vinyl halide
Less than or equal to 100 ppm	(1) Supplied-air respirator equipped with half-mask facepiece, operated in continuous-flow, pressure-demand, or other positive pressure mode (2) Supplied-air hood, helmet, or suit operated in continuous-flow mode
Less than or equal to 200 ppm	Supplied-air respirator equipped with full facepiece, operated in continuous-flow, pressure-demand, or other positive pressure mode
Greater than 200 ppm and Entry into area of unknown concentration for emergency purposes	(1) Self-contained breathing apparatus with full facepiece, operated in pressure-demand or other positive pressure mode (2) Combination Type C supplied-air respirator with full facepiece, operated in pressure-demand mode, and auxiliary self-contained air supply

II. INTRODUCTION

This report presents the criteria and the recommended standard based thereon that were prepared to meet the need for preventing impairment of health from occupational exposure to vinyl halides. The criteria document fulfills the responsibility of the Secretary of Health, Education, and Welfare under Section 20 (a)(3) of the Occupational Safety and Health Act of 1970 to "develop criteria dealing with toxic materials and harmful physical agents and substances which will describe exposure levels...at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience."

After reviewing data and consulting with others, NIOSH formalized a system for the development of criteria on which standards can be established to protect the health and provide for the safety of employees exposed to hazardous chemical and physical agents. The criteria and recommended standards should enable management and labor to develop better engineering controls resulting in more healthful work environments. Simply complying with the recommended standard should not be the final goal.

These criteria for a recommended standard for vinyl halides are part of a continuing series of criteria developed by NIOSH. The recommended standard applies to the handling, processing, manufacture, use, or storage of the vinyl halides. The standard was not designed for the population-at-large, and its application to situations other than occupational exposure is not warranted. The standard is intended to: (1) protect against the development of short- and long-term systemic effects from exposure to vinyl halides; (2) protect against local effects on the skin and eyes; (3) minimize the risk of induction of cancer; (4) be measurable by techniques that are valid, reproducible, and available to industry and government agencies; and (5) be attainable with existing technology.

The diagnosis of a rare liver cancer, angiosarcoma, in employees involved in polymerization processes involving exposure to vinyl chloride has generated research on related compounds, including vinylidene chloride and vinyl bromide. The available data from studies with animals confirm the carcinogenic potential of vinyl chloride. The available information on vinylidene chloride and vinyl bromide suggests that these compounds also are carcinogenic and may induce the same type of characteristic tumor that is associated with exposure to vinyl chloride.

Although no reports of animal experiments have been located in which the effects of long-term exposure to vinyl fluoride or vinylidene fluoride were investigated, these compounds have been found to be mutagenic in bacteria, and they may have metabolic products and pathways similar to those of the other vinyl halides. Examination of the chemical and physical properties of the

vinyl halides indicates that all of them or their metabolites may have similar macromolecular binding potentials. The limited data on vinyl fluoride and vinylidene fluoride suggest that they probably exert nearly the same tumorigenic propensities as vinyl chloride, vinylidene chloride, and vinyl bromide.

To permit accurate assessment of the health hazards associated with the vinyl halides, additional research is necessary. This research should include attempts to: (1) develop less toxic substitutes; (2) develop improved control technology; (3) develop respiratory protective devices, especially those with end-of-service-life indicators, for the vinyl halides other than vinyl chloride; and (4) develop improved sampling and analytical methods and continuous monitoring equipment.

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 Gamma-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.

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(a) Vinyl Chloride

In 1975, Prodan et al [104] published estimates of LC50 values for a 2-hour exposure to vinyl chloride for several animal species. The values were 27,419 ppm for mice, 47,640 ppm for rats, and 236,215 ppm for both guinea pigs and rabbits. However, there was an error in the authors' calculations, and these values should actually have been 117,500 ppm (300.8 g/cu m) for mice, 156,000 ppm (399.4 g/cu m) for rats, and 238,000 ppm (609.3 g/cu m) for guinea pigs and rabbits. The recalculated LC100 values were 150,000 ppm for mice, 210,000 ppm for rats, and 280,000 ppm for guinea pigs and rabbits. The authors reported that death was preceded by excitement, contractions and convulsions, and accelerated respirations. The excitement phase progressed to a state of "tranquility" characterized by Cheyne-Stokes breathing and circulatory disturbances as indicated by cyanosis and conjunctival congestion. This phase then progressed into a state of deep narcosis that was followed by respiratory failure and death.

Abreu and coworkers [105] surveyed the anesthetic effects of 18 halogenated hydrocarbons, including vinyl chloride, on mice. The minimal certain anesthetic concentration (EC100 for anesthesia), highest tolerated concentration (LC0), 50% anesthetic concentration (EC50 for anesthesia) and 50% lethal concentration (LC50) on inhalation were estimated. To establish each point on each substance's effect-concentration of the curve, the authors exposed 10-40 mice to vinyl chloride for 10 minutes by inhalation. The ratio of the highest tolerated concentration to minimal certain anesthetic concentration was calculated as the "certain safety factor." The ratio of the 50% lethal concentration to the 50% anesthetic concentration was calculated as the "50% safety factor." Vinyl chloride had a minimal certain anesthetic concentration of 5.0 millimoles/liter (122,000 ppm; 312.3 g/cu m), a highest tolerated concentration of 9.0 millimoles/liter (220,000 ppm; 563.2 g/cu m), a "certain safety factor" of 1.8, a 50% anesthetic concentration of 4.1 millimoles/liter (100,000 ppm; 256 g/cu m), a 50% lethal concentration of 9.9 millimoles/liter (242,000 ppm; 619.5 g/cu m), and a "50% safety factor" of 2.4.

Aviado and Smith [106] reported the results of studies on sodium phenobarbital anesthetized rhesus monkeys exposed to vinyl chloride at concentrations of 2.5, 5.0, or 10.0% (25,000, 50,000, or 100,000 ppm; 64, 128, or 256 g/cu m). The vinyl chloride was administered to one animal at each concentration through a tracheal cannula for 5 minutes, alternating with 15 minutes of room air. Pulmonary resistance and compliance were estimated from measurements of tracheal airflow and transpulmonary pressure. Although control procedures were not discussed, it is assumed that each animal served as its own control.

Pulmonary resistance increased and pulmonary compliance and respiratory minute volume decreased with increasing vinyl chloride concentrations [106]. The only values of the exposed animals that were significantly different ($P<0.05$) from those of controls were pulmonary resistance (15.35% higher than

controls) and respiratory minute volume (12.30% lower than controls) at vinyl chloride concentrations of 10%. No significant changes in heart rate or aortic blood pressure were observed in these animals.

Oster et al [107], in 1947, investigated the anesthetic effects on dogs of vinyl chloride gas mixed with oxygen. Two dogs were "momentarily" exposed to vinyl chloride at a 50% concentration (500,000 ppm; 1,280 g/cu m) which was then decreased to 7% (70,000 ppm; 179.2 g/cu m) by volume. During exposure, the dogs maintained good abdominal relaxation, but their legs became rigid and muscular movements became uncoordinated. A third dog, anesthetized with 25% vinyl chloride, had signs similar to those in the first two dogs. After exposure the dogs continuously "crowed" and salivated heavily.

Four additional dogs received a local anesthetic, monocaine hydrochloride, and their blood pressures were checked by cannulation of the femoral artery [107]. After control blood pressure measurements were obtained, the animals were anesthetized with 10% vinyl chloride (100,000 ppm; 256 g/cu m) in oxygen. During the vinyl chloride exposure, the dogs had normal blood pressures, but they showed such cardiac irregularities as intermittent tachycardia, ventricular extrasystoles, and vagal beats. Similar irregularities were detected with a stethoscope in noncannulated dogs on the same exposure regimen.

Six other dogs were anesthetized with 10% vinyl chloride (100,000 ppm) in oxygen [107]. Electrocardiographic (ECG) records (lead II) were obtained at exposures to vinyl chloride (not further defined) sufficient to produce light surgical anesthesia, surgical anesthesia, and threatened respiratory collapse. At exposures producing surgical anesthesia, several changes were noted in the cardiac rhythm, especially marked tachycardia followed by bradycardia. In addition, two of the six dogs showed R-wave inversions, and one dog showed incipient ventricular fibrillation. All six dogs showed abnormalities in the ECG record, ranging from sinus arrhythmia and transitory extreme left axis deviation to atrioventricular (A-V) block, ventricular tachycardia, ventricular multifocal extrasystoles, and inversion of the T-wave with elevated ST segments. As the concentration of vinyl chloride was increased toward that necessary for respiratory failure, the ECG abnormalities disappeared except for the greatly reduced R-wave amplitude. The authors concluded that vinyl chloride caused muscular incoordination in the extremities and serious cardiac arrhythmias. They also concluded that vinyl chloride was not safe as an anesthetic and that its use in humans was not warranted.

In 1974, Belej et al [108] reported the changes in cardiac function of rhesus monkeys exposed to vinyl chloride at concentrations of 2.5, 5.0, and 10.0% (25,000, 50,000, and 100,000 ppm; 64, 128, and 256 g/cu m). Three animals were exposed at each concentration. They were anesthetized with sodium phenobarbital, their tracheae were cannulated for artificial respiration, and their chests were opened by midsternal incisions to allow measurement of myocardial contractility, pulmonary arterial, aortic, and left

atrial pressure. The vinyl chloride mixtures were administered for periods of 5 minutes alternating with 10-minute exposures to room air. The number of test periods for each animal was not specified. Control procedures were not reported, but each animal probably served as its own control.

The heart rate and aortic, left atrial, and pulmonary arterial pressures were not significantly different between any of the experimental and control groups [108]. The force of myocardial contraction in animals exposed to 10% vinyl chloride was significantly different ($P<0.05$) from control values, showing a decrease of 28.5%. At 5% vinyl chloride there was a 9.1% decrease, and at 2.5% vinyl chloride there was a 2.3% decrease; however, these latter changes were not significant. Decreases in aortic blood pressure, while not significant, paralleled decreases in contractility.

Carr et al [109] demonstrated that inhalation of certain compounds increased the sensitivity of the canine heart to epinephrine. Lead II of the ECG was recorded from each of seven unanesthetized dogs in the experiment. Epinephrine hydrochloride was injected iv at a dose of 0.01 mg/kg during 25-40 seconds, and the ECG was again recorded. Subsequently, the animals were exposed to vinyl chloride at concentrations of from 15 to 90% with oxygen. After the dogs had inhaled the vinyl chloride for 10-20 minutes, the ECG recording and epinephrine injection were repeated. Three of the seven dogs developed sensitization of the myocardium with multifocal ventricular ectopic tachycardia after vinyl chloride exposure. The authors concluded that vinyl chloride produced sensitization of the myocardium, but less frequently than did its saturated analog, ethyl chloride. The total exposures used were too high to allow a conclusion about whether inhalation of vinyl chloride may pose an acute threat to workers in times of fear-provoking stress or to those who may take medication containing epinephrine for asthma control or other reasons.

Clark and Tinston [110] exposed beagle dogs to vinyl chloride at various concentrations by mask for 5 minutes. During the final 10 seconds of exposure, a 5-μg/kg injection of adrenaline was administered iv. ECG's were recorded and analyzed for serious arrhythmias, such as multifocal ventricular ectopic beats or ventricular fibrillation. At each concentration, four to seven dogs were exposed. Vinyl chloride was calculated, by a moving average interpolation technique, to have induced cardiac sensitization in 50% of the animals at a concentration of 5%.

In 1970, Viola [111] reported on the effects on rats of exposure to vinyl chloride. Twenty-five male albino Wistar rats with an average weight of 150 g were exposed to vinyl chloride at a concentration of 3% (30,000 ppm; 76.8 g/cu m) for 4 hours/day, 5 days/week, for 1 year. Twenty-five similar rats served as controls. Throughout the exposure period, the general physical appearance, behavior, and body weight of the animals were monitored. After the exposures, some of the exposure survivors and some of the controls were killed at 20-day intervals, and gross and microscopic changes in the paws,

brain, liver, kidneys, and thyroid were noted. The number of rats surviving, the number of examinations conducted, and the number of rats killed at each interval were not specified.

Exposure to vinyl chloride did not significantly affect growth but was slightly soporific to the animals during the first 10 months of exposure [111]. During the 11th month, the exposed rats had lower body weights and showed less aggressiveness and less reaction to external stimuli than the controls; they also suffered disturbances in equilibrium. No details about the observations made were presented. Of the rats exposed to vinyl chloride, 13 died from cardiopulmonary complications and 2 died from hematoperitoneum. On microscopic examination, the authors observed that most of the animals showed pathologic changes in the brain, liver, kidneys, and thyroid, and that six rats showed skeletal alterations. He did not report whether these changes were observed in the rats that died during exposure or in those that were killed after the exposure. The paws of the vinyl chloride-exposed rats had areas of hyperkeratosis, superficial thickening of the epidermis, and disappearance of the cutaneous "adnexa." In addition, vacuolization and degeneration of the basal layer, a modest increase in the papillar layer, and edema of the epidermis were noted. The connective tissue of the skin showed fragmentation and decreased elastic reticulum and dissociation of collagen bundles. The small arterial vessels of the paws showed signs of endothelial fibrosis, and some vessels were completely occluded by proliferation of connective tissue.

Extensive metaplastic proliferation of cartilage-like material was found around the small metatarsal bones [111]. The edges of the material were irregular, with differential growth that resulted in outward bending of toes. In areas of mature compact bone, the cartilaginous elements were grouped around a central nucleus of the bone, giving the appearance of chondroid metaplasia. In small bones, this chondroid metaplasia was often extensive, and the bones appeared to be impregnated with a mucoid substance that obliterated the cement lines by altering the characteristic deposition of the bone tissue.

Microscopic examination of the brains of rats exposed to vinyl chloride showed diffuse degenerative lesions of the gray and white matter [111]. Fibrotic processes had often surrounded and invaded the small nerve bundles of the gray matter. There was also evidence of neuronal phagokaryosis with satellitosis and deposition of neuroglial elements around the altered nerve cells of the white matter. In the cerebellum, there were signs of atrophy of the granular layer and profound degenerative changes in some areas of the Purkinje cell layer.

Animals exposed to vinyl chloride had enlarged livers [111]. Some livers appeared yellowish with smooth surfaces and were slightly more brittle than normal. Microscopic examination revealed signs of diffuse interstitial hepatitis, functional degeneration or necrosis of the hepatic cells, and marked cytoplasmic and nuclear polymorphism. The Kupffer cells were often hypertrophic and showed evidence of abnormal proliferation. Numerous areas of

partial necrosis and diffuse fatty degeneration often blocked the portal capillaries, centrilobular veins, and sinusoids. Intense fibrosclerotic reactions were also noted in the areas of degenerative change in the livers of a few exposed rats.

In contrast, the kidneys of the exposed animals were relatively unaltered except for signs of tubulonephrosis and occasional chronic interstitial nephritis [111]. The author also noted colloid goiters and a marked increase in parafollicular cells in the thyroids of several animals. Examination of the controls showed no alterations in any of the organs.

The author [111] concluded that his investigation confirmed that rats were sensitive to vinyl chloride and that the lesions of bone and connective tissue were similar to those described in workers affected by acroosteolysis of the hands and to those in experimental "osteolathyrism." This report is valuable for its characterization of the systemic toxic effects resulting from chronic exposure to vinyl chloride. An assessment of the hazard posed by exposure to vinyl chloride is not possible; however, because the information was not presented in sufficient detail to permit a statistical analysis. Observations on tumors produced in animals that were probably the same as those in this paper were presented in a second paper by Viola et al [112] and are discussed in a subsequent section of this chapter.

In 1961, Torkelson et al [113] reported a three-part investigation on the effect of repeated exposure of rats, rabbits, dogs, and guinea pigs to vinyl chloride at 50, 100, 200, or 500 ppm (128, 256, 512, 1,280 mg/cu m). In the first experiment, groups of 10 male and 10 female rats were placed in a 160-liter inhalation chamber containing vinyl chloride at a nominal concentration of 500 ppm for 7 hours/day, 5 days/week, for 4.5 months. The control group consisted of five male and five female rats.

Male rats exposed repeatedly at 500 ppm for 4.5 months showed a significantly higher ($P<0.001$) liver-to-body weight ratio than the controls [113]. Of the 20 exposed rats, 3 males and 1 female died during the exposure. Microscopic examination showed an increased centrilobular granular degeneration of the liver and interstitial and tubular changes in the kidneys.

In the second experiment, the animals exposed to vinyl chloride at nominal concentrations of 100 or 200 ppm (±15%) for 7 hours/day, 5 days/week, for 6 months, included 20-24 male and 24 female rats, 10 male and 8 female guinea pigs, 3 male and 3 female rabbits, and 1 male and 1 female dog [113]. In addition, eight groups of five male rats each were exposed at nominal concentrations of 100 or 200 ppm (±15%) for 0.5, 1, 2, or 4 hours/day, 5 days/week, for 6 months. For each species and regimen, two control groups carefully matched on the basis of age, condition, and weight were used, one group of colony controls, and the other air-exposed in the chamber on a regimen similar to that of the experimental groups.

Of the 24 rats exposed at 100 ppm for 7 hours/day, 5 males and 1 female died [113]. All rats exposed repeatedly for 7 hours/day showed slight but significant increases ($P<0.05$) in liver weight.

Repeated exposure to vinyl chloride at 200 ppm for 7 hours/day for 6 months resulted in the deaths of 3 of 12 rats [113]. Of the five rats in each "short exposure" group, one, two, one, and one died after exposure for 0.5, 1, 2, and 4 hours/day, respectively. Organ weights were normal in all species, except that liver weights increased in rats exposed repeatedly for 7 hours/day. At 8 weeks after exposure, male rats continued to have increased liver weights, but the weights appeared to be returning to normal. Increases in liver weight of rats exposed for 2 or 4 hours/day were not statistically significant. All the rats exposed for 0.5 or 1.0 hour/day had normal organ weights compared with those of control rats. Microscopic examination showed liver changes characterized by centrilobular granular degeneration and necrosis with some foamy vacuolization in male rabbits and periportal cellular infiltration in female rabbits.

In the third experiment, 24 male and 24 female rats, 12 male and 12 female guinea pigs, 3 male and 3 female rabbits, and 1 male and 1 female dog were exposed to vinyl chloride at a concentration of 50 ppm for 7 hours/day, 5 days/week, for 6 months [113]. Three additional groups of 10 male rats each were exposed for 1, 2, or 4 hours/day, 5 days/week, for 6 months. Matched groups of control animals were again used. Vinyl chloride concentrations in the chamber were determined by micro-Volhard titration. Repeated exposures to vinyl chloride at 50 ppm did not produce toxic signs in any of the animals. A decrease in the kidney weight was observed in the female rats, but it was not attributed to the exposure since it was not observed at higher concentrations.

Animals exposed repeatedly at 100, 200, or 500 ppm were found to have normal biochemical and hematologic values and urinalysis tests [113]. Serum enzyme activities were normal in all dogs, rats, and rabbits. None of the organs examined had macroscopic tissue changes at any exposure concentration. The authors concluded that repeated exposures for 7 hours/day at 100 ppm could cause increased liver weight.

Lester et al [18] conducted four experiments with Sherman strain rats. In the first experiment, an unspecified number of rats were exposed in pairs to vinyl chloride at various concentrations for up to 2 hours in an exposure chamber. No control animals were described. In the rats exposed to vinyl chloride at a concentration of 5% (50,000 ppm; 128 g/cu m), the righting reflex was lost; at 6% (60,000 ppm; 153.6 g/cu m), however, it was said to be still present, but it was absent in rats exposed at 7% (70,000 ppm; 179.2 g/cu m). The corneal reflex disappeared at a vinyl chloride concentration of 10% (100,000 ppm; 256 g/cu m). The animals rapidly returned to normal after removal from the chamber. One rat was killed after exposure to vinyl chloride at 10% but showed no gross signs of adverse effects. Two rats exposed to vinyl chloride at 15% were deeply anesthetized within 5 minutes. One rat had

effusions of fluid from the mouth and died of asphyxia in 42 minutes; autopsy revealed edema and congestion of the lungs. The other rat remained under deep anesthesia for 2 hours but recovered promptly when removed from the exposure.

In their second experiment with rats, Lester et al [18] randomly assigned 18 male and 18 female rats to an experimental group and a control group. The experimental animals were exposed to vinyl chloride at a concentration of 10% (reduced to 8% after 2 days) between 8:30 am and 4:30 pm. Two female rats and an unspecified number of male rats in the experimental group died early in the experiment and were replaced. A total of three female rats died (days 2, 5, and 14) in the course of vinyl chloride exposure, and only two males survived all 15 days of exposure. In addition to mortality, exposure to vinyl chloride at a concentration of 8% was associated with a failure to gain weight until day 9, followed by weight gain at a slower rate than the controls until the cessation of exposure, after which the rates were equal. Neither gross nor microscopic differences were noted between experimental and control livers and kidneys at necropsy. Some rats had parasitic liver cysts and focal necrotizing pneumonia, but kidneys were within normal limits of variability. Microscopic examination of the spleens of experimental rats showed a significantly higher incidence of severe abnormality than was found in controls, although some individual rats in the control group manifested equally severe splenic abnormalities.

Lester et al [18] performed another experiment to ascertain whether vinyl chloride was a lung irritant. Three female and five male rats, matched with controls, were exposed as before for 8 hours daily for 19 consecutive days to vinyl chloride at a concentration of 5% in air. All animals were deprived of food and water while in the exposure chamber. Hemoglobin determinations were made during the exposure period. On the 20th day, all animals were anesthetized with ether, and blood was drawn by cardiac puncture. The animals were killed by an overdose of ether, and necropsies were performed. The terminal blood sample was tested for hemoglobin, prothrombin time, hematocrit, red cell, white cell, and differential white cell counts, and unspecified serum transaminase activities. Prothrombin time, hematocrit, and the serum transaminase activities were normal for both groups. The experimental group had a statistically significant increase ($P<0.05$) in red blood cells and a decrease ($P<0.01$) in white blood cells. The differential white cell counts of control and experimental groups were not significantly different. The ratio of the weight of the liver to the body weight was significantly elevated (males, $P<0.01$; females, $P<0.001$) in the experimental group. The five male experimental animals had thinner coats than normal and scaly tails; all other rats were normal in appearance. One of the experimental males had fibrous pleural adhesions, but these appeared to be old and unrelated to the experimental exposure. Microscopic examination of all organs and tissues failed to disclose abnormalities other than those in the liver in either group. There were no differences in intracellular or total fat in the liver, but livers in the experimental group had widespread swelling and vacuolization of cells with compression of the sinusoids. This difference was significant ($P<0.001$).

In the last experiment of the series, rats were exposed to vinyl chloride at a concentration of 2.0% for 8 hours/day, 5 days/week, for 3 months [18]. Sixty rats weighing about 75 g were separated randomly into two groups, each consisting of 15 males and 15 females. In the week before the rats were exposed to vinyl chloride, they were observed and weighed and blood was taken for hemoglobin determinations. All rats were weighed weekly, and hemoglobin determinations were made monthly. Four control and one experimental animal died in the course of the experiment. After 3 months, all animals were killed for necropsy after blood samples were drawn. The livers and spleens were weighed before being fixed in formalin. No significant differences were noted between the experimental and control body weights, hemoglobin levels, hematocrits, prothrombin times, or white cell monocyte and eosinophil counts. The livers of the experimental animals were significantly heavier ($P<0.001$) and the spleens significantly lighter (males, $P<0.02$; females, $P<0.05$) than in the control group. The experimental rats also had a statistically significant decrease ($P<0.01$) in white blood cell and neutrophil counts and an increase ($P<0.01$) in lymphocyte counts, when compared to the controls. Microscopically, the experimental group had fewer signs of kidney damage but more extensive liver damage, as indicated by swelling of cells and compression of sinusoids, than controls. No microscopic differences between the spleens of the two groups were noted.

In this 1963 paper, Lester and coworkers [18] concluded that the only suggestion of a specific toxic action of vinyl chloride was the increase in liver weight; the increase was not only statistically significant, but also of substantial magnitude (30% heavier than controls). The authors stated that they did not know the significance of the increase in liver weight after exposure to vinyl chloride, nor whether the liver returned to normal after exposure ceased. In addition, the authors pointed out the increasing neurologic deficits with increasing concentrations of vinyl chloride, finally terminating in death from respiratory insufficiency at concentrations of 15% for a single exposure or of 10% for repeated exposures.

(b) Vinylidene Chloride

In 1963, Irish [114], stated that there were at that time essentially no published data on vinylidene chloride toxicity and summarized data from unpublished reports of the Dow Chemical Company. He presented no detailed information on the animals exposed in these studies. "Brief" exposure to vinylidene chloride at concentrations around 4,000 ppm (15.9 g/cu m) was said to have rapidly produced "drunkenness," which progressed to unconsciousness if the exposure was continued. The author stated that vinylidene chloride irritated the eyes, and, in liquid form, irritated the skin. Animals exposed at concentrations of 25, 50, and 100 ppm (99.3, 198.5, and 397 mg/cu m) for 8 hours/day, 5 days/week, for several months exhibited unspecified liver and kidney damage. Irish concluded that vinylidene chloride produced adverse effects at concentrations below those necessary to produce irritation and below the odor threshold of 500-1,000 ppm.

Jaeger et al [115] estimated the LC50's for fed and fasted rats exposed to vinylidene chloride. One group of male Holtzman rats weighing 250-400 g was allowed continuous access to food; another group was fasted for 18 hours before exposure.

Eight groups of fasted rats and six groups of fed rats, each group consisting of five or six animals, were exposed to vinylidene chloride at various concentrations for 4 hours [115]. The 4-hour LC50 at 24 hours for the fasted rats was 600 ppm (2,382 mg/cu m) and the 24-hour minimum lethal concentration was 200 ppm (794 mg/cu m). The estimated 4-hour LC50 at 24 hours for the fed rats was 15,000 ppm (59.6 g/cu m), and the minimum lethal concentration for these animals was 10,000 ppm (39.7 g/cu m).

The authors [115] suggested that decreases in glutathione concentration in the livers of fasted rats was a possible explanation for the differences in lethality. They pointed out that this could be of importance with regard to the occupational risk because of the known circadian pattern of glutathione concentrations in the liver.

Siegel et al [116] published the results of experiments on several dichloroacetylene mixtures. For comparative purposes, they determined LC50's for vinylidene chloride and several other compounds. The 14-day LC50 of vinylidene chloride for male Sprague-Dawley rats was estimated to be 6,350 ppm (25.2 g/cu m) for a 4-hour exposure.

Short et al [117] reported the LC50 at 14 days and the 20-ppm LT50 for CD-1 mice exposed to vinylidene chloride for 22-23 hours. The LC50 for males was 98 ppm (389 mg/cu m) (95% confidence limits, 82-118 ppm), and for females it was 105 ppm (416.9 mg/cu m; 92-121 ppm). When the exposure periods were increased to 2 days at 22-23 hours/day, the LC50 for male mice was 35 ppm (139 mg/cu m). The LT50 for males was 4 days (3.6-4.4) at 20 ppm (79.4 mg/cu m). Concentrations of vinylidene chloride were measured by gas-liquid chromatography; other experimental details for these determinations were not given.

Carpenter et al [118] reported the effects of inhalation of vinylidene chloride on Sherman albino rats weighing 100-150 g. The authors reported that the concentration of vinylidene chloride sufficient to kill two to four of six test animals within 14 days after a 4-hour exposure was 32,000 ppm.

Balmer et al [119] also performed a study to determine the inhalation toxicity of vinylidene chloride in rats. A group of 104 male and 104 female Sprague-Dawley rats was exposed to vinylidene chloride at a concentration of 10 ppm (39.7 mg/cu m) for 6 hours/day, 5 days/week, for up to 18 months. A similar group was exposed at 40 ppm (158.8 mg/cu m) on the same schedule, and another group served as controls. After 30 days, four males and four females from each group were killed and examined. Because examination showed no effects, at the end of week 5 exposure concentrations were increased to 25 and 75 ppm (99.3 and 297.8 mg/cu m). After 6 months, five males and five females

from each group were killed and examined, and after 7 months, four animals of each sex from each group were killed, and bone marrow cells were prepared for cytogenetic examination. After 12 months of exposure, five additional animals of each sex from each group were killed and examined. Exposure ended at 18 months, and any animals remaining alive at 24 months were killed and examined.

Balmer et al [119] stated that "no clinical signs of toxicity were seen at any time." There were no signs of cytogenetic effects, and no hematologic or clinical chemical changes were relatable to the vinylidene chloride exposure. No significant differences in mortality, tumor formation, or gross pathology of the internal organs were observed. On microscopic examination, the livers of the animals exposed at both concentrations showed increased cytoplasmic vacuolation in the hepatocytes.

The authors [119] concluded that inhalation of vinylidene chloride at concentrations of 25 or 75 ppm resulted in "minimal liver changes" and did not cause an increase in tumors in rats.

Gage [120], in 1970, presented the results of an inhalation study of several industrial chemicals, including vinylidene chloride, on Alderley Park specific-pathogen-free rats weighing an average of 200 g. Groups of four male and four female rats were exposed to vinylidene chloride vapor at concentrations of 200 or 500 ppm (794 or 1,985 mg/cu m) for 6 hours/day, 5 days/week, for 4 weeks. Concentrations of vinylidene chloride in the exposure chamber were monitored by gas chromatography. During the exposures, the animals were checked for any change in weight and activity. The rats were killed at the end of the exposures, and blood and organs were collected and tested. Macroscopic and microscopic examinations were performed on organs and fixed tissues. Rats exposed at 500 ppm developed nasal irritation (sneezing), did not gain weight normally, and suffered liver cell degeneration. Rats exposed at 200 ppm suffered only slight nasal irritation, and all organs were normal on necropsy. No further data were presented by the author.

Siletchnik and Carlson [121] published the results of a study to determine the cardiac sensitizing effects of vinylidene chloride. Adult male Charles Rivers rats weighing 250-400 g were lightly sedated with 25 mg of sodium pentobarbital/kg ip, restrained, and then exposed to vinylidene chloride at 25,600 ±700 ppm (101.6 ±2.8 g/cu m) for periods of 10 minutes or longer. The rats were pretreated with 4 μg of epinephrine/kg, and the minimum amount of epinephrine necessary to produce cardiac arrhythmias or demonstrate a difference between pairs of animals was determined. The effect of phenobarbital was determined using weight-matched pairs of animals. One animal of each pair was administered phenobarbital, 50 mg/kg ip, daily for 4 days and exposed to vinylidene chloride 24 hours after the last dose. The pair mate in each case received injections of saline and was similarly exposed to vinylidene chloride.

In rats exposed to air alone, epinephrine at 4 μg/kg did not elicit any cardiac arrhythmias [121]. The authors stated that vinylidene chloride alone

caused sinus bradycardia and such arrhythmias as A-V-block, multiple continuous premature ventricular contractions, and ventricular fibrillation; they presented no further information. Epinephrine at doses as low as 0.5 μg/kg elicited cardiac arrhythmias in 29 animals exposed to vinylidene chloride. Sensitivity to epinephrine increased with increasing length of exposure to vinylidene chloride. The increased sensitivity to epinephrine was reversible, since 5 minutes after removal from exposure the animals were again able to tolerate high doses of epinephrine without showing arrhythmias.

Premature ventricular contractions were seen in animals pretreated with phenobarbital, exposed to vinylidene chloride, and challenged with epinephrine [121]. No arrhythmias were seen in the saline-treated animals challenged with the same amount of epinephrine. Arrythmias were produced in the phenobarbital-treated animals at a lower epinephrine dose and a shorter exposure to vinylidene chloride.

The authors [121] concluded that the phenobarbital probably induced vinylidene chloride metabolizing hepatic enzymes and that a metabolite caused the cardiotoxic effects. They further stated that, since the adrenal gland in humans may release up to 4 μg/kg/minute of adrenalin during stress, workers exposed to high concentrations of vinylidene chloride may be under a risk of these cardiotoxic events.

Prendergast et al [122] conducted a series of inhalation studies to determine the effects of vinylidene chloride and other chlorinated hydrocarbons on Sprague-Dawley or Long-Evans rats, Hartley guinea pigs, New Zealand White rabbits, beagle dogs, or squirrel monkeys. The exposed animals were subjected either to continuous 90-day exposures or to repeated 8-hour exposures, 5 days/week, for 6 weeks. The animals repeatedly exposed to vinylidene chloride included 15 rats, 15 guinea pigs, 3 rabbits, 2 dogs, and 3 monkeys. Continuous exposures involved groups of 15 or 45 rats, 15 or 45 guinea pigs, 3 rabbits, 2 or 6 dogs, and 3, 9, or 21 monkeys. A control group consisted of 304 rats, 314 guinea pigs, 48 rabbits, 34 dogs, and 57 monkeys. The concentrations of vinylidene chloride were monitored by gas-liquid chromatography. The concentrations of vinylidene chloride in the chamber during the continuous exposure were 20 ±2.1, 61 ±5.7, 101 ±4.4, or 189 ±6.2 mg/cu m (5, 15.4, 25.5, or 47.6 ppm), and the concentration during the repeated exposure was 395 ±32 mg/cu m (99.5 ppm).

Immediately after each experiment, the animals were killed and necropsies were performed [122]. To estimate the effects of vinylidene chloride inhalation, the authors measured liver alkaline phosphatase, SGPT, serum urea nitrogen, and liver lipid content, and made hematologic determinations. In the control populations, 7/304 rats, 2/314 guinea pigs, 2/48 rabbits, and 1/57 monkeys died prematurely.

Animals repeatedly exposed to vinylidene chloride at 395 mg/cu m (99.5 ppm) showed no microscopic tissue changes relatable to the exposure when compared with control tissues [122]. Gross examination of tissues showed no

changes in any animals except for one rat that had a gelatinous substance on its kidney and bloody urine in the bladder. The microscopic examination showed only nonspecific respiratory inflammation, which the authors considered not to be the result of vinylidene chloride exposure. They did not give any reasons for this conclusion. None of the repeatedly exposed animals died during the exposure, and only rabbits and monkeys lost weight.

Of the animals exposed continuously at 189 mg/cu m (47.6 ppm), seven guinea pigs died between days 4 and 9, and three monkeys died, one each on days 26, 60, and 64 [122]. Gross examination showed mottled livers in a majority of the experimental animals. Exposed rabbits, dogs, and monkeys lost weight, while rats and guinea pigs gained weight during the exposure. There were increases in liver alkaline phosphatase and SGPT activity in rats and guinea pigs, but there were no significant changes in any other biochemical parameters. Two rats also showed increases of 20% and 34.4% in liver lipid content. Serum urea nitrogen concentrations in exposed rats were comparable with those of control rats. Three of the 15 guinea pigs that were exposed at 101 mg/cu m (25.5 ppm) died between the 3rd and 6th exposure days, and 2 of the 3 monkeys exposed at 101 mg/cu m died, 1 on day 39 and the other on day 47. White or bluish-gray spots and nodules were visible on the lungs of several guinea pigs and rats. Serum urea nitrogen concentrations of exposed guinea pigs were comparable with those of the control group.

Continuous exposure at 61 mg/cu m (15.4 ppm) resulted in the deaths of 3 of the 45 guinea pigs on days 3 and 4 of exposure [122]. The exposed monkeys lost weight, and exposed rats gained less weight than the controls. Several animals of all species had mottled livers and spleens.

Two of the 45 rats, 2 of the 45 guinea pigs, and 1 of the 21 monkeys exposed continuously at 20 mg/cu m (5 ppm) died [122]. The dogs lost weight, and the rats gained less than controls. Gross examination showed mottled livers in about one-third of the exposed animals. Microscopic changes were seen in the kidneys and liver of the exposed monkeys and nonspecific inflammatory changes in the lungs of all animals exposed at each concentration. The authors did not attribute the lung changes to the vinylidene chloride exposure. They did not give any reasons for this conclusion. Liver damage was noted in animals exposed to vinylidene chloride at 189 mg/cu m (47.6 ppm). Although animals exposed at 61 and 20 mg/cu m (15.4 and 5 ppm) also had signs of liver damage, the authors did not consider these attributable to the exposures to vinylidene chloride, since those exposed at 101 mg/cu m (25.5 ppm) did not exhibit these changes. Hematologic test results for exposed animals were similar to those for the controls.

In 1977, Humiston et al [123] and Rampy et al [124] reported the results of a study of the oral toxicity of vinylidene chloride. Groups of 48 male and 48 female Sprague-Dawley rats were given access to vinylidene chloride in their drinking water at nominal concentrations of 50, 100, or 200 ppm (equivalent ranges of daily intake: 5-12, 8-20, 16-40 mg/kg) for 730 days. Eighty male and 80 female rats served as controls. The typical impurities of

the vinylidene chloride used in this study was reported by Rampy et al [124] as: vinyl bromide, 4 ppm; vinyl chloride, 3-5 ppm; trans-1,2-dichloroethene, 138-1700 ppm; cis-1,2-dichloroethene, 24-680 ppm; 1,1,1-trichloroethane, 2-60 ppm; 1,1,2-trichloroethane, 48 ppm; hydroquinone monomethyl ether, 2 ppm.

The appearance and demeanor of the rats ingesting vinylidene chloride were not different from those of controls throughout the study [123]. Body weight gains and food and water consumption were similar for experimental and control animals. No compound-related abnormalities were noted in the results of hematologic studies, urinalyses, or serum chemistry analyses. No significant differences were noted in mean organ weights or organ to body weight ratios.

Gross and microscopic examinations revealed occasional statistical differences between exposed and control animals [123]. The differences considered compound-related were fatty changes or fatty degeneration of the liver in female rats in the 50, 100, and 200 ppm groups and in male rats in the 200-ppm group. Although the incidence of these liver lesions in the males of the 100-ppm group was not significantly increased, it was higher than that in the controls. Centrilobular atrophy and periportal hypertrophy were also seen in the liver of the exposed animals. No target organ was found that showed a tumorigenic effect which was considered compound-related, and the total tumor incidence in male and female rats in the various exposure groups was not considered different from that in the controls.

Humiston et al [123] concluded that the only compound-related deviations in these rats were the fatty changes or fatty degenerations of the liver. All other statistically significant deviations observed were considered to be within the normal variation encountered in lifetime studies with this strain of rat. They also concluded that these results did not indicate an "oncogenic effect for vinylidene chloride ingested by rats." The data indicate that if a carcinogenic potential for rats exists for vinylidene chloride, these cumulative doses must be lower than that necessary to promote the expression of that potential.

Jaeger et al [125] gave single doses of vinylidene chloride dissolved in corn oil by stomach tube to lightly ether-anesthetized male Holtzman rats weighing 250-350 g. The rats were fasted for 4 hours before they received the vinylidene chloride. Anesthetized control rats received corn oil only. Some of the experimental rats were given ip injections of sodium phenobarbital (30 mg/kg) to aid in measuring the time-response relationship for vinylidene chloride. This was indicated by the time between loss and recovery of the righting reflex. Three spontaneous rightings within a minute was considered evidence that the reflex had returned. The liver glucose-6-phosphatase activity, serum alanine-alpha-ketoglutarate transaminase activity, liver triglyceride values, and the phenobarbital sleeping time were determined at different times after the animals received doses of vinylidene chloride and were used as indices of liver damage. The rats were killed at intervals up to 24 hours after they were given the vinylidene chloride or corn oil, and their

blood was collected for preparation of serum. The livers were removed and used to make homogenates for biochemical assays.

The phenobarbital sleeping time increased significantly ($P<0.05$) within 2-4 hours in rats given 400 mg/kg of vinylidene chloride, and the maximum increase was observed at 12-16 hours, although there were no statistical differences between the sleeping times at 4-8, 12-16, and 20-24 hours [125]. Liver damage, as evidenced by either decreased hepatic glucose-6-phosphatase activity or increased serum alanine-alpha-ketoglutarate transaminase activity, was marked at 8 and 16 hours after the vinylidene chloride was given to the rats. Serum alanine-alpha-ketoglutarate transaminase activity increased significantly ($P<0.05$) at 4, 8, 16, and 24 hours and the glucose-6-phosphatase activity decreased significantly ($P<0.05$) at 8 and 16 hours in animals given vinylidene chloride at 400 mg/kg. The serum enzyme activity began to decline after 8 hours. The liver triglyceride concentration increased with increasing doses of vinylidene chloride; at doses of 800 mg/kg, it was almost double the control concentration. None of the control animals showed a change in any of the indices of hepatic toxicity considered.

Jenkins et al [126] studied the effect of vinylidene chloride on adrenalectomized male Holtzman rats weighing 200-470 g. Sham-operated rats were used as controls. Both the adrenalectomized and control rats were fasted for 18 hours before being given single oral doses of 400 mg/kg of vinylidene chloride in corn oil, 2 ml/kg by volume. After 20 hours, more adrenalectomized rats than control rats had died. Biochemical responses to vinylidene chloride could not be measured as a result of the high mortality rate. The LD50 in adrenalectomized rats after 24 or 96 hours was 84 (64-111) and 81 (70 94) mg/kg, respectively. However, with control rats, the LD50 was 1,550 (1,520-1,581) and 1,510 (1,445-1,578) mg/kg after 24 and 96 hours, respectively.

In the same study, Jenkins and associates [126] observed the effects of vinylidene chloride on 9- to 11-week-old male and female rats given single oral doses of 400 mg/kg. They also studied the effects of vinylidene chloride on 21- to 24-week-old male and female rats given single oral doses of 200 mg/kg. Liver and plasma enzyme activities were measured 20 hours after oral administration. The older female rats showed a greater increase in liver glucose-6-phosphatase activity than the older male rats, and both groups of females had increased liver alkaline phosphatase activity in comparison with their respective male counterparts. From these observations, the authors concluded that female rats were more susceptible to the hepatotoxic effects of vinylidene chloride than male rats.

(c) Vinyl Bromide

Abreu et al [105] published the results of a study on the anesthetic properties of 18 halogenated hydrocarbons, including vinyl bromide. Groups of 10-40 mice were exposed to vinyl bromide at several unspecified concentrations to determine the minimal certain anesthetic concentration (EC 100 for

anesthesia), highest tolerated concentration (LCO), and "certain safety factor" (highest tolerated concentration divided by minimal certain anesthetic concentration). Vinyl bromide showed a minimum certain anesthetic concentration of 3.5 millimoles/liter (86,000 ppm; 376.7 g/cu m) and a highest tolerated concentration of 7.0 millimoles/liter (171,000 ppm; 749 g/cu m), for a certain safety factor of 2.0 [105].

Leong and Torkelson [127] conducted two studies of the effects of inhaled vinyl bromide (99.7% pure) on various animal species, including rats, rabbits, and monkeys. The impurities in the vinyl bromide included a polymerization inhibitor (paramethoxy phenol, 0.1%), ethylene oxide (0.12%), vinyl chloride (0.06%), and traces of ethyl bromide, methylene chloride, acetylene, and various aldehydes. The first study involved exposing four groups of five male Wistar rats each to vinyl bromide at 10,000 ppm (43.8 g/cu m) in a 160-liter stainless steel chamber for 7 hours/day, 5 days/week, for either 3 days or, 1, 2, or 4 weeks. Concentrations of vinyl bromide in the chamber were determined by infrared spectroscopy. Two control groups were exposed to room air. Immediately after the exposure, the surviving animals were killed, and macroscopic and microscopic examinations were performed on their organs and on fixed tissue specimens.

The rats exposed to vinyl bromide at 10,000 ppm became hypoactive during the 7-hour exposure period [127]. They seemed drowsy after 1 hour of the first exposure and looked "sluggish" by the 13th exposure. The control animals remained active throughout the exposure period. Exposed animals showed a significantly lower ($P<0.05$) weight gain than controls between the 15th and 20th days of exposure, and the difference was greater ($P<0.01$) after the 20th exposure. Gross examination of killed animals showed multifocal gray areas in the lungs, but the authors stated that no "compound related" tissue changes were observed microscopically.

In the second study, 2 groups of animals each consisting of 60 Charles River rats, 6 New Zealand white rabbits, and 6 cynomologus monkeys, all equally divided according to sex, were exposed to vinyl bromide at 250 or 500 ppm (1,095 or 2,190 mg/cu m) for 6 hours/day, 5 days/week, for 6 months [127]. A third group of 30 male and 30 female rats, 3 male and 3 female rabbits, and 4 female and 2 male monkeys was exposed to filtered room air. The experiments were conducted in the evening during the first 20 weeks of exposure and then were changed to daytime. The authors did not state whether the concurrent control animals were also switched to a daytime schedule. Vinyl bromide concentrations in the chamber were monitored by gas chromatography. Gross and microscopic examinations were performed on organs and fixed tissue of exposed animals at the end of the experiment. The animals exposed for 6 months were observed for changes in activity, body weight, indications of respiratory distress, eye and nasal irritation, and skin condition. Hematologic tests were performed on rats, rabbits, and monkeys in the control and 500-ppm groups prior to exposure and after 2, 10, and 24 weeks of exposure. All monkeys were examined for nonvolatile bromide in whole blood at the end of weeks 1, 2, 4, 8, 16, and 26.

At the end of the 6 months of exposures, all the animals exposed to vinyl bromide at 250 or 500 ppm showed weight increases at rates comparable with controls [127]. Only rats had a decrease in mean weight when the exposure schedule was changed from evening to daytime during the 20th week of exposure. Microscopic examination of major organs of all groups and species showed no changes that resulted from exposure to vinyl bromide. Analysis of blood showed elevated concentrations of bromide in all exposed animals, with monkeys that had been exposed at 250 and 500 ppm having the highest levels. No statistically significant changes were observed in the other measurements.

In the same report, Leong and Torkelson [127] summarized the results from unpublished data on the effects of vinyl bromide on rats. An unspecified number of rats was exposed to vinyl bromide at nominal concentrations of 100,000 (437,600 mg/cu m), 50,000 (218,800 mg/cu m), or 25,000 ppm (109,400 mg/cu m) for 1.5 and 7 hours. Two weeks after exposure to vinyl bromide at 25,000 or 50,000 ppm, the rats that survived were killed and examined for microscopic tissue changes.

Exposure at 100,000 ppm caused deep anesthesia and death within 15 minutes [127]. None of the rats exposed at 50,000 ppm for 1.5 hours died, but an unspecified number of deaths occurred during the 7-hour exposure. Within 25 minutes, the rats became unconscious. Vinyl bromide at 25,000 ppm anesthetized the rats, but they recovered rapidly when removed from exposure. Microscopic examination of tissues showed slight to moderate liver and kidney damage in rats exposed at 50,000 ppm. Examination of tissues from rats exposed at 25,000 ppm showed no abnormalities.

Leong and Torkelson [127] also gave male rats a 50% solution of vinyl bromide in corn oil by oral intubation to determine the LD50. They reported an LD50 of approximately 500 mg/kg but presented no supportive data. They also reported that vinyl bromide was irritating to the eyes but not to the skin of rabbits; data were not presented to support these findings.

(d) Vinyl Fluoride

In a book on the toxicity of anesthetics [128], Clayton reported that a mixture of 800,000 ppm (1,504 g/cu m) of vinyl fluoride in oxygen was not lethal for rats exposed to it for 12.5 hours. He also stated that unpublished data of Limperos (no further identification given) showed that male and female rats exposed to vinyl fluoride at concentrations of 100,000 ppm (188 g/cu m) for 7 hours/day, 5 days/week, for 6 weeks gained weight normally, exhibited no behavioral changes, had no fatalities, and had no tissue changes as evaluated by microscopic examination. Clayton did not supply details of these experiments.

In 1950, Lester and Greenberg [129] reported the effects of single exposures to vinyl fluoride on adult white rats. Rats were exposed for 30 minutes at concentrations ranging from 20 to 80% (200,000 to 800,000 ppm; 376

to 1,504 g/cu m) in an 11-liter glass chamber for 30 minutes. The rats were tested for any abnormalities in the postural, righting, and corneal reflexes after the exposure.

At the 30% (300,000 ppm; 564 g/cu m) concentration, the rats exhibited "hindleg instability" which the authors considered a sign of "slight intoxication" [129]. At 80%, the rats experienced difficulty in breathing but recovered after a 1-minute exposure to room air. Postural and righting reflexes were lost between 50 and 60% and between 60 and 70%, respectively. Loss of the postural reflex was also evident in rats exposed to vinyl fluoride at 80% for 12.5 hours, but these rats also regained the reflexes soon after breathing room air.

Results of an investigation on repeated exposures of rats to vinyl fluoride were summarized in a technical report from E I du Pont de Nemours and Company [130]. An unspecified number of rats were exposed to vinyl fluoride at a concentration of 100,000 ppm for 7 hours/day, 5 days/week, for a total of 30 exposures. There were no differences in the rate of weight gain, in the results of necropsies, of microscopic examinations of fixed tissues, of organ weights, or of clinical observations. It was concluded that vinyl fluoride did not constitute "much of" an inhalation hazard. However, the technical report did not present any data for evaluation.

(e) Vinylidene Fluoride

In a book on the toxicity of anesthetics [128], Clayton reported that a mixture of 800,000 ppm (2,096 g/cu m) of vinylidene fluoride in oxygen was not lethal to rats exposed to it for 19 hours. No experimental details or data were offered to support this statement.

Lester and Greenberg [129], in 1950, reported the effects of inhaled vinylidene fluoride on an unspecified number of adult white rats. The rats were exposed to vinylidene fluoride at concentrations ranging from 10% to 80% (100,000 to 800,000 ppm; 262 to 2,096 g/cu m) in an 11-liter glass chamber for 30 minutes. After the rats were removed from the chamber, their postural, righting, and corneal reflexes were tested.

The rats exposed to vinylidene fluoride at 10%-80% for 30 minutes lost none of the reflexes tested, but those exposed at concentrations of 40% (400,000 ppm; 1,048 g/cu m) or higher showed slight intoxication, which was manifested at 80% by the development of an unsteady gait without loss of the postural reflex [129]. Rats exposed at 80% for 19 hours showed no progressive signs of intoxication, and autopsies showed no evidence of pulmonary irritation.

Carpenter et al [118] reported the effects of short-term static inhalation exposures of Sherman albino rats weighing between 100 and 150 g to vinylidene fluoride. The authors reported that exposure to vinylidene fluoride at a concentration of 128,000 ppm (335.4 g/cu m) for 4 hours was sufficient to kill

two to four of the six test animals. From this observation, they concluded that vinylidene fluoride was slightly hazardous to rats. No further information was presented.

Burgison et al [131] studied the myocardial sensitizing properties of vinylidene fluoride in eight dogs and two cats. The animals were first injected with epinephrine and then exposed by inhalation to vinylidene fluoride at 250,000-500,000 ppm (655-1,310 g/cu m) for 5-15 minutes, at which time the epinephrine injection was repeated. ECG's, lead II, of each animal were recorded. None of the animals developed myocardial sensitization to epinephrine.

(f) Summary

The results of these studies show that each of the vinyl halides is capable of causing CNS effects. Changes in liver function and structure were also observed in some experiments. The adverse effects noted after exposure were similar to those noted in worker populations exposed to the vinyl halides.

Teratogenicity and Effects on Reproduction

Only two experiments with animals have been located in which the teratogenic, embryotoxic, and fetotoxic potentials of the vinyl halides were evaluated.

(a) Vinyl Chloride

John et al [132] evaluated the effects of the inhalation of vinyl chloride on mouse, rat, and rabbit embryonal and fetal development. Female CF-1 mice (25-30 g) were exposed at nominal concentrations of 50 or 500 ppm (128 or 1,280 mg/cu m), and Sprague-Dawley rats (250 g) and New Zealand white rabbits (3.5-4.5 kg) were exposed at nominal concentrations of 500 or 2,500 ppm (6,400 mg/cu m). Actual concentrations were determined by infrared spectrophotometry. Rats (20-35) and mice (30-40) were exposed on days 6-15 of gestation, and rabbits (15-20) were exposed on days 6-18 of gestation. Controls were matched to each exposure group and exposed in a similar manner to filtered room air. The authors examined the exposed dams for resorption sites in their uteri and the litters for the ratio of the sexes, body weights, and other gross features of the fetuses. The authors also examined the fetuses of each species for soft tissue and skeletal anomalies.

Maternal weight gain, food consumption, and final liver weights were decreased in mice exposed at 500 ppm (1,280 mg/cu m), but these effects were not observed at 50 ppm (128 mg/cu m) [132]. Ethanol (15%) in drinking water was also given to mice, rats, and rabbits exposed at 50 and 500 ppm, at 2,500 ppm (6,400 mg/cu m), and at 2,500 ppm, respectively. The authors stated that

ethanol altered the metabolism of vinyl chloride by blocking the primary and most rapid metabolic pathway. Ethanol with vinyl chloride at concentrations of 50 or 500 ppm decreased food consumption, weight gain, and liver weight in mice. In animals exposed to vinyl chloride at 50 and 500 ppm with 15% ethanol, weight gain and liver weight were lower than in those exposed to vinyl chloride alone. In rats exposed at 500 ppm, there was a significant decrease ($P<0.05$) in maternal weight gain during days 6-21 of gestation. At 2,500 ppm, the liver weight of the rats was increased significantly ($P<0.05$) at day 21 of gestation. There was also a significant difference in food consumption but no difference between exposed and control animals in weight gain. Rabbits showed a significantly decreased ($P<0.05$) food consumption rate at 500 ppm, but no effects were noted at 2,500 ppm. Giving ethanol in addition to exposure to vinyl chloride at 2,500 ppm significantly increased the effects on rabbits and rats. Maternal mortality in mice exposed at 500 ppm was significantly increased ($P<0.05$) over concurrent control mortality. Also, there was an increase ($P<0.05$) in the incidence of resorptions, a decrease ($P<0.05$) in fetal body weight, and a reduction ($P<0.05$) in litter size. No significant effects other than an increase in crown-rump length ($P<0.05$) were seen at 50 ppm. Fetuses from mice exposed to vinyl chloride at 500 ppm differed significantly ($P<0.05$) from concurrent control fetuses in incidences of unfused sternebrae, delays in ossification of the sternebrae, and delays in ossification of bones of the skull. The addition of 15% ethanol to the drinking water of the dams significantly increased ($P<0.05$) the incidence of skeletal anomalies in the fetuses of these mice, including anomalies in the sternebrae, vertebrae, and skull at 50 and 500 ppm, and in the ribs as well at 500 ppm.

There was only one maternal death in rats exposed to vinyl chloride at 2,500 ppm (6,400 mg/cu m) [132]. The only significant ($P<0.05$) fetal effects observed after exposure at 500 ppm (1,280 mg/cu m) were a reduction of the body weights, an increase in crown-rump length, and a significant increase ($P<0.05$) in the number of lumbar spurs. Examination of the fetuses for soft tissue anomalies showed a significant increase ($P<.05$) in the incidence of dilated ureters at 2,500 ppm. Skeletal anomalies at 2,500 ppm included significant decreases ($P<0.05$) in the incidence of unfused sternebrae and delayed skull ossifications.

One of the seven rabbits exposed to vinyl chloride at 2,500 ppm died during the experiment [132]. A significant decrease ($P<0.05$) was seen in the number of live fetuses/litter at 500 ppm, but not at 2,500 ppm. No other gross differences were observed. The incidence of delayed ossification of the fifth sternebra was significantly increased ($P<0.05$) at 500 ppm. No other skeletal or soft tissue anomalies were seen in rabbits.

John et al [132] concluded that exposure to vinyl chloride at concentrations causing some maternal toxicity did not cause teratogenic effects on or embryonal or fetal toxicity in mice, rats, or rabbits. However, it is apparent that adverse effects did occur on the fetuses of the mice exposed at 500 ppm (1,280 mg/cu m) (sternebrae and skull anomalies) and in the

fetuses of rats exposed at 2,500 ppm (6,400 mg/cu m) (dilated ureters). The authors' determination that these effects did not substantiate an embryotoxic or fetotoxic potential and were secondary to the maternal toxicity were not supported by clinical tests. The authors regarded the changes as minor skeletal and soft tissue variations and concluded that the incidence of "major" skeletal or soft tissue malformations was not significantly greater in exposed animals than in the control groups. In mice exposed at 500 ppm, there were significant increases in the incidence of resorptions and decreases in the fetal body weight and in litter size. In rats exposed at 500 ppm, there was a significant decrease in the fetal body weight and an increase in crown-rump length, and, in rabbits exposed at 500 ppm, there was a significant decrease in the number of live fetuses/litter. In both rats and rabbits, however, there was not a corresponding adverse effect at the 2,500-ppm exposure concentration. Ethanol at 15% in the drinking water enhanced the effects of inhaled vinyl chloride, but the authors concluded that maternal toxicity was more enhanced than was fetotoxicity.

(b) Vinylidene Chloride

In 1977, Murray [133] reported the preliminary results of a study of the effects of inhalation of vinylidene chloride on Sprague-Dawley rats and New Zealand white rabbits. Groups of 40, 28, and 26 pregnant rats were exposed for 7 hours/day to vinylidene chloride at 20, 80, and 160 ppm (79.4, 317.6, and 635.2 mg/cu m), respectively, during days 6-15 of gestation. Eighteen and 15 rabbits were exposed to vinylidene chloride for 7 hours/day at 80 and 160 ppm during days 6-18 of pregnancy. Controls for both species were exposed to filtered chamber air only. The animals were observed for changes in appearance and "demeanor," body weight gain, and food and water consumption. Fetuses were removed by cesarean section, the litters were counted, and the ratio of resorptions to implants, the sex ratio in the litters, and the body weights, crown-rump lengths, external abnormalities, and soft tissue and skeletal alterations of the offspring were noted. The skeletal examinations were performed on the skulls, vertebrae, and ribs.

After exposure at 80 or 160 ppm (317.6 or 635.2 mg/cu m), the rats showed a decrease in their food consumption and body weight gain ($P<0.05$) but an increase in their water consumption ($P<0.05$) [133]. The only change noted in rats exposed at 20 ppm was an increase in water consumption ($P<0.05$). The appearance and demeanor, body weight gain, and food consumption of the exposed animals were comparable with those of controls. Fetuses of rats exposed at 80 or 160 ppm had significantly increased numbers of skeletal abnormalities, but these were not seen in fetuses of rats exposed at 20 ppm (79.4 mg/cu m) Skeletal examinations showed significant increases ($P<0.05$) in the incidences of delayed ossification of the parietal bone, "wavy" ribs, and lumbar spurs in the 292 rats exposed to vinylidene chloride at 80 ppm. Exposures at 160 ppm caused significant increases ($P<0.05$) in delayed ossification of skull bones and cervical vertebrae and "wavy" ribs. No adverse effects were seen on rats exposed at 20 ppm.

For the rabbits exposed to vinylidene chloride at 80 and 160 ppm (317.6 and 635.2 mg/cu m), only those exposed at 160 ppm showed significant decreases ($P<0.05$) in body weight gain [133]. In addition, exposure at 160 ppm produced a significant increase ($P<0.05$) in the ratio of resorptions to implants, from 3% (4/115) in the controls to 31% (41/132) in the exposed rabbits. The author stated that high ratios of resorptions to implants in particular females were correlated with high loss of body weight. No increase in resorptions was noted at 80 ppm. Examination of fetuses from dams exposed at 160 ppm found significant ($P<0.05$) skeletal abnormalities characterized by a decreased incidence of delayed ossification of the fifth sternebrae and by an increased incidence of 13 pairs of ribs. The investigators concluded that only minor and "questionable" adverse effects resulted from exposure of rats and rabbits to vinylidene chloride at concentrations above 20 ppm. They suggested that 20 ppm should be considered as a no-adverse-effect concentration. They further noted that vinylidene chloride was embryotoxic by inhalation in both species, but that the embryotoxic effects were associated with exposure concentrations that were toxic to the mothers.

In another experiment, the investigators [133] gave 26 Sprague-Dawley rats access to vinylidene chloride at a concentration of 200 ppm (0.8 mg/liter) in drinking water during days 6-15 of pregnancy. Twenty-four control rats were given access to water alone. Similar observations to those noted in the inhalation exposures were reported. The only significant difference ($P<0.05$) reported was an increase in the fetal crown-rump length (controls 46.6 ±2.4 mm; exposed 47.8 ±1.3 mm). The authors concluded that vinylidene chloride in the drinking water was not teratogenic in rats and did not cause adverse effects on rat embryos.

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

No reports of studies that examined the teratogenic potential of vinyl bromide, vinyl fluoride, or vinylidene fluoride have been located.

Carcinogenicity

Angiosarcoma of the liver has been shown to be a characteristic tumor in workers exposed to vinyl chloride. Other cancers, of the lungs and brain, have also been linked to vinyl chloride exposure, but these latter types are more common than the former and may have been induced by a variety of other factors. Laboratory animals exposed to the vinyl halides have also shown a wide variety of tumors, especially angiosarcoma of the liver.

(a) Vinyl Chloride

In 1971, Viola et al [112] investigated tumor formation in rats exposed to vinyl chloride by inhalation. Twenty-five 3-month-old male albino Wistar rats were exposed to vinyl chloride at a concentration of 30,000 ppm (76.8 g/cu m)

for 4 hours/day, 5 days/week, for 1 year; 25 similar rats served as controls. Rats were killed at unspecified intervals, and their tissues were examined microscopically. These exposed animals were apparently the same ones used in the study by Viola [111] that was discussed in Animal Toxicity.

Skin tumors, the most frequent types, were found in 65-70% of the animals after 10 months of exposure [112]. These tumors developed in the paraauricular region, and most were epidermoid carcinomas. The authors also found two mucoepidermoid carcinomas and one papilloma of the skin. In addition to the tumors, they found warty subauricular growths and papillary epithelial proliferation with progressive increases in the thickness of the epidermis in a few rats. In four rats, adenocarcinomas of the respiratory tract were found, and in one rat an epidermoid tumor was found. The authors also found osteochondromas in the metacarpal and metatarsal regions of all four limbs in five rats. None of the control rats developed any of the types of tumors observed in the exposed animals.

In addition to the carcinomas, Viola et al [112] observed the same range of nontumorigenic adverse effects that Viola had reported previously [111]. They [112] concluded that the tumorigenic potential of vinyl chloride was greatest for the "cutaneous system." They also suggested that the mucoepidermoid carcinomas could have been caused by ingestion of vinyl chloride from the fur during cleansing, with subsequent concentration of it in the salivary glands. The authors did not analyze their data statistically, and they did not present them in terms of adverse changes/animal. Either of these formats would have allowed a more accurate hazard assessment than is possible from the data as presented by the authors.

In 1974, Caputo et al [134] extended the previous studies of Viola [111] and Viola et al [112] by exposing 3-month-old Wistar rats of both sexes for 4 hours/day, 5 days/week, for 12 months to vinyl chloride at concentrations of 20,000, 10,000, 5,000, 2,000, 500, or 50 ppm [134]. A minimum of 150 animals was exposed at each concentration.

At 50 ppm (128 mg/cu m), no tumors were observed among 200 exposed animals [134]. At 500 ppm (1,280 mg/cu m) and above, a significantly greater ($P<0.03$) percentage of tumors was seen in the exposed animals than was seen in a group of control animals. Tumors most frequently observed included squamous cell carcinoma of the skin, angiosarcoma of the liver and adenocarcinoma of the lung. The authors stated that rabbits exposed to vinyl chloride at concentrations of 10,000 ppm (25.6 g/cu m) also had significantly increased incidences ($P<0.02$) of acanthoma of the skin and adenocarcinoma of the lung appearing during the 9th through the 15th months of exposure. No further information concerning this experiment was reported.

The authors [134] concluded that these results clearly confirmed the carcinogenicity of vinyl chloride and that almost all tissues and organs were sensitive to it. Angiosarcoma of the liver appeared in 4/150 animals (3%) exposed at 500 ppm, 10/200 (5%) at 2,000 ppm (5,120 mg/cu m), 12/200 (6%) at

5,000 ppm (12.8 g/cu m), 16/200 (8%) at 10,000 ppm (25.6 mg/cu m), and 18/150 (12%) at 20,000 ppm (51.2 g/cu m). The prevalences of other tumors showed similar increases with increasing concentrations of vinyl chloride, indicating dose-related responses.

In 1976, Maltoni [135] reported interim and final results of a series of 17 experiments designed to evaluate the carcinogenic properties of vinyl chloride. A detailed plan for the conduct of these experiments [136] and preliminary results [137-139] had previously been published by Maltoni and coworkers. The experiments included inhalation exposure of Sprague-Dawley and Wistar rats, Swiss mice, and golden hamsters to vinyl chloride at concentrations of up to 30,000 ppm (76.8 g/cu m) for 4 hours/day, 5 day/week, for 30-52 weeks. Observation periods in some cases were as short as 46 weeks, because the experiments had not yet been concluded. Other experiments with Sprague-Dawley rats included inhalation exposures at concentrations of 6,000 or 10,000 ppm (15.4 or 25.6 g/cu m) for a total of 100 hours on various schedules; inhalation exposures of pregnant rats at 6,000 or 10,000 ppm for 4 hours/day during days 12-18 of gestation and subsequent examination of the fetuses; and oral administration of vinyl chloride in olive oil at doses of 0.03-50 mg/kg.

The most common malignant tumors seen in Sprague-Dawley rats were Zymbal gland carcinoma (26%), angiosarcoma of the liver (22%), and nephroblastoma (9%), as indicated in Table III-2 [135]. It should be noted that most other species do not have Zymbal glands. With increasing exposure, the percentage of animals with tumors generally increased and the average latent period generally decreased. Angiosarcoma of the liver developed in 1 of 59 rats exposed at 50 ppm (128 mg/cu m) for 52 weeks, with a mean latency of 135 weeks, and in 18 of 60 rats (30%) exposed at 30,000 ppm (76.8 g/cu m) for 52 weeks, with an average latency of 53 weeks. None of the 480 animals exposed at concentrations below 50 ppm had been observed for longer than 46 weeks at the time of publication, and no tumors were seen in them. Preliminary information [139] on tumor formation in the Wistar rats (Table III-3) indicated that these animals might have been less susceptible to vinyl chloride than the Sprague-Dawley rats; however, with the data presented, it was not possible to determine this likelihood mathematically.

Decreased latency with increasing exposure was also observed in the Swiss mice (Table III-4); latency ranged from 51 weeks for lung tumors in animals exposed for 30 weeks at 50 ppm (128 mg/cu m) to 36 weeks for animals exposed at 10,000 ppm (25.6 g/cu m) for the same period [135]. However, the percentage of animals with each tumor reached a maximum concentrations that were different for each tumor. The majority of the tumors in mice were adenomas of the lungs (45%). Angiosarcoma of the liver accounted for 12% of the tumors observed in these animals. The golden hamsters (Table III-5) did not show a dose-related response for tumor induction, and the latent periods seen in this species were not reported.

TABLE III-2

TUMORS OBSERVED IN SPRAGUE-DAWLEY RATS
EXPOSED TO VINYL CHLORIDE BY INHALATION*

Concentration (ppm)	No. Animals Exposed**	Animals with Tumors										
		Zymbal Gland Carcinomas			Nephroblastomas			Liver Angiosarcomas			All Tumors***	
		No.	%	Latency (wk)	No.	%	Latency (wk)	No.	%	Latency (wk)	No.	%
30,000	60	35	58	43	0	0	-	18	30	53	51	85
10,000	61	16	26	50	5	8	59	9	15	64	38	62
6,000	60	7	12	62	4	7	65	13	22	70	31	52
2,500	59	2	3	33	6	10	74	13	22	78	32	54
500	59	4	7	79	4	7	83	7	12	81	22	37
250	59	0	0	-	6	10	80	4	7	79	16	27
50	59	0	0	0	1	2	135	1	2	135	10	17
Controls	58	0	0	-	0	0	-	0	0	-	6	10

*Results after 135 wk in animals exposed 4 hrs/d, 5 d/wk, for 52 wk
**Number of animals surviving at 24 wk, when first tumor was observed
***Includes angiosarcomas of other sites, angiomas, fibroangiomas, fibroadenomas, adenomas, carcinomas, papillomas, hepatomas, neuroblastomas, neurilemmomas, ependymomas, rhabdomyosarcomas, lymphomas; several animals had two or more tumors

Adapted from Maltoni [135]

TABLE III-3

TUMORS OBSERVED IN WISTAR RATS
EXPOSED TO VINYL CHLORIDE BY INHALATION*

Concentration (ppm)	No. Animals Exposed	No. Animals with Tumors**			
		Zymbal Gland Carcinomas	Nephro-blastomas	Liver Angiosarcomas	All Tumors***
10,000	30	1 (10/69)	1 (3/69)	8 (4/69)	11 (20/69)
6,000	30	0 (3/72)	3 (3/72)	2 (3/72)	8 (13/72)
2,500	30	0 (1/74)	0 (4/74)	3 (5/74)	4 (14/74)
500	30	0 (2/67)	0 (2/67)	3 (0/67)	4 (5/67)
250	30	0 (0/67)	0 (1/67)	1 (1/67)	3 (1/67)
50	30	0 (0/64)	0 (0/64)	0 (0/64)	1 (1/64)
Controls	40	0 (0/68)	0 (0/68)	0 (0/68)	2 (0/68)

*Results after 95 wk in animals exposed 4 hr/d, 5 d/wk, for 52 wk
**Numbers in parentheses indicate proportion of Sprague-Dawley rats at the same exposures with tumors after 95 wk
***Includes angiosarcomas of other sites, adenomas, hepatomas, mesotheliomas, fibroangiomas, carcinomas, lymphomas, pericytosarcomas; several animals had two or more tumors

Adapted from Maltoni [139]

TABLE III-4

TUMORS OBSERVED IN SWISS MICE
EXPOSED TO VINYL CHLORIDE BY INHALATION*

Concentration (ppm)	No. Animals Exposed**	Animals with Tumors									
		Lung Tumors			Mammary Carcinomas			Liver Angiosarcomas		All Tumors***	
		No.	%	Latency (wk)	No.	%	Latency (wk)	No.	%	No.	%
10,000	50	35	70	36	13	47	31	8	16	36	72
6,000	54	38	70	38	8	28	33	5	9	39	72
2,500	53	30	57	43	9	30	35	11	21	31	58
500	58	38	66	41	7	24	37	11	19	43	74
250	58	33	57	45	11	32	39	11	19	40	69
50	57	2	4	51	12	33	43	1	2	18	32
Controls	141	8	6	44	0	0	-	0	0	13	9

*Results after 81 wk in animals exposed 4 hr/d, 5 d/wk, for 30 wk
**Number of animals surviving at 16 wk, when first tumor was observed
***Includes angiosarcomas of other sites, angiomas, fibroangiomas, adenomas, carcinomas, papillomas, acanthomas, adenocarcinomas, basaliomas, leiomyosarcomas, lymphomas; several animals had two or more tumors

Adapted from Maltoni [135]

TABLE III-5

TUMORS OBSERVED IN GOLDEN HAMSTERS
EXPOSED TO VINYL CHLORIDE BY INHALATION*

Concentration (ppm)	No. Animals Exposed	No. Animals with Tumors			
		Liver Angiosarcomas	Skin Tricho-epitheliomas and Basaliomas	Forestomach Epithelial Tumors	All Tumors**
10,000	35	0	6	4	4
6,000	32	1	2	7	10
2,500	33	0	1	10	12
500	33	2	3	7	12
250	32	0	3	2	6
50	33	0	6	4	10
Controls	70	0	2	0	5

*Results after 105 wk in animals exposed 4 hr/d, 5 d/wk, for 30 wk
**Includes angiomas, fibroangiomas, adenocarcinomas, melanomas, lymphomas, hepatomas; several animals had two or more tumors

Adapted from Maltoni [135]

The Sprague-Dawley rats exposed at 6,000 or 10,000 ppm (15.4 or 25.6 g/cu m) had been followed for only 59 weeks at the time of this report [135]. Zymbal gland carcinoma was observed in some exposed animals, but no nephroblastoma or angiosarcoma of the liver was found. The preliminary results shown in Table III-6 suggest that exposure at 6,000 ppm for 100 hours during 25 weeks has a lower carcinogenic potential than exposure at 10,000 ppm on the same schedule or at 6,000 ppm for 100 hours during 5 weeks. These findings indicate that the severity of exposure was more important than the total mass to which the rats were exposed and suggest that metabolic and excretory processes may affect the carcinogenic potential; however, more complete data are needed to substantiate this inference.

The offspring of pregnant rats exposed to vinyl chloride at concentrations of 6,000 or 10,000 ppm (15.4 and 25.6 g/cu m) for 4 hours/day from the 12th to the 18th day of gestation developed tumors [135]. In 54 offspring from dams exposed at 10,000 ppm, the following tumors developed: 3 Zymbal gland carcinomas, 1 nephroblastoma, 1 subcutaneous angiosarcoma, 1 angiosarcoma of the leg, 1 Zymbal gland fibrosarcoma, and 1 ovarian leiomyosarcoma. In the 32 offspring from dams exposed at 6,000 ppm, 1 Zymbal gland carcinoma, 1 subcutaneous angiosarcoma, 1 intraabdominal angiosarcoma, 1 Zymbal gland adenoma, 1 skin carcinoma, 1 subcutaneous fibrosarcoma, and 1 mammary carcinoma were observed following a 143-week observation period. Unfortunately, details of this experiment, including reproduction indices and signs of toxicity to the dams, were not reported. The author's suggestion that the results of this experiment indicate that vinyl chloride has a transplacental effect is reasonable, but it cannot be thoroughly evaluated without more detailed information than was presented.

The experiments outlined by Maltoni and coworkers [135-139] were well designed. The presentation of data in these papers, however, was often confusing, and the information contained in the tables frequently disagreed with that presented in the text. It was often unclear whether they were presenting the number of animals with tumors or simply the number of tumors. Furthermore, preliminary data on tumors when the followup period was less than the probable latent period are of little value. Maltoni's observations and data do show that vinyl chloride induces various tumors in a variety of rodents, and that angiosarcoma of the liver is a characteristic lesion induced by vinyl chloride. The data also indicate that there are strain and species differences in the magnitude of the tumorigenic response elicited by exposure to vinyl chloride.

Lee et al in 1977 [140] and in 1978 [141] reported results of inhalation studies on 2-month-old albino CD-1 mice and CD rats exposed to vinyl chloride (99.8% pure, Matheson Gas Products) at 50, 250, or 1,000 ppm (128, 640, or 2,560 mg/cu m). Groups of 36 females and 36 males of each species were exposed for 6 hours/day, 5 days/week, for 12 months. Two similar control groups were exposed to uncontaminated air. Throughout the exposure period, the animals were observed for changes in weight gain, food consumption, and

TABLE III-6

TUMORS OBSERVED IN SPRAGUE-DAWLEY RATS EXPOSED TO VINYL CHLORIDE BY INHALATION FOR 100 HOURS ON VARIOUS SCHEDULES*

Concentration (ppm)	Exposure Schedule	No. Animals Exposed	No. Animals with Tumors		
			Zymbal Gland Carcinomas	Liver Angiosarcomas	All Tumors**
10,000	4 hr/d, 5 d/wk x 5 wk	120	4	0	4
10,000	1 hr/d, 4 d/wk x 25 wk	120	4	0	4
10,000	4 hr/d, 1 d/wk x 25 wk	120	2	0	3
6,000	4 hr/d, 5 d/wk x 5 wk	120	3	0	4
6,000	1 hr/d, 4 d/wk x 25 wk	120	0	0	1
6,000	4 hr/d, 1 d/wk x 25 wk	120	0	0	1
Controls	-	249	0	0	0

*Results after 59 wk
**Includes 1 angiosarcoma, 1 angiopericitosarcoma, 2 lymphomas

Adapted from Maltoni [135]

mortality. Four animals of each species and sex exposed at each concentration were killed at the end of exposure months 1, 2, 3, 6, and 9. Their organs were examined grossly, and tissues were fixed and examined microscopically. Additional laboratory determinations, including hematologic and blood chemistry examinations, cytogenetic analyses of bone marrow cultures, pulmonary macrophage counts, DNA synthesis assays, and urinary analyses were performed at the interim examinations and at the termination of the experiment at 12 months. Roentgenograms of the limbs of those animals exposed for the longest periods were made also.

Of the mice exposed at 1,000 ppm (2,560 mg/cu m), two males and one female died between the 3rd and 9th days of exposure [140]. Between the 6th and 9th months, 13 male and 21 female mice died or were removed from exposure because their health had deteriorated. By the end of the 9th month, all animals had been removed from exposure.

By the 6th month, the most evident effects on exposed mice were rough hair coat, lethargy, loss of appetite, and rapid weight loss [140]. Additionally, abdominal distention and external tumor masses, such as mammary tumors in females, were noticeable between the 7th and 9th months. During the first 8 months of the experiment, exposed and nonexposed mice showed comparable weight gains; however, the exposed group showed a decline in weight by the 9th month. Also, by the 9th month of exposure, one female and most of the male mice had elevated pulmonary macrophage counts (from pulmonary washings) and had developed bronchioloalveolar adenomas.

Microscopic examination of hepatic and renal tissues from one female and two male mice that died after being exposed at 1,000 ppm for 3-9 days revealed a number of lesions characterized by acute toxic hepatitis, focal to marked congestion, diffuse coagulation necrosis of hepatocytes in the centrilobular area, and tubular necrosis in the renal cortex [140]. During the 8th and 9th months of exposure, mitotic figures were observed in mouse livers, but were not seen in livers of mice killed at other times.

Bronchioloalveolar adenomas were observed in 48 of the 72 mice exposed at 1,000 ppm, whereas only 1 of the 72 control mice developed this tumor [140]. These tumors were first noted during the 2nd month of exposure to vinyl chloride and in the 9th month in the control. Mammary tumors, first observed in exposed female mice during the 6th and 7th months, included adenocarcinoma and carcinoma of squamous cells and of anaplastic cells; metastasis was prevalent to the lungs and pleurae. None of the control mice developed mammary tumors. Angiosarcoma of the liver was found in 31 exposed mice, being observed first during the 6th month of exposure. In addition, angiosarcoma was occasionally seen in the mammary glands, heart, gastrointestinal tract, pancreas, kidneys, epididymis, testis, mesenteric lymph nodes, and skeletal muscles. Angiosarcoma of the liver was more prevalent in females than in males. Two male and three female mice developed malignant lymphoma between the 6th and 9th months of exposure, whereas none were seen in controls.

All female mice exposed to vinyl chloride at 250 ppm (640 mg/cu m) died or had to be removed from exposure by the 9th month because of morbidity [140]. Male mice were more resistant to the toxic actions of vinyl chloride than female mice, and some survived the 12-month exposures. No differences in body weight between the exposed and control mice were noted. One female mouse examined after the 9th month of exposure showed an increased pulmonary macrophage count. Bronchioloalveolar adenomas were first detected in exposed mice during the 2nd month; a total of 48, 22, and 12 mice exposed at 1,000, 250, or 50 ppm, respectively, developed this tumor. Only one control male mouse developed bronchioalveolar adenoma during the 9th month. Female mice also developed mammary tumors consisting of adenocarcinomas and squamous and anaplastic cell carcinomas. Of the mice exposed at 250 ppm, 23 (16 females) developed liver angiosarcomas, which were first evident after the 6th month of exposure. During the 9th month of exposure, malignant lymphomas developed in two female mice.

Between the 6th and 12th months of exposure to vinyl chloride at 50 ppm (128 mg/cu m), 6 male and 14 female mice either died or were removed from exposure because of deteriorating health [140]. Throughout the exposure period, the body weights of exposed mice were comparable with those of control mice. Microscopic examination also showed mitotic figures in the liver during the 8th and 9th months of exposure. A significant increase in DNA synthesis, as measured by incorporation of 14C-thymidine, was detected in the livers of male mice exposed at 50 ppm for 11 months. There was no increase in the number of mitotic figures in the livers of these mice. During the 12th month of exposure, one of two surviving male mice had an elevated pulmonary macrophage count.

Bronchioloalveolar adenomas were seen in 12 mice exposed at 50 ppm (128 mg/cu m) [140]. Three male mice developed angiosarcoma of the liver. Mammary tumors were observed in nine of the exposed mice, the first at 7 months. One female mouse developed a malignant lymphoma during the 6th month and another developed a hemangioma in the mediastinum. Control mice developed none of the tumors discussed.

From the effects observed in mice exposed to vinyl chloride at 1,000, 250, and 50 ppm (2,560, 640, and 128 mg/cu m), the authors [140] concluded that weight loss, mortality, and tumor incidence were dependent on the concentration of vinyl chloride and the duration of exposure. Vinyl chloride inhaled at 50-1,000 ppm for 6 hours/day, 5 days/week, was found to be highly carcinogenic in mice. The duration of exposure before tumors were observed varied from 2 months for bronchioloalveolar adenomas to 6 months for mammary gland tumors and for angiosarcoma. The latter tumors occurred first in the liver and then in other organs. Angiosarcoma was more prevalent in female mice than in male mice exposed at 250 or 1,000 ppm. It was found mostly in the livers of mice exposed to vinyl chloride for 7-9 months. Mammary gland tumors were considered to be a complex type and were characterized by anaplastic and squamous cell metaplasia during the early stages of their development. Metastasis of anaplastic and squamous cell carcinomas to the

lungs was common. Bronchioalveolar adenomas occurred in both male and female mice at a very young age and after a short period of exposure. More deaths and tumors were observed at 250 and 1,000 ppm than at 50 ppm. Other types of tumors observed in the exposed mice were hepatic cell carcinomas, renal adenomas, and keratoacanthomas of the skin.

In the second part of the experiment, Lee et al [140] exposed 72 adult male and female rats to vinyl chloride at concentrations of 50, 250, or 1,000 ppm (128, 640, or 2,560 mg/cu m) for up to 12 months, using the same exposure schedule previously reported. During the first 7 months of exposure, no remarkable adverse effects were seen in any rats. However, of the rats exposed at 1,000 ppm, 8 male and 13 female rats either died or were removed from exposure during the 8th-12th months. None of the controls died during the experiment. After the 4th week of exposure, female rats had gained less weight than the controls. During the 9th month, the first cases of angiosarcoma of the liver were observed in four rats. By the end of the study, 22 rats had developed angiosarcoma of the liver, more females than males having the tumors. Of the 22 rats with angiosarcoma of the liver, 13 also developed angiosarcoma of the lungs. Additional angiosarcoma was found in the omentum of one rat, and two rats had hemangiomas in the adrenal glands.

Four male and 10 female rats died or were removed from exposure during months 8-12 of exposure to vinyl chloride at 250 ppm (640 mg/cu m) [140]. None of the control rats died during the exposure period. Body weight gain by exposed rats was comparable with that by the controls. Two rats developed angiosarcoma of the liver during the 9th month of exposure. By the end of the 12th month of exposure, 13 rats, 10 of them females, had developed angiosarcoma of the liver. Of the 10 female rats, 3 also had angiosarcoma of the lungs; angiosarcoma of the omentum or mesentery was also found in two rats. None of the control rats had angiosarcoma.

During months 8-12 of exposure to vinyl chloride at 50 ppm (128 mg/cu m), two female rats died [140]. Exposed and control rats had comparable body weight gain. Subcutaneous angiosarcoma was found in two rats. No angiosarcoma of the liver, lungs, or other organs was observed in any of the rats exposed at 50 ppm, nor did any of the control rats develop angiosarcoma.

None of the laboratory tests performed on rats exposed to vinyl chloride at 1,000, 250, or 50 ppm showed any persistent changes [140]. The authors indicated that female rats were more sensitive to the toxic action of vinyl chloride and that more females than males died between the 8th and 10th months of exposure. In general, rats were considered more resistant to both the carcinogenic and toxic actions of vinyl chloride than mice.

The experiments by Lee et al [140,141] indicate that vinyl chloride is carcinogenic in mice and rats, and that mice are more susceptible to its carcinogenic effects than rats. Since the experiments were conducted at various exposure concentrations, it can be concluded that the different responses probably were a function of species-specific factors and were not

caused by structural differences between the species such as lung surface area. Since there are differences between species, there may be differences between strains within a species also. Such a situation would account for the apparent inconsistencies between the reports of various authors using different strains of the same species. This confounding factor must be considered in any attempt to extrapolate the results from animal experiments to human exposure situations.

Maltoni et al [137], in 1975, gave vinyl chloride by gastric intubation to 13-week-old Sprague-Dawley rats. Groups of 40 male and 40 female rats were given 50.00, 16.65, or 3.33 mg/kg of vinyl chloride dissolved in olive oil 5 times/week for 52 weeks. A fourth group of rats, 40 males and 40 females, was given olive oil without vinyl chloride as the control group. The number of tumors that developed in the rats of each group were recorded.

At 50 weeks, no tumors were apparent in the rats given the lowest dose (3.33 mg/kg), but one of the male rats given 16.65 mg/kg developed angiosarcoma of the liver, which was identified during the 49th week of the experiment, and a female rat given 50 mg/kg had angiosarcoma in the thymus.

In an update of this study [137], Maltoni [135] in 1976 reported that after 84 weeks the rats receiving the 50.00-mg/kg dose had developed eight cases of angiosarcoma of the liver and four other tumors. At 16.65 mg/kg, angiosarcoma of the liver had developed in five rats, a Zymbal gland carcinoma in one, and a nephroblastoma in one. No tumors were observed in animals given 3.33 mg/kg.

(b) Vinylidene Chloride

Lee et al in 1976 [140] and 1978 [141] described the effects of inhaled vinylidene chloride (99% pure, Aldrich Co.) on 36 male and on 36 female 2-month-old albino CD-1 mice and 36 male and 36 female albino CD rats exposed at 55 ppm (218.4 mg/cu m) for 6 hours/day, 5 days/week, for 12 months. Vapor concentrations were monitored by gas-liquid chromatography during the exposures. Control animals were exposed to uncontaminated air. Organs and tissues from rats and mice were examined for microscopic changes at the end of the 1st, 2nd, 3rd, 6th, 9th, and 12th months of exposure.

Two male mice died on the 13th day of exposure and were replaced in the study with healthy males [140]. Microscopic examination showed a number of lesions in the two dead male mice. They were characterized by acute toxic hepatitis, focal to marked congestion, marked diffuse coagulation necrosis of hepatocytes, and marked tubular necrosis in the renal cortex. No additional deaths occurred, nor did any control animals die. Six mice were observed to have small nodules of bronchioalveolar adenoma by the 12th month of exposure; only one control male mouse developed a bronchioalveolar adenoma. The mice removed from exposure after the 9th month (two males) and 10th month (one

female) had developed angiosarcoma in the liver. Neither mammary tumors nor malignant lymphomas were found.

After exposures at 55 ppm (218.4 mg/cu m), fatty changes were seen in the livers of rats [140]. Two rats had also developed extrahepatic angiosarcoma (mesenteric lymph node, subcutaneous) by the end of the exposure period. None of the control rats developed liver tumors of any type.

In 1977, Maltoni et al [142] reported the research plan and preliminary results for a series of experiments with vinylidene chloride. Groups of 60-120 Sprague-Dawley rats were exposed by inhalation to vinylidene chloride at concentrations of 10, 25, 50, 100, or 150 ppm (39.7, 99.3, 198.5, 397, or 595.5 mg/cu m) for 4 hours/day, 4-5 days/week, for 12 months. An increased incidence of mammary tumors was noted in the exposed animals; however, there was no apparent dose-related effect. One Zymbal gland carcinoma was found in an animal exposed at 100 ppm.

Swiss mice were exposed to vinylidene chloride at 10 and 25 ppm (39.7 and 99.3 mg/cu m) on the same schedule [142]. Exposure of these mice at concentrations of 50 ppm or higher produced an unacceptably high mortality in the study population within 4 days. Adenocarcinoma of the kidneys was observed in two groups exposed at 25 ppm with an incidence of 8% and 4%. None of these tumors were observed in animals exposed at 10 ppm or in control animals.

Sprague-Dawley rats were given vinylidene chloride in olive oil by gavage at dose rates of 0.5, 5, 10, and 20 mg/kg/day, 4-5 days/week for 52 weeks [142]. No increase in mammary tumors was observed; one rat developed a Zymbal gland carcinoma at the 10-mg/kg dose.

Although Lee et al [140,141] had reported that their mice were exposed at 55 ppm of vinylidene chloride, Maltoni et al [142] found that exposure of his mice at concentrations of 50 ppm or more produced unacceptable mortalities within 4 days. Maltoni's mice exposed at 25 ppm of vinylidene chloride for 12 months did not develop angiosarcoma of the liver, whereas Lee et al stated that 3 of 72 mice exposed at 55 ppm for 12 months did develop this tumor. The discrepancies in the results of these studies may be caused by differences in the strains of animals used, and has been discussed previously. Maltoni et al [142] stated that neither inhalation exposures nor ingestion experiments with rats demonstrated a specific carcinogenic effect from vinylidene chloride such as had been demonstrated for vinyl chloride (Zymbal gland carcinoma and angiosarcoma of the liver). It should be remembered that these data are preliminary for rats, and that a longer followup period may reveal that these tumor types will be formed. The authors also stated that mice were susceptible to a specific carcinogenic effect, adenocarcinoma of the kidney, and that this species difference probably resulted from a more "favorable metabolic condition for expressing the oncogenic potentiality." The authors pointed out that further research using different species was necessary to evaluate this hypothesis.

(c) Vinyl Bromide

In 1977, BL Van Duuren, in a written communication to NIOSH, reported unpublished results of bioassays with vinyl bromide. Thirty female ICR/Ha Swiss mice were injected subcutaneously (sc) with 25 mg of vinyl bromide in 0.05 ml of trioctanoin once a week for 420 days, and none of the mice developed tumors at the site of injection.

Van Duuren also tested the effect of vinyl bromide on mouse skin. Thirty female ICR/Ha Swiss mice had vinyl bromide in acetone (15.0 mg/0.1 ml) applied to their skin three times/week for 420 days. Control mice received no exposures. After 412 days of applications of vinyl bromide, one mouse developed a papilloma and another developed a subcutaneous fibrosarcoma. None of the control mice developed skin tumors. These data indicate that vinyl bromide is not carcinogenic by these routes of exposure.

Dorato et al [143], in 1978, submitted to NIOSH the 1-year interim results of a 2-year study on the inhalation toxicity of vinyl bromide. Rats were exposed to vinyl bromide at nominal concentrations of 1,250, 250, 50, and 10 ppm (5,475, 2,095, 219, and 43.8 mg/cu m) for 6 hours/day, 5 days/week. Hematologic values did not show dose-related effects that were attributed by the authors to the vinyl bromide exposure, and the only clinical chemistry abnormalities considered significant were elevations in serum LDH and bromide in the rats exposed at 1,250 ppm. These rats also showed decreases in body weight beginning at week 16 for the females and week 45 for the males.

Increased liver weights were noted in the rats exposed to vinyl bromide at 250 and 1,250 ppm, and increased spleen weights were noted in rats exposed at 50, 250, and 1,250 ppm [143]. Angiosarcoma of the liver seen in 9/48 rats exposed at 1,250 ppm and in 2/30 exposed at 250 ppm. Zymbal gland carcinoma was observed in 8/47 exposed at 1,250 ppm and in 2/30 exposed at 250 ppm. Lung, mammary, and brain tumors were also observed in these animals. Metastatic angiosarcoma was present in the lungs of four animals. The authors concluded that vinyl bromide after exposure for up to 52 weeks at 250 and 1,250 ppm had a carcinogenic effect on rats.

A comparison of the frequencies of angiosarcomas at these exposure concentrations in this experiment [143] with the frequencies of angiosarcoma observed in rats exposed to vinyl chloride after a similar followup period [139] suggests that vinyl bromide may be more effective in inducing this tumor than vinyl chloride. Further comparison with the vinyl chloride data indicates that after a longer observation period, angiosarcoma will be seen in those rats exposed to vinyl bromide at lower concentrations.

(d) Vinyl Fluoride and Vinylidene Fluoride

No reports examining the carcinogenic potential of vinyl fluoride or vinylidene fluoride have been located.

Mutagenicity

Each of the vinyl halides has been shown to be mutagenic in one or another test system. The mutagenic activity of these compounds increases with metabolic activation by mammalian microsomal systems, showing that metabolites as well as the parent compounds have mutagenic potential.

(a) Vinyl Chloride

Because the reported carcinogenic action of vinyl chloride in workers attracted considerable attention, several investigators became interested in evaluating its mutagenicity and that of its known or presumed metabolites. Ames et al [144] showed that many known carcinogens activated by mammalian liver enzymes produced back mutations in auxotrophs of the bacterium Salmonella typhimurium. Studies of the genetic activities of vinyl chloride and some of its metabolites have been performed in several bacterial species, yeasts, Neurospora, Drosophila, mammalian cell cultures, and mice.

In 1974, Rannug et al [145] used the system described by Ames and his coworkers [144] to investigate the mutagenicity of vinyl chloride. Four histidine-requiring strains of Salmonella typhimurium were exposed to vinyl chloride under various experimental conditions and then cultured on histidine-deficient media to determine the frequency of back mutations to histidine independence. Strain TA1535 reverts to histidine independence by a base-pair substitution, while in the other strains used, TA1536, TA1537, and TA1538, reversion results from addition or deletion of a base pair (frameshift mutation). In addition to their inability to synthesize histidine, these test strains include a mutation that increases the permeability of the cell and another that decreases the repair of damaged DNA; these deletions enhance the sensitivity of the bacteria to certain mutagenic agents.

Because bacteria may not duplicate mammalian metabolic processes in activating potentially mutagenic substances, the substances under test were incubated with a 9,000 x gravity (G) microsomal extract from the livers of Sprague-Dawley rats [145]. For some experiments, a microsomal system was produced by mixing the microsomal supernatant with a dihydronicotinamide adenine dinucleotide phosphate (NADPH) generating system.

In preliminary tests with strain TA1535, Rannug and coworkers [145] bubbled vinyl chloride gas through either water or a suspension containing the microsomal system, or they exposed the bacteria for 75 minutes to an atmosphere containing 11% (281.6 g/cu m) vinyl chloride. The vinyl chloride was analyzed by gas chromatography and mass spectroscopy and was reported to be of "very high" purity, containing only trace amounts of isopropanol. In a subsequent experiment, strain TA1535 was exposed to an atmosphere of 20% vinyl chloride with the microsomal system or with the microsomal supernatant with no NADPH-generating system, and to vinyl chloride alone, for intervals of 30, 60, or 90 minutes. Controls were incubated with the microsomal system without vinyl chloride. Finally, all four strains were exposed for 90 minutes under

similar conditions. To evaluate the lethality of the vinyl chloride preparations, identically treated bacteria were cultured on a medium containing histidine, and the number of surviving cells was determined. To evaluate the comparative mutagenicity of the vinyl chloride preparations, histidine-independent mutant colonies were counted on five plates of minimal media for each test, and the number of mutants/100 million surviving cells was compared to the spontaneous mutation rate using the Student's t-test.

In the initial tests, Rannug et al [145] found that vinyl chloride dissolved in water or directly in the microsomal suspension had no effect on the rate of back mutation to histidine independence in strain TA1535. However, exposure to an atmosphere of 11% vinyl chloride gas for 75 minutes resulted in 17.6 ±2.6 (SE) mutants/100 million surviving cells, compared with 5.3 ±0.2 in controls, significant at the 1% level ($P<0.01$). A mutation rate two to three times that of controls was observed in strain TA1535 exposed to 20% vinyl chloride in the presence of a microsomal system for intervals of 30 minutes ($P<0.01$) and 60 or 90 minutes ($P<0.001$). Bacteria exposed to vinyl chloride without the microsomal system showed no increase in mutagenic response. Exposure of strain TA1535 to vinyl chloride and the microsomal supernatant in the absence of the NADPH-generating system also caused no significant change in the mutation rate. In the final experiment, involving all four test strains, only TA1535 showed a mutagenic response to vinyl chloride. At the concentrations tested, vinyl chloride with the microsomal system did not affect bacterial survival on a complete medium, although vinyl chloride alone reduced the survival rate slightly.

Rannug et al [145] concluded that vinyl chloride was mutagenic in Salmonella only after metabolic activation by mammalian microsomal enzymes. They suggested that the most plausible primary metabolite from vinyl chloride would be chloroethylene oxide, which could be formed in the NADPH-dependent oxidation by microsomal enzymes. Since only strain TA1535 was affected, the mutagenically active metabolites of vinyl chloride appeared to be capable of causing base-pair substitutions but not frameshift mutations. The ineffectiveness of water solutions in inducing mutations was attributed to the low solubility and high volatility of vinyl chloride.

In 1975, Bartsch et al [146] reported tests of vinyl chloride on Salmonella, in which they evaluated the mutagenic response as a function of dose and exposure duration and compared the effectiveness of several mammalian tissue fractions in manifesting the mutagenic potential of vinyl chloride. The Salmonella typhimurium strains used in this series of experiments were TA1535, TA1530, and G-46, which are reverted to histidine-independence by base-pair substitutions, and TA1538, which is reverted by a frameshift mutation. Bacteria were exposed to vinyl chloride (99.9% pure) at nominal concentrations of 0.2, 2.0, and 20% (5.1, 51.2, and 512 g/cu m) in air for up to 48 hours. Gas chromatography showed that these nominal concentrations of vinyl chloride in air produced viryl chloride concentrations in the media of 0.04, 0.4, and 4 millimoles, respectively, after 6 hours, with no further increase in up to 48 hours.

Fractions of liver, kidney, and lung tissue were prepared from BD-IV rats and OF-1 mice, some of which had been pretreated with sodium phenobarbital to increase hepatic microsomal enzyme activity [146]. Microsomal supernatants were prepared by centrifuging homogenized tissue at 9,000 x G. For some experiments, the microsomal supernatant was then centrifuged at 100,000 x G to produce a purified microsomal fraction and a supernatant containing microsomal protein. The 9,000 x G microsomal supernatants from four human liver biopsy specimens were also tested.

In the presence of a microsomal fraction derived from mice treated with sodium phenobarbital, with an NADPH-generating system, the mutation rate in TA1530, the most sensitive of the strains tested, increased 6, 12, and 28 times over the spontaneous rate after 48 hours of exposure to vinyl chloride in air at 0.2, 2.0, and 20% [146]. Strains TA1535 and G-46 showed similar mutagenic response, while TA1538 showed no significant increase over control rates after exposure to 20% vinyl chloride for 48 hours. Exposure of strain TA1530 to 20% vinyl chloride without the microsomal system caused a linear increase in the mutation rate as a function of length of exposure, reaching 20 times the spontaneous rate after 48 hours. The prevalence of mutations in the presence of the microsomal system was seven times as high as with vinyl chloride alone after 1.5 hours, but only twice as high after 48 hours; the difference in the mutation rate induced by vinyl chloride alone and in the presence of a microsomal system reached a plateau after about 9 hours of exposure.

Bartsch et al [146] attempted to characterize the enzymes involved in vinyl chloride mutagenicity by testing the activity of various mouse liver fractions on strain TA1530. In the absence of the NADPH-generating system, the 9,000 x G microsomal supernatant with 2% vinyl chloride produced no increase above the mutation rates produced by exposure to vinyl chloride alone for periods of up to 48 hours. Purified microsomes with an NADPH-generating system produced an increase in the vinyl chloride-induced mutation rate of about half of that obtained with the 9,000 x G microsomal system after 48 hours. The 100,000 x G liver protein supernatant (cytosol) did not increase the mutagenic response compared to that induced by vinyl chloride alone. Addition of alcohol dehydrogenase and NAD^+ to the microsomal systems did not affect the mutation rate, although alcohol dehydrogenase would be expected to convert any chloroethanol produced to chloroacetaldehyde. This compound is known to be mutagenic to TA1530 [147].

Comparison of tissues from various sources showed that rat liver microsomal supernatant was comparable to that from mouse liver in activating the mutagenic response to vinyl chloride [146]. Pretreating the animals with phenobarbital increased the activity of the liver microsomal supernatant 15-40%. Kidney and lung fractions from either pretreated or untreated animals increased the mutagenic activity of vinyl chloride only marginally over control values. One of the four human liver specimens tested was nearly twice as active as those of rat or mouse liver, while the remaining three were somewhat less active than liver tissue from phenobarbital-treated rats and

mice. Based on data from pretreated animals, the relative mutagenic activities of tissue fractions for strain TA1530 were: mouse liver 100%; rat liver, 80%; mouse kidney, 20%; rat kidney, 16%; mouse and rat lung, 7%; and human liver, 170, 70, 64, and 46%.

Bartsch et al [146] concluded that vinyl chloride was mutagenic to Salmonella in the absence of mammalian microsomal enzymes, probably through the action of breakdown products produced either by bacterial enzymes or nonenzymatically. They pointed out that their findings strongly supported the enzymatic formation of mutagenic vinyl chloride metabolites. Since the 9,000 x G microsomal extract gave a stronger response than purified microsomes, the authors concluded that soluble liver proteins (cytosol) played a role in the metabolic activation of vinyl chloride, either by involvement in a two-step activation mechanism or by prolonging the viability of the microsomal enzymes.

In a subsequent review paper, Bartsch [148] noted that the wide variation in human liver enzymatic activity, which was confirmed in mutagenicity testing of N-nitrosomorpholine, indicated that some individuals are genetically liable to a higher risk from exposure to carcinogens. Bartsch suggested that those estimating acceptable environmental levels of such substances should consider the possible risk for the most susceptible individuals.

In 1976, Garro et al [149] reported studies of the modification of the mutagenic activity of vinyl chloride on Salmonella typhimurium TA1530 by suspensions of untreated and Aroclor 1254-pretreated rat or mouse hepatic microsomes in the presence of an NADPH-generating system and by a system generating free radicals from riboflavin and N,N,N',N'-tetramethylethylenediamine (TMED) under irradiation from fluorescent lamps. They described TMED as an accelerator of vinyl chloride photopolymerization. Although incubation of vinyl chloride with native microsomal suspensions increased its mutagenic activity by about 65%, incubation of this chemical with similar suspensions that had been heated to destroy their enzymatic activity also increased, but at a somewhat reduced level, its mutagenic activity. Mutagenesis in the presence of liver extracts was not NADPH dependent. Incubation of vinyl chloride with the free-radical generating system apparently increased its mutagenic activity by nearly tenfold. The authors took these findings to indicate "that the stimulatory effect of liver extracts on the mutagenic activity of vinyl chloride in the Salmonella auxotroph reversion test cannot be ascribed to enzymatic activation by a microsomal mixed function oxidase and...that the mutagenic effect of vinyl chloride may involve a free radical mechanism."

Although Garro et al [149] found that riboflavin and the tertiary amine had an effect on the mutagenic activity of vinyl chloride for Salmonella typhimurium TA1530 only in the presence of light, they made no measurements that would confirm the relationship of the presence of free radicals in their photoactivated test system to increased mutagenic activity of vinyl chloride. Also, they did not rule out the possibility that the light itself altered the apparent mutagenic activity of vinyl chloride. These two uncertainties about

the photochemical activation experiments makes the conclusion that free radicals may have a special importance in increasing the mutagenic activity of vinyl chloride questionable.

In 1976, Andrews et al [150] confirmed the earlier reports that exposure to vinyl chloride increased the mutagenic frequency in Salmonella TA 1535 in the absence of a microsomal enzyme system.

Greim et al [151], Henschler [152], and Henschler et al [153] reported a study of the mutagenic effects of vinyl chloride and several related compounds on Escherichia coli K12. This bacterium, they suggested, might be a more useful test organism than Salmonella because it was more resistant to the nongenetic toxic effects of some of the test compounds [152]. E. coli K12 can be evaluated for mutagenic response at four loci by plating on selective media; back mutations at the gal+, arg+, and nad+ loci cause reversions to prototrophy, while forward mutations are measured at the gal+ and MTR loci [154]. Vinyl chloride (99.9% pure) was bubbled through a medium containing the bacteria, a microsomal supernatant from mice pretreated with phenobarbital, and an NADPH-generating system [152]. This produced a concentration of vinyl chloride in the medium of 10.6 millimoles, as determined by gas chromatography. The mutagenic response at the four test loci, as a percentage of the spontaneous mutation frequency, was 231 ±20 (SD) for gal+, 663 ±141 for arg+, 148 ±24 for nad+, and 172 ±35 for MTR. Vinyl chloride was by far the most mutagenically active of the compounds tested.

In 1976, Loprieno et al [155] reported on the genetic effects of vinyl chloride activated by mammalian enzymes both in vitro and in vivo (host-mediated assays). Two species of yeasts were used as the test organisms. A haploid strain of Schizosaccharomyces pombe containing a mis-sense mutation in the ade6 locus and a mutation in the rad10 locus was used to study forward mutations at the five loci involved in the biosynthesis of adenine. A diploid strain of Saccharomyces cerevisiae with double heterozygotic alleles in the ade2 and trp5 loci was used to study the induction of gene conversion at these loci. For the in vitro experiments, vinyl chloride (about 99.9% pure) at concentrations of 5 and 50% (128 and 1,280 g/cu m) in air was bubbled through a suspension containing the yeast cells for up to 4 hours, resulting in vinyl chloride concentrations in the treatment flasks of 16 and 48 millimoles, respectively. The vinyl chloride was activated with a purified microsomal fraction (105,000 x G) from the livers of Swiss albino mice combined with an NADPH-generating system. For the host-mediated assays, Swiss albino mice weighing 25 g each were administered orally 1 ml of olive oil containing 1.85% vinyl chloride, ie, at 740 mg/kg. Controls were given olive oil. Cells of Schizosaccharomyces were injected into the peritoneum of four to six mice and permitted to incubate for 3-12 hours before being plated to study mutation frequency.

Mutagenic activity was observed in the in vitro studies with Schizosaccharomyces only when a purified microsomal system was included in the preparation [155]. Maximum mutagenic activity was reached after 30-60 minutes

of treatment, and the activity increased with the vinyl chloride concentration in the medium. At a vinyl chloride concentration of 48 millimolar for 60 minutes, the mutation frequency at the five loci was 62.43/10,000 surviving cells, compared with a spontaneous mutation rate of 2.00/10,000. In studies with Saccharomyces, treatment with 48 millimoles vinyl chloride for 300 minutes in the presence of purified microsomes produced a gene conversion frequency of 8.47/100,000/locus in the ade2 system and 4.36/100,000/locus in the trp5 system; spontaneous frequencies for these systems were 0.49/100,000/locus and 0.85/100,000/locus.

In the host-mediated assay, Loprieno et al [155] found that Schizosaccharomyces showed a mutagenic response after incubation for 12 hours in the peritoneum of mice given vinyl chloride orally at 740 mg/kg. The observed mutation frequency was 6.89 (±0.60)/10,000 cells compared with a control rate of 1.33 (±0.19)/10,000 in yeast incubated in rats not given vinyl chloride; regression analysis showed the effect to be significant at the 1% level. Comparing the mutagenic effectiveness of the 16 millimoles of vinyl chloride used in vitro with that of 11.2 millimoles of vinyl chloride administered to the mice for in vivo studies, the authors concluded that in vitro treatment was more effective. They attributed this to the fact that, in the host-mediated assay, the presence of an active concentration of the purported mutagenic metabolite was minimal as a consequence of its short half-life.

In a later study with Saccharomyces cerevisiae, Shahin [156] reported that vinyl chloride added directly to the medium in concentrations of 0.275-0.55% caused neither mutagenesis nor recombination (crossing-over) in the absence of a microsomal activating system. He did not describe any experiments in which a microsomal system was used.

Drozdowicz and Huang [157] tested the mutagenic activity of vinyl chloride in the fungus Neurospora crassa. The test organisms were a wild-type strain, which was scored for forward mutation to acriflavin resistance, and a nicotinic acid-deficient auxotrophic strain. Amounts of a 1.78 M ethanol solution of vinyl chloride (apparently up to 10%) were added directly to the medium containing the fungal conidia for 3- to 4-hour exposures, or cultures were exposed to gaseous vinyl chloride at concentrations of up to 50% in oxygen for 3.5 or 24 hours.

Neurospora conidia were then plated on nonselective and selective media and incubated for 5-7 days for scoring of survival and mutation frequencies. Activating systems used were a 9,000 x G hepatic microsomal supernatant from phenobarbital-induced rats for the 3.5-hour exposures and a purified microsomal fraction from uninduced Buffalo rats for the 24-hour exposures, both mixed with an NADPH-generating system. Ultraviolet light and methyl methanesulfonate were used as positive mutagenic controls. Both of the latter treatments induced dose-dependent increases in mutation rates, but vinyl chloride showed no mutagenic activity under any of the test conditions.

Two possible explanations for this lack of vinyl chloride-induced mutagenicity in Neurospora were suggested by the authors [157]. Vinyl chloride or its mutagenic metabolites might have been unable to penetrate into the conidia; however, the authors also noted that the Salmonella [146,150] and yeast tester strains [155] used carried mutations affecting genetic repair, while the Neurospora crassa strains used in this study [157] were not repair deficient and thus might not have been sensitive enough to indicate mutagenicity for vinyl chloride. Drozdowicz and Huang also mentioned unpublished data by Huang et al showing that vinyl chloride was not mutagenic in Haemophilus influenzae when DNA from this bacterium was subjected to vinyl chloride treatment and used in transformation assays. No additional details were provided.

Bartsch and Montesano [158], in a 1975 review of the mutagenic and carcinogenic effects of vinyl chloride, mentioned a personal communication from F Verburgt reporting unpublished observations of positive results in a recessive lethal test on Drosophila. Verburgt exposed male Drosophila to vinyl chloride at 800 ppm for 4 or 17 days. He observed a significant increase in the frequency of recessive lethals and noted that peak mutagenic activity was found in metabolically active germ cells. No further information was provided. Magnusson and Ramel [159], in 1976, also obtained positive results in recessive lethal tests with Drosophila. Male Drosophila were exposed to vinyl chloride at unspecified concentrations in air for 3 hours and then mated to Muller 5 females. The authors reported a significant increase of recessive lethals in both the first and second generations after treatment, indicating that vinyl chloride induced recessive lethal mosaics, but no quantitative data were given.

In 1977, Verburgt and Vogel [160] reported the results of recessive lethal tests on Drosophila males exposed to vinyl chloride at concentrations of 200, 850, 10,000, 30,000, or 50,000 ppm for 2 days and to 30 or 850 ppm for 17 days. At each concentration, chromosomes were tested and the number of lethals was scored during days 0 to 12 after exposure.

Vinyl chloride exposure for 2 days at concentrations of 0, 30, and 200 ppm produced 0.10, 0.18, and 0.09% lethals, respectively [160]. Concentrations of 850 ppm for 2 or 4 days produced 0.39 and 0.59% lethals, respectively, and concentrations of 10,000, 30,000, and 50,000 ppm for 2 days induced lethals in 2.19, 2.22, and 2.30%, respectively. After 17 days of exposure and examination for 10 subsequent days, lethals were found in 0.19% of those exposed at 0 ppm, 0.35% of those exposed at 30 ppm, and 1.02% of those exposed at 850 ppm.

Verburgt and Vogel [160] stated that the data, which demonstrated an increasing frequency of lethal effects between concentrations of 0 and 10,000 ppm, demonstrated that the mutagenic activity of vinyl chloride was concentration dependent. Since exposure at 30,000 and 50,000 ppm did not significantly increase the mutation frequency above that seen at 10,000 ppm,

they inferred that above a certain concentration (between 850 and 10,000 ppm) Drosophila was incapable of metabolically "activating" (for mutagenesis) further vinyl chloride, and that the enzymatic mechanisms were saturated.

Anderson et al [161] conducted a dominant lethality study with mice to determine whether vinyl chloride can induce genetic effects. Male CD-1 mice were exposed in groups of 20 to vinyl chloride (purity not described) at concentrations of 3,000, 10,000, and 30,000 ppm (7.68, 25.6, and 76.8 g/cu m) 6 hours/day for 5 days. A concentration of 30,000 ppm was the highest exposure level chosen because it had been shown in preliminary tests to be in the "toxic range" and it was desired that the maximum tolerated dose or higher be included in the study protocol. Control mice were exposed to air alone. Two positive control groups of 15 and 25 mice were given 200 mg/kg of ethyl methanesulphonate orally for 5 days or one ip dose of 200 mg/kg of cyclophosphamide on the 5th day. After the exposure period, each of the surviving males, then 10-12 weeks old, was mated with two 8- to 10-week-old females each week for 8 consecutive weeks. The females were killed 13 days after the assumed date of mating, and their uteri were examined for live implantations, early fetal deaths, and late fetal deaths.

Of the male mice, only those exposed to vinyl chloride at 30,000 ppm showed significant mortality, with only 9 of 20 mice surviving 5-day exposures [161]. In females mated to vinyl chloride-exposed males, the frequency of pregnancy and the number of early and late fetal deaths did not differ significantly from untreated control values. The number of implantations/pregnant female was not affected by vinyl chloride, except that it was significantly below the negative control value in females mated during the 4th week to mice that had been exposed at 30,000 ppm (10.00 vs 12.38, $P<0.05$); however, implantation frequency in this group was slightly above control values for 3 of the 8 weeks of mating. Both positive control groups were significantly higher than negative (air) controls in all the indicators of dominant lethality examined, attesting to the sensitivity of the system. The authors [161] concluded that vinyl chloride at the stated exposure concentrations was not mutagenic in mice as measured by the dominant lethal test. This suggests that the active mutagenic compound in the metabolism of vinyl chloride did not affect the germinal cells of these mice.

Several investigators have attempted to obtain information on the mechanism of mutagenic and carcinogenic activity of vinyl chloride by testing its known or suspected metabolites for their ability to cause mutations in microorganisms. Malaveille et al [147] used Salmonella strain TA1530 to evaluate the mutagenic activity of three presumed metabolites, chloroacetaldehyde, chloroethanol, and chloroethylene oxide (chlorooxirane), and a known urinary metabolite, chloroacetic acid. The substances were tested, with and without a liver microsomal system from phenobarbital-pretreated mice, at concentrations of 40, 4.0, and 0.4 μmol/ml of medium; chloroethylene oxide was also tested at 0.04 μmol/ml.

Chloroacetaldehyde was highly toxic to bacteria at each test concentration used, reducing survival to less than 0.004% of control levels [147]. Chloroacetic acid was toxic at concentrations of 4 and 40 μmol/ml and was the only substance tested that showed no mutagenic activity. Chloroacetaldehyde caused a sixfold increase over the spontaneous rate at a concentration of 4 μmol/ml in combination with the microsomal system; this substance also showed direct mutagenic activity in the absence of mammalian microsomes. At a concentration of 40 μmol/ml, chloroethanol, which did not affect bacterial survival, increased the mutation frequency more than 10 times in the presence of the microsomal system and about 6 times in its absence; at 4 μmol/ml, chloroethanol approximately doubled the mutation frequency of the bacteria, and its mutagenic activity was apparently unaffected by the microsomal system. Chloroethylene oxide was tested without microsomal activation only.. At a concentration of 0.4 μmol/ml, it reduced bacterial survival to 11% and produced a sixfold increase in the mutation frequency; at 0.04 μmol/ml, it caused no increase over spontaneous mutation frequency. These findings indicate that chloroethylene oxide is a far more effective mutagen than chloroacetaldehyde, supporting the suggestion of Henschler and his colleagues [151-153] that the unstable oxirane was directly involved in vinyl chloride mutagenesis.

McCann et al [162] compared the mutagenicity of vinyl chloride with that of its probable metabolites chloroacetaldehyde and chloroethanol, both with and without activation by a rat liver microsomal system. They used Salmonella strains TA1535 and TA100, the latter being identical with TA1535 except that it contains a factor that interferes with DNA repair, thus increasing its sensitivity to many mutagens. Bacteria were exposed to 20% vinyl chloride in air for 3-9 hours, while chloroacetaldehyde and chloroethanol were added directly to the media in concentrations of up to 30 μg/plate and 1-5 mg/plate, respectively.

The mutagenic responses of strains TA1535 and TA100 to vinyl chloride were similar, and McCann et al [162] observed very little activation by a microsomal system from phenobarbital-pretreated rats with exposure periods of up to 9 hours. From the authors' graphs, the direct action of vinyl chloride on strain TA100 produced about 25 revertants/plate above spontaneous levels (which averaged 150 revertants/plate) with 3 hours of exposure and 200 at 9 hours; the corresponding levels with the microsomal system added were 65 and 225 revertants/plate above control levels. However, the authors added in a footnote that increasing the concentration of microsomes in the system had produced a twofold increase over the direct activity of vinyl chloride in both TA100 and TA1535.

At the concentrations tested, chloroacetaldehyde, with no microsomal system, effectively reverted strain TA100 to histidine independence but did not affect strain TA1535 [162]. The mutagenic activity in strain TA100 increased with the concentration of chloroacetaldehyde, reaching 285 revertants/plate above the spontaneous rate at a concentration of 30 μg/plate. Chloroethanol increased the mutagenic reponse of strain TA100 to over twice

the spontaneous levels and showed a trace of activity with strain TA1535. However, addition of the microsomal supernatant caused a small increase in the mutagenic response of strain TA1535 and a much greater increase in that of strain TA100; quantitative data were not given. The authors noted that an NADPH-generating system was not necessary for this activation. Comparing the mutagenic activity of the three substances in strain TA100 on an equimolar basis, the authors found that the number of revertants/μmol, with control levels subtracted, was 1.0 for vinyl chloride, 0.6 for chloroethanol, and 746 for chloroacetaldehyde.

Despite the high mutagenic activity of chloroacetaldehyde in strain TA100, McCann and coworkers [162] concluded that this substance was probably not the active metabolite involved in vinyl chloride mutagenicity. Vinyl chloride, with or without microsomes, was about equally active in the two bacterial strains tested, while chloroacetaldehyde affected only strain TA100. By contrast, activation of chloroethanol by a microsomal system produced a relatively large increase in the mutation rate of TA100, indicating that chloroacetaldehyde might be the mutagenically active metabolite of chloroethanol. The authors suggested that chloroethylene oxide might be the metabolic intermediate responsible for vinyl chloride mutagenicity. This conclusion is supported by the findings of Malaveille et al [147] and of Rannug et al [163] that chloroethylene oxide was several times more active than chloroacetaldehyde in the nonrepair-deficient strains TA1530 and TA1535.

In 1976, Rannug et al [162] compared the mutagenicity of chloroethlyene oxide, chloroacetaldehyde, 2-chloroethanol, and chloroacetic acid in Salmonella typhimurium strain TA1535. The test substances were added to the bacteria before plating, in concentrations ranging from 0.1 to 1.5 millimolar; 2-chloroethanol and chloroacetic acid were also studied at concentrations of up to 1 M. Ethylene oxide, described as a "well known mutagen," was used as a positive control. The authors also tested vinyl chloride at a concentration of 2% (51.2 g/cu m) in air for 3 hours, using the procedure described in their earlier study [145].

Chloroethylene oxide showed both a definite toxic effect and strong mutagenic activity [163]. At a concentration of 0.75 millimolar, it produced 180 revertants/100 million surviving cells, 60 times the spontaneous mutation rate. Chloroacetaldehyde also showed a mutagenic effect in this concentration range but was only about 5% as effective as chloroethylene oxide on a molar basis. 2-Chloroethanol and chloroacetic acid showed no mutagenic effect up to 1.5 millimolar and were therefore retested at higher concentrations. 2-Chloroethanol produced a weak mutagenic response only at 1 molar. Chloroacetic acid was highly toxic to bacteria at concentrations up to 0.5 molar, and no increase in mutagenic response could be detected. Ethylene oxide, the positive control substance, did not produce an increase in mutagenic response at concentrations below 5 millimolar, and ethylene oxide at 95.5 millimolar produced an increase in the mutation rate equivalent to that produced by chloroethylene oxide at a concentration of 0.15 millimolar.

In their experiments with 2% (51.2 g/cu m) vinyl chloride, Rannug et al [163] found that vinyl chloride at this concentration in the presence of a microsomal system produced 10.0 ±0.9 (SE) revertants/100 million cells, significantly more ($P<0.001$) than the control rate of 3.8/100 million cells; neither vinyl chloride alone nor the microsomal system alone produced a significant increase. Noting the difficulty of comparing vinyl chloride mutagenicity to that of the other compounds because of the difference in experimental conditions, the authors estimated that only if all the vinyl chloride was converted to 2-chloroethanol would the concentration of this compound be great enough to account for the observed mutagenic activity of activated vinyl chloride.

Calculating that chloroethylene oxide was 10,000-15,000 times as mutagenic as ethylene oxide, Rannug et al [163] concluded that this was in reasonable agreement with the ratio of the preliminary rate constants of the two compounds for reaction with the appropriate nucleophiles. They considered this to be an indication that chloroethylene oxide acts in the same way as ethylene oxide, as a monofunctional alkylating agent. The authors concluded on the basis of interpretations by Hussain and Osterman-Golkar [164] that chloroacetaldehyde was far more active as a mutagen than would be expected from its reactivity as an alkylating agent.

In an addendum to the paper by Rannug et al [163], Hussain and Osterman-Golkar [164] analyzed the data of Rannug et al on a kinetic basis. They noted that the higher-than-expected mutagenic activity of chloroethylene oxide, based on comparison of its rate constant for alkylation with that of ethylene oxide, indicated "a certain role of the aldehyde groups." Chloroacetaldehyde, however, was several orders of magnitude more effective than expected, indicating "a reaction mechanism different from simple alkylation."

In 1977, Loprieno et al [165] tested vinyl chloride metabolites for mutagenic activity in yeasts. Chloroethylene oxide, 2-chloroacetaldehyde, and 2-chloroethanol, added to the media in various concentrations, were tested in vitro; 2-chloroacetaldehyde was also tested in the host-mediated assay. Test organisms and experimental procedures were the same as those used in their previous study [155].

Chloroethylene oxide showed the highest mutagenic activity in all systems examined [165]. At a concentration of 0.1 millimole, the forward mutation frequency in S. pombe was 340 times the control rate, and at 1 millimole the gene conversion rate in S. cerevisiae was 40-50 times that in controls. 2-Chloroethanol in concentrations up to 50 millimoles showed no mutagenic activity in yeast cells, with or without microsomes. 2-Chloroacetaldehyde showed a weak mutagenic effect in vitro, increasing mutation rates 2-7 fold at concentrations up to 12.5 millimoles. When administered to male Swiss albino mice (25 g) in oral doses of 250 mg/kg, 2-chloroacetaldehyde produced no increase in the mutation rate of S. pombe incubated in the peritoneum for 3-6 hours.

Elmore et al [166] evaluated vinyl chloride and its metabolites in a study designed to permit accurate comparisons of their mutagenic activity and to provide additional insight as to the mechanism of this activity. Since previous investigators had not ascertained the purity of the metabolites used, Elmore and coworkers tested pure forms of chloroethanol, chloroacetic acid, chloroethylene oxide, and chloroacetaldehyde. The last compound can exist in combinations of four forms, depending on its preparation. The authors therefore tested pure preparations of the monomer, dimer hydrate, and trimer, plus the 50:50 mixture of monomer and monomer hydrate formed when the monomer is dissolved in water or physiologic systems. They also tested a solution of 0.0106 M vinyl chloride in nutrient broth.

Salmonella typhimurium strain TA100 was used for quantitative mutagenicity testing [166]. The authors also tested DNA repair-deficient strains of Bacillus subtilis in repair assays, as an indirect test for mutagenicity. 4-Nitroquinoline-N-oxide was used as a positive mutagenic control. The number of replicate plates used in these studies was not mentioned and the authors did not indicate the statistical significance of their results.

Incubation of Salmonella for 48 hours in a medium containing initially 0.0106 M vinyl chloride produced no increase over the spontaneous mutation rate [166]. Chloroethanol and chloroacetic acid at concentrations of 1 millimole also showed no mutagenic activity. All forms of chloroacetaldehyde were mutagenic to Salmonella strain TA100. Chloroacetaldehyde monomer, the most active form, caused a maximum mutagenic response of 404 revertants/plate above spontaneous levels at a concentration of 0.84 μmol. The mixture of monomer and monomer hydrate caused 512 revertants/plate at 14 μmol. The dimer hydrate at 120 μmol and the trimer at 240 μmol produced 193 and 159 revertants/plate, respectively. Mutagenic response was linear up to these concentrations but became nonlinear at high concentrations for all four forms of chloroacetaldehyde.

Chloroethylene oxide, which decomposed rapidly to chloroacetaldehyde, with a half-life of 1.6 minutes under the 37 C incubation conditions, was preincubated with the bacteria at 3 C for up to 6 hours before plating to ensure that the undecomposed compound penetrated the cells [166]. With 4 hours of preincubation, chloroethylene oxide at a concentration of 0.26 millimole produced 114 revertants/plate above spontaneous levels.

The repair assay used by Elmore et al [166] involves incubating Bacillus subtilis strains on 6-mm filter paper discs saturated with the test substances, as described by Kada et al [167]. Lethality and mutagenic potential were evaluated by comparing inhibition zones in the wild-type strain 168 with those in strains deficient in their ability to repair DNA lesions due to lack of either excision repair (hcr- or uvr-) or recombination repair (rec-) capability.

Vinyl chloride, chloroethanol, and chloroacetic acid did not inhibit bacterial growth in the repair assay [166]. The various forms of

chloroacetaldehyde affected growth of the wild type and excision repair-deficient strains only slightly but had a much greater effect on the recombination-deficient strain, with the monomer and monomer hydrate again being the most active forms. Chloroethylene oxide also selectively inhibited growth of the recombination-deficient strain.

Since the wild-type and excision repair-deficient strains of B. subtilis (both capable of recombination repair) were essentially unaffected by these substances, Elmore and colleagues [166] concluded that recombination repair is induced to correct DNA lesions caused by vinyl chloride metabolites. They suggested that the post-replication repair of DNA in mammalian cells, which, like recombination repair in bacteria, is an error-prone process, might be responsible for the production of human cancer by vinyl chloride. The ultimate carcinogenic metabolites of vinyl chloride, the authors considered, are chloroacetaldehyde monomer hydrates, known to react with DNA, and chloroethylene oxide, which rearranges to chloroacetaldehyde or to a stabilized diradical intermediate also known to react with DNA. They suggested that the lower mutagenicity of chloroethylene oxide might result from its being detoxified faster than chloroacetaldehyde.

Laumbach et al [168] extended the investigation of Elmore et al [166] by studying the effect of chloroacetaldehyde on transforming DNA extracted from Bacillus subtilis. Previous studies [169,170] had shown that chloroacetaldehyde could bind to DNA in vitro, modifying bases and causing mismatched base pairs; however, Laumbach et al [168] found that transforming DNA isolated from wild-type B. subtilis and treated with chloroacetaldehyde did not affect the number of transformants in any of four auxotrophic B. subtilis strains used as recipients. When the wild-type strain was treated with chloroacetaldehyde for 15 minutes before the DNA was extracted, there was a major depression of biologic activity in the transforming DNA, as evidenced by a decrease of 50% or more in the number of transformants produced. This depression showed genetic-marker specificity, reducing transformation at some loci by over 90%. The authors noted that DNA segments that have previously been shown to be associated with macromolecular structures such as the cell wall or cell membrane appeared to be selectively protected from attack by chloroacetaldehyde. The addition of a mammalian microsomal system did not significantly alter the effect of chloroacetaldehyde on transformation efficiency.

Huberman et al [171] evaluated the mutagenicity of chloroethylene oxide and 2-chloroacetaldehyde directly on mammalian cells, using cultures of V79 cells derived from the kidneys of Chinese hamsters; this cell system had been successfully used in detecting mutagenic activity of other carcinogenic substances. Cells were seeded on media containing 8-azaguanine or ouabain and exposed to the test substances at concentrations of up to 25 μmol for 3 hours. After an additional period of incubation, colonies resistant to 8-azaguanine were scored for 10-12 plates at each concentration and ouabain-resistant colonies were scored for 32-40 plates at each concentration.

The mutagenic response at both loci increased as a function of the concentrations of chloroethylene oxide and 2-chloroacetaldehyde [171]. At a concentration of 6 μmol, chloroethylene oxide produced mutation frequencies 4 times that of controls for 8-azaguanine resistance and 10 times the control frequency for ouabain resistance. The corresponding values for 2-chloroacetaldehyde at these concentrations were 13 and 2 times control frequencies. Chloroethylene oxide at 13 μmol produced mutation frequencies exceeding control frequencies by factors of 8 at the 8-azaguanine locus and 23 for ouabain. 2-Chloroacetaldehyde at this concentration was strongly cytotoxic, and no mutagenic effect could be detected.

(b) Vinylidene Chloride

In a 1975 study of vinyl chloride mutagenicity, Bartsch et al [146] stated that they had unpublished data showing that vinylidene chloride metabolically activated by rat or mouse liver microsomal enzymes was a more active mutagen than vinyl chloride. A subsequent 1975 paper by Bartsch et al [172] presented data on the mutagenicity of vinylidene chloride in Salmonella typhimurium, using histidine-deficient tester strains TA1530 and TA100. Plated bacteria, in a medium containing a microsomal system from the livers of phenobarbital-pretreated OF-1 mice supplemented with an NADPH-generating system, were exposed to vinylidene chloride, containing 0.3% 4-methoxyphenol as an antioxidant, at concentrations of 0.2, 2.0, or 20% (7.94, 79.4, or 794 g/cu m) in air [172]. This produced respective vinylidene chloride concentrations of 0.33, 3.3, and 33 millimoles in the media after 2 hours of exposure, as determined by gas chromatography. After exposure, the bacteria were cultured for up to 48 hours, and histidine-revertant colonies were counted on each plate. From one to four experiments were conducted at each concentration, each using a pool of four mouse livers; bacteria were plated in triplicate for each experiment. The authors also compared the efficiency of liver, kidney, and lung microsomal systems from male OF-1 mice and female BD-VI rats in inducing mutagenic response to vinylidene chloride in strain TA100.

Both Salmonella strains showed a positive mutagenic response to vinylidene chloride in the presence of a mammalian microsomal system [172]. No mutagenic activity was observed in the absence of the NADPH-generating system. In strain TA100, exposure to vinylidene chloride for 4 hours at 0.2% produced an average of about 300 revertants/plate, compared with control levels of less than 50. At 2% vinylidene chloride, the number of revertants/plate in strain TA100 reached 500 ±23 (SE) above control levels, while at 20% vinylidene chloride, the number was only 330 ±29. Strain TA1530 followed the same pattern but was somewhat less sensitive. The authors suggested that the reduction in mutagenic response at the highest exposure concentration might have resulted from inhibition of the microsomal enzymes responsible for the metabolic activation of vinylidene chloride.

The mutagenic response of the bacteria to 2% vinylidene chloride increased linearly with time up to 4 hours, and this test period was therefore used in experiments comparing various tissue fractions [172]. All of the mouse tissue

fractions tested induced some mutagenic response to vinylidene chloride, although the liver fraction was the most active. Rat tissue fractions were much less active than those of mice, and rat lung tissue showed minimal activity. Phenobarbital pretreatment, used only in mice, approximately doubled the mutagenic activity of vinylidene chloride. Exposure to 2% vinylidene chloride in the presence of microsomal systems from untreated mouse liver caused 330 ±49 revertants/plate above control levels. Using this value as a standard (100%), relative activities of the other tissue fractions from untreated animals were: mouse kidney, 20%; mouse lung, 6%; rat liver, 30%; rat kidney, 5%; rat lung, less than 3%. In a 1976 review paper, Bartsch [148] also noted that the relative activities of four human liver biopsy specimens, under similar experimental conditions, were 38, 17, 16, and 11% of the corresponding mouse liver values.

In another set of experiments, using Salmonella strain TA1530, Bartsch et al [172] attempted to explicate the mechanism whereby vinylidene chloride exerted mutagenicity by adding sulfur-containing compounds to the media. With exposure to 2% (79.4 g/cu m) vinylidene chloride, the addition of 12 µmol/ml of N-acetyl cysteine and the same amount of N-acetyl-methionine to the medium, in the presence of a mouse liver microsomal system, caused an 80% reduction in the number of revertants. The authors concluded that the mutagenic metabolites of vinylidene chloride are trapped by nucleophilic sulfur groups, thus competing for binding to bacterial DNA.

In a review published in 1976, Bartsch et al [173] again noted that vinylidene chloride was more mutagenically active than vinyl chloride, based on calculations from linear dose- and time-dependent response curves from separate experiments. They indicated that vinyl chloride produced 3.7 revertants/µmol of substrate/hour of exposure/plate in strain TA1530 and 5.6 in strain TA100, while vinylidene chloride produced 9.5 and 14.6 revertants/µmol/hour/plate, respectively, in these test strains.

Greim et al [151], Henschler [152], and Henschler et al [153] reported on the mutagenic activity of vinylidene chloride, as well as that of vinyl chloride and related compounds, in Escherichia coli strain K12. Analytical grade vinylidene chloride was injected into the incubation medium to produce a concentration of 2.5 millimoles, as determined by gas chromatography.

Like vinyl chloride, vinylidene chloride was most active in causing mutations at the arg+ locus, producing revertants at 229 ±26% of the spontaneous mutation rate [151-153]. Revertants at the gal+ locus increased to 120 ±14% of the spontaneous rate in bacteria exposed to vinylidene chloride, while the MTR and nad+ loci were not observably affected. No mutagenic activity was observed in the absence of a microsomal system.

The authors [151-153] stated that the mutagenic activity of vinyl chloride, which caused a 563% increase in mutations at the arg+ locus, was "several times higher" than that of vinylidene chloride. It should be noted, however, that the measured concentration of vinyl chloride in the medium (10.6

millimoles) was over four times that of vinylidene chloride. In addition, the difference in exposure technique required for the highly insoluble gaseous vinyl chloride necessitates that such comparisons be made with caution. Since Bartsch et al [172] exposed bacteria to both vinyl chloride and vinylidene chloride in air, and thus determined the concentration in the medium under similar conditions, their comparisons of relative mutagenic activity are probably more accurate. Furthermore, Henschler et al [153] pointed out in their discussion that vinylidene chloride is the most polar of the chlorinated ethylenes they tested, and its oxirane, which has not been successfully synthesized, would be expected to be the least stable. Thus, it should be expected to have a higher mutagenic activity than vinyl chloride.

(c) Vinyl Bromide

VF Simmon and R Mangham, in a written communication to NIOSH in August 1977, reported the results of a study on the mutagenic effects of vinyl bromide on Salmonella typhimurium strains TA100 and TA1535. Plated bacteria, with and without a liver microsomal system from male rats pretreated with Aroclor 1254, were exposed for 12 hours to atmospheres containing 0-20% vinyl bromide (source and purity not described). After an additional 48-hour incubation period, histidine revertants were counted on three replicate plates for each concentration.

Vinyl bromide at concentrations of 2-20% (87.6-876 g/cu m), in the absence of a microsomal activation system, increased the mutagenic response in both Salmonella test strains as compared with control activity according to Simon and Mangham. Addition of a microsomal system enhanced the mutagenic activity of vinyl bromide. At 20% vinyl bromide in the presence of a microsomal system, there was an average of 1,129 revertants/plate in strain TA100 and 959/plate in TA1535; without the activating system, the mutation rates were 620/plate for TA100 and 721/plate for TA1535. Control rates of about 130/plate for TA100 and less than 20/plate for TA1535 were not significantly affected by the addition of the microsomal system alone.

Although Simmon and Mangham did not conduct simultaneous studies of vinyl chloride or measure the concentration of vinyl bromide produced in the medium, they postulated that vinyl bromide was slightly more mutagenic by these procedures than vinyl chloride. No data were offered in support of this comparison. The authors' findings do support a conclusion that vinyl bromide induces mutations in Salmonella strain TA100 and TA1535 without microsomal activation, although microsomes enhance its mutagenic activity. The mutagenic responses of both strains were concentration-dependent in a nearly straight-line relationship, which showed a tendency to level out at the highest concentration tested (20%). Since Simmon and Mangham did not provide data on bacterial survival, it is not possible to determine whether this saturation resulted from a toxic effect of vinyl bromide at high concentrations.

In a 1976 review, Bartsch [148] mentioned unpublished data on vinyl bromide mutagenicity and noted that microsomal systems from three human liver

samples were 23-36% as effective as a mouse liver microsomal system in inducing the mutagenic effects of vinyl bromide on Salmonella. No experimental data were presented, nor did Bartsch make any comparison of vinyl bromide mutagenicity with that of other vinyl compounds.

(d) Vinyl Fluoride and Vinylidene Fluoride

Putative mutants of Escherichia coli B and E. coli Sd-4 were isolated by the penicillin method of Lederberg and Zinder and by plating in the absence of streptomycin, respectively [174]. The authors stated that the E. coli B cultures exposed to vinyl fluoride and vinylidene fluoride mutated at about 100 times the rate at which the control cultures mutated. They also noted a similar influence of vinylidene fluoride on the Sd-4 strain of E. coli.

Despite this apparent observation of extremely high mutation rates, the authors were unable to isolate any auxotrophic strains from the treated cultures [174]. They presented some evidence for the induction of heritable changes in the fermentation patterns of certain carbohydrates, although it was not unequivocal.

While it is possible that qualitative changes in the mutation frequencies may have occurred, the failure to isolate auxotrophic strains from the treated cultures suggests that any such effects were minimal [174]. Also, the selection method used by these authors does not allow the direct measurement of either the spontaneous or induced mutation rates or frequencies of a culture, although it may greatly enrich the ratio (frequency) of mutated cells to normal cells in the culture.

Vinylidene fluoride has been tested for mutagenic potential in the "Ames" Salmonella auxotroph reversion assay procedure, and the "in vitro transformation of BALB/3T3 cell assay (J Watson, written communication, April 7, 1978). The "Ames" analysis was conducted with Salmonella typhimurium strains TA-1535, TA-1537, TA-1538, TA-100, and TA-98, with and without activation by rat liver microsomes. Solvent and positive control plates were run concurrently with test plates. Test plates were exposed to vinylidene chloride gas for 1, 24, 48, or 72 hours and incubated at 37 C for 48 hours, after the 1-hour exposure, and 24 hours after the 24, 48, and 72-hour exposures.

Without activation, strain TA-1535 exposed for either 24 or 48 hours showed a threefold increase in the number of revertants/plate and those exposed for 72 hours showed a sevenfold increase when compared with solvent controls according to Watson. Ten micrograms of methylnitrosoguanidine/plate (positive control) increased the number of revertants 43-fold. With activation, the increases in revertants/plate were reported as sevenfold for one 24-hour exposure, eightfold for one 48-hour exposure, and tenfold for a 72-hour exposure. A positive control of 2-anthramine at 100 μg/plate gave eightfold increases. Other Salmonella strains did not show substantial increases in revertants/plate when compared with solvent controls in either the activated or nonactivated systems.

These results show that vinylidene fluoride induces a base-pair substitution, but no frameshift mutations according to Watson. Although strain TA-100 should also identify any potential mutagen capable of inducing base-pair substitution, the results were negative for this strain in these tests. The most plausible explanation for this apparent discrepancy is that the presence of the resistance transfer factor on the TA-100 was in this case protective. The results also indicate that some product of the metabolism of vinylidene fluoride is more mutagenic than the parent compound.

Watson also tested the ability of vinylidene fluoride to transform BALB/3T3 cells. Cells were exposed for various periods ranging from 0 to 48 hours, with and without tissue culture media. Only the cells exposed with culture media showed an elevated number of transformations above background; however, these elevations were not significant.

Metabolism

Metabolic pathways have not been completely and convincingly delineated for any of the vinyl halides. That for vinyl chloride apparently is nearest to completion, but, even here, several key steps in the initial reactions are only postulated and have not been conclusively proven by experimentation designed specifically to elucidate intermediate metabolic products in vivo. The proposed pathways for vinylidene chloride are sketchy at best, while the determinations of pathways for vinyl bromide, vinyl fluoride, and vinylidene fluoride have only just begun.

(a) Vinyl Chloride

Vinyl chloride metabolism has been studied extensively since the discovery of vinyl chloride-induced angiosarcoma in humans in early 1974. The major urinary excretion products of vinyl chloride have been characterized following both inhalation and oral exposures, and the compound has been shown to be readily absorbed and widely distributed in body tissues and to be metabolized into several major and minor metabolites.

(1) Distribution and Elimination

Hefner et al [4], in 1975, found that the metabolism of vinyl chloride during the first 15 hours after exposure of three male rats to 14C-(1,2-)vinyl chloride at 49 ppm (125.4 mg/cu m; a total estimated intake of 0.49 mg/kg) for 65 minutes resulted in the formation of polar metabolites that were excreted predominantly in the urine (58% of the 14C activity). Lesser amounts of radioactivity were excreted in the feces (2.7%) and in the expired air as carbon dioxide (9.8%). At 75 hours after administration, 67.1% of the radioactivity had been excreted in the urine, 3.8% in the feces, and 14.0% as expired carbon dioxide. Trace amounts of radioactivity (0.02% of that administered) were eliminated in expired air as unchanged vinyl chloride. A small but significant amount of radioactivity (1.6%) was retained in the liver

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Hefner et al [4], in 1975, found that the metabolism of vinyl chloride during the first 15 hours after exposure of three male rats to 14C-(1,2-)vinyl chloride at 49 ppm (125.4 mg/cu m; a total estimated intake of 0.49 mg/kg) for 65 minutes resulted in the formation of polar metabolites that were excreted predominantly in the urine (58% of the 14C activity). Lesser amounts of radioactivity were excreted in the feces (2.7%) and in the expired air as carbon dioxide (9.8%). At 75 hours after administration, 67.1% of the radioactivity had been excreted in the urine, 3.8% in the feces, and 14.0% as expired carbon dioxide. Trace amounts of radioactivity (0.02% of that administered) were eliminated in expired air as unchanged vinyl chloride. A small but significant amount of radioactivity (1.6%) was retained in the liver

for as long as 75 hours after exposure. The skin retained 3.6% of the radioactivity, 0.2% was found in the kidneys, and 7.6% was found in the remaining carcass.

Hefner et al [4] also reported that the in vivo kinetics of uptake (metabolism) of inhaled vinyl chloride, determined for four male rats exposed together in a chamber at initial concentrations ranging from 50.5 to 1,167.0 ppm (129.3 to 2,987.5 mg/cu m) for 52.5-356.3 minutes, differed at different concentrations of vinyl chloride. For concentrations of 50-105 ppm, the apparent first-order rate constant derived after seven separate exposures was 0.00804 ±0.0034/minute, corresponding to a half-life of 86 minutes. After five separate exposures to vinyl chloride at concentrations ranging from 220 to 1,167 ppm, the first-order rate constant was determined to be 0.00265 ±0.00135/minute, a half-life of 261 minutes. Based on these results, Hefner et al concluded that there were different pathways for vinyl chloride metabolism and that at least one of them was readily saturated, so that the amounts of substrate degraded by the individual pathways were dependent on the concentration of vinyl chloride presented to the organism. However, these variations in apparent first-order constants are equally consistent with the existance of a single saturable process and do not provide any conclusive experimental evidence for the existence of multiple biochemical pathways.

Watanabe et al [175] reported that the largest amounts of radioactivity in rats exposed to 14C-(1,2-)vinyl chloride at 10 or 1,000 ppm (25.6 or 2,560 mg/cu m) for 6 hours remained, 72 hours after exposure, in the liver and skin. For the liver, skin, carcass, muscle, lungs, and kidneys, μg equivalents of radioactivity per g of tissue were higher at 1,000 ppm than at 10 ppm. When the data were normalized for metabolized vinyl chloride, an apparent increase, although not a statistically significant one, was observed in the 14C activity of the liver and skin at 1,000 ppm.

In the rats exposed at 10 ppm, a greater percentage of the total recovered radioactivity was excreted in the urine and a smaller percentage in the expired air than in rats exposed at 1,000 ppm [175]. The apparent first-order rate constants for pulmonary excretion at 10 and 1,000 ppm were 0.034 ±0.002 and 0.031 ±0.01/hour, respectively, equivalent to half-lives of 20.4 and 22.4 minutes, respectively.

The urinary excretion of radioactivity as a function of time for both concentrations of airborne vinyl chloride was nonlinear [175]. This could indicate that elimination was occurring from at least two compartments [176]. From the initial linear portions of these data, apparent first-order rate constants were 0.151 ±0.009 and 0.168 ±0.001/hour, corresponding to half-lives of 4.6 and 4.1 hours for 10 and 1,000 ppm, respectively. No kinetic analysis was performed on the slow phase, or second part, of the curve, since it represented less than 3% of the total urinary radioactivity.

In 1976, Watanabe et al [177] reported that, in male rats given 14C-(1,2-)vinyl chloride in single oral doses of 0.05, 1.0, or 100 mg/kg, the

percentage of radioactivity in the expired air varied in a dose-dependent manner. At 100 mg/kg, 67% of the administered radioactivity was recovered as unmetabolized 14C-vinyl chloride, while at the lower doses, only 1-2% was recovered as 14C-vinyl chloride. The percentage of 14C activity detected as carbon dioxide was greater (13%) at 1.0 mg/kg than at 0.05 (9%) or at 100 mg/kg (2%). Urinary and fecal excretion of 14C activity was higher at 0.05 and 1.0 mg/kg than at 100 mg/kg. The same trend was observed for the carcass and tissues. Analysis of tissues for 14C activity at 72 hours indicated that the liver contained three to six times as much radioactivity/g of tissue as the other tissues. The proportion of the dose remaining in the tissues after 72 hours in the 0.05- and 1.0-mg/kg dose groups was greater than that in the 100-mg/kg group.

Watanabe et al [177] indicated that the kinetics of the pulmonary elimination of oral doses of vinyl chloride at 0.05 and 1 mg/kg were essentially similar and monophasic. The apparent first-order rate constants for the lower doses were 0.013 ±0.001 and 0.012 ±0.001/minute, corresponding to half-lives of 53.3 and 57.8 minutes, respectively. The characteristics of excretion of a dose of 100 mg/kg, however, indicated a biphasic response during the first 4 hours after administration. Separation of the response into a rapid and a slow component gave apparent first-order rate constants of 0.048 ±0.005 and 0.017 ±0.008/minute, equivalent to half-lives of 14.4 and 40.8 minutes.

Urinary excretion curves after single oral doses of vinyl chloride indicated a multiphasic mode of elimination [177]. The linear portion of each curve extended from 12 to 36 hours after administration. The first-order rate constants were estimated to be 0.155 ±0.006, 0.15 ±0.002, and 0.152 ±0.011/hour, equivalent to half-lives of 4.5, 4.6, and 4.6 hours for doses of 0.05, 1.0, and 100 mg/kg, respectively. Ninety-seven percent was excreted within 36 hours. After 36 hours, the excretion curves were quite variable and represented less than 3% of the total urinary activity; hence, no estimates of rate constants were made.

Hefner et al [178], in 1975, reported that when the whole body (excluding the head) of a male rhesus monkey was exposed to 14C-(1,2-)vinyl chloride at 7,000 ppm (17.9 g/cu m) for 2 hours, and a second monkey was similarly exposed at 800 ppm (2.1 g/cu m) for 2.5 hours, radioactivity could be detected only in the liver, bile, and kidneys. They also reported that very little gaseous vinyl chloride was absorbed percutaneously, 0.023 and 0.031% of the total available radioactivity at 7,000 and 800 ppm, respectively.

Gehring et al [179] reported that metabolism of vinyl chloride by rats did not increase proportionately as the concentrations increased from 1.4 to 4,600 ppm (3.58 to 11,776 mg/cu m). The nonlinearity of the amount of vinyl chloride metabolized during the 6 hours of exposure was reported to be in accordance with Michaelis-Menten kinetics, rather than with apparent first-order kinetics. From the Michaelis-Menten kinetic model, the authors

estimated that the theoretical maximum amount (Vm) of vinyl chloride that could be metabolized in 6 hours was 8,558 ±1,147 μg and the apparent Michaelis constant (Km) was 860 ±159 μg/liter of air.

Gehring et al [6] analyzed the results obtained by Watanabe et al [177] and concluded that vinyl chloride elimination tended to be dose dependent and that the primary pathways of vinyl chloride metabolism became saturated as the oral dose of vinyl chloride increased, permitting elimination by another pathway(s). From the urinary excretion curves of Watanabe et al [177], Gehring et al [6] concluded that, since the slopes, and therefore the rate of elimination (half-lives of 4.5 hours), did not change, urinary excretion was not affected by dose. They also concluded that elimination kinetics of vinyl chloride in expired air after a dose of 0.05 or 1.0 mg/kg indicated a monophasic process, whereas at a higher dose (100 mg/kg), biphasic elimination kinetics were indicated. The half-life for elimination for the 100-mg/kg dose was found to be 14 minutes, which corresponded with the half-life for vinyl chloride in blood reported by Withey [180]. Gehring et al [6] interpreted these results to mean that "vinyl chloride is bound reversibly to some site in the body having a finite capacity. As the dose increases, the availability of the binding sites decreases and the chemical is free to find its way to other sites as well or to be eliminated." The authors also concluded that the fate of vinyl chloride within the body changed with dose, and that pulmonary excretion of vinyl chloride was not a rate-limiting step in metabolism.

In 1975, Green and Hathway [5] reported on a whole-body autoradiographic study in which rats were given single oral doses of 30 microcuries of 14C-(1,2-)vinyl chloride, which showed that, at 4 hours after administration, the gastrointestinal tract was free of radioactivity except for the large intestine, which contained trace amounts. After 2 hours, a distinct localization of 14C was noted within sectioned tubules of the paraauricular region, which the authors thought might be localized in the Zymbal glands.

Green and Hathway [5] also found that excretion of radioactivity by four rats given single iv or ip doses of 250 or 450 mg/kg of 14C-(1,2-)vinyl chloride, containing 2 microcuries of 14C, in a beta-hydroxyethyllactamide solution was completed within 72 hours. Rats given similar oral doses of 14C-vinyl chloride were still excreting small amounts of 14C after 72 hours. The greatest percentage of the radioactive label in the lower oral dose was excreted in the urine; only small amounts of radioactivity were eliminated in expired air as unchanged vinyl chloride and [4,6,175,177,186,187] the high oral dose, approximately 92% of the label, was eliminated in expired air as unchanged vinyl chloride and less than 1% as carbon dioxide. The authors stated that, nevertheless, about 100 times more vinyl chloride was metabolized at the higher oral dose than at the lower one.

At an iv dose of 250 μg/kg, 99% of the vinyl chloride was excreted unchanged in expired air within an hour after injection, including 80% within 2 minutes [5]. The excretion profile of vinyl chloride after a single ip injection at the low dose was intermediate between that occurring with oral or

iv administration. The authors suggested that some of the vinyl chloride in blood was excreted unchanged through the lungs and some was absorbed into the hepatic-portal system and metabolized by the liver.

From these data, the authors [5] concluded that the change in excretion pattern between high and low doses was due to a "saturable drug metabolism and to a highly efficient arterial-alveolar transfer of unchanged vinyl chloride from systemic blood that leaves a relatively low concentration of material available for biotransformation in successive passes through the liver."

In another experiment by Green and Hathway [5], three rats that received 3, 30, or 300 mg/kg/day of nonradioactive vinyl chloride by oral intubation for 60 days were given single oral doses of 14C-(1,2-)vinyl chloride (0.6 mg/kg, containing 2 microcuries) on days 1 and 60. For the first 24 hours after administration of the radiolabeled vinyl chloride, urine and expired air were monitored for radioactivity. The authors concluded that chronic exposure for 60 days did not affect the excretion rate for a single oral dose of 14C-vinyl chloride. The authors also concluded that vinyl chloride did not induce its own metabolism and that excretion data for a single dose also applied to the chronic situation.

(2) Identification of Metabolites

Gothe et al [3], in 1974, analyzed the metabolites produced from vinyl chloride in vitro by a microsomal supernatant from rat liver in the presence of an NADPH-generating system. Vinyl chloride was bubbled through the microsomal system, to which 3,4-dichlorobenzenethiol had been added as a trapping agent for reactive metabolites. After 2 hours of exposure, the products identified were consistent with the formation of chloroethylene oxide, chloroacetaldehyde, or both.

A similar study by Barbin et al [2], using a mouse liver microsomal system and 4-(4-nitrobenzyl)pyridine, showed that a volatile metabolic adduct of vinyl chloride was formed that had an absorption spectrum identical to that of the adduct of chloroethylene oxide but different from the adduct of chloroacetaldehyde. They concluded that chloroethylene oxide was the primary metabolite of vinyl chloride in their system.

Chloroethylene oxide was chemically synthesized by Zief and Schramm [181] and Gross and Freiberg [182]. Upon standing, chloroethylene oxide was observed to readily rearrange to chloroacetaldehyde. In an aqueous solution at pH 7.4 and 37 C, chloroethylene oxide had a half-life of 1.6 minutes and its rearrangement followed first-order kinetics [183].

Radwan and Henschler [184] reported that small quantities of monochloroacetic acid could be detected when vinyl chloride at 100-2,000 ppm (256-5,120 mg/cu m) was perfused through isolated rat livers. They reported a slight increase in the concentration of methemoglobin in the system, which they considered indicative of the formation of peroxide intermediates.

Watanabe et al [175] reported that during the first 24 hours after exposure of rats to 14C-(1,2-)vinyl chloride 10 or 1,000 ppm (25.6 or 2,560 mg/cu m) the nonvolatile urinary metabolites were N-acetyl-S-(2-hydroxyethyl)cysteine, thiodiglycolic acid, and a third metabolite that was not identified. They concluded that the proportion of 14C eliminated by various routes was concentration dependent. Moreover, the dominant route of excretion at both concentrations was in the urine and the metabolites were predominantly nonvolatile or polar. This finding supports the earlier conclusions of Hefner et al [4] and Watanabe et al [177] that the elimination of vinyl chloride metabolites was dose dependent. The authors also suggested that metabolism occurred at a reduced rate because body burden in terms of equivalents of radioactivity increased by only 27-fold as the concentration of vinyl chloride was increased from 10 to 1,000 ppm. They concluded that this also indicated that the primary metabolic pathway for vinyl chloride was saturable at high concentrations, specifically at 1,000 ppm. This work, in addition to the work of Hefner et al [4], tends to support a hypothesis that, at concentrations of vinyl chloride above 220 ppm, alternate metabolic pathways exist.

Hefner et al [4] reported that the urinary metabolites from rats exposed for 4, 5, or 7 weeks to vinyl chloride at 5,000 ppm (12.8 g/cu m) were similar. The polar metabolites in the urine appeared to be conjugated with glutathione or cysteine through covalent linkages to the sulfhydryl groups. Chromatographic analysis suggested the presence of S-(2-hydroxyethyl)cysteine. Two theoretically possible metabolites, S-(2-chloroethyl)cysteine and S-(2-carboxymethyl)cysteine, were not detected, but Hefner et al postulated that S-(2-carboxymethyl)cysteine might not have been adequately resolved from the urine background. When rats were exposed to vinyl chloride at 5,000 ppm for 9 weeks, chromatographic analysis of their urine showed the additional presence of monochloroacetic acid. Muller et al [185] exposed male rats continuously to vinyl chloride at 1,000 ppm for 48 hours, and they found thiodiacetic acid as well as S-(carboxymethyl)cysteine in the urine.

To identify the probable urinary metabolites of vinyl chloride after its administration by oral intubation, Green and Hathway [5] gave each of four rats three doses of 50 mg of 14C-(1,2-)vinyl chloride/kg at 3-hour intervals, for a total dose of about 10 microcuries of 14C. Major metabolites of vinyl chloride were identified by mass spectral analysis as thiodiglycolic acid, S-(2-chloroethyl)cysteine, and N-acetyl-S-(2-chloroethyl)cysteine. Thiodiglycolic acid contained 47% of the excreted label, whereas S-(2-chloroethyl)cysteine and N-acetyl-S-(2-chloroethyl)cysteine each accounted for 23% of the urinary label. Urea, glutamic acid, and monochloroacetic acid were responsible for 6, 0.5, and 0.5% of the urinary 14C, respectively. Radiolabeled methionine and serine were present in trace amounts. The authors also stated that thiodiglycolic acid is the major metabolite (61%) of monochloroacetic acid in the rat.

Watanabe et al [177] also found three major and several minor high-pressure liquid chromatographic peaks that contained about 95% of the total

14C activity in urine samples from rats after oral doses of 0.05, 1.0, or 100 mg of 14C-(1,2-)vinyl chloride/kg. Two of the major peaks were identified as N-acetyl-S-(2-hydroxyethyl)cysteine and thiodiglycolic acid; the third major peak could not be identified.

(3) Proposed Pathways

Investigators have postulated that there are at least two pathways for the metabolism of vinyl chloride, both leading to similar end products [4,6,175,177,186,187]. Some have stated that one pathway, suggested to be active at low levels of absorption, begins with a hydration reaction whose product is chloroethanol. A proposed second pathway, suggested to be predominant at high absorption levels, involves the oxidation of vinyl chloride to chloroethylene oxide by microsomal enzymes. These two pathways converge with the formation of chloroacetaldehyde as the second step in each. Investigators have also postulated that the metabolism of vinyl chloride involves the formation of free radicals [5,157].

Reynolds et al [188], in 1976, proposed a scheme in which an epoxide (chloroethylene oxide) was produced as a primary reactive metabolite of vinyl chloride. This would involve the hepatic mixed-function oxidase system [189,190], particularly the cytochrome P-450 component [191,192]. A wide variety of oxidative reactions, including epoxidation, can be mediated by these enzymes, located in the membranes of the endoplasmic reticulum of liver cells, with NADPH serving as an electron donor. Rearrangement of the epoxide could then occur, producing a beta-chlorinated acetaldehyde, a diol, or a glutathione conjugate as a secondary metabolite. These products could be formed by interaction of the epoxide with epoxide hydrase or with glutathione epoxide transferase [188].

Watanabe et al [177] reported that, at oral doses of 0.05 or 1 mg of 14C-(1,2-)vinyl chloride/kg, 14C was consistently eliminated in the urine as nonvolatile, polar metabolites and in the expired air as carbon dioxide. At an oral dose of 100 mg/kg, however, the primary route of excretion was by expiration of unchanged vinyl chloride. This indicated to the authors not only that metabolic pathways for vinyl chloride are dose dependent, but also that the process contains a saturable component. Comparing these results with their previous findings [175], the authors also concluded that the metabolic fate of vinyl chloride is independent of the route of administration.

In both oral and inhalation exposures to vinyl chloride, N-acetyl-S-(2-hydroxyethyl)cysteine was a major urinary metabolite [175,177]. One study [193] has indicated that this compound could be formed from S-formylmethyl cysteine and S-formylmethyl glutathione, which at one time were considered either not to be formed or to be metabolized to S-carboxymethyl cysteine [193]. Although Green and Hathway [5] identified (2-chloroethyl)cysteine and N-acetyl-S-(2-chloroethyl)cysteine as urinary metabolites of vinyl chloride in rats, the formation of these products may be an artifact [177,185] of the

method of separation (methanol derivatization produces the chloro-compound, whereas diazomethane derivatization produces the hydroxy-compound) [194,195].

From data presented by other authors [5,175,177], showing the formation of 14C-carbon dioxide after administration of 14C-vinyl chloride, Plugge and Safe [196] proposed two additional alternatives for its pulmonary metabolism. The first assumed that the metabolism of vinyl chloride proceeded by the addition and transfer of a chloroacetyl group to coenzyme A and by subsequent metabolism in the Krebs cycle. The second scheme assumed formation of glycolate followed by oxidation to glyoxylate, which entered the C-2 and C-1 pools. By analogy with the metabolic pathway for chloroethylene oxide, the glycolate alternative seems to be the more feasible one [163].

Chloroethanol has been reported to be transformed in vivo and in vitro via rat liver enzymes to S-carboxymethyl glutathione, which can also be derived from the two compounds, S-formylmethyl glutathione and chloroacetate [193]. Chloroacetate has been detected as a metabolite of chloroethanol [197]. Metabolism of either chloroethanol or chloroacetate yields S-carboxymethyl cysteine, thiodiacetate (thiodiglycolate), and small amounts of glycolate [197,198]. In another investigation, thiodiacetate was detected as a product of the metabolism of S-carboxymethyl cysteine [199]; this conversion has been confirmed by Yllner [198].

Bonse and Henschler [1], in a 1976 review of the metabolism of chlorinated ethylenes, concluded that their oxidation via monooxygenases to corresponding oxiranes (epoxides) consituted the initial metabolic reaction. The authors suggested that electrophilic reactions or alkylation of cellular components were essentially responsible for the toxicity of the chlorinated ethylenes and that the other pathways were generally part of a detoxification mechanism. After rearrangement, additional metabolic steps, including oxidation of either aldehydic or alcoholic derivatives to carboxylic acids were suggested. The authors also suggested hydrolysis of acyl chlorides to acids as an alternate pathway.

Green and Hathway [5,195] speculated that several routes might exist for vinyl chloride metabolism in rats. Their first suggestion was oxidative biotransformation involving molecular oxygen and the formation of chloroethylene oxide, which would then spontaneously rearrange to chloroacetaldehyde. Both chloroethylene oxide and chloroacetaldehyde can react with glutathione to form S-(formylmethyl)glutathione, which in turn can be converted to S-(2-hydroxyethyl)cysteine. Chloroacetic acid is also formed from chloroacetaldehyde and subsequently metabolized via the Krebs cycle to glutamic acid. Formaldehyde would also be formed and metabolized to carbon dioxide and urea. Since serine and methionine are synthesized in part from formaldehyde, they also could be formed. The second suggested reaction was the formation of the previously identified metabolites, S-(2-chloroethyl)cysteine and N-acetyl-S-(2-chloroethyl)cysteine. These reaction products were thought to be the result of equilibrium interactions of S-(2-

hydroxyethyl)cysteine and N-acetyl-S-(2-hydroxyethyl)cysteine through cyclic intermediates [195]. The third suggested reaction was conversion of S-(carboxymethyl)cysteine, by oxidation and transamination, to thiodiglycol, and its subsequent oxidation to thiodiglycolic acid. The authors [195] concluded that chloroacetic acid was not a part of the major degradative pathway for vinyl chloride, but simply a byproduct of chloroacetaldehyde metabolism, unless however, the glutathione conjugation mechanism were inhibited, whereupon the conversion of chloroacetaldehyde to chloroacetic acid would become an important detoxification alternative. They further supported this hypothesis by administering several vinyl chloride metabolites to rats and showing that chloroacetaldehyde and S-(carboxymethyl)cysteine, but not chloroacetic acid, were in the direct pathway for the formation of thiodiglycolic acid. These authors [195] also identified small quantities of N-acetyl-S-vinylcysteine as a urinary metabolite of vinyl chloride in rats, thus lending credence to the hypothesized pathway of an equilibrium between the chloro- and the hydroxy-ethyl glutathione derivatives, possibly through an episulphonium ion intermediate.

Plugge and Safe [196], in a 1977 review postulated that the metabolism of vinyl chloride occurs both in vivo and in vitro via the mixed-function oxidase system, primarily through the cytochrome P-450 system, to an oxirane [153], in this case chloroethylene oxide. The oxirane (epoxide) formed from vinyl chloride would be a strong electrophilic molecule, and it may be unstable because of the presence of its asymmetric chlorine. This instability could result in intramolecular rearrangement of the chloroethylene oxide to chloroacetaldehyde. The authors considered that both chloroethylene oxide and chloroacetaldehyde would bind either directly or enzymatically to glutathione, thereby forming S-formylmethyl glutathione. Via an NAD+-dependent aldehyde dehydrogenase, chloroacetaldehyde could also be oxidized to chloroacetate. This particular compound, if it was not excreted, could bind with glutathione to form S-carboxymethyl glutathione, which in turn could be hydrolyzed to S-carboxymethyl cysteine. S-carboxymethyl cysteine could be either deaminated and decarboxylated to form thiodiglycolate, N-acetylated, or excreted.

Van Duuren [200], in 1975, hypothesized that when rats were given large amounts of vinyl chloride, an epoxidation reaction would occur in which vinyl chloride was converted to chloroethylene oxide by the microsomal mixed-function oxidase system. Chloroethylene oxide would subsequently be reacted or would spontaneously rearrange to chloracetaldehyde [201].

Hefner et al [4] conjectured that, with exposures below 100 ppm of vinyl chloride, its metabolism would occur by hydration to 2-chloroethanol followed by oxidation to 2-chloroacetaldehyde by the very rapid alcohol dehydrogenase pathway. Since chloroacetaldehyde reacts rapidly with the sulfhydryl of glutathione, only a trace amount of monochloroacetic acid would be formed.

At higher concentrations of vinyl chloride, Hefner et al [4] suggested that the alcohol dehydrogenase pathway could easily be saturated. Compensatory mechanisms, in terms of alternate pathways, were suggested to

these authors by the fact that two different rate constants were obtained from the results of their kinetic analyses. The rate constant was reduced, from 0.00804 ±0.0034/minute (half-life of 86 minutes) for concentrations ranging from 50 to 105 ppm to 0.00265 ±0.00135 (half-life of 261 minutes) for concentrations ranging from 220 to 1,167 ppm, suggesting that additional pathways were mobilized in conjunction with the alcohol dehydrogenase pathway. Hefner et al speculated that one of the mobilized metabolic paths may involve the oxidation of accumulated 2-chloroethanol, and a second plausible alternative appeared to involve direct epoxidation of vinyl chloride. The authors stated that their results were preliminary and inconclusive for support of their hypotheses. Gehring et al [6] concluded that the reactive metabolites formed from the first pathway should possess a lower carcinogenic potential.

In 1977, Bolt et al [202] stated that vinyl chloride in the atmosphere of a closed system equilibrated with that in the tissues of rats within 15 minutes at various concentrations below 250 ppm (the concentration at which the authors stated that saturation of the vinyl chloride-metabolizing enzymes is achieved) when metabolism of vinyl chloride was blocked by 6-nitro-1,2,3-benzothiadiazole (an inhibitor of some cytochrome P-450-dependent oxidations). When rats not given the metabolic blocking agent were tested, the concentration of vinyl chloride in the atmosphere declined exponentially with a half-life of about 1.1 hours.

Bolt et al [202] also reported that exposure of rats to vinyl chloride at concentrations below 250 ppm (640 mg/cu m) produced a straight first-order decline of vinyl chloride in the exposure system indicating concentration dependence, while exposures at concentrations above 250 ppm produced decline curves best described by zero-order kinetics indicating no concentration dependence. They stated that vinyl chloride leaves the body rapidly due to urinary excretion. They observed that approximately 50% of the dose from a 1-hour exposure at an initial concentration of 50 ppm appeared in the urine after 8 hours; approximately 70% appeared after 22 hours. Excretion via feces and via expiration of carbon dioxide was not taken into account. The authors also noted that the calculated rate constant for urinary excretion of 0.19/hour is valid only in their system. They concluded that on continuous or repeated exposure below 220 ppm, no appreciable accumulation of either unchanged vinyl chloride or its major metabolites should be expected. This is consistent with the conclusions of other authors [146,200,203-205], who support the theory that a reactive, short-lived metabolite occurring in low concentrations is responsible for the adverse effects of vinyl chloride, primarily liver damage and carcinogenesis.

Barrio et al [170], Secrist et al [206], and Barbin et al [2] reported that chloroacetaldehyde reacts directly with adenosine or cytidine at pH 3.5-4.5 and 37 C to produce either 3-beta-D-ribofuranosyl-imidazo-(2,1-i) purine or 5,6-dihydro-5-oxo-6-beta-D-ribofuranosyl-imidazo-(I,2-c) pyrimidine. Bartsch and Montesano [158] postulated that covalent binding of

chloroacetaldehyde directly to DNA in the cell could explain the induction of mutagenesis by base-pair substitutions in Salmonella typhimurium TA1530.

An integrative scheme of putative metabolic pathways for vinyl chloride is presented in Figure XVII-3.

(4) Mechanisms

Hefner et al [4] evaluated the effects of potential inhibitors of vinyl chloride metabolism. Pyrazole, an inhibitor of alcohol dehydrogenase, xanthine oxidase, and other enzymes, administered to rats 1 hour before exposure to vinyl chloride at 65 or 1,234 ppm (166.4 or 3,159 mg/cu m) inhibited the metabolism of vinyl chloride by 71.2 and 86.9%, respectively. Other rats were pretreated with ethanol 1.5 hours before exposure to vinyl chloride at 56 or 97 ppm (143.4 or 248.3 mg/cu m) to competitively inhibit alcohol dehydrogenase activity. This resulted in 96.0 and 82.9% inhibition of vinyl chloride metabolism, respectively. Exposure to vinyl chloride at 1,025 or 1,035 ppm (2,624 or 2,649.6 mg/cu m) after pretreatment with ethanol produced inhibition of vinyl chloride metabolism by 46.5 and 35.7%, respectively. Rats pretreated with SKF-525A (a mixed function oxidase inhibitor) before being exposed to vinyl chloride at 65 ppm (166.4 mg/cu m) exhibited no metabolic inhibition. However, when SKF-525A pretreated rats were exposed to vinyl chloride at 1,038 ppm (2,657.3 mg/cu m), inhibition of vinyl chloride metabolism was 18.8%.

Jaeger et al [207,208], Conolly et al [209], and Conolly and Jaeger [210] also evaluated the effects of various inhibitors and promoters of vinyl chloride metabolism in male and female rats. Female rats were not susceptible to hepatotoxic effects of vinyl chloride in any of the experiments. In polychlorinated biphenyl (Aroclor 1254) or phenobarbital-pretreated male rats, pyrazole and SKF-525A protected against acute hepatotoxicity, while disulfiram (an inhibitor of acetaldehyde dehydrogenase) and ethanol potentiated the toxic effects of vinyl chloride. The authors speculated that the protection afforded by SKF-525A was due to mixed-function oxidase inhibition, indicating a disruption in the metabolism of vinyl chloride to an active metabolite. Protection by pyrazole was probably due partially to inhibition of mixed-function oxidases and partially to inhibition of acetaldehyde dehydrogenase. The lack of competitive effects by ethanol indicated to the authors that the conversion of chloroethylene oxide to chloroethanol was decreased, possibly because of increased spontaneous rearrangement of chloroethylene oxide to chloroacetaldehyde (bypassing the acetaldehyde dehydrogenase conversion step) or because of catalase conversion of chloroethanol to a peroxide and subsequent rearrangement to chloroacetaldehyde (again bypassing acetaldehyde dehydrogenase).

Hefner et al [4] determined the effects of vinyl chloride on liver sulfhydryl levels. Male rats were exposed for 7 hours/day to vinyl chloride at concentrations of 15,000 ppm (38.4 g/cu m) for 5 days, 5,000 or 500 ppm (12.8 or 1.3 g/cu m) for 5 days/week for either 1, 3, or 7 weeks, or 50 ppm

(128 mg/cu m) for either 1 hour, 7 hours, or 5 days. No overt signs of toxicity were observed in rats exposed at any concentration. Significant reductions in nonprotein sulfhydryl levels were found in rats exposed to vinyl chloride at 50 ppm for 7 hours, at 500 and 5,000 ppm for 1 and 3 weeks, and 15,000 ppm for 1 week. Although the reduction in nonprotein sulfhydryl levels could not be definitively correlated with exposure concentration, the authors concluded that there was a tendency for such reduction to become less obvious with repeated exposures. Four rats treated with ethanol before exposure to vinyl chloride at 1,070 ppm (2.7 g/cu m) for 105 minutes had significant decreases in hepatic nonprotein sulfhydryl levels (77.0 ±12.8%) as compared with the controls (95.0 ±3.4%). The authors indicated that ethanol alone did not affect the liver nonprotein sulfhydryl levels.

Reynolds et al [211], in 1975, showed that male rats given drinking water containing 0.1% pentobarbital 7 days before either one or five consecutive 6-hour exposures to airborne vinyl chloride at a concentration of 5% (128 g/cu m) exhibited a diffuse vacuolization of the cytoplasm of cells of the centrilobular liver parenchyma and focal areas of necrosis of midzonal parenchyma after the exposure. In the livers of pretreated rats exposed to vinyl chloride for 5 consecutive days, the authors found broad tracts of stroma depleted of parenchymal cells that corresponded in distribution and extent to the areas of necrosis found 24 hours after a single exposure. Since pentobarbital, an inducer of mixed-function oxidase activity, appeared to increase the liver toxicity of vinyl chloride, the authors concluded that the endoplasmic reticulum was the primary site for generation of toxic vinyl chloride metabolites. Moreover, Reynolds and colleagues suggested that these metabolites, possioly epoxides, were presumably responsible for the observed cellular injury as well as the potential for tumorigenesis.

Several reports [202,204,205,212,213] have detailed the in vivo and in vitro requirements for covalent binding of vinyl chloride (or its metabolites) with cellular macromolecular constituents, including DNA, RNA, and protein. In addition, these reports have identified some effects of various chemical inducers or inhibitors of cellular metabolic processes on the metabolism of vinyl chloride.

In 1975, Bolt et al [204] reported that rat liver microsomes metabolized vinyl chloride to more polar metabolites during a 90-minute incubation and that these metabolites became covalently bound to the microsomal proteins. In addition, vinyl chloride metabolites became covalently bound to other sulfhydryl-containing proteins or to RNA when added to the incubation mixture. NADPH was reported to be essential to the binding process, hence essential to this metabolic route for vinyl chloride. Similar results were reported with microsomes from human liver, but the authors did not give experimental data.

Kappus et al [205], using the same incubation procedure as that used by Bolt et al [204], confirmed the essentiality of NADPH in the covalent binding process. In an additional paper, Kappus et al [212] reported that continued uptake of 14C-vinyl chloride by liver microsomes depended on NADPH. Without

NADPH, uptake of 14C-(1,2-)vinyl chloride increased rapidly during the first 2 minutes and reached saturation after 5 minutes. With NADPH, the uptake of vinyl chloride continued beyond the incubation time of 60 minutes and a tenfold increase in the uptake of 14C-vinyl chloride by the microsomal preparation was noted. The authors also showed that vinyl chloride could be taken up by both protein and lipid components of microsomal membranes; the single difference noted was that the time course differed from that for uptake by microsomes. Their data also suggested a greater ability on the part of liposomes to bind vinyl chloride reversibly. From these studies, the authors inferred that the NADPH-independent part of microsomal vinyl chloride uptake was at least partially due to the reversible binding of vinyl chloride to the lipids and proteins of the microsomal membranes.

Kappus et al [212] also found that, of the total 14C-(1,2-)vinyl chloride taken up by the microsomes, about 1% was bound irreversibly to the microsomal protein. Moreover, irreversible binding of the vinyl chloride metabolites to the microsomal proteins appeared to depend on the presence of NADPH, the incubation time, and the concentration of the metabolites. In addition, the authors demonstrated that when atmospheric air was replaced by nitrogen in the presence of NADPH, vinyl chloride uptake was reduced. The amount of vinyl chloride metabolites irreversibly bound to protein also was lowered.

Kappus et al [205] reported that vinyl chloride metabolites were also bound to added albumin, but not to concanavalin A, which contains no sulfhydryl groups. They found that the addition of glutathione or glutathione-containing cytosol to the incubation medium caused a 30% depression in covalent binding to cellular proteins [204,212], thus indirectly supporting the concept that free sulfhydryl groups must be present for binding to proteins to occur or for detoxification to occur. In further support of this concept, they reported that inhibition of the microsomal cytochrome P-450-dependent mixed-function oxidases by 4-(1-naphthyl)imidazole inhibited covalent binding by about 85%. Microsomal uptake of vinyl chloride was completely blocked by carbon monoxide, an inhibitor of cytochrome P-450 oxidation reactions [212]. Irreversible binding of vinyl chloride metabolites to proteins was also blocked by carbon monoxide, whether NADPH was present or not. Boiling of the microsomes prior to incubation reduced vinyl chloride uptake in the presence of NADPH, and no irreversibly protein-bound vinyl chloride metabolites were detected. Addition of reduced glutathione to the microsomal incubation mixture with NADPH resulted in very little change in vinyl chloride uptake by the microsomes, but did result in a 25% inhibition of irreversible protein binding.

Microsomal uptake of vinyl chloride was not affected by trichloropropene oxide, an inhibitor of epoxide hydrase [212]. However, irreversibly protein-bound vinyl chloride metabolites were increased twofold. No induction effect on vinyl chloride uptake could be demonstrated in microsomes from phenobarbital-pretreated rats. There also were no changes in irreversible protein binding. Cytochrome P-450, however, was increased in the liver

microsomes from rats pretreated with phenobarbital. Vinyl chloride uptake was similar in liver microsomal preparations containing added glutathione and cytosol obtained from control and pretreated rats. From the data presented, the authors suggested that the initial step in vinyl chloride metabolism involved an oxygenation reaction catalyzed by an enzyme system containing cytochrome P-450. In addition, the authors concluded that chloroethylene oxide was probably the initial reactive metabolite.

Kappus et al [205] presented additional evidence for involvement of the epoxide in the covalent binding reaction by using the xanthine oxidase model system, which generates hydrogen peroxide and an oxygen-radical. They concluded that demonstration of the binding of vinyl chloride metabolites to albumin in the presence of a complete xanthine oxidase system strongly suggested that oxygen radicals, known to be involved in epoxidation by the microsomal enzyme system, convert vinyl chloride to a metabolite that then binds covalently to a protein, such as albumin.

Watanabe et al [214], in 1977, attempted to characterize the binding of vinyl chloride to hepatic macromolecules and nucleic acids by exposing male rats to 14C-(1,2-)vinyl chloride at nominal concentrations of 1, 10, 25, 50, 100, 250, 500, 1,000, or 5,000 ppm (range 2.96-12,800 mg/cu m). The results suggested that increases in exposure concentration did not proportionately increase the total amounts of radioactivity bound to hepatic macromolecules. The percentage of total 14C activity bound to hepatic macromolecules ranged between 20 and 22%, except in rats pretreated with phenobarbital where it reached 39%. Both the metabolized and bound vinyl chloride increased with increasing nominal concentration, but the ratio of bound to metabolized vinyl chloride declined with increasing nominal concentration.

In rats exposed at nominal concentrations of 1, 10, 25, or 50 ppm (range 2.56-128 mg/cu m), Watanabe et al [214] found that the nonprotein sulfhydryl content of the liver was depleted, but not significantly so. However, at 100 ppm (256 mg/cu m) and above, a significant depletion ($P<0.05$) was noted. Since it seemed a reasonable assumption that the major detoxification of the reactive metabolites of vinyl chloride occurs by reaction with nonprotein sulfhydryl groups [186], Watanabe et al [214] considered it important that at nominal concentrations of 100 ppm and higher, a signficant dose-related depletion of that pool could be demonstrated. They also suggested that the carcinogenicity of vinyl chloride was related to the decreased ability of exposed organisms to detoxify the reactive metabolites of vinyl chloride.

Watanabe et al [214] reported that no evidence could be found that would suggest covalent binding of 14C from vinyl chloride to the isolated nucleic acids in their experiments. The authors concluded that vinyl chloride did not preferentially react with intracellular nucleic acids. They mentioned, however, that this finding conflicted with the findings of a previous study by Bolt et al [215] which demonstrated that covalent binding to RNA and DNA occurred after a static exposure to 14C-vinyl chloride at 145 ppm (371.2 mg/cu m). Both Watanabe et al [214] and Bolt et al [215] concluded that vinyl

chloride does not preferentially react with hepatic nucleic acids. However, Watanabe et al [214] reported that five rats pretreated with phenobarbital (80 mg/kg/day) by ip injection 3 days before exposure to 14C-vinyl chloride at a nominal concentration of 100 ppm showed a markedly increased binding of 14C to hepatic macromolecules when compared with nonpretreated animals, even though there was no observable increase in vinyl chloride metabolism.

Watanabe et al [214] concluded that their findings did not associate the carcinogenicity of vinyl chloride with a disproportionate increase in binding of its electrophilic metabolites to hepatic macromolecules as the exposure concentration was increased. Because there was no demonstrable evidence to support preferential binding of the electrophilic metabolites to nucleic acids of the hepatocytes, they raised the possibility that the carcinogenic potential of vinyl chloride could not be associated with this commonly accepted mechanism for carcinogenesis. The authors suggested, however, that before alkylation of nucleic acids was excluded as the carcinogenic mechanism, more studies to determine the absence of such alkylation activity in the target tissue rather than the hepatocytes are required. They suggested that the hepatocyte itself, since it is susceptible to the toxicity of vinyl chloride, may function as a detoxifier. This would imply that tissues having a lesser ability to detoxify the reactive metabolites of vinyl chloride may themselves become the victims of toxicity.

Gehring et al [6] stated that since "Toxicity, including carcinogenesis, is a dynamic process involving absorption of a chemical into the body, distribution to various tissues, reversible or irreversible reactions with cellular components, and ultimately clearance from the tissues and the body via metabolism and/or excretion," it follows that "the predictability of animal toxicological data for assessing the hazard of a chemical to man is enhanced if the fate of the chemical per se and/or its degradation products in animals is equated to the fate in man." They stated that under ordinary conditions and over a selected range of doses, chemical kinetics fit a linear differential equation, the implication being that a known increase in dose will result in a linear increase in tissue levels. They added, however, that many metabolic and excretory processes were easily overwhelmed and saturated, thus leading to a situation in which nonlinear Michaelis-Menten pharmacokinetics would prevail. The authors suggested that the results of Hefner et al [4], in which the rate of metabolism of vinyl chloride at low concentrations was rapid and the primary metabolic pathways were overwhelmed at high concentrations, supported this theoretical model.

The data presented above suggest that alkylating metabolites of vinyl chloride, such as chloroacetaldehyde and chloroethylene oxide, are formed in vivo. Both chloroacetaldehyde and chloroethylene oxide can conjugate with glutathione and cysteine and subsequently form the vinyl chloride metabolites that have been identified in urine, such as N-acetyl-S-(2-chloroethyl)cysteine [195], which may itself be a potent alkylating agent by virtue of its half-mustard forming ability. In terms of assessing the hazard of exposure to vinyl chloride, experimental data support the conclusion that the

carcinogenicity of vinyl chloride is a function of the metabolic formation of alkylating metabolites. The urinary metabolites identified so far indicate that the primary deactivation mechanism is conjugation with glutathione, a nonprotein, free-sulfhydryl containing compounds. Experimental data have indicated that as the nonprotein, free-sulfhydryl groups are depleted as a sequel of the absorption and metabolism of vinyl chloride reaction of the alkylating metabolites with tissue macromolecules, such as DNA or RNA, may be more likely to occur. As a result, toxicity of a different order of magnitude may be elicited at higher exposure concentrations.

(b) Vinylidene Chloride

McKenna et al [216] showed that in rats exposed to airborne 14C(1,2-) vinylidene chloride at concentrations of 10 and 200 ppm (39.7 and 794 mg/cu m) for 6 hours covalent bonding occurred in the liver. At 10 ppm, 1-2% of the body burden was expired as unchanged vinylidene chloride, and at 200 ppm, between 4 and 8% was expired unchanged, ie, a twentyfold increase in the exposure concentration increased the total body burdens of vinylidene chloride of both fasted (fasting depletes liver glutathione) and fed rats only fifteenfold.

The pulmonary elimination of vinylidene chloride at both 10 and 200 ppm (39.7 and 794 mg/cu m) was found to be biphasic [216]. First-order rate constants for the rapid and slow portions of the biphasic curve were 0.0345 ±0.0095 and 0.0032 ±0.0013/minute (half-lives of 20 and 217 minutes) at 10 ppm and 0.0324 ±0.002 and 0.0052 ±0.0042/minute (half-lives of 19 and 133 minutes) at 200 ppm. The largest amounts of radioactivity at both concentrations were found in the liver and kidneys. The fasted rats exposed at 10 ppm (39.7 mg/cu m) had more radioactivity in the liver and plasma than the fed animals exposed at 10 ppm. The amount of covalently bound radioactivity in the liver, as compared with body burden of 14C and total metabolism of vinylidene chloride, increased about 26 times with a twentyfold increase in exposure concentrations for the fed rats. The percentage of covalently bound radioactivity in the livers of fasted rats exposed at 200 ppm also was greater than that in the fed animals, although the fasted rats metabolized less vinylidene chloride than the fed animals.

The elimination of radioactivity in rat urine at both 10 and 200 ppm was also biphasic [216]. First-order rate constants for the rapid and slow portions of the biphasic curve were 0.226 ±0.041 and 0.036 ±0.005/hour, (half-lives of 3.1 and 19.3 hours) at 10 ppm and 0.155 ±0.015 and 0.043 ±0.007/hour, (half-lives of 4.5 and 16 hours) at 200 ppm. The urinary metabolites, at 24 hours after exposure, were identified as N-acetyl-S-(2-hydroxyethyl)cysteine and thiodiglycolic acid, with two additional unidentified 14C-labeled fractions.

McKenna et al [217] reported that rats given single oral doses of 50 mg/kg of 14C-(1,2-)vinylidene chloride exhaled 19-29% of the radioactivity as unchanged vinylidene chloride while rats receiving 1 mg/kg exhaled only 1-3%

of the radioactivity as unchanged vinylidene chloride. The increase in pulmonary elimination of vinylidene chloride at the higher dose was accompanied by decreases in 14C carbon dioxide production and in urinary and fecal excretion of 14C. Fasted rats excreted less radioactivity in the urine (35%) than fed animals (47%) at 50 mg/kg. The pulmonary elimination of radioactivity was inconsistent after administration of vinylidene chloride at a dose of 1 mg/kg, although these elimination curves also were biphasic. Rate constants were not calculated, but half-lives for the rapid and slow portions of the curves were estimated to be 25 and 117 minutes, respectively, for both fed and fasted rats. The pulmonary elimination curve at 50 mg/kg was biphasic, with rate constants for the rapid and slow portions of the curve being 0.0332 ±0.0036 and 0.0105 ±0.001/minute (half-lives of 21 and 66 minutes). Elimination reached a peak at 30 minutes in fed rats and at 60 minutes in fasted rats.

The greatest tissue concentrations of 14C after 72 hours were found in the liver [217]. A fiftyfold increase in dose resulted in only a 35-fold increase in nonvolatile radioactive compounds. There was a fiftyfold increase in covalently bound radioactivity in the liver, however, which was greater than the observed increase in metabolism. The urinary excretion profiles were biphasic, with apparent first-order rate constants for the rapid and slow phases of 0.116 and 0.042/hour (half-lives of 6 and 16.8 hours) at both 1 and 50 mg/kg. The major urinary metabolites were the same as those identified after inhalational exposure [216], ie, N-acetyl-S-(2-hydroxyethyl)cysteine and thiodiglycolic acid. McKenna et al [217] also reported that unchanged vinylidene chloride was eliminated only in expired air and was not retained in the tissues for longer than a few hours.

Madrid et al [218] identified two of the four major urinary metabolites isolated from rats exposed to 14C-vinylidene chloride by inhalation at 10 or 200 ppm (39.7 or 794 mg/cu m) for 6 hours and by oral administration (1 or 50 mg/kg) as N-acetyl-S-(2-hydroxyethyl)cysteine and thiodiglycolic acid. The former compound represented about 45% of the total urinary radioactivity, whereas the latter accounted for 25%. The authors concluded that the identification of these two compounds as urinary metabolites supported the hypothesis that glutathione conjugation was a major step in the biotransformation of vinylidene chloride.

Jaeger et al [219], in 1977, reported that fed and fasted male rats exposed to 14C-vinylidene chloride at 2,000 ppm (7.9 g/cu m) for 2 hours did not differ significantly in the rate of vinylidene chloride uptake or of urinary excretion of 14C during the first 24 hours. Of the calculated dose, 36.7 and 36.5% were recovered within 24 hours in the urine of fed and fasted animals, respectively. Thirty minutes after a 2-hour exposure, the kidneys of fasted rats contained both the greater amount of total radioactivity and the larger amount of metabolites that were soluble in trichloroacetic acid (hence, not bound). Fasted rats also had significantly greater amounts of total radioactivity in the spleen, heart, and serum than did fed rats. There was no

significant difference between the 14C contents of the brains of fed and fasted rats.

The livers of fasted rats contained substantial amounts of radioactivity that was trichloroacetic acid-insoluble [219]. This component represented either 14C that was tightly bound to microsomal or mitochondrial macromolecules or that had entered the metabolic pool. The rates of disappearance of the trichloroacetic acid-insoluble 14C from the microsomal and mitochondrial fractions of the liver in fed and fasted rats were similar, although the amounts differed significantly; both had estimated half-lives of less than 3 hours. Significantly more radioactivity was found in the hepatic cytoplasmic fractions of fasted rats than in those of fed rats. The authors suggested that on the basis of their data metabolism of vinylidene chloride was quite rapid, with trichloroacetic acid-soluble components being excreted by the kidney and trichloroacetic acid-insoluble components entering the metabolic pool. They concluded that since a rapid turnover of bound 14C material occurred (half-life less than 3 hours), covalent binding to protein or tissue constituents must have been minimal.

Jaeger et al [219] concluded that fasting had no effect on the rate or on the amount of in vivo metabolism, but that the in vivo metabolic pathway appeared to be significantly different in fasted rats than in fed rats. They also reported that pretreatment with trichloropropane epoxide (an epoxide hydrase inhibitor) significantly increased the toxicity of vinylidene chloride in rats, and on this basis, suggested the possible formation of an epoxide intermediate as a result of the hepatic metabolism of vinylidene chloride.

Several studies [115,220-224] have shown the hepatotoxic effects of inhaled vinylidene chloride on rats to be associated with decreased glutathione concentrations in the liver and liver mitochondria. Fasting of rats before exposure to vinylidene chloride at concentrations of 2,000 ppm (7.9 g/cu m) for 4 hours [115,221], 1,980 ppm (7.9 g/cu m) for 4 hours [220], 250 ppm (992.5 mg/cu m) for 1-24 hours [223], or 200 ppm (794 mg/cu m) for 4 hours [222] resulted in markedly enhanced hepatotoxicity as compared with that seen in fed control rats. Hepatic necrosis was reported in fasted but not in fed rats and was associated with glutathione depletion Elevation of serum alanine alpha-ketoglutarate transaminase activity levels (indicative of liver injury) occurred in fasted rats at 150-200 ppm but only at or above 2,000 ppm in fed rats [115,220]; this difference was also evident in an isolated perfused rat liver system [115].

Diethylmaleate, a material that depletes glutathione, potentiated the hepatotoxic effects of vinylidene chloride on fed rats and on perfused livers from fed rats [115]. Surgical or chemical thyroidectomy (resulting in increased liver glutathione) reduced the severity of hepatotoxic injury in fasted rats exposed to vinylidene chloride at a concentration of 2,000 ppm for 4 hours, whereas thyroxine (which increases the general metabolic rate and decreases glutathione) enhanced the hepatotoxicity of vinylidene chloride [224]. SKF-525A (an inhibitor of mixed-function oxidases) did not affect the

response of fed rats exposed to vinylidene chloride nor did it protect fasted rats from the hepatotoxic effects of such exposure [222]. However, Reichert and Bashti [225] reported that SKF-525A in perfused rat liver preparations diminished the rate of metabolism of vinylidene chloride. These data support the hypothesis that a major pathway for the detoxification of vinylidene chloride involves conjugation with glutathione and that blockage of its conjugation with glutathione greatly enhances its hepatotoxicity.

Jaeger [223] noted that a significant elevation ($P<0.05$) of hepatic citric acid occurred after exposure of rats to vinylidene chloride at a concentration of 250 ppm. He concluded that vinylidene chloride probably affected the mitochondria, leading to inhibition of the Krebs cycle and subsequent mitochondrial damage. Jaeger et al [219], on the basis of prior work [5,152], hypothesized that chloroacetyl chloride, a metabolite of vinylidene chloride, was converted to monochloroacetic acid, which in turn was converted into chlorocitric acid, an inhibitor of the enzyme aconitase. Inhibition of this enzyme would result in an accumulation of citric acid. This hypothesis was predicated by analogy on the hypothesis of lethal synthesis, which suggests that fluoracetic acid is converted to fluorocitric acid, which inhibits aconitase [226].

Short et al [117] reported that the lethality of vinylidene chloride in male and female mice exposed at various concentrations for 22-23 hours was reduced substantially by pretreatment with disulfiram. When exposures were increased to 22-23 hours/day for 2 days, pretreatment with disulfiram, diethyldithiocarbamate, or thiram reduced the lethality of vinylidene chloride in male mice. Pretreatment with methionine or cysteine also reduced the lethality of vinylidene chloride, but instead of protecting in terms of increasing the acute LC50 (as did the other three compounds), these compounds protected by delaying the onset of mortality after exposure.

Short et al [117] also reported that disulfiram pretreatment protected male mice from the hepatotoxic effects of exposure to vinylidene chloride at 60 ppm (238.2 mg/cu m) for 22-23 hours. However, after two consecutive 22- to 23-hour exposures at 60 ppm, there was no protection from hepatotoxicity.

Short et al [117] showed that covalently bound radioactivity could be detected in the macromolecules of the liver and kidneys of mice 4 and 24 hours after an ip injection of 3 mg of 14C-vinylidene chloride/kg. The kidneys contained more bound 14C/mg of protein than did the liver at 4 and 24 hours after administration of vinylidene chloride. Pretreatment with disulfiram greatly reduced the bound 14C in both tissues at both time periods.

Bonse and Henschler [1] proposed in a 1976 review of polychlorinated aliphatic compound metabolism that an oxirane, a postulated metabolic intermediate of vinylidene chloride, spontaneously rearranged to chloroacetyl chloride and was then hydrolyzed to monochloroacetic acid. Since monochloroacetic acid is also a product of vinyl chloride metabolism, they speculated that its formation and fate in vinylidene chloride metabolism followed a similar scheme.

An integrative scheme for vinylidene chloride metabolism is presented in Figure XVII-3.

(c) Vinyl Bromide

In 1940, Abreu and Emerson [227] reported that a slight increase (approximately 2.7 times control value, 0.016-0.043 mg/g wet liver) occurred in the amount of total inorganic bromide in the livers of mice exposed to vinyl bromide vapor at a concentration of 2.5 millimoles/liter (267,400 mg/cu m) for 60 minutes. The authors concluded that this increase in liver bromide content was caused by the in vivo hydrolysis of vinyl bromide.

Barbin et al [2], in 1975, showed that a volatile metabolite was formed when a 50% vinyl chloride-oxygen mixture was passed through an incubation medium containing phenobarbital-pretreated mouse liver microsomes and an NADPH-generating system. The volatile metabolite was identified as chlorethylene oxide. A 1:1 mixture of vinyl bromide and air, when passed through the same microsomal system, produced a reaction product having an absorption spectrum identical to that of the vinyl chloride/oxygen mixture. From these data, the authors concluded that vinyl chloride and vinyl bromide were converted in vitro by microsomal enzymes to the corresponding epoxides.

Conolly et al [209] and Conolly and Jaeger [210] reported that polychlorinated biphenyl (Aroclor 1254)-treated male rats that were then exposed to vinyl bromide at concentrations of 10,000-51,000 ppm (43.8-223.4 g/cu m) for 4 hours developed acute hepatic injury as indicated by increases in serum sorbitol dehydrogenase activity. The authors [209,210] concluded that these data, along with observations of increased toxicity in fasted animals and those treated with an inhibitor of epoxide hydrase, suggested that the acute hepatotoxicity of vinyl bromide was mediated through epoxide intermediates. They felt that the similarity between the acute effects of vinyl bromide and of other vinyl halides indicated that hepatic mixed-function oxidase induction had occurred to such an extent that the rate of epoxidation exceeded the rate of detoxification, so that hepatic damage occurred. Conolly and Jaeger [210] concluded also that both glutathione and epoxide hydrase were involved in the detoxification of vinyl bromide metabolites in polychlorinated biphenyl-treated rats.

(d) Vinyl Fluoride and Vinylidene Fluoride

Dilley et al [228] found that vinyl fluoride and vinylidene fluoride could undergo biotransformation and that the carbon-fluorine bond could be broken. They reported that male rats exposed by inhalation to vinyl fluoride or vinylidene fluoride for 30 minutes at concentrations of 3,000 and 2,200 ppm (6.64 and 5.76 g/cu m), respectively, excreted significantly increased ($P<0.01$) amounts of fluoride ion daily when compared with the nonexposed control animals. The value for excreted fluoride ion 6 days after exposure to vinyl fluoride was 3.77 ±0.23 μmol. There was a significant increase ($P<0.05$) in urinary output for vinyl fluoride-exposed animals that persisted for the 14

days of measurement. The values for excreted fluoride 1, 5, 6, and 7 days after exposure to vinylidene fluoride ranged from 3.02 ±0.14 to 4.30 ±0.49 μmol. No diuresis was observed in vinylidene fluoride-exposed animals.

The authors also noticed a cyclic excretion pattern for vinylidene fluoride in which there was major excretion directly after exposure and again 5 days after exposure [228]. The authors proposed that either the fluoride ion, the parent compound, or the fluorine-containing metabolites were stored in some biologic compartment and then released with a turnover rate of about 5 days.

Conolly and Jaeger [210] reported that fasting had no effect on hepatotoxicity in polychlorinated biphenyl-treated rats exposed to vinyl fluoride at 10,000 ppm (18.8 g/cu m) for 4 hours. Three consecutive daily doses of trichloropropane epoxide (an inhibitor of epoxide hydrase) before exposure to vinyl fluoride produced increased mortality in rats; however, fasting in addition to administration of trichloropropane epoxide did not exert a synergistic effect. This indicated to the authors that glutathione may not be important in the detoxification of vinyl fluoride metabolites in polychlorinated biphenyl-pretreated rats, but that epoxide hydrase may be involved in detoxifying fluoroethylene oxide.

Structure-Activity Considerations

Vinyl chloride has been shown to be a human and animal carcinogen, inducing characteristic angiosarcoma of the liver [79,84,87,134,135,140]. Vinylidene chloride [140,141] and vinyl bromide [143] have also been shown to induce this characteristic tumor in animals. No information is available concerning the induction of tumors by vinyl fluoride or vinylidene fluoride. An assessment of the carcinogenic potential of the vinyl halides as a group can be attempted by applying the available carcinogenicity and mutagenicity data to the structure-activity interrelationships of the five compounds.

Such an assessment of the carcinogenic potential of the vinyl halides requires an understanding of their mechanisms of action. A review of the available metabolic data on vinyl chloride indicates that several reactive intermediates are produced (Figure XVII-3). These intermediates are electrophiles, which have been shown to form covalent bonds with cellular macromolecules. A similar metabolic route may be operative for the other vinyl halides, producing similar intermediates that also may bind covalently to cellular constituents. The carcinogenic potential of each of the vinyl halides would therefore be the resultant potentials of these possible metabolites and of any unmetabolized compound.

One hypothesis for the mechanism by which vinyl chloride expresses its carcinogenic potential involves its metabolism, via the microsomal cytochrome P-450 mixed-function oxidase system, to the oxirane (epoxide), chloroethylene oxide [1,196,200,212]. One basis for predicting the carcinogenicity of

inadequately tested vinyl compounds is the assumption that metabolic epoxidation is involved in their metabolism as well, and that the epoxide is the major reactive intermediate. The relative carcinogenic potential would then be influenced by the relative ease with which the epoxides are formed from the corresponding halo-olefins and the relative reactivity of a particular epoxide toward cellular nucleophiles.

The propensities of vinyl halides to undergo chemical transformation to epoxides are dependent on the electronegativities of the substituents on the olefinic nucleus [229]. Increasing electronegativity results in rarefaction of the electron density of the double bond, and thereby in a decrease in the susceptibility of the olefin to epoxidation. Thus, for the vinyl halides under consideration, the expected order of non-enzymatic epoxidation would appear to be vinyl bromide > vinyl chloride > vinylidene chloride > vinyl fluoride > vinylidene fluoride. Bonse and Henschler [1] supported this scheme of epoxidation by showing that the order of the rate of ozonization of a series of olefins was ethylene > vinyl chloride > trichloroethylene > tetrachloroethylene. Also, a study of the reaction rates of ozone, a strong oxidizing agent, with chlorinated and conjugated olefins showed that the rate of ozone attack decreased strongly (1,000-fold from vinyl chloride to tetrachloroethylene) as the number of chlorine atoms in the olefin molecule increased [230].

Hanzlik et al [231] found that a series of para-substituted styrenes (vinyl benzenes) underwent metabolism via the cytochrome P-450 system of rat-liver microsomes at rates that were essentially substituent independent. From the kinetic data of these authors, RL Schowen (written communication, August 1977) calculated a Hammett rho value (a measure of the sensitivity of the reaction series to ring substitution) of around -0.2. Using this value and the Hammett equation, Schowen suggested that substituted vinyl compounds for which the substituents have effective Hammett sigma values (measures of the substituents' abilities to attract or repel electrons by inductive and resonance effects) which differ by as much as 2 units, should differ in rates of oxidation by only a factor of 2.5. Since the sigma* values (measures of inductive effects alone) for the halogens are fluoride, 1.10; chloride, 1.05; and bromide, 1.02 [232], Schowen concluded that these vinyl compounds would be expected to generate epoxide metabolites at similar rates.

Schowen also addressed the problem of estimating the reactivity of the epoxide intermediates that are assumed to be formed. He made two analyses, each dependent on an experimentally derived measure of reactivity for halide compounds. One analysis used Swain-Scott substrate factors, S, which reflect electrophilicity [232]. Based on S values determined for other halide alkylating agents, ag, S = 1.00 for $ClCH_2CO_2^-$, 1.10 for $BrCH_2CO_2^-$, 1.33 for $ICH_2CO_2^-$, and for nonhalide agents, Schowen suggested that alkylating potentials of the vinyls relative to vinyl chloride would vary over a range of no more than 16. In a second analysis using a leaving group parameter, L, from the Swain-Lohmann equation [233] for the halides (bromine, 0.0; chlorine, -1.61; fluorine, -3.60) and reaction constants determined from these L values

for halide compounds, he estimated that the relative reaction rates of chloro to fluoro compounds would range from 63 to 1,585 and that those of bromo to chloro would range from 25 to 398. Thus, the fluoro derivatives could be roughly 1,500-fold less reactive than the chloro derivatives, while the bromo derivatives could be roughly 400 times more reactive. Although the second method predicts less alkylating potency for the fluoro compounds than the first method, both methods indicate that at least the chloro- and bromo-vinyls would be expected to form active alkylating intermediates.

The available experimental evidence lends some support to the theoretical considerations regarding epoxidation, but the information is spotty, and comparative studies on the relative rates of epoxidation of the five vinyl halides under consideration are not available. Besides the evidence for formation of the epoxide of vinyl chloride, the production of epoxides in the metabolism of vinylidene chloride [1,173] and vinyl bromide [2] has only been postulated. No evidence has been located for the metabolic epoxidation of vinyl fluoride or vinylidene fluoride. Other chlorinated olefins whose metabolism via an epoxide has been postulated are trichloroethylene and tetrachloroethylene. Evidence in support of the formation of the corresponding epoxides has been reviewed [1].

Bonse and Henschler [1] also attempted to estimate the relative reactivities of vinyl intermediates. They noted that a common feature of those vinyl halides found to be mutagenic is their potential for the formation of asymmetric oxirane intermediates. Asymmetrically substituted oxiranes have been found to be less stable and, hence, presumably more reactive than the symmetrical ones such as those that would be expected to be formed from some of the vinyl halides that have been tested and found inactive as mutagens, eg, cis- and trans-1,2-dichloroethylene [151-153]. The authors suggested that the formation of an asymmetrical intermediate might be a useful criterion for predicting mutagenic and carcinogenic potentials of the vinyl halides.

The solubilities of the vinyl halides in water increase in the following order: fluoride, difluoride, chloride, dichloride, and bromide. Their molar solubilities are essentially zero, 0.003, 0.018, 0.026, and 0.053, respectively (see Table XVII-1). Their solubilities in blood might well follow this same order although lipid solubility and various types of macromolecular binding cannot be ignored. That is to say, the relative amount absorbed through the lungs may be about 20 times greater for vinyl bromide than for vinylidene fluoride.

The experimental evidence and theoretical considerations are compatible with the hypothesis that the five vinyl halides are capable of undergoing biochemical epoxidation but that the two fluoro olefins may be somewhat less susceptible than the other vinyl halides to this reaction. Extrapolation of the estimates of Schoven suggests that vinylidene chloride, and vinyl bromide, may have a similar or greater carcinogenic potential than vinyl chloride, but that vinyl fluoride and vinylidene fluoride, although possibly carcinogenic,

on the basis of limited mutagenicity data, are likely to be less reactive (possibly up to 1,500 times less) than the other three.

The suggestion that the other vinyl halides resemble vinyl chloride in their effects and mechanism of action is debatable on the basis that normal mammalian biochemical constituents such as steroids and unsaturated fatty acids contain the vinyl moiety and are not suspected of carcinogenicity. It should be noted that variation either above or below a physiologically critical concentration range for many of these compounds may lead to toxic effects. NIOSH is unable to suggest any systematic relationship between the toxicities of all compounds containing the vinyl group, although vinyl halides are treated here as a group because of the similarities in chemical and physical properties. It may well be that it is the presence of the halide moiety which imparts a particular toxicity range to these agents by allowing them to be activated, epoxidated, or hydrated at sufficiently high rates, and, at the same time imparting to the metabolites a characteristic stability and intrinsic activity that allows them to reach and interact with vital cellular constituents.

In the absence of additional toxicologic data on the vinyl halides under consideration, the relevance of the theoretical considerations discussed above to estimation of the potential toxicity of these compounds might be tested by developing mathematical relationships between biologic activities and physicochemical parameters. These parameters could also consider any variations in steric interactions. Sufficient consistent biologic data are not yet available, however, to permit the development of such equations.

Correlation of Exposure and Effect

The vinyl halides have been shown to induce effects on the nervous, circulatory, respiratory, integumentary, skeletal, and digestive systems in humans and laboratory animals. These effects are summarized in Tables III-2 to III-10. The modes of action of the vinyl halides are not clearly understood, and there is little published information on any of them other than vinyl chloride. It has been proposed that expression of the tumorigenic and mutagenic potential of vinyls depends on metabolic intermediates; this possibility is discussed in the section on Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction.

Lethal concentrations of the vinyl halides have been determined. For vinyl chloride, the LC50 for mice exposed for 10 minutes and observed for an unspecified period was 239,580 ppm [105]. In another study, the LC50's for 2-hour exposures were calculated as 117,500 ppm for mice, 156,000 ppm for rats, and 238,000 ppm for guinea pigs and rabbits [104]. The LC100's were also

determined in this experiment; they were 150,000 ppm for mice, 210,000 ppm for rats, and 280,000 ppm for guinea pigs and rabbits. The duration of the observation period was not reported.

For vinylidene chloride, the 4-hour LC50 in rats has been reported as 6,350 ppm with a 14-day observation period [116]. Other authors [118] reported that from two to four of six rats died within 14 days after one 4-hour exposure at a concentration of 32,000 ppm. A single 22- to 23-hour exposure of rats produced LC50 values of 98 ppm for males and 105 ppm for females [117]. Two exposures for 22-23 hours gave LC50 values of 35 ppm for male rats, and the LT50 for exposure at 20 ppm was reported as 4 days. This experiment showed that mortality in rats exposed to vinylidene chloride is in part a function of the total accumulated dose. The 24-hour LC50 value in rats after one 4-hour exposure was determined as 15,000 ppm for fed animals and 600 ppm for animals fasted for 18 hours [115]. The oral LD50 has also been calculated for adrenalectomized rats as 84 mg/kg for 24 hours and 81 mg/kg for 96 hours; in sham-operated controls, the LD50 was 1,550 mg/kg for 24 hours and 1,510 mg/kg for 96 hours [126]. This indicated that adrenal hormones provide some protection against the acute effects of vinylidene chloride in rats.

Exposure to vinyl bromide at concentrations of 171,000 ppm has been tolerated by rats for 10 minutes [105]. In another experiment [127], concentrations of 100,000 ppm were shown to be 100% lethal in rats after 15 minutes, and some rats died (percentage unspecified) at concentrations of 50,000 ppm for 7 hours. An oral LD50 of 500 mg/kg (given in corn oil) for vinyl bromide was also determined for rats [127].

Vinyl fluoride has been reported to be not lethal to rats exposed at a concentration of 80%, with 20% oxygen, for 12.5 hours [128]. Vinyl fluoride at 100,000 ppm, 7 hours/day, 5 days/week, for 6 weeks caused no observed adverse effects on rats according to Lorieno, quoted by Carpenter [128]. However, Connoly et al [209] reported that four of seven rats pretreated with Aroclor 1254 and exposed to vinyl fluoride at concentrations of 102,000 ppm died after a 4-hour exposure.

Vinylidene fluoride has been reported not to be lethal to rats exposed at a concentration of 80%, with 20% oxygen, for 19 hours [128]. Another author [118], however, stated that a static exposure to vinylidene fluoride at 128,000 ppm for 4 hours was sufficient to kill from two to four of six rats within 14 days. Not enough information was presented to evaluate whether or not the static exposure conditions, eg, decreased partial pressure of oxygen, were directly responsible for this difference in lethality.

These studies indicate that vinyl chloride, vinylidene chloride, and vinyl bromide present a low degree of acute toxic hazard in animals, and that, as the duration of exposure increases, the concentration necessary to produce lethal effects decreases. One study [117] showed that exposure of male mice to vinylidene chloride at concentrations as low as 20 ppm was lethal after daily exposures of 22-23 hours for 4 days. The information available suggests

that the acute toxicity of these compounds is dependent in part on the rates of metabolism and excretion and the subsequent total accumulated dose. The variability of the estimates of LC50 values, resulting in part from variability in the experimental protocols used, does not allow a ranking of the compounds according to acute toxicity, except that vinyl fluoride and vinylidene fluoride are less toxic than the other vinyls and have not been found to have acute lethal actions on dynamic inhalation exposure in normal rats.

Cardiovascular effects have been reported for vinyl chloride, vinylidene chloride, and vinylidene fluoride. Twenty percent of 51 workers examined in 1965, who were exposed to vinyl chloride at a TWA concentration of 49 ppm, and 42% of 60 workers examined in 1969, exposed at a TWA concentrations of 43 ppm, showed elevated pulmonary arterial pressure [19]. Durations of exposure for these workers were not presented. In another report [78], workers who were currently exposed to vinyl chloride or who had been exposed in the past had a 39.4-41% frequency of diastolic hypertension, while workers from the same plant with no known exposure to vinyl chloride had a frequency of diastolic hypertension of 24.3% ($P<0.05$). Symptoms of circulatory disturbances in workers exposed to vinyl chloride have been reported in several studies. The symptoms included cold hands and feet (13%) [33], cold fingers and hands (25.7%), numbness or tingling in fingers or toes (31.4%), and other indications of Raynaud's syndrome (8.6%) [20]. Raynaud's syndrome (155) and unspecified circulatory disturbances (12%) appeared in another population also [32]. Cardiac sensitization to epinephrine has also been demonstrated in dogs exposed to vinyl chloride at 50,000 ppm for 5 minutes [110]. Changes, such as tachycardia, sinus arrhythmia, and ventricular multifocal extrasystoles, have been observed in the ECG records of dogs exposed to vinyl chloride at 100,000 ppm without epinephrine stimulation [107]. A significant decrease ($P<0.05$) of 28.5% in myocardial force of contraction has been observed in monkeys exposed to vinyl chloride at the same concentration for 5 minutes [108]. Monkeys exposed at 50,000 ppm showed a decrease of 9.1% in myocardial force of contraction, and those exposed at 25,000 ppm showed a 2.3% decrease in force of contraction. Decreases in aortic blood pressure followed a similar pattern in the monkeys. This experiment indicates that the cardiovascular effects of vinyl chloride are dose dependent.

Vinylidene chloride, inhaled at concentrations of 25,000 ppm for 10 minutes, caused sinus bradycardia and such cardiac arrhythmias as AV-block and ventricular fibrillation in rats [121]. Vinylidene chloride also enhanced the cardiac sensitivity to epinephrine, and this sensitivity increased with increasing duration of vinylidene chloride exposure.

No cardiac sensitization to epinephrine was noted in cats or dogs exposed to vinylidene fluoride at concentrations of 250,000-500,000 ppm for 5-15 minutes [131]. This suggests that vinylidene fluoride does not have the same mode of action on the cardiovascular system as vinyl and vinylidene chlorides. Similar information is not available for vinyl bromide or vinyl fluoride.

CNS effects have been observed on animals after exposure to each of the vinyl halides. In some instances, these effects might have been secondary to systemic effects caused by cardiovascular changes. The authors of the reports did not address this possibility. Vinyl chloride caused "certain anesthesia" in mice after a 10-minute exposure at 122,000 ppm, and 50% anesthesia after exposure a 10-minute exposure at 100,000 ppm [105]. Exposures at LC50's caused excitement, convulsions, and contractions in mice, rats, and rabbits [104]. Exposure of dogs to vinyl chloride at 500,000 ppm momentarily, then at 70,000 ppm for an unspecified period, caused rigidity of the legs and uncoordinated muscular movements [107].

An experiment with human subjects showed that 5-minute exposures to vinyl chloride at 12,000 ppm caused dizziness in two, dizziness, nausea, lightheadedness, and dulling of vision and hearing at 16,000 ppm in five, and the same symptoms with more intensity in all six, and a headache in one of them at 20,000 ppm [18]. Among 168 workers exposed to vinyl chloride at a TWA concentration of 899 ppm for up to a few months, 47% complained of dizziness, 45% of somnolence, 36.6% of headache, 13% of loss of memory, 11% of euphoria, and 9% of nervousness [19]. Of 168 workers exposed to vinyl chloride at a TWA concentration of 98 ppm (prior exposure information not available), 10.2% reported dizziness, 16.6% somnolence, 6.9% headache, 8% loss of memory, 1.2% euphoria, and 0.6% nervousness. Frequent dizziness and weakness in the legs were also reported by other workers exposed to vinyl chloride [20,33], as was fatigue in 38.6% and headache in 12.9% [20] and in 13.7% of another group of workers [78]. These data indicate that a decrease in the TWA concentration of vinyl chloride led to a decrease in the frequency of CNS symptoms, and that exposure at TWA concentrations as low as 38 ppm produced adverse effects.

Other findings that might be considered manifestations of CNS effects have included a "large proportion of accidents" occurring in a worker population [32] and an excess of suicides as the actual causes of death in another worker population (10 observed vs 5.3 expected) [84]. Effects on brain cells have also been observed, ie, a localized atrophy of cerebellar Purkinje cells and necrosis of the frontoparietal cerebral cortex in one worker [41]. Also, fibrotic processes surrounding and invading the small nerve bundles of the gray matter, neuronal phagokaryosis with satellitosis and deposition of neurologic elements around altered nerve cells of the white matter, and atrophy of the granular layer and degenerative changes in the Purkinje cell layer were observed in rats exposed at 30,000 ppm, 4 hours/day, 5 days/week, for 1 year [111].

Exposure to vinylidene chloride at about 4,000 ppm for a brief period caused "drunkenness" that progressed to unconsciousness in animals [114]. Workers exposed to a vinylidene chloride copolymer while cleaning tanks developed pains in the lips, nose, and eyes, headache, somnolence, facial anesthesia, corneal anesthesia, hypoesthesia, difficulty in speaking and eating [72], and fatigue, weakness, nausea, and dizziness [70,71]. Because of the composition of the copolymers to which these workers were exposed in

aqueous suspension, it is not reasonable to assume that vinylidene chloride was the only causative agent of these CNS effects.

Vinyl bromide caused a "certain anesthesia" at a concentration of 86,000 ppm for a 10-minute exposure in rats [105]. In another experiment, a 1.5-hour exposure at 25,000 ppm anesthetized all rats, and a 7-hour exposure at 10,000 ppm caused drowsiness in rats [127].

Rats exposed for 30 minutes to vinyl fluoride at 300,000 ppm showed instability of the hindlegs; at 500,000 ppm there was loss of postural reflexes, and at 600,000 ppm there was loss of the righting reflex [129].

Rats exposed to vinylidene fluoride for 30 minutes at 400,000 ppm showed slight intoxication, and at 800,000 ppm showed an unsteady gait without loss of the postural reflexes [129].

The available data indicate that vinyl chloride and vinylidene chloride can produce similar CNS manifestations that may be secondary to the cardiovascular effects of these compounds. Human exposure information is not available concerning CNS symptoms for vinyl bromide, vinyl fluoride, or vinylidene fluoride, and anesthetic effects from vinyl fluoride and vinylidene fluoride have only been observed at very high concentrations.

Workers exposed to vinyl chloride have also experienced adverse respiratory effects ranging from coughing and sneezing to bronchial rales, pulmonary emphysema, decreased respiratory volume, decreased vital capacity, decreased maximum expiratory volume/second, and linear type pulmonary fibrosis [19]. Pulmonary function changes were also noted in 12 of 180 workers with "vinyl chloride disease" [32]. Monkeys exposed to vinyl chloride at 100,000 ppm for 5 minutes have shown a significantly increased ($P<0.05$) pulmonary resistance (15.35%) and significantly lowered ($P<0.05$) respiratory minute volume (12.3%) [106]. In addition, bronchioalveolar adenomas have been observed in mice exposed to vinyl chloride at 50 ppm, 6 hours/day, 5 days/week, for up to 12 months [140].

Bronchioalveolar adenomas have been found in mice exposed to vinylidene chloride at 55 ppm for 6 hours/day, 5 days/week, for up to 12 months [140]. Respiratory irritation was seen in rats, guinea pigs, rabbits, dogs, and monkeys when exposed to vinylidene chloride at 87.6 ppm continuously for 90 days or 1,730 ppm for 8 hours/day, 5 days/week, for 6 weeks [122]. Nasal irritation was seen in rats exposed to vinylidene chloride at 200 ppm for 6 hours/day, 5 days/week, for 4 weeks [120]. Inflammation of the epipharynx was also noted in two workers exposed to the emanations from an aqueous polyvinylidene chloride copolymer suspension [70,71]. Because of the mixed composition of this suspension, the authors did not attribute the effect to vinylidene chloride alone. No data were located on respiratory effects of vinyl bromide, vinyl fluoride, or vinylidene fluoride.

Scleroderma of the hands and forearms was observed in 8 of 70 workers exposed to vinyl chloride at unspecified concentrations [20]. Fourteen of 36 workers from whom samples of skin for biopsy were taken had fragmentation of the elastic fibers of the skin of the fingers. Dermatologic complaints were also elicited from 80% of 168 workers during the 1st month of exposure to vinyl chloride at a TWA concentration of 899 ppm [19]. These changes progressed over a period of time from pruritus to contact dermatitis with papules to scleroderma. In the 1st year, 4.4% of the workers developed contact dermatitis, and this frequency increased to 7.4% during 7 years, even though the TWA concentration decreased from 899 to 43 ppm. Other possible routes of exposure of the skin were not evaluated by the authors. Scleroderma was diagnosed in 10% of 180 workers with "vinyl chloride disease" [32]. Another four workers found to have scleroderma showed thickening of the skin of the fingers, adhesions on the deep layers, palmar erythema, hyperhydrosis, and hard projecting nodules in the areas of the flexor tendons [21]. The paws of rats exposed to vinyl chloride at 30,000 ppm, 4 hours/day, 5 days/week, for 1 year showed hyperkeratosis, superficial thickening of the epidermis, disappearance of the cutaneous adnexa, vacuolization and degeneration of the basal layer, a thickening of the papillar layer, with edema, and a decrease in the elastic reticulum and dissociation of the collagen bundles [111]. Arterial vessels of the paws also showed endothelial fibrosis. The same rats also showed skin papillomas and warty subauricular growths [112]. No reports were located of integumentary effects with exposure to vinylidene chloride, vinyl bromide, vinyl fluoride, or vinylidene fluoride.

Skeletal changes have also been observed in humans and animals exposed to vinyl chloride. Acroosteolysis has been observed in workers [20,21,32,35,74,75,78]. In one study [78], exposures to vinyl chloride were estimated at 50-100 ppm in air and 600-1,000 ppm close to the workers' hands during reactor cleaning operations. No information was available in any of these reports on the duration of employment or exposure for the workers with acroosteolysis. It was noted that all workers with acroosteolysis had been employed in reactor cleaning, whereas only 21% of the entire vinyl chloride-exposed population had had experience as reactor cleaners [74,75]. In rats exposed to vinyl chloride at 30,000 ppm for 4 hours/day, 5 days/week, for 1 year, observed effects included alteration in the characteristic bone deposition in the small bones with a mucoid impregnation [111] and osteochondromas in the metacarpal and metatarsal regions of all of the limbs of of 25 rats [112]. No information concerning skeletal abnormalities was located for vinylidene chloride, vinyl bromide, vinyl fluoride, or vinylidene fluoride.

Liver and spleen abnormalities have been observed in humans and animals exposed to vinyl chloride. Hepatomegaly was observed in 65% of 48 workers [30], in one worker exposed 3-4 hours/day, 2-3 days/week, for 3 years and 5 months [41], in 1 of 17 workers [33], in 64% of 11 workers [37], and in 30.2% of 168 workers exposed at a TWA concentration of 899 ppm, and in 11.4% of 168 workers exposed at a TWA concentration of 38 ppm [19] (durations of exposure not reported). Hepatomegaly was also reported in 13.2% of 126 workers

estimated as having "moderate" exposures to vinyl chloride, while only 7.3% of 80 workers estimated to have "light" exposures and 7.1% of 134 workers with "no" exposure showed hepatomegaly [78]. Degenerative changes found in the livers through biopsy included single cell necrosis, hyperplasia, hydropic swelling of the cells, periportal and centrilobular fibrosis and fatty degeneration [31]; dilatation of sinusoids, formation of connective tissue septa, fibroblastic activation, and enlarged hepatocytes with hyperchromatic nuclei [39]; nonalcoholic-type cirrhosis [36]; and fibrosis [30,34,37,40,41].

Several authors have reported clinical test results indicative of liver damage. Workers exposed to vinyl chloride showed abnormal SGOT values in 31% of 277 [78], in 73% of 11 [37], in 50% of 36 [19], in 28% of 68 [34], and in 46.9% of 59 [35]. Results of BSP retention tests were found to be abnormal in 47% of 15 workers [33], in 85% of 26 workers [19], in 9% of 11 workers [37], and in 67.2% of 70 workers [20] and to increase significantly ($P<0.001$) with increasing exposure to vinyl chloride [76]. LDH values were elevated in 36% of 11 workers [37], in 11.1% of 72 workers [34], and in 9.4% of 59 workers [35]. Alkaline phosphatase values were also found to be abnormal in 13% of 277 workers [78], in 55% of 11 workers [37], in 49.4% of 72 workers [34], and in 59.4% of 59 workers [35]. Other clinical values found to be abnormal in vinyl chloride-exposed workers in some of these reports included thrombocyte counts, leukocyte counts, reticulocyte counts, erythrocyte sedimentation rates, total bilirubin, albumin, cholesterol, icterus index, SGPT, isocitrate dehydrogenase, and gamma-glutamic transpeptidase activities, serum beta-globulin, and 17-ketosteroids [19,20,32-35,37,76-78]. Unfortunately, the authors of these studies did not supply information concerning exposure concentrations or durations that might facilitate a correlation of the exposures with the effects. It should also be noted that the frequencies of these abnormal test results were often not significantly different from those in other cohorts of workers such as rubber workers.

Splenic abnormalities, including enlargement, were observed in 57.4% of 70 workers [20], 45% of 11 workers [39], 10% of 1,180 workers [38], 26% of 180 workers with "vinyl chloride disease" [32], and 77% of 48 workers [30] exposed to vinyl chloride. No information is available on exposure concentrations or durations for these workers.

In 30 rats exposed to vinyl chloride at 20,000 ppm, 8 hours/day, 5 days/week, for 3 months, the livers were significantly heavier ($P<0.001$) than those of controls, there was widespread swelling and vacuolization of the liver cells and compression of the sinusoids; the spleens of the rats were significantly lighter ($P<0.05$) [18]. Rats and guinea pigs exposed to vinyl chloride at 100 ppm for 7 hours/day, 5 days/week, for 6 months also showed significantly increased liver weights ($P<0.05$) [113].

No abnormal clinical chemical values were noted either in mice or rats exposed to vinyl chloride at 50, 250, or 1,000 ppm for 6 hours/day, 5 days/week, for up to 12 months [140] or in rats, guinea pigs, rabbits, or dogs exposed at 100 or 200 ppm for 7 hours/day, 5 days/week, for 6 months [113].

In a group of 46 affected workers exposed to vinylidene chloride at TWA concentrations of 0-5 ppm with occasional peaks of 300 ppm, 11% showed hepatomegaly, 13% showed abnormal serum alkaline phosphatase values, and 21-39% showed abnormalities in serum LDH, GGTP, GOT, and GPT values [69]. Of 256 additional workers tested, 29% had abnormal clinical values, and these workers averaged 5.11 years of exposure, whereas the employees who showed normal values averaged 3.64 years of exposure. Serum alkaline phosphatase and GPT values were increased in rats and guinea pigs exposed to vinylidene chloride at 47.6 ppm continuously for 90 days [122]. These animals also had mottled livers and spleens. In rats exposed to vinylidene chloride at 25 or 75 ppm 6 hours/day, 5 days/week, for 17 months, there was increased hepatocytic cytoplasmic vacuolization [119]. Liver cell degeneration was also noted in rats exposed to vinylidene chloride at 500 ppm for 6 hours/day, 5 days/week, for 4 weeks, but not in animals exposed at 200 ppm for the same period [120]. Necrosis and fatty focal vacuolization was also seen in mice and rats exposed at 55 ppm for 6 hours/day, 5 days/week, for up to 12 months [140]. Liver damage has also been demonstrated in rats given vinylidene chloride orally in corn oil in a single dose of 200 mg/kg [125,126], and in drinking water at normal concentrations of 50, 100, or 200 ppm for 730 days [123].

In a 1-year interim report [143], vinyl bromide was stated to have caused increased liver weights in rats exposed at 250 and 1,250 ppm and increased spleen weights in rats exposed at 50, 250, and 1,250 ppm. Gross examinations indicated mottled livers in a few of the animals exposed at these concentrations. Significant elevations in serum LDH and bromide values were also reported in those rats exposed at 1,250 ppm.

No information was located concerning the hepatotoxicity of vinyl fluoride or vinylidene fluoride.

The systemic effects that reportedly resulted from exposure to vinyl halides suggest that the vinyls or their metabolites interfere with cellular processes primarily in the liver and the cardiovascular system. Exposures to large quantities may also involve the skeletal, integumentary, and central nervous systems; however, these systems may also be affected secondarily by changes in the cardiovascular system, and the relative magnitudes of the effects resulting from primary action of the vinyl halides or their metabolites and from the suggested secondary ones are uncertain.

Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

The vinyl halides produce reactive metabolic intermediates, possibly including asymmetric oxiranes. Several proposed intermediates in the metabolic pathways of the vinyl halides are capable of covalent binding with cellular macromolecules, and may therefore induce carcinogenesis and mutagenesis. Although few experiments have been reported in which the carcinogenic or mutagenic potentials of the vinyl halides other than vinyl

chloride are evaluated, the vinyl halides considered in this document, as suggested earlier in this chapter, may be qualitatively if not quantitatively similar in their induction potentials.

One report has suggested that exposure of male workers to vinyl chloride can induce excess fetal deaths among their offspring [101]. However, as has been previously discussed, the methods of data collection used in this report are considered inappropriate.

The fetuses of mice, rats, and rabbits from dams exposed to vinyl chloride during pregnancy showed significant abnormalities, including increased crown-rump length, in mice exposed at 50 ppm, and increased incidence of resorptions, decreased fetal body weight, reduction in litter size, increased numbers of unfused sternebrae, and delayed ossification of the bones of the skull in mice exposed at 500 ppm [132]. Fetuses from rats exposed at 500 ppm showed a significant reduction in the fetal body weights and a significant increase in the number of lumbar spurs and in crown-rump length. Fetuses from rats exposed at 2,500 ppm showed a significant increase in the incidence of dilated ureters and significant decreases in the incidence of unfused sternebrae and delayed skull ossifications. The only other significant difference noted was an increase in the incidence of delayed ossification of the fifth sternebra in rabbits exposed at 500 ppm. The authors of this study regarded these effects as due to maternal toxicity and not to direct toxicity to embryos and fetuses. However, the observation of characteristic cancers in progeny of dams exposed to vinyl chloride during their pregnancies [135] suggests that vinyl chloride or its metabolites cross the placental barrier and may have induced the abnormalities reported.

Pregnant rats exposed to vinylidene chloride at 80 ppm had significantly increased numbers of resorptions/implants and fetuses with significant increases in skeletal abnormalities such as delayed ossification of parietal bones, wavy ribs, and lumbar spurs [133]. Delayed ossification of skull bones and cervical vertebrae, along with wavy ribs, were also observed in fetuses of rats exposed at 160 ppm. No adverse effects were observed at 20 ppm. In the rabbits exposed at 160 ppm, there was a significant increase in the number of resorptions/implants and a significantly decreased incidence of delayed ossification of the fifth sternebra, and an increased incidence of a 13th pair of ribs. No adverse effects were noted on the fetuses from dams exposed at 80 ppm. In the fetuses of rats given access to drinking water containing vinylidene chloride at 200 ppm, the only significant difference from controls was an increase in the fetal crown-rump length.

No reports have been located of studies in which the reproductive or teratogenic effects of vinyl bromide, vinyl fluoride, or vinylidene fluoride were investigated.

Covalent binding of the vinyl halides to cellular macromolecules such as DNA, RNA, and proteins may be a critical step in a genotoxic effect [1]. Vinyl chloride, after metabolic activation by microsomal enzymes, has been

shown to enhance mutagenesis in Salmonella [151,152,155,156]. Similar metabolic enhancement has been shown for vinylidene fluoride (J Watson, written communication, April 1978), vinyl bromide (VF Simmon and R Mangham, written communication, August 1977) and vinylidene chloride [151,152,172]. The common molecular features of these compounds, the formation of the asymmetrical oxirane and the subsequent spontaneous rearrangement to the aldehyde or acyl halide, have been suggested as producing the most reactive intermediates [1-3,210], although the oxirane of vinylidene chloride has not yet been synthesized in the laboratory [1]. Direct binding with proteins in vitro has been reported for chloroethylene oxide (the oxirane of vinyl chloride) [196,212] and for chloroacetaldehyde [170,206]. In vitro and in vivo binding of vinyl chloride or its metabolites to microsomal proteins has also been reported [204,205,212,214,215] as has macromolecular binding of vinylidene chloride or its metabolites [117,219]. In addition to direct binding to proteins, metabolites of vinyl chloride have been reported to bind to RNA in vitro [170,204,205] and in vivo [215].

Even when the route of administration of the vinyl halides differ, the metabolic end products, and, presumably, the intermediates, with each route are the same [4,5,175,177]. Only unchanged vinyl chloride or vinyl chloride-derived carbon dioxide were exhaled after oral, ip, iv, or inhalation exposures [4,5,175,177]. Urinary metabolites from all routes of exposure include cysteine-conjugated products and small amounts of monochloroacetate [5,175,177].

Absorption of vinyl chloride through the intact skin was reportedly minimal, amounting to less than 0.031% of the total available gaseous vinyl chloride in 2.5 hours [178]. Vinyl chloride concentrations in the air rapidly equilibrated (within 15 minutes) with vinyl chloride in the tissue when metabolism was blocked [202]. Under these conditions, the half-life of vinyl chloride was 4.3 minutes. Absorption and subsequent metabolism of vinyl chloride has been reported to be concentration dependent, with a saturable enzyme system responsible for metabolism at low concentrations and a secondary oxidative system predominant at higher concentrations [4-6]. It has been postulated that the oxirane is formed only at the higher concentrations through the secondary oxidative pathway, but that halogenated acetalydehyde is common to both pathways. Thus, even without the formation of the oxirane at low concentrations, the possibility of macromolecular alkylation exists through the action of the aldehyde intermediate.

Vinyl chloride has been shown to produce a characteristic tumor, angiosarcoma of the liver, in both humans [31,32,34,36,37,40,41] and animals [134,135,140]. The cases of angiosarcoma of the liver in workers exposed to vinyl chloride are summarized in Table XVII-4 [61]. This summary shows that the average exposure of the affected workers was 17.3 ±6.3 years (range 4-30 years) and the average latency for diagnosis of the tumor was 20.5 ±6 years (range 9-38 years). Accurate exposure information, to allow calculation of total accumulated dose, is not available for these workers. Kuzmack and McGaughy [62], using data derived from epidemiologic studies, calculated that

the incidence rates of angiosarcoma in workers exposed at concentrations of 350 ppm, 7 hours/day, for 5 days/week should be 0.0031/person/year of exposure. An incidence rate of 0.0052/person/year of exposure was also calculated from the incidence rate in rats.

Angiosarcoma of the liver was also observed in 1 of 59 rats exposed to vinyl chloride at 50 ppm, 4 hours/day, 5 days/week, for 52 weeks [135]. The percentage of animals with angiosarcoma of the liver increased from 2% at 50 ppm, to 7% at 250 ppm, 12% at 500 ppm, 22% at 2,500 ppm, 22% at 6,000 ppm, 15% at 10,000 ppm, and 30% at 30,000 ppm. Average latency increased with decreasing exposure concentration, from 53 weeks at 30,000 ppm to 135 weeks at 50 ppm. In another experiment [134], rats exposed at 50 ppm for 4 hours/day, 5 days/week, for 12 months showed no tumors over an unspecified observation period. At 500 ppm, however, there was a significant increase ($P<0.03$) in the number of tumors seen, with 3% of the animals having angiosarcomas of the liver. Increasing exposure concentrations to 2,000, 5,000, 10,000, and 20,000 ppm increased the frequency of all tumors and of angiosarcoma of the liver to 5, 6, 8, and 12%, respectively. Other tumors in rats, such as Zymbal gland carcinoma and nephroblastoma, have been reported to have similar latencies [135]. Statistical estimates were made by CR Norwood and FW Dresch (written communication, December 1977) using the data in these reports [134,135,140] and based on the assumptions that the background incidence of this tumor is zero and that the no-observable-effect concentration is that at which the probability of one tumor developing in 100 replications of the same experiment is less than 0.01. They found that conservative, no-observable-effect concentrations for angiosarcoma of the liver could be calculated as any of 0.2 ppm [140], 0.01 ppm [134], or 0.000004 ppm [135].

A variety of other tumors have been seen in workers exposed to vinyl chloride, such as cancer of the respiratory system [80,81,84], buccal cavity, pharynx, and peritoneum [64,81], brain [84,89], gall bladder [84], and glioblastoma, reticulum cell sarcoma, and lymphosarcoma [87]. Similar tumors have been seen in animals exposed to vinyl chloride [112,135,136,138,140]. These tumors are much more common than angiosarcoma of the liver, however, and can be induced by a wide variety of other carcinogens; they are therefore not considered pathognomonic of vinyl chloride exposure. The relatively long latent period for induction of angiosarcoma of the liver in both humans and animals, along with the lack of adequate followup information in most cases, makes a purely objective assessment of risk on the basis of the available data unwarranted.

No cases of cancer in humans have been reported to be related to occupational exposure to vinylidene chloride, and only three animal experiments relative to its carcinogenicity have been located. In one experiment [140], 3 of 72 CD-1 mice exposed to vinylidene chloride at a concentration of 55 ppm, 6 hours/day, 5 days/week, for up to 12 months developed angiosarcoma of the liver. Two of 72 rats similarly exposed

developed extrahepatic angiosarcoma. In another experiment [119], 208 rats exposed at 40 ppm for 6 hours/day, 5 days/week, for 1 month and then exposed at 75 ppm on the same schedule for 17 more months developed no angiosarcoma. In addition, these rats did not show increased incidences of other tumors compared with those in controls. A further experiment [142] showed an increased incidence of adenocarcinoma of the kidney in Swiss mice exposed to vinylidene chloride at 25 ppm for 4 hours/day, 4-5 days/week, for 12 months, but no increase in other tumors. The authors [142] stated that exposures at 50 ppm and higher were lethal to these animals. Sprague-Dawley rats exposed on the same schedule at concentrations of from 10 to 150 ppm showed an increased incidence of mammary tumors; however, this increase was not dose dependent.

No cases of cancer in humans have been attributed to vinyl bromide exposure. The preliminary results of one animal experiment [143] indicated that vinyl bromide at 1,250 or 250 ppm induced a significant increase in angiosarcoma of the liver and other tumors in rats after 1 year of exposure. At 1,250 ppm, 9/48 rats developed angiosarcoma, and, at 250 ppm, 2/30 rats developed angiosarcoma. No increase in tumor formation was observed in rats exposed at 10 and 50 ppm for 1 year.

No reports concerning the carcinogenicity of vinyl fluoride or vinylidene fluoride in humans or animals have been located.

Comparison of the limited animal data available on induction of angiosarcoma by the vinyl halides supports the postulations outlined in the Structure-Activity Considerations section of this chapter. The expected order of susceptibility of the olefins toward epoxidation, calculated from the sum of the electronegativities of the substituents, is vinyl bromide > vinyl chloride > vinylidene chloride > vinyl fluoride > vinylidene fluoride. The carcinogenicity data show that vinyl bromide at a concentration of 250 ppm induced angiosarcoma in 7% of the animals after 1 year of exposure [143], and that vinyl chloride at a concentration of 250 ppm also induced angiosarcoma in 7% of the animals, but after 2 years of exposure [135]. This indicates that, for this characteristic tumor, vinyl bromide has a stronger induction potential, since it is reasonable to assume that, within another year, more of the vinyl bromide exposed animals would develop the tumors. A comparison of the induction potential of vinylidene chloride with that of vinyl chloride or vinyl bromide is more difficult. One experiment with vinylidene chloride showed 4% angiosarcoma of the liver in CD-1 mice exposed at a concentration of 55 ppm for 85,800 ppm-hours [140], another experiment showed no angiosarcoma in Swiss mice exposed to vinylidene chloride at 25 ppm for 23,000 ppm-hours [142], while an experiment with Swiss mice exposed to vinyl chloride at a concentration of 50 ppm for 30,000 ppm-hours showed a 2% incidence of angiosarcoma of the liver [135]. These data are not so easily compared as the data from the vinyl bromide and vinyl chloride experiments, but they do suggest that vinylidene chloride may be less active in inducing angiosarcoma of the liver than vinyl chloride. Because the behaviors of these compounds appear to fit the expected structure-activity relationship, it is reasonable

to suppose that vinyl fluoride and vinylidene fluoride might also fit this relationship. Because of the lack of information concerning the vinyl fluorides, it is not possible to substantiate this hypothesis at the present time.

No mutagenic effects on humans have been related to exposure to any of the vinyl halides. Studies of chromosomal aberrations in the lymphocytes of workers exposed to vinyl chloride [94-99] have indicated a significant increase in abnormalities; however, the combined frequency of abberations in these studies was only a fraction of the background frequency [100].

Each of the vinyl halides has been found to be mutagenic in some test system. Vinyl chloride has been shown to produce mutations in Salmonella, in the Ames test procedure [145,146,149,150,162,163], in E. coli [151-153], in yeasts, both in vitro and by host-mediated assay [155], and in Drosphila by the recessive lethal test [158,159]. Negative results have been obtained in Neurospora [157].

Several investigators have shown that vinyl chloride has a direct mutagenic effect on Salmonella [149,150,162,163]. One study [146] reported a twentyfold increase over the spontaneous mutation rate after 48 hours of exposure to a medium containing 4 millimoles of vinyl chloride. Activation by a 9,000 x G mammalian microsomal system increased the mutation rate to 28 times the spontaneous rate [146], and exposures of as short as 30 minutes at vinyl chloride concentrations of 200,000 ppm induced twice the spontaneous rate of mutation [145]. Purified microsomal fractions (100,000 x G) have been shown to be less active than the 9,000 x G fraction [146], while the supernatant cytosol produced no increase in mutagenic activity above that found for vinyl chloride alone. Vinyl chloride has been shown to affect only loci at which mutation occurs by substitution [145,146]. One dominant lethal study [161] with male mice exposed to vinyl chloride at 30,000 ppm for 6 hours/day for 5 days showed no mutations, which suggests that mammalian gametes may not be affected by exposure.

Vinylidene chloride has been shown to be similarly mutagenic in bacterial systems [172,173]. Exposure of Salmonella for 2 hours, in media containing 0.33-33 millimoles of vinylidene chloride and a mammalian microsomal system, resulted in 6-10 times the spontaneous number of revertants [172]. Bartsch et al [173] reported that vinylidene chloride was about three times as active as a mutagen as vinyl chloride on an equimolar basis. In a study using E. coli, Greim et al [151] concluded that vinyl chloride was "several times" more mutagenically active than vinylidene chloride; their data showed that vinylidene chloride produced a onefold increase over the spontaneous number of mutations at a concentration of 2.5 millimolar, while vinyl chloride produced six times the spontaneous number of mutations at the same locus at a concentration of 10.6 millimolar.

Vinyl bromide at concentrations of 20% in air was shown to be mutagenic in Salmonella TA100 after a 12-hour exposure (VF Simmon and R Mangham, written

communication, August 1977). This exposure produced revertants at 10 times the spontaneous rate with microsomal activation and at about 5 times the spontaneous rate without activation.

Both vinyl fluoride and vinylidene fluoride have been shown to produce direct mutagenic responses in E. coli at up to 100 times the spontaneous rate [174]. However, no data were given on the exposure concentrations for these experiments and no auxotrophic mutants were isolated from the putative mutant colonies. Vinylidene fluoride has also been reported to increase the frequency of mutations in Salmonella both with and without microsomal activation (J Watson, written communication, April 1973).

Several investigators have tested known or presumed metabolites of vinyl chloride in an attempt to identify the mutagenically active agents. The most active compounds tested were chloroacetaldehyde and chloroethylene oxide [166,147,163,165]. Chloroethanol showed lower mutagenic activity [147,162, 163], and chloroacetic acid was not mutagenic in Salmonella [147,163,166]. The direct activity of chloroethanol resembled that of vinyl chloride in that it affected Salmonella strain TA1535 and strain TA100 (identical to TA1535 except that it is DNA repair-deficient) about equally [162]. Chloroethanol, like vinyl chloride, was also further activated by the addition of mammalian microsomes [147,162].

McCann et al [162] suggested that, although chloroacetaldehyde was the most active of the metabolites of vinyl chloride that they tested, it was probably not the major mutagenic metabolite of vinyl chloride, since chloroacetaldehyde affected only the repair-deficient Salmonella strain TA100. These authors suggested that chloroethylene oxide was the most likely mutagenic metabolite, although they did not test its activity. However, the compound has been tested by other investigators on both repair-deficient [166] and nonrepair-deficient [147,163] strains, and it appears, like vinyl chloride, to be similarly active in each.

These studies show that each of the vinyl halides is mutagenic in various test systems and that the putative metabolites are more strongly mutagenic than the parent compounds. The studies support the conclusions drawn from the limited carcinogenic data available and, further, raise a suspicion that the fluorides also may be carcinogens. The failure of vinyl chloride to be mutagenic in the mouse dominant-lethal test may indicate that the mutagenic factor may not be distributed to mammalian gametes in sufficient concentrations to produce significant changes; however, further research is necessary to determine fully the potential of these compounds for mammalian mutagenicity.

The available evidence concerning the vinyl halides indicates that each produces similar biologic effects, albeit possibly at different concentrations. Indications from the experiments on mutagenicity suggest that these compounds are able to exert their action directly but that metabolism of the parent compounds produces intermediates that are much more reactive.

TABLE III-7

EFFECTS ON HUMANS FROM EXPOSURE TO VINYL CHLORIDE OR VINYLIDENE CHLORIDE*

Subjects	Concentration (ppm)	Duration	Signs and Symptoms	Reference
6 Volunteers	20,000	5 min	Dizziness, nausea, lightheadedness, dulling of vision and hearing in 6; headache in 1	18
"	16,000	"	Dizziness, nausea, lightheadedness, dulling of vision and hearing in 5	18
"	12,000	"	Dizziness in 2	18
"	4,000-8,000	"	No effects	18
168 Workers	899	a few mo	Dizziness (37%), somnolence (69%), headache (36.6%), anorexia (23%), epigastric pain (16%), loss of memory (13%), euphoria (11%), nervousness (9%); hepatomegaly (30.2%); dermatologic complaints (80%); Raynaud's syndrome (6%)	19
51 Workers	69	-	Elevated pulmonary arterial pressure in 20%	19
60 Workers	63	-	Elevated pulmonary arterial pressure in 42%	19
157 Workers	"	-	Decrease in respiratory volume, FVC, FEV 1	19
168 Workers	38	-	Dizziness (10.2%), somnolence (16.6%), headache (6.9%), anorexia (10.3%), epigastric pain (9%), loss of memory (8%), euphoria (1.2%), nervousness (0.6%); hepatomegaly (11.4%); dermatitis (7.4%); Raynaud's syndrome (2.9%)	19
1,673 Workers	20-39	-	Acroosteolysis in 1%	74, 75
46 Workers*	0-5 (peaks to 300)	-	Hepatomegaly (11%), abnormal alkaline phosphatase (13%); abnormal LDH (39%), GGTP (30%), SGOT (23%), SGPT (21%)	69
73 Workers*	"	avg 5.11 yr	Abnormal clinical blood values	69
181 Workers*	"	avg 3.64 yr	Normal clinical blood values	69

TABLE III-8

NONTUMORIGENIC EFFECTS ON ANIMALS FROM EXPOSURE TO VINYL CHLORIDE BY INHALATION

Species	Concentration (ppm)	Duration	Effects	Reference
Rat	210,000	2 hr	LC100	104
"	136,000	"	LC50; contractions, convulsions	104
"	30,000	4 hr/d, 5 d/wk x 1 yr	Nerve cell changes, thickening of skin, papillomas, warty growths	111
"	20,000	8 hr/d, 5 d/wk x 3 mo	Liver weight increase, cellular changes; spleen weight decrease	18
"	2,500	d 6-15 of gestation	Dilated ureters in offspring	132
"	500	"	Decreased fetal weight, increased lumbar spurs in offspring	132
"	100	7 hr/d, 5 d/wk x 6 mo	Increased liver weight	113
Mouse	242,000	10 min	LC50	105
"	150,000	2 hr	LC100	104
"	122,900	10 min	Anesthesia in 100%	105
"	117,500	2 hr	LC50; contractions, convulsions	104
"	100,000	10 min	Anesthesia in 50%	105
"	500	d 6-15 of gestation	Decreased litter size, fetal weight; increased resorptions;	132
"	50	"	Increased crown-rump length in offspring	132
Guinea pig	280,000	2 hr	LC100	104
"	238,000	"	LC50	104
"	100-200	7 hr/d, 5 d/wk x 6 mo	Liver weight increase; no blood changes	113
Rabbit	280,000	2 hr	LC100	104
"	238,000	"	LC50; contractions, convulsions	104
"	2,500	d 6-18 of gestation	Death of 1/7; no reproductive effects	132
"	500	"	Delayed ossification, wavy ribs	132
"	100-200	7 hr/d, 5 d/wk x 6 mo	Liver weight increase; no blood changes	113
Dog	100,000	-	Cardiac irregularities	107
"	50,000	5 min	Cardiac sensitization to epinephrine	110
"	100-200	7 hr/d, 5 d/wk x 6 mo	Liver weight increase; no blood changes	113
Monkey	100,000	5 min	Increased pulmonary resistance,	106
"	"	"	Myocardial force decreased 28.5%	108
"	50,000	"	Myocardial force decreased 9.1%	108
"	25,000	"	Myocardial force decreased 2.3%	108

TABLE III-9

NONTUMORIGENIC EFFECTS ON ANIMALS FROM EXPOSURE TO VINYLIDENE CHLORIDE BY INHALATION

Species	Concentration (ppm)	Duration	Effects	Reference
Rat	32,000	4 hr	Death of 2-4 of 6 in 14 d	118
"	25,000	10 min	Cardiac irregularities, sensitization to epinephrine	121
"	15,000	4 hr	LC50 (24 hr) for fed animals	115
"	6,350	"	LC50 (14 d)	116
"	600	"	LC50 (24 hr) for fasted animals	115
"	500	6 hr/d, 5 d/wk x 4 wk	Liver cell degeneration	120
"	200	"	Nose irritation; no liver effects	120
"	160	d 6-15 of gestation	Delayed ossification, wavy ribs in offspring	133
"	105	22-23 hr	LC50--14 d (females)	
"	100	8 hr/d, 5 d/wk x 6 wk	Respiratory irritation	122
"	98	22-23 hr	LC50--14 d (males)	
"	80	d 6-15 of gestation	Increased fetal resorptions; skeletal abnormalities	133
"	25-75	6 hr/d, 5 d/wk x 17 mo	Liver cell degeneration	119
"	48	90 d	Mottled livers; elevated SGPT, alkaline phosphatase	122
"	55	6 hr/d, 5 d/wk x 12 mo	Fatty infiltration of liver	140
"	35	22-23 hr x 2	LC50 (males)	117
"	20	4 d	LT50	117
"	5	90 d	Respiratory irritation	122

TABLE III-9 (CONTINUED)

NONTUMORIGENIC EFFECTS ON ANIMALS FROM EXPOSURE TO VINYLIDENE CHLORIDE BY INHALATION

Species	Concentration (ppm)	Duration	Effects	Reference
Mouse	55	6 hr/d, 5 d/wk	Necrosis of liver	140
Guinea pig	100	8 hr/d, 5 d/wk x 6 wk	Respiratory irritation	122
"	48	90 d	Mottled livers, elevated	122
"	5	90 d	Respiratory irritation	122
Rabbit	160	d 6-18 of gestation	Increased fetal resorptions, extra ribs in offspring	133
"	100	8 hr/d, 5 d/wk x 6 wk	Respiratory irritation	122
"	5	90 d	Respiratory irritation	122
Dog	100	8 hr/d, 5 d/wk x 6 wk	"	122
"	5	90 d	"	122
Monkey	100	8 hr/d, 5 d/wk x 6 wk	"	122
"	5	90 d	"	122

TABLE III-10

NONTUMORIGENIC EFFECTS ON ANIMALS FROM EXPOSURE TO VINYL BROMIDE BY INHALATION

Species	Concentration (ppm)	Duration	Effects	Reference
Rat	171,000	10 min	Not lethal	105
"	100,000	15 min	Lethal to 100%	127
"	86,000	10 min	Anesthesia in 100%	105
"	50,000	7 hr	Death of unspecified number	127
"	25,000	1.5 hr	Anesthesia in 100%	127
"	10,000	7 hr	Drowsiness, sluggishness	127

TABLE III-11

NONTUMORIGENIC EFFECTS ON ANIMALS FROM EXPOSURE TO VINYL FLUORIDE BY INHALATION

Species	Concentration (ppm)	Duration	Effects	Reference
Rat	800,000 in oxygen	12.5 hr	Not lethal	128
"	800,000 in oxygen	30 min	Breathing difficulty, loss of postural reflex	129
"	600,000	"	Loss of righting reflex	129
"	500,000	"	Loss of postural reflex	129
"	300,000	"	Instability of hindlegs	129
"	100,000	7 hr/d, 5 d/wk x 6 wk	No effects	128

TABLE III-12

NONTUMORIGENIC EFFECTS ON ANIMALS FROM EXPOSURE TO VINYLIDENE FLUORIDE BY INHALATION

Species	Concentration (ppm)	Duration	Effects	Reference
Rat	800,000 in oxygen	19 hr	Not lethal	128
"	800,000	30 min	Unsteady gait	129
"	400,000	"	Slight intoxication	129
"	128,000 static exposure	4 hr	Death of 2-4 of 6 in 14 d	113

TABLE III-13

TUMORIGENIC EFFECTS ON ANIMALS FROM EXPOSURE TO VINYL CHLORIDE BY INHALATION

Species	Concentration (ppm)	Duration	Effects	Reference
Rat	30,000	4 hr/d, 5 d/wk x 12 mo	Tumors in 85%; liver angiosarcomas in 30%, average latency 53 wk	135
"	20,000	"	Liver angiosarcomas in 12%	134
"	10,000	"	Tumors in 62%; liver angiosarcomas in 15%, average latency 64 wk	135
"	"	"	Liver angiosarcomas in 8%	134
"	6,000-10,000	4 hr/d d 12-18 of gestation	Tumor induction in offspring	135
"	6,000	4 hr/d, 5 d/wk x 12 mo	Tumors in 52%; liver angiosarcomas in 22%, average latency 70 wk	135
"	5,000	"	Liver angiosarcomas in 6%	134
"	2,500	"	Tumors in 54%; liver angiosarcomas in 22%, average latency 78 wk	135
"	2,000	"	Liver angiosarcomas in 5%	134
"	500	"	Liver angiosarcomas in 3%	134
"	"	"	Tumors in 37%; liver angiosarcomas in 12%, average latency 81 wk	135
"	250	"	Tumors in 27%; liver angiosarcomas in 7%, average latency 73 wk	135
"	50	"	Tumors in 17%; liver angiosarcomas in 2%, average latency 135 wk	135
"	"	"	No tumors	134

TABLE III-13 (CONTINUED)

TUMORIGENIC EFFECTS ON ANIMALS FROM EXPOSURE TO VINYL CHLORIDE BY INHALATION

Species	Concentration (ppm)	Duration	Effects	Reference
Mouse	10,000	4 hr/d, 5 d/wk x 30 wk	Tumors in 72%; liver angiosarcomas in 16%	135
"	2,500	"	Tumors in 58%; liver angiosarcomas in 21%	135
"	250	"	Tumors in 69%; liver angiosarcomas in 19%	135
"	50	"	Tumors in 32%; liver angiosarcomas in 2%	135
"	"	6 hr/d, 5 d/wk x 12 mo	Bronchiolar adenomas	140
Hamster	50-10,000	4 hr/d, 5 d/wk x 30 wk	Tumor induction; liver angiosarcomas; not dose related	135
Rabbit	10,000	-	Increase in skin acanthomas and lung adenocarcinomas	134

TABLE III-14

TUMORIGENIC EFFECTS ON ANIMALS FROM EXPOSURE TO VINYLIDENE CHLORIDE BY INHALATION

Species	Concentration (ppm)	Duration	Effects	Reference
Rats	10-150	4 hr/d, 4-5 d/wk x 12 mo	Increase in mammary tumors	142
"	55	6 hr/d, 5 d/wk x 12 mo	Extrahepatic angiosarcomas in 3%	140
"	40-75	6 hr/d, 5 d/wk x 18 mo	No angiosarcomas; no increase in tumors	119
Mice	55	6 hr/d, 5 d/wk x 18 mo	Liver angiosarcomas in 4%; bronchiolar adenomas	140
"	25	4 hr/d, 4-5 d/wk x 12 mo	Increase in kidney adenosarcomas and lung adenocarcinomas	142

TABLE III-15

TUMORIGENIC EFFECTS ON ANIMALS FROM EXPOSURE TO VINYL BROMIDE BY INHALATION

Species	Concentration (ppm)	Duration	Effects	Reference
Rat	1,250	12 mo	Liver cancer in 19%; significant increase	327
"	250	"	Liver cancer in 7%; significant increase in other tumors	327
"	10-50	"	No tumors	327

IV. ENVIRONMENTAL DATA

Sampling and Analytical Methods

Most of the sampling and analytical procedures for airborne vinyls in occupational environments have been developed and tested for vinyl chloride. While these procedures may provide some guidance for choosing sampling and analytical conditions for the other vinyl halides, caution must be exercised in extrapolating or interpolating from vinyl chloride to vinylidene chloride, vinyl bromide, vinyl fluoride, and vinylidene fluoride. Certain physical and chemical properties of the latter compounds are quite different from those of vinyl chloride at ambient temperatures and pressures (see Table XVII-1). The collection media used for sampling the various vinyls should be selected to permit reproducible air sampling, adequate collection efficiency, storage stability, retention, and minimum breakthrough of the specific compounds.

(a) Sampling

(1) Vinyl Chloride

Denenberg and Miller [234] reported on several types of sampling equipment that can be used for the collection of workplace samples of vinyl chloride. These included evacuated glass flasks, glass syringes, and evacuated bottles for the collection of grab samples, and inflatable sampling bags (Saran, Mylar, or Teflon) and charcoal tubes for the collection of integrated samples.

Murdoch and Hammond [235] used evacuated glass bottles to collect grab samples for the determination of vinyl chloride concentrations in polyvinyl chloride work areas. After the samples were collected, the bottles were sealed with silicone rubber septa. Aliquots were later removed by syringe for analysis by gas chromatography.

Williams et al [236] also reported using evacuated stainless-steel containers equipped with critical orifices for collecting grab or integrated samples of air that contained mixtures of vinyl chloride, vinylidene chloride, and other compounds under laboratory conditions. Identical results were obtained for samples collected in steel containers from a chamber and for samples taken directly from the chamber.

Stainless steel canisters and Tedlar bags have both been used for sampling for vinyl chloride. Losses of 0-10% vinyl chloride/day were reported for samples stored in Tedlar bags [10]. The losses were attributed either to leakage from the bags or to reactions of vinyl chloride with other air contaminants, such as nitrogen dioxide and ozone.

Levine et al [237] compared the storage stability of vinyl chloride collected in Teflon and aluminized Scotchpak gas sampling bags. The comparison showed the loss from Teflon bags to be about 20%/day, but it was not determined whether the loss resulted from the permeability of the Teflon, from chemical reaction, or from mechanical problems. No detectable loss occurred during a 1-week period from aluminized Scotchpak bags that contained samples of vinyl chloride at concentrations of 0.1-1.1 ppm (0.256-2.8 mg/cu m).

Ketterer [238] found Teflon bags to be satisfactory for holding samples that would be analyzed for vinyl chloride soon after collection but did not report the time between sample collection and analysis. The relative standard deviations for seven samples of vinyl chloride at a concentration of 25 ppm (64 mg/cu m) and for eight samples at a concentration of 52.2 ppm (133.6 mg/cu m) were 2.24 and 1.77%, respectively, and the reported accuracy at both concentrations was 95%. The author concluded that this degree of accuracy and reproducibility should be readily attainable in field use, since fluctuations in temperature and humidity and the presence of other volatile organic materials had little effect [238].

The major advantage of bag sampling is that it permits direct analysis of the sampled air, ie, without the adsorption and desorption steps required for collection on solid sorbents [239]. Its disadvantages include the bulky equipment required for personal sampling and the relatively high detection limit, approximately 50 ppb (0.13 mg/cu m) that results from the sample not being concentrated. Another disadvantage of bag sampling is that the sample volume is limited.

The most widely used sampling technique involves adsorption on solid sorbents such as Tenax-GC resin and activated charcoal. The major sampling problem in collecting vinyls on solid media is that vinyls have appreciable vapor pressures, which can result in sample migration or loss.

Tenax-GC resin was used by Ives [240] to concentrate grab samples of contaminated air. Average recoveries of 90% for vinyl chloride at 6 ppb (0.015 mg/cu m) and 100% at 60 ppb (0.15 mg/cu m) were reported when contaminated air in a 500-ml gas sampling tube was flushed with nitrogen through the Tenax-GC resin trap at a flowrate of 85 ml/minute for 35 minutes. The trap was cooled in dry ice. Ahlstrom et al [241] reported that Tenax-GC resin did not quantitatively adsorb vinyl chloride from the atmosphere, but they presented no data supporting this conclusion. Zado and Rasmuson [242] reported that the breakthrough volume for vinyl chloride on Tenax-GC resin was 170 ml at a flowrate of 50 ml/minute, but they did not specify the concentration sampled nor the dimensions of the resin bed. They stated that Tenax-GC resin had the next to the poorest breakthrough performance of 10 adsorbents tested.

Nelms et al [243] described a permeation sampling technique using a charcoal badge, 41 x 48 mm and 7 mm thick, pinned to the worker's clothing for

monitoring 8-hour exposures of vinyl chloride at concentrations of 5 ppb to 50 ppm (0.01-128 mg/cu m). Vinyl chloride passed through a permeable membrane and was adsorbed on activated charcoal. The vinyl chloride concentration was later determined by gas chromatography. The authors stated that temperature and humidity had no measurable effect on the determination of vinyl chloride. Of the compounds tested (including sulfur dioxide, nitrogen dioxide, and ozone) only ethylene chloride was reported to cause positive interference during analysis.

Hill et al [244] evaluated breakthrough volumes for vinyl chloride on 20 sorbents, 6 activated charcoals and 14 gas-chromatographic column packings, each contained in 1.5-cm sections of glass tubing with inner diameters of 4 mm. Breakthrough volume was defined as the air volume sampled when 5% of the synthetic atmospheric concentration of vinyl chloride was detected in the tube effluent. Vinyl chloride was measured using a portable gas chromatograph with a flame ionization detector. The results are shown in Table XVII-5. Breakthrough volume for Dow carbon XF 4175 L and MSA-6 coconut charcoal increased with decreasing flowrate, and the amount of vinyl chloride adsorbed increased with increasing concentrations of vinyl chloride in the air. The authors concluded that the MSA-6 coconut charcoal was suitable for collecting vinyl chloride at concentrations of about 1 ppm (2.56 mg/cu m) or lower, at flowrates of 50-100 ml/minute. High humidity or high concentrations of other organic contaminants could reduce the breakthrough volume, but this was not investigated [244]. The authors suggested that maximum sample volumes of 5 liters at a flowrate of 50 ml/minute would not result in significant breakthrough. These suggested values have been adopted for the NIOSH-accepted method [245].

Cuddeback et al [246] tested commercially available charcoal tubes from two manufacturers. By examining the packings of the front sections of the tubes, they determined that MSA tubes averaged 99.7 mg of charcoal (±6%) for three samples in 16.5 mm (±10.9%) tubes, and SKC tubes averaged 86.2 mg (±3.1%) for six samples in 15.9 mm (±7.8%) tubes. Breakthrough volumes, defined as those at which the effluent concentration of vinyl chloride was 10% of the inlet concentration, were measured using the front sections of the MSA tubes. As shown in Table XVII-6, there was no consistent correlation between breakthrough volume and sampling rate.

Several activated charcoals were evaluated for vinyl chloride collection and breakthrough by Severs and Skory [247]. They concluded that the Pittsburgh PCB had superior breakthrough characteristics for vinyl chloride sampling. Breakthrough volumes for commercial tubes with different packings were also compared. Tubes packed with 600 mg of SKC (Lot 105) charcoal or 700 mg of Pittsburgh PCB carbon had a breakthrough of less than 2% for vinyl chloride at 25 ppm (64 mg/cu m) at a flowrate of 1 liter/minute for 30 minutes. The same tubes packed with 150 mg of the SKC charcoal had breakthrough of 2% within 2 minutes for vinyl chloride at 1 ppm (2.56 mg/cu m) sampled at 1 liter/minute.

(2) Vinylidene Chloride

Severs and Skory [247] used charcoal tubes for collecting vinylidene chloride in workplace samples. No data on collection efficiency or storage stability were reported. Tubes packed with 600 mg of SKC charcoal had "good" retention capacity for vinylidene chloride. At 31 ppm (123 mg/cu m) of vinylidene chloride, samples collected at a flowrate of 1 liter/minute had a breakthrough below 0.08% after 75 minutes. Russell [248] reported that the breakthrough volume of vinylidene chloride on Carbosieve B was greater than 10 liters of air.

(3) Vinyl Bromide

Russell [248] collected vinyl bromide on Porapak N porous polymer in a 4-inch by 0.19-inch inner diameter stainless steel sampling tube. The breakthrough volume was 1 liter at a sampling flowrate of 100 ml/minute of air that was nearly saturated with water and that contained 1-5 ppm (4.38-21.9 mg/cu m) of vinyl bromide. Bales [249] used a charcoal tube to collect vinyl bromide in a production facility. No data on breakthrough volume, collection efficiency, or storage stability were reported.

(4) Vinyl Fluoride

Bales [250] used Teflon bags for collecting air samples to be analyzed for vinyl fluoride. DW Yeager (written communication, August 1977) stated that there was no measurable leakage of vinyl fluoride from Teflon bags in a 4-day period; however, within 2 weeks a 50% loss had occurred. Only a limited number of samples were analyzed for this study.

(5) Vinylidene Fluoride

Pennwalt Corporation [251] recommended that charcoal tubes be used to collect vinylidene fluoride. No data regarding efficiency and stability were reported.

NIOSH recommends using the sampling methods as outlined in Appendices II-V. Charcoal tubes are recommended for sampling vinyl chloride in the NIOSH-accepted method (Appendix II) and for sampling vinylidene chloride in the NIOSH-proposed method (Appendix III). There are no validated methods for vinyl bromide, vinyl fluoride, or vinylidene fluoride; however, NIOSH recommends that charcoal tubes be used for vinyl bromide (Appendix IV) and vinylidene fluoride (Appendix VI). Teflon air bags, as used by Bales [250], are recommended for sampling vinyl fluoride in the proposed method (Appendix V).

(b) Analysis

The available methods for determination of vinyls in the workplace include gas-chromatographic and infrared techniques, among others, but vinyl chloride

has most often been analyzed by gas chromatography. This method has the advantages of being more specific and less expensive than infrared analysis.

(1) Gas Chromatography

Analysis by gas chromatography generally involves direct injection of a portion of the air sample taken from a sampling bag or canister or injection of an aliquot of sample desorbed from a suitable adsorption material through which ambient air has been drawn. Ives [240] used both procedures in series to sample and analyze for vinyl chloride. Grab samples in a 500-ml gas sampling tube were flushed with nitrogen through a Tenax-GC cold trap. Vinyl chloride was subsequently thermally desorbed directly onto a gas chromatographic column. Severs and Skory [247], on the other hand, thermally desorbed vinyl chloride from charcoal into a gas sampling bag. While the injection of contaminated air obtained from a bag or canister is straightforward, samples from activated carbon or gas-chromatographic packings must be desorbed before analysis.

(A) Desorption

Desorption from sampling tubes is accomplished thermally or by solvent extraction. A variety of operating conditions for these two techniques have been investigated.

Three variations of thermal desorption have been applied to vinyl chloride. The first variation involved heating charcoal in a flow of prepurified nitrogen and collecting the vinyl chloride containing effluent in a bag [247]. Heating the charcoal to 430 C eliminated low and erratic recoveries. The nitrogen flow was maintained at 500-800 ml/minute.

In the second variation [239,241,248], activated charcoal or gas-chromatographic packing was heated, and the vinyl chloride-laden effluent was flushed directly onto the analytical column with carrier gas. Purcell [239] maintained the desorption chamber at 260-300 C and the column at 25 C for 4 minutes during desorption. After desorption, the column temperature was raised to 70 C, and the vinyl chloride was eluted. When this technique was used to analyze the front section (100 mg) of the charcoal tube, an overall recovery of 90% was determined for a 278-ml sample spiked with vinyl chloride at 1 ppm (2.56 mg/cu m). Good reproducibility was demonstrated by obtaining a relative standard deviation of 4.1% in the analysis of 11 sampling tubes, each containing a 278-ml sample spiked with vinyl chloride at 1 ppm.

Ahlstrom et al [241] also thermally desorbed vinyl chloride directly onto a gas-chromatographic column. The sample, collected on 150 mg of petroleum-derived charcoal (SKC Lot 104) packed in a 5- x 3/16-inch U-shaped stainless steel tube, was desorbed by pulse heating the tube for 2 minutes at 400 C. The desorbed vinyl chloride was swept by the helium carrier gas onto the column, which was maintained at 90 C. The carrier gas flow was 20 ml/minute. Recovery of a 45-ppm vinyl chloride synthetic atmosphere sampled at 50

ml/minute for 1, 2, and 3 minutes averaged 99 ±2%. For four runs of a 1-ppm vinyl chloride standard, the relative standard deviation was 1.2%.

Russell [248] thermally desorbed vinyl bromide from Porapak N and vinyl chloride and vinylidene chloride from Carbosieve B adsorbents. In each case, the recovery was 100 ±3%. Samples were collected at a flowrate of 100 ml/minute, but specific concentrations and sample volumes were not reported. Desorption from Porapak N was performed by heating for 5 minutes at 200 C, and desorption from Carbosieve B was accomplished by heating for 5 minutes at 270 C. The adsorbent column was maintained at 60 C for desorption from Porapak N and at 80 C for desorption from Carbosieve B.

The third thermal desorption variation [240,252] is similar to that of Ahlstrom et al [241]. It differs from that of Russell [248] in that the sample is injected into the analytical column only after desorption is complete, rather than being continuously flushed into the column during desorption while elutriation is retarded by a relatively low column temperature.

Ives [240] used Tenax-GC sorbent cooled to dry ice temperature to concentrate air bag samples, with thermal desorption directly onto the chromatography column. Ives heated the Tenax for 5 minutes at 150-180 C before flushing it with carrier gas through the gas-chromatographic column. Recovery was 100% for a 579-ml sample spiked with vinyl chloride at 60 ppb and 90% for a similar sample spiked with vinyl chloride at 6 ppb.

Myers et al [252] collected vinyl chloride on activated charcoal (GC grade, 60/80 mesh, Coast Engineering Laboratory) packed in glass columns 6.5 cm long and 5-mm outside diameter. For desorption, the tubes were heated for 30 seconds at 300 C. The analytical column, 6-feet x 1/8-inch Chromosorb 101, was maintained at 100 C. Replicate analysis of 13 samples of a standard atmosphere containing vinyl chloride at approximately 1 ppm indicated an average of 1.25 ±0.037 ppm (3.2 ±0.09 mg/cu m). The authors concluded that vinyl chloride could be detected at 100 ppb (0.256 mg/cu m), in a 1-liter sample and at 20 ppb (0.05 mg/cu m) in a 5-liter sample. They speculated that 1 ppb (0.003 mg/cu m) could be detected by increasing the instrument's operating sensitivity.

The advantages of the thermal technique for desorption of vinyl chloride, according to Zado and Rasmuson [242], are that it is simple to handle, free of interferences, and highly sensitive. The authors noted that its disadvantages include the requirement of expensive equipment and the inability to make repeated injections of the sample. They suggested using the less expensive Porapak N instead of Carbosieve B. However, the disadvantage of Porapak N is its low breakthrough volume of 976 ml, compared with greater than 2,000 ml for Carbosieve B, at a flowrate of 50 ml/minute.

For solvent desorption of vinyl chloride and other vinyls, carbon disulfide has generally been used. However, tetrahydrofluran and a bromine-hexane mixture have also been used.

Hill et al [244] reported using a 2-ml vial containing 0.5 or 1.0 ml of carbon disulfide for desorption of vinyl chloride from the front section of a charcoal tube (100 mg of charcoal). The 13-μg samples were analyzed after desorption periods of 10-30 minutes at ambient temperature. The authors found that desorption efficiencies were generally in the 80-90% range. Hill et al also determined that the addition of the charcoal to the carbon disulfide enabled more precise analyses at ambient temperatures than if the solvent were added to the charcoal. They concluded that solvent temperature and volume had little effect on precision, although only one set of tests was performed at other than ambient temperature (0 C). Studies of the stability of vinyl chloride samples by the same authors [244] demonstrated that vinyl chloride was stable on charcoal for periods of over 2 weeks, but that migration from the front to the back section occurred when the tubes were stored at ambient temperatures. Cooling to -20 C retarded this effect. The authors suggested using two tubes in series as the front and backup sections to obviate the need for storage at low temperatures.

Severs and Skory [247] studied a desorption technique by which 1 g of PCB 12/30 charcoal was added slowly to 10 ml of carbon disulfide, the mixture was cooled in a dry ice/acetone slurry and agitated for 30 minutes. Samples were stored under refrigeration and held in a wet ice bath while they were analyzed. An average recovery of 98% (93-101%) was reported. When the same procedure was applied to the desorption of vinylidene chloride, recovery ranged from 95 to 100%. In neither case was sample loading specified.

Lao et al [253] added 15 ml of carbon disulfide, cooled to -15 C, to 1-g aliquots of 20/50 carbon in a 25-ml flask fitted with mini-inert valves. The system was allowed to equilibrate for 15 minutes at 15 C before samples were withdrawn for analysis. Recovery was 88% for 2.7 ng of vinyl chloride, 95% for 14.1 ng, 98% for 54 ng, and 97% for 126 ng. The concentration of vinyl chloride in the headspace of the flasks never exceeded 2% of its concentration in the liquid.

Still another desorption technique was used by Cuddeback et al [254]. The charcoal (100 mg) was placed in a 2-ml glass vial, which was sealed with a silicone rubber septum. The vial was cooled to dry ice temperature, and 0.5 ml of carbon disulfide at room temperature was injected through the septum. When bubbling produced by the mixing ceased, the vial was removed from the dry ice and allowed to stand at room temperature for 5 minutes before samples were withdrawn for analysis. Recoveries from a 2.55-μg sample were 85% for immediate analysis, 83% after 7 days, and 71% after 14 days. For a 31.9-μg sample, respective recoveries for these intervals were 89, 79, and 81%.

Hoffmann et al [255] used a mixture of 0.5 ml of bromine and 11 ml of n-hexane, cooled to -30 C in a Reacti-flask, to desorb vinyl chloride from 1 g

of charcoal. After the charcoal was added, the flask was sealed and covered with dark paper, and the contents were stirred magnetically for 7 minutes. During this procedure, vinyl chloride is converted to 1,2-dibromo-1-chloroethane, which has a much greater sensitivity to electron-capture detection than vinyl chloride. For samples enriched by column chromatography and determined by gas chromatography using an electron-capture detector, the authors reported a recovery of at least 85%.

Desorption of vinyl chloride with tetrahydrofuran was reported in an Environmental Protection Agency (EPA) publication [10]. Recovery was 88%, and there was less diffusion into the headspace than was evident with carbon disulfide desorption; however, the solvent volume and the desorption conditions were not reported.

Ethyl Corporation [14] reported that a carbon disulfide-pentane mixture was used to desorb vinyl bromide from about 14 g of Pittsburgh 20x50 activated carbon.

No data were located on the desorbing agent for vinyl fluoride and vinylidene fluoride samples.

(B) Chromatographic Columns

The choice of column materials and operating parameters for analysis of vinyls will depend on the interfering compounds that may be present and their relative retention times. For vinyl chloride analysis, potential interferences include light hydrocarbons, other halocarbons, Freons, and sulfur dioxide [240,247,256,257]. Contaminants often found during analyses for vinyl chloride include acetylene, methyl chloride, 1,3-butadiene, and vinylidene chloride [253]. Table XVII-7 shows the retention times relative to vinyl chloride for a number of interfering compounds on various column materials. Foris and Lehman [258] listed the Kovats retention indices for four vinyl halides on Poropak Q.

Severs and Skory [247] separated vinyl chloride and vinylidene chloride on a 20-foot x 1/8-inch stainless steel column containing Carbowax 4,000 on 80/100-mesh Supelcoport and with a 6-foot x 1/8-inch column of 20% DC 200 on 80/100-mesh Chromosorb W.

For vinylidene chloride separation, the NIOSH-proposed method [259] recommends that a silanized glass column (10-foot x 1/4-inch outer diameter) packed with 100/120-mesh Durapak OPN be used. The Manufacturing Chemists' Association (MCA) reported use of a stainless-steel column (10 feet x 1/8 inch) packed with 100/120-mesh Durapak OPN chemically bonded to Porasil C [260].

Rein et al [261] reported using a 50-foot x 1/4-inch column packed with 33.5% DC-200 oil on 30/60-mesh Chromosorb P to analyze for vinyl fluoride and vinylidene fluoride at about 30 C. The packed column was conditioned for 8-12

hours in the instrument under operating conditions. The authors noted that the column was excellent for separating compounds with low boiling points at ambient temperatures. The retention times for vinyl fluoride and vinylidene fluoride were 16.4 and 12.4 minutes, respectively. Rein et al [261] also reported analyzing for vinyl fluoride and vinylidene fluoride on combined 6-foot and 12-foot columns packed with 33.5% DC-200 oil on 30/60-mesh Chromosorb P, but they found that resolution of any low-boiling fractions that were present was poor at ambient temperatures.

The Ethyl Corporation [14] has analyzed for vinyl bromide using a 25-foot x 1/8-inch stainless steel column packed with 30% SE-52 on 80/100-mesh Gas Chrom Q conditioned for 16 hours at 200 C; Lao et al [253] have used a 6-foot x 1/8-inch column of Chromosorb 102, similarly conditioned. The Ethyl Corporation report [14] noted that isopentane interfered with the determination of vinyl bromide on an SE-52 column, and suggested that a combined column of 12 feet of SE-52 and 6 feet of 10% Carbowax 20M gave a good separation of vinyl bromide from isopentane. The SE-52 on Gas Chrom Q column was used to determine vinyl bromide at concentrations of less than 1 ppm.

(C) Chromatographic Detectors

Detection methods used in gas chromatography to quantitate vinyls, particularly vinyl chloride, include electron capture [10,255], microcoulometry and electroconductivity [256], chemiluminescence [262], mass spectroscopy [257,263], and flame-ionization [238,239,242,247,253,264]. Table XVII-8 shows the specificity and approximate detection limit of each of these detectors for vinyl chloride.

Electron-capture detectors belong to the general class of direct-current ion chambers. Nitrogen or argon is used as the carrier gas, and 3H or 63Ni is used as the radioactive source to excite the gas. As compounds are eluted from the gas chromatographic column, they become ionized by the excited carrier gas and produce an increased current flow across parallel electrodes. The current flow is proportional to the amount of compound present. Electron-capture detection is more selective than flame-ionization detection, but it is less reliable and has a smaller dynamic range [10]. A further disadvantage of electron-capture detection with respect to vinyl chloride analysis is that response to aromatic halides and polychlorinated hydrocarbons is relatively low [264]. Hoffmann et al [255] have extended the electron-capture detection limit for vinyl chloride by brominating vinyl chloride to produce 1,2-dibromo-1-chloroethane. The detection limit for this compound was 15 pg/injection, and the response was linear between 50 and 300 pg [255].

Microcoulometric detection is highly sensitive and accurate for chloride ions [10]. As chlorinated hydrocarbons are eluted from the gas chromatograph column, they are pyrolyzed to form hydrogen chloride gas. The hydrogen chloride causes silver chloride to precipitate, and to disturb the electrical balance at the positive silver electrode. The coulometer regenerates silver ions until the electrical balance is restored, and the current generated to

restore the balance is proportional to the number of chloride ions generated. Ernst and Van Lierop [256] used a Hall detector (microcoulometer) for the analysis of vinyl chloride; the vinyl chloride was pyrolyzed in a quartz tube in the presence of hydrogen and the hydrogen chloride formed was detected as a function of the increased conductivity of an aqueous reservoir. A detection limit of 0.07 ng, slightly better than the flame-ionization detection limit, has been reported [264]. The major advantage of microcoulometry is its sensitivity to organohalides [264]. Its disadvantage is its electrical power requirements, which make the detector impractical for field use [10].

Chemiluminescence detection of vinyl chloride has been used by McClenny et al [262]. This method is based on light emission from the products of the gas phase reaction of vinyl chloride with ozone. The authors determined the lower detection limit to be 50 ppb (0.13 mg/cu m), and response was linear from 50 ppb to 10 ppm (0.13-25.6 mg/cu m).

Mass spectroscopy specific ion monitoring is a highly sensitive and selective detection method, but it is relatively expensive to install. According to Rosen et al [257], it offers a detection limit for vinyl chloride of 8.7 pg/10 ml injection. Detection depends on the response of the instrument to the vinyl chloride molecular ion (m/e 62) and the 37Cl ion (m/e 64) [257,263]. For qualitative confirmation of vinyl chloride, the ratio of the m/e 62 and m/e 64 peaks should be about 3:1, conforming to the natural abundance ratio of 35Cl and 37Cl [253,257].

The flame-ionization detector is perhaps the most commonly used instrument for the analysis of vinyls. This detector responds to most organic compounds and is insensitive to almost all inorganic compounds [10]. It has a wide linear range covering several orders of magnitude, and it can detect vinyls in the ppb range. According to reports of the NIOSH-accepted method for the analysis of vinyl chloride [245], and the MCA method for vinylidene chloride [260], a sample of 0.2 ng/injection of vinyl chloride and vinylidene chloride, respectively, can be detected by flame-ionization. However, the conditions under which the MCA method was tested were not specified. For vinylidene chloride analysis, the NIOSH-proposed method [259] reports that a sample loading of 7 μg (about 35 ng/injection) had a desorption efficiency of greater than 80%. Detector response is generally a function of the number of carbon atoms in a molecule of a compound, although a reduced response or no response may occur when the carbon atom is attached to atoms other than hydrogen, such as chlorine, oxygen, or sulfur. A lower detection limit of 0.01 ppm (0.03 mg/cu m) for vinyl chloride in a 10-ml sample of air has been reported for the flame-ionization detector [10]. The major disadvantage of the flame-ionization detector is its relatively nonselective response [264].

(2) Infrared and Other Analytical Methods

According to a personal communication by Keenan cited in an EPA publication [10], the analysis for vinyl chloride by infrared spectrophotometry has one major problem: several substances that are present

in ambient air act as interferences, and thus the method is not specific for vinyl chloride. The EPA report [10] noted that vinyl chloride is detectable at an absorption frequency of 941 or 917 1/cm. The authors pointed out that these major problems could be circumvented by additional instrumentation, but they cautioned that the cost would be high. Effective optical paths of 20 meters are required in order for infrared analyzers to achieve a detection limit of 1 ppm (2.56 mg/cu m).

Other methods that have been used to determine vinyl chloride concentrations include colorimetry and polarography [10]. The sensitivities of the colorimetric methods are very much affected by such interferences as ethylene and methanol, and the sensitivity of the polarographic method is affected by any other volatile materials that may be present.

Gronsberg [265] used a photometric method to determine concentrations of vinylidene chloride in air. His method is based on the reaction of vinylidene chloride with pyridine and on subsequent condensation of the reaction products with aniline or barbituric acid. After the reaction, a polymethine dye complex is formed. The method has a sensitivity of 2 μg/photometric cuvette volume and is capable of determining vinylidene chloride in air at concentrations of 10 mg/cu m (2.5 ppm). The author reported that vinyl chloride, acrylonitrile, dichloroethane, and hydrogen chloride had no effect on the analysis for vinylidene chloride but noted that trichloroethylene and 1,1,2-trichloroethane produced analogous reactions.

Color-specific detector tubes are available for the determination of vinyl chloride or vinylidene chloride in the work environment. Two types of color reactions, one using chromate and bromophenol blue, and the other using permanganate and o-tolidine, were used for analyzing for vinyl chloride [266]. Their ranges of linearity were 0.5-3 ppm (1.28-7.68 mg/cu m) and 1-50 ppm (2.56-128 mg/cu m), respectively. Vinylidene chloride can be determined with twice the sensitivity with which vinyl chloride can be determined. No detector tubes for vinyl bromide, vinyl fluoride, or vinylidene fluoride are known to be available.

Murdoch and Hammond [235] reported using detector tubes to determine concentrations of vinyl chloride in polyvinyl resin production environments. Vinyl chloride was determined at concentrations of 0-3 ppm (0-7.68 mg/cu m). The tubes had a lower detection limit of 0.5 ppm (1.28 mg/cu m).

Detector tubes have the advantages of being simple and inexpensive, and do not require that samples be transported for analysis. Their major disadvantages are their susceptibility to interferences and lack of sensitivity.

(3) Continuous Monitors

Continuous monitoring systems can be used to warn employees of overexposure to vinyl chloride at high concentrations, permit reduction of

emissions by locating sources of leaks, and produce permanent records for areas where employees have been exposed to vinyl chloride.

Continuous systems with multiple sampling points have been reported to be effective for monitoring concentrations of vinyls in work area atmospheres [239,267-270]. The air samples were analyzed by infrared spectrometry or gas chromatography. Other continuous-analysis methods that have been used for vinyl chloride include impregnated paper tape [234,271], Stark spectroscopy with a carbon monoxide or carbon dioxide laser [272], and an ultraviolet (UV) conductivity system [273].

Portable infrared analyzers with 20- to 25-meter folded-path absorption cells have been used to detect vinyl chloride at a working lower detection limit of about 1 ppm (2.56 mg/cu m) [267,274]. Also, portable gas chromatographs with flame-ionization or electron-capture detectors have been used for "continuous" monitoring for vinyl chloride, and a sensitivity of 0.1 ppm has been reported for such systems [10]. Purcell [239] found lower detection limits for vinyl chloride of 50 ppb with gas-liquid chromatography and 1 ppm with infrared spectrometry.

Baker and Reiter [275] described an automatic monitoring system, based on a gas chromatograph equipped with a flame-ionization detector and an alarm device that has been used for the determination of vinyl chloride in workplace atmospheres. Each analyzer in the system could monitor 20 sample points, and each analysis required 2 minutes from collection to readout. An analytic range of 0.1-25 ppm (0.256-64 mg/cu m) was reported. The compounds found to interfere with the analysis of vinyl chloride included methyl chloride, isobutylene, n-butyl acrylate, and toluene, and the interference from the last two compounds occurred after approximately 40 minutes. The authors concluded that the monitoring system had the advantages of being very sensitive, very accurate, and relatively maintenance free.

Denenberg et al [234,271] reported the use of impregnated paper tape for monitoring vinyl chloride. With this method the intensity of light reflected from the tape surface is theoretically proportional to the concentration of analyte. The double bond in the vinyl chloride molecule is broken by means of an oxidant converter, releasing free chlorine. The chlorine reacts to darken the paper tape. A lower detection limit of between 0.05 and 0.1 ppm (0.13 and 0.256 mg/cu m) is claimed, and performance and sensitivity are unaffected over ranges of 0-100% relative humidity and 0-40 C [234]. Trichloroethylene, which produces a response three times as great as vinyl chloride, will interfere, and vinylidene chloride, with a double bond and two chlorine atoms, will produce twice as great a response as vinyl chloride [271].

Stark spectroscopy was used by Freund and Sweger [272] for the measurement of vinyl chloride concentrations. Carbon monoxide and carbon dioxide lasers were investigated and the extracavity absorption cell contained two 40-cm stainless steel Stark electrodes spaced 1 mm apart. The method is capable of detecting vinyl chloride at 1 ppm (2.56 mg/cu m).

A UV method for measuring vinyl chloride in air has been developed by Confer [273], in which vinyl chloride exposed to UV light decomposes to produce chlorine, hydrogen chloride, phosgene, and other products, and the concentrations of the decomposition materials are measured by changes in conductivity of deionized water. A 6-inch UV lamp with an output of 2.5 watts, 90% of which is at a wavelength of 253.7 nm, was positioned in a 600-ml gas washing flask directly upstream from the sensor of a conductivity analyzer. Air was passed over the lamp at 2 liters/minute, and the deionized-water absorber was set at a flowrate of 6 ml/minute. Degradation efficiency was 80%, and, with a 2.5-minute holdup time in the conductivity cell, response reached 90% of the final reading. A lower detection limit of 0.05 ppm (0.13 mg/cu m) was found. Response was linear for concentrations up to 25 ppm (64 mg/cu m). Interferences by sulfur dioxide, chlorine, and hydrogen sulfide can be removed by scrubbing in a 100-ml gas-washing bottle equipped with a fritted bubbler and containing 20 ml of deionized water. Interferences by nitric oxide, carbon disulfide, and trichloroethylene, however, are not removed by this scrubbing method.

(4) Recommendations

The analytical methods described in detail in Appendices II-VI offer the necessary quantitative sensitivity and precision. Their accuracy, technical requirements, and cost requirements are easily within the range of most analytical laboratories.

For the analysis of vinyl chloride and vinylidene chloride, NIOSH recommends desorption of samples with carbon disulfide and analysis by gas chromatography with flame-ionization detection. A stainless steel column (20 feet x 1/8 inch) packed with 10% SE 30 on 80/100-mesh Chromosorb W is recommended for vinyl chloride [245]. For analysis of vinylidene chloride, a silanized glass column (10 feet x 1/4 inch) packed with Durapak OPN (oxypropionitrile) chemically bonded to 100/120-mesh Porasil C is recommended [259].

There are no NIOSH-validated methods for the sampling and analysis of vinyl bromide, vinyl fluoride, or vinylidene fluoride. However, NIOSH recommends that samples of vinyl bromide and vinylidene fluoride, collected on charcoal tubes, be desorbed with carbon disulfide and that samples of vinyl fluoride, collected in Teflon bags, be injected directly into the chromatograph. For analysis of these compounds, gas chromatography with flame-ionization detection is recommended. The column recommended for vinyl bromide analysis is an SE-30 (20-ft) column, the column recommended for vinyl fluoride is also a 20-foot, SE-30 column (DW Yeager, written communication, February 1978), and the recommended column for vinylidene fluoride is a stainless steel (6 feet x 1/8 inch) column packed with 80/100-mesh Chromosorb 102 (JL Sadenwasser, written communication, March 1978). However, other columns with high separation efficiencies can also be used. All work with the desorbing agent should be performed in an exhaust hood because of the high toxicity of carbon disulfide.

NIOSH also recommends that a continuous monitoring system with alarm-indicator devices be installed to monitor area concentrations of vinyl chloride or vinylidene chloride in accordance with 29 CFR 1910.1017(g)(6)ii. Continuous monitors should be installed to monitor vinyl bromide, vinyl fluoride, or vinylidene fluoride as soon as systems sensitive enough become available. The system ideally should be highly sensitive and specific to the vinyl halides sampled and free of interferences.

Environmental Levels

In 1975, Barnhart et al [276] reported the results of NIOSH industrial hygiene surveys of vinyl chloride monomer producers and polyvinyl chloride processers. Three vinyl chloride manufacturing plants and seven polyvinyl chloride processing plants were included in the study. Workplace air samples were collected on charcoal tubes and analyzed by gas chromatograph after desorption with carbon disulfide. The survey found concentrations in the range of 0.1-9.20 ppm (0.256-23.55 mg/cu m) in the monomer plants and 0.01-0.85 ppm (0.03-2.18 mg/cu m) in the polyvinyl chloride processing plants. The authors concluded from these data that polyvinyl chloride processors were rarely exposed to vinyl chloride at concentrations greater than 0.5 ppm (1.28 mg/cu m), which was the Federal action level at that time. Monomer production workers, on the other hand, had a greater risk of vinyl chloride exposure. Polyvinyl chloride producers were not included in this study.

Results of other vinyl chloride monitoring surveys have also been reported [277-280] and the data are presented in Tables IV-1 and IV-2.

Baretta et al [269] monitored the concentrations of vinyl chloride in a vinyl chloride polymerization plant, apparently before and during 1967, continuously with an infrared spectrometer. Five sampling probes were placed in the work area for each of four job classifications, and mean vinyl chloride concentrations were calculated weekly. Mean area concentrations for the coagulator operator, dryer operator, blender-packager, and polymer operator declined steadily during the 7 months of the study. The authors attributed the decline to undescribed "actions undertaken to reduce the atmospheric concentration" of vinyl chloride. Weekly average vinyl chloride concentrations decreased from 205 to 40 ppm (524.8 to 102.4 mg/cu m) for coagulator operators and from 90 to 20 ppm (230 to 51 mg/cu m) for dryer operators. Blender-packagers and polymer operators were consistently exposed at concentrations below the target concentration of 50 ppm (128 mg/cu m) used in the plant at that time.

Kramer and Mutchler [76], in 1972, reported 8-hour TWA concentrations for vinyl chloride of from 0 to 300 ppm (0 to 768 mg/cu m) in a vinyl chloride polymerization plant. They stated that the mean TWA concentration was 155 ppm (396.8 mg/cu m) in 1950 and 30 ppm (76.8 mg/cu m) in 1965. Concentrations were estimated on the basis of area sampling data.

TABLE IV-1

SUMMARY-VINYL CHLORIDE MONITORING

Operation	Year	Mean Concentration	Concentration Range	Reference
Ethyl Corporation				
Vinyl chloride unit (monthly averages-October to April)	1973	2.7 ppm (6.9 mg/cu m)	- -	279
	1973	2.3 ppm (5.9 mg/cu m)	- -	279
	1973	1.6 ppm (4.1 mg/cu m)	- -	279
	1974	1.7 ppm (4.4 mg/cu m)	- -	279
	1974	1.6 ppm (4.1 mg/cu m)	- -	279
	1974	1.4 ppm (3.6 mg/cu m)	- -	279
	1974	1.3 ppm (3.3 mg/cu m)	- -	279
Dow Chemical USA				
Loading area (TWA concentrations)	1975	0.5 ppm (1.28 mg/cu m)	0.1 - 6.2 ppm (0.256- 15.87 mg/cu m)	280
	1976	0.3 ppm (0.77 mg/cu m)	0.1 - 0.6 ppm (0.256- 1.54 mg/cu m)	280
Production unit (TWA concentrations)				
378 samples	1975	0.3 ppm (0.77 mg/cu m)	0.1 -173 ppm (0.256-443 mg/cu m)	280
304 samples	1976	0.3 ppm (0.77 mg/cu m)	0.1 - 29 ppm (0.256- 74.24 mg/cu m)	280

TABLE IV-1 (CONTINUED)

SUMMARY-VINYL CHLORIDE MONITORING

Operation	Year	Mean Concentration	Concentration Range	Reference
Reactor operator (TWA concentrations)				
No. 1	1976-1977	0.8 ppm (2.0 mg/cu m)	- -	280
No. 2	1976-1977	0.2 ppm (0.5 mg/cu m)	- -	280
First operators	1976-1977	0.3 ppm (0.77 mg/cu m)	nd - 1.2 ppm (nd - 3.1 mg/cu m)	280
Utility operators	1976-1977	0.3 ppm (0.77 mg/cu m)	0.1 - 0.5 ppm (0.256- 1.28 mg/cu m)	280
Union Carbide Corp				
Solvent Process Area				
Personal samples	1974	- -	0.6 - 8.1 ppm (1.5 - 20.7 mg/cu m)	277
Area samples	1974	-	0.7 - 6.8 ppm (1.8 - 17.4 mg/cu m)	277
Dynel Process Area				
Personal samples	1974	- -	0.2 - 2.7 ppm (0.5 - 6.9 mg/cu m)	277
Area samples Control room	1974	1.4 ppm (3.58 mg/cu m)	- -	277
Dispersion Process Area				
Personal samples	1974	- -	3.0 - 43.7 ppm (7.68 -111.87 mg/cu m)	277
Area samples Control room	1974	- -	1.2 - 11.7 ppm (3.1 - 30.0 mg/cu m)	277

TABLE IV-2

SUMMARY-VINYL CHLORIDE MONITORING

Operation	Mean Concentration	Standard Deviation	Concentration Range
B.F. Goodrich Chemical Company 1974			
Mass Polymerization Process Area			
Office	1.0 ppm (2.56 mg/cu m)	1.4 ppm (3.6 mg/cu m)	nd- 3.8 ppm (nd- 9.7 mg/cu m)
Lead technician	4.4 ppm (11.2 mg/cu m)	7.0 ppm (17.9 mg/cu m)	nd- 22.6 ppm (nd- 57.8 mg/cu m)
Operating technician	3.6 ppm (9.2 mg/cu m)	3.9 ppm (10.0 mg/cu m)	nd- 13.7 ppm (nd- 35.0 mg/cu m)
Serviceman	6.4 ppm (16.4 mg/cu m)	12.9 ppm (33.0 mg/cu m)	nd- 71.4 ppm (nd-182.78 mg/cu m)
Bagger	nd	- -	- -
Suspension Resin Process Area			
Office	14.5 ppm (37.1 mg/cu m)	25.3 ppm (64.8 mg/cu m)	nd- 96.5 ppm (nd-247.0 mg/cu m)
Pearl technician	27.7 ppm (70.9 mg/cu m)	60.7 ppm (155.4 mg/cu m)	nd-245.0 ppm (nd-627.0 mg/cu m)
Paste technician	28.2 ppm (72.2 mg/cu m)	41.1 ppm (105.2 mg/cu m)	1.6-158.8 ppm (4.1-406.5 mg/cu m)
Rover technician	11.9 ppm (30.5 mg/cu m)	12.6 ppm (32.3 mg/cu m)	nd- 46.7 ppm (nd-119.6 mg/cu m)

TABLE IV-2 (CONTINUED)

SUMMARY-VINYL CHLORIDE MONITORING

Operation	Mean Concentration	Standard Deviation	Concentration Range
Suspension Resin Process Area			
Utility man	8.2 ppm (21.0 mg/cu m)	8.7 ppm (22.3 mg/cu m)	nd- 23.6 ppm (nd- 60.4 mg/cu m)
Bagger	0.2 ppm (0.5 mg/cu m)	0.4 ppm (1.0 mg/cu m)	nd- 0.9 ppm (nd- 2.30 mg/cu m)

Adapted from Jones [278]

Cook et al [75], in 1971, reported that concentrations of airborne vinyl chloride inside a reactor during scraping operations tended to be below 100 ppm (256 mg/cu m) and were usually about 50 ppm (128 mg/cu m). These estimates were developed from information supplied by a "small number" of unspecified plants, and the dates of the analyses were not reported.

In 1975, Ott et al [86] summarized 8-hour TWA concentrations of vinyl chloride measured by area sampling techniques from 1950 to 1966 in a polymerization facility. From 1950 to 1959, TWA concentrations ranged from 5 to 825 ppm (12.8 to 2,112 mg/cu m) with excursions to 4,000 ppm (10,240 mg/cu m). Large variations in the TWA concentrations were reported for different job classifications, and even within a single job classification, eg, dry end packer, 5-10 ppm (12.8-25.6 mg/cu m) and coagulator, 135-825 ppm (345.6-2112 mg/cu m). From 1960 to 1966, TWA concentrations ranged from 5 to 240 ppm with excursions to 500 ppm. The TWA concentration for the dry end packer during this period was listed as 5 ppm and that for the coagulator was 30-240 ppm (76.8-614 mg/cu m).

Ott et al [73], in 1976, also estimated TWA concentrations of vinylidene chloride from data gathered by area monitoring in production and polymerization facilities from 1956 through 1965. Estimated concentrations ranged from 5 to 70 ppm (19.85-277.9 mg/cu m) with excursions to 1,900 ppm (7,543 mg/cu m).

Dow Chemical USA [280] has provided NIOSH with vinylidene chloride monitoring data. These data are summarized in Table IV-3.

Bales [250], in 1977, provided NIOSH with the results of two industrial hygiene surveys conducted at a vinyl fluoride polymerization and monomer production plant. Samples were collected in 7.7-liter Teflon bags and were analyzed for vinyl fluoride by gas chromatography. TWA concentrations of vinyl fluoride ranged from 1 to 5 ppm (1.88 to 9.4 mg/cu m) for 11 samples collected from employees' breathing zones. Both personal and area samples collected in the monomer plant showed that concentrations of vinyl fluoride were less than 2 ppm (3.76 mg/cu m) for all but one (21 ppm or 39.5 mg/cu m) sample taken at the start of the operation.

Bales [249] also reported results from an industrial hygiene survey in a vinyl bromide monomer plant. The data are shown in Table IV-4.

Engineering Controls

Engineering controls should be used to eliminate the potential for exposure to vinyl halides in the workplace and to prevent fire and explosion. These goals can be achieved with properly constructed and maintained closed-system operations and appropriate safety precautions.

Closed-system operations provide the best means for eliminating employee exposures to vinyl halides. Closed-system operations are effective only when the integrity of the system is maintained by frequent inspection and by prompt repair of any leaks that are found. Closed-system operations should be performed under negative pressure.

Where closed systems cannot be adequately designed and effectively used, local exhaust ventilation systems should be provided to direct vapors and gases away from employees and to prevent the recirculation of contaminated exhaust air. Contaminated air should be directed to an incinerator equipped with scrubbers to remove any toxic combustion products. Exhaust ventilation systems for quality control laboratories or laboratory hoods where samples are prepared for analysis should be equipped with sorbers. Guidance for designing a local exhaust ventilation system can be found in Recommended Industrial Ventilation Guidelines [281], Industrial Ventilation--A Manual of Recommended Practice [282], or more recent revisions, and in Fundamentals Governing the Design and Operation of Local Exhaust Systems, ANSI Z9.2-1971 [283]. Ventilation systems of this type require regular inspection and maintenance for effective operation. These inspections should include face-velocity measurements of the collecting hood or duct, inspection of the air mover and collector, and measurements of vinyl concentrations in workroom air. Continuous airflow indicators, such as oil or water manometers, are recommended and should be properly mounted on collection hoods, ductwork, or laboratory hoods and marked to indicate the appropriate airflow.

TABLE IV-3

SUMMARY-VINYLIDENE CHLORIDE MONITORING

Operation	Year	Mean TWA Concentration	Mean TWA Concentration Range
Area samples			
Louisiana Division			
Loading area			
6 samples	1975	0.4 ppm (1.59 mg/cu m)	0.1- 1.7 ppm (0.4- 6.75 mg/cu m)
7 samples	1976	0.6 ppm (2.38 mg/cu m)	0.1- 2.2 ppm (0.4- 8.7 mg/cu m)
Production unit			
30 samples	1974	1.5 ppm (5.96 mg/cu m)	0.1- 4.2 ppm (0.4-16.7 mg/cu m)
69 samples	1976	1.9 ppm (7.5 mg/cu m)	0.2- 8.5 ppm (0.8-33.7 mg/cu m)
Texas Division			
311 samples	1975	0.4 ppm (1.59 mg/cu m)	0.1- 9.5 ppm (0.4-37.7 mg/cu m)
600 samples	1976	0.5 ppm (1.99 mg/cu m)	0.1-10.0 ppm (0.4-39.7 mg/cu m)
Personal samples			
Reactor operators			
No. 1	1976-1977	0.2 ppm (0.8 mg/cu m)	- -
No. 2	1976-1977	0.2 ppm (0.8 mg/cu m)	- -
First operators (5)	1976-1977	6.7 ppm (26.6 mg/cu m)	- -
Utility operators (4)	1976-1977	1.7 ppm (6.75 mg/cu m)	- -

Adapted from reference 280

TABLE IV-4

SUMMARY-VINYL BROMIDE SURVEY

Operation	Year	Median TWA Concentration	TWA Concentration Range
Operators	1977	0.27 ppm (1.2 mg/cu m)	0.1 -0.43 ppm (0.44-1.88 mg/cu m)
Loading crewman	1977	1.2 ppm (5.3 mg/cu m)	- -
Lab technician	1977	0.4 ppm (1.8 mg/cu m)	0.29-0.51 ppm (1.27-2.23 mg/cu m)
Loading crewman (Observed during 61-min loading operation)	1977	6.3 ppm (27.6 mg/cu m)	- -

Adapted from Bales [249]

Although it may be unnecessary to ventilate monomer production equipment, since it is usually located outdoors, proper ventilation must be provided for the building from which the process is controlled [276]. The control building should be maintained under positive pressure, and its air intake should be positioned so as to provide clean fresh air.

The procedures developed for vinyl chloride as discussed in the following paragraphs can also be used to control exposure to the other vinyl compounds.

Vinyl chloride monomer is manufactured in closed systems. The maintenance of the integrity of such systems is dependent on careful inspection of seals, especially at joints, valves, and pumps. Generally, where seals are closely inspected and maintained, escape of vinyl chloride can be prevented during monomer production. Several reports, however, have mentioned processes, periods, or areas of potential exposure [279,280,284,285]. These include quality control sampling points [284], tank car loading [286], tank car gauging [285], storage and transfer systems [286], distillation areas [280], and leaks from other equipment [297,284]. These potential sources of exposure in monomer production should be avoided by the use of alternative methods of

tank car gauging [284] (slip-tube gauging has been a source of exposure and should be controlled and monitored [285]), by the use of purge gas in loading and storage operations, prior to maintenance entry, and in quality-control sample collection [284], by the careful collection and purification of purge gas, by the use of closed-loop systems for tank car loading and quality control sampling [276], and by the use of properly maintained laboratory hoods for quality control laboratory procedures.

Most of the cases of angiosarcoma of the liver found in vinyl chloride workers have occurred among employees of vinyl chloride polymerization plants. Controls are needed to reduce worker exposure to vinyl chloride during the opening and cleaning of reaction vessels, at discharge points from relief valves and piping joints, while monomer is being stripped from the polymer, and while tank cars are being loaded or unloaded. A reduction in the frequency of manual cleaning of reactor vessels is absolutely necessary. The crust on the vessel can contain up to 3-5% monomer, and 30-50% of this may be liberated during cleaning [287]. Automatic high-pressure water, steam, or organic solvent vessel-cleaning systems can reduce the frequency of worker entry into reactor vessels [286,288,289]. Organic solvents are also toxic to varying degrees, however, and their use should therefore be carefully controlled. A proposed proprietary system for lining reactor vessels is claimed to eliminate resin buildup on the reactor vessel surfaces [286].

Because vinyl chloride polymerization reactions do not go to completion, polyvinyl chloride resins should be stripped of unreacted monomer. Stripping vessels, slurry tanks, centrifuges, and dryers must be enclosed and exhaust-ventilated [286].

If amount of residual monomers in polymers is reduced, the exposure of fabricating workers to vinyl chloride will be substantially reduced. The quantity of residual monomer that is released from a resin depends on the process temperature, the surface area of the resin, and the quantity of unreacted monomer in the resin [290]. Manufacturers should control their process to reduce these factors to the greatest extent consistent with the demands of the process. Fabricators should know the residual monomer content of the polyvinyl chloride resins that they use. Methods are available, eg, aspiration and air stripping [291], for reducing the residual monomer content of resins early in the fabricating cycle, preferably during the compounding and dry-blending stages. Oberg [292] found vinyl chloride concentrations of 0.04-1.5 ppm during laboratory blending operations.

Unless adequate ventilation is provided, the escape of residual vinyl chloride from bagged or boxed resin can result in buildup of the vinyl chloride concentration in warehouses and storerooms [293]. According to Oberg [292], vinyl chloride concentrations of 0.8-1.5 ppm have been found in storage areas. A manufacturer of vinylidene chloride reported that a latex containing 2,000 ppm of unreacted vinylidene chloride released 1,000 ppm of vinylidene chloride in 1 week of storage [294]. High storage or processing temperatures

may also accelerate the release of unreacted monomer. Oberg found ranges of vinyl chloride concentrations of 1.5-2.2 ppm at 46-68 C and 60-120 ppm at 71-110 C.

In vinyl production areas, employers should install automatic, multipoint continuous monitoring systems with alarm devices sensitive to airborne vinyls at the recommended exposure limits. Baker and Reiter [275] reported on a highly sensitive automatic monitoring system using a gas chromatograph equipped with a flame-ionization detector and an alarm device that activated when either the vinyl chloride concentration exceeded a preselected level, the check sample analysis was out of range, or the sample flow was insufficient. The system required 2 minutes for an analysis, and each analyzer could monitor up to 20 locations. Areas in which high vinyl concentrations are detected should immediately be monitored for gas leaks with a portable organic vapor analyzer. Also, entry into such areas should be limited to authorized personnel with proper protective clothing and equipment. As soon as a leak is located, properly equipped maintenance personnel familiar with emergency procedures should try to repair it.

Efforts should be made to minimize the extent to which vinyl vapors mix with air in confined or regulated areas and to prevent vapors from being exposed to any ignition source. A flexible hose ventilation unit and recovery system which can be moved to the source of the leakage should be available to control leaks which are not readily repaired.

Unloading vinyls from railroad tank cars is especially hazardous while lines and hoses are being coupled and uncoupled. Vinyl chloride vapor and vapor from other vinyl halides also remain in tank cars after the liquid is removed. If compressors and pumps are used to remove the vapor, care should be taken to avoid leaks from this equipment. It has been suggested that tank cars be emptied down to only the vinyl chloride vapor pressure, which eliminates the need to purge the car and reduces the use of pumps and compressors [286].

Storage and process areas where vinyl halides are stored as liquids should be diked to prevent the uncontrolled spread of any spilled material. The diked areas should be designed with drainage systems to carry spilled material into holding ponds or other areas where the product can be recovered or disposed of in a safe manner.

The flammability of some of these compounds mandates careful design and operation of all spark- or heat-producing equipment in vinyl halide work areas. Electric systems and motors must be spark- and explosion-proof. Sump pumps in diked areas must also be explosion-proof.

Achievement and maintenance of reduced concentrations of airborne vinyls in the workplace are dependent on the implementation of the engineering control recommendations. According to an unpublished report [295] submitted

to NIOSH, the available data suggest that a combination of many control measures is required to keep vinyl chloride concentrations at or below the current Federal occupational limit of 1 ppm (2.56 mg/cu m). Since the promulgation of the vinyl chloride standard in 1974, many different types of control techniques have been employed in work areas, and employee vinyl chlorides to vinyl chloride have been greatly reduced. Table IV-5 shows the apparent reductions in vinyl chloride concentrations that have been achieved in typical vinyl chloride polymerization plants, especially during 1974-1975, when most of the controls were installed [295].

TABLE IV-5

8-HOUR TWA EXPOSURE OF WORKERS TO VINYL CHLORIDE, 1974-1977

Process-Year	Average Distribution of Vinyl Chloride Concentrations			
	<1	1-5	>5	ppm
PVC Mass Polymerization No. 1				
1974	2%	52%	46%	
1975	43%	45%	12%	
1976	73%	20%	7%	
PVC Mass Polymerization No. 2				
1974-1975	0%	45%	55%	
1977	80%	20%	0%	
PVC Suspension Polymerization				
1975	17%	66%	17%	
1976	83%	17%	0%	
PVC Dispersion Polymerization				
1975	50%	50%	0%	
1976	67%	33%	0%	
PVC Dispersion and Suspension Polymerization				
1974	0%	38%	62%	
1975	42%	44%	14%	
1976	55%	36%	9%	
1977(first half)	65%	30%	5%	

Adapted from reference 295

V. WORK PRACTICES

In all workplaces where the vinyl halides are produced, handled, used, or stored, employers should supplement engineering and administrative controls with appropriate work practice programs. Work practice programs should be oriented toward methods for handling vinyl halides, procedures for cleaning up spills and responding to emergencies, and use and care of personal protective clothing and equipment. In addition, a regular program of instruction should be established to ensure that all potentially exposed employees are familiar with the specific hazards of each vinyl halide and with appropriate procedures for handling them. Employers should inform employees of any adverse effects that could be caused by inhalation of decomposition products. If contractors are employed for maintenance and repair activities or cleaning of vinyl contaminated equipment, employers should ensure that the contractor personnel are also familiar with the hazards of the compounds and with precautions to be taken when performing their duties. Employers may use the Material Safety Data Sheet presented in Appendix XVI as a guide in providing employees with the necessary information.

The vinyl halides vary in their toxicities (Chapter III) and their chemical and physical properties (see Table XVII-1). Although this chapter and the literature cited in it deal mainly with vinyl chloride, all of the vinyl halides are similarly produced, handled, stored, and transported. Similar practices and engineering controls will usually be applicable, therefore, to all vinyl halides; those specific for each halide are discussed separately. The control procedures outlined in Chapter IV for specific processes involving vinyl chloride are not a substitute for good general work practices.

Since the promulgation of the 1974 Federal occupational exposure limit of 1 ppm (2.56 mg/cu m) for vinyl chloride, many papers have been published on various ways to reduce worker exposure to this compound. Although some practices are applicable to work with vinyl chloride at any time, most controls and practices can be separated into those that apply to monomer production, those that apply during polymer production, and those that apply during polymer fabrication or processing.

Although closed loop systems may be used for quality-control sampling, the proximity of the employee to the sample cylinder connections greatly increases the likelihood of exposure in the event of leaks [280]. Therefore, caution should be used in collecting quality-control samples even where closed loops are used.

All work areas in which exposure to vinylidene chloride or vinyl bromide may occur should be posted with warnings that a potential human carcinogen is

present. For potential exposure to vinyl chloride, the area should be posted to warn that a human carcinogen is present.

Entry into regulated areas, as defined in Appendix I (29 CFR 1910.1017 (e)), or confined or enclosed spaces should be carefully controlled by a permit system or the equivalent. A confined or enclosed space is usually thought of as any reactor, autoclave, tank, chamber, vat, pit, pipe, flue, duct, bunker, or undergrade room and only properly protected personnel trained in emergency procedures should be permitted to enter such areas [305,297]. Unauthorized personnel and those not properly protected should not be permitted to enter regulated areas or confined or enclosed spaces. Records of those who enter these spaces should be kept by means of a daily log, employment records, or the equivalent. Properly fitted protective clothing and equipment should be worn by anyone entering such areas, and suitable respiratory equipment should be worn if vinyl concentrations exceed the permissible exposure limits.

Whenever airborne vinyl halide concentrations exceed the recommended environmental limits, respirators must be used in accordance with Table I-1. The current Federal standard for vinyl chloride allows the use of a chemical cartridge respirator or a gas mask, front- or back-mounted canister, at concentrations of vinyl chloride not exceeding 10 ppm or 25 ppm, respectively. Service life requirements, 1 hour for a cartridge and 4 hours for a canister, are also listed (29 CFR 1910.1017 (g)). NIOSH, however, has also required that end-of-service-life indicators be used with cartridge and canister air-purifying respirators. In December 1974, NIOSH and MSHA published the requirements for a canister or cartridge respirator with end-of-service-life indicators for use in vinyl chloride atmospheres (30 CFR 11.200-11.208). NIOSH has recently approved the 3M No. 8716 vinyl chloride cartridge respirator, which has an end-of-service-life indicator, for use in vinyl chloride at concentrations up to 10 ppm (DP Wilmes, written communication, February 1978). End-of-service-life indicators for canister gas masks for vinyl halides have yet to be developed. To prevent exposure through leakage, NIOSH recommends that each employee be provided an appropriate individually-fitted respirator in good, clean condition, and that employees be drilled in the use of these respirators and in testing them for leakage, proper fit, and proper operation.

Since vinyl chloride, vinyl bromide, vinyl fluoride, and vinylidene fluoride are gases at ambient conditions and are liquids only under pressure, a hazard from splashes rarely exists under normal working conditions. These compounds can nevertheless cause eye and skin irritation, and contact with them should be avoided. Vinylidene chloride is a liquid at ambient conditions. Because the pressurized materials evaporate rapidly on release, excessive exposure to undiluted liquid vinyls could cause a "frostbite" type of "burn" [298,299,300]. Warnings against skin irritation and burns from contact with liquid vinylidene chloride and vinyl chloride have been published [299,301]. Phenolic inhibitors of polymerization, formerly used widely, have been implicated in the causation of burns by contact with surfaces from which

the inhibited vinyl monomer had evaporated, leaving a film of the inhibitor [301]. If a vinyl halide is splashed on the skin, the affected areas should immediately be washed with soap and water. If eye exposure occurs, the affected eye should be rinsed with water for at least 15 minutes, and medical attention should be obtained as soon as possible [297]. Eyewash fountains and emergency showers should be located near all vinyl exposure areas and should be readily accessible.

Employees who handle vinyls or enter vinyl exposure areas should be provided with appropriate clothing. Protective clothing should be provided clean and dry for each use. To prevent contamination of other work areas, employees should not wear protective clothing outside exposure areas. In most vinyl operations, employees should use coveralls made of any nonsparking material [305]. Employees should also wear safety goggles or glasses with side shields, hardhats, respiratory protective equipment, rubber gloves, and boots whenever they enter confined or regulated areas [297]. One vinyl bromide manufacturer has recommended that neoprene gloves and boots be worn by employees opening process lines and repairing pumps and that a one-piece nylon suit, vinyl-coated on both sides, with attached neoprene boots and gloves be worn by employees entering a reactor vessel or tank [14]. Employers should warn employees that heat stroke may result from the wearing of impervious clothing.

Vinyl-contaminated work clothing should be kept separate from street clothing and should not be removed from the work area. Employers should provide shower and change rooms with locker room facilities that allow for complete separation of work and street clothing. Employers should encourage all employees working in areas where exposure to vinyls might occur to shower before changing from work clothes into street clothes. Employers should be responsible for the laundering of contaminated or soiled clothing, and no employee should be allowed to take or wear home any work clothing. All work clothing should be adequately cleaned after each wearing. Employers should inform laundry personnel of the possible hazard from vinyl contaminants on work clothing. Although the vinyl halides are at most only slightly soluble in water, clothing contaminated with liquid vinyls should be allowed to dry before being laundered. This should be done in a vacuum or other enclosed system provided with air ventilation devices in order to prevent vinyl halide release into the laundry or work area. Waste water should be handled in accordance with all applicable Federal, state, and local regulations.

The vinyl halides addressed in this document are flammable over wide ranges of concentrations in air, and contact with ignition sources should therefore be avoided. Vinyl chloride, vinylidene chloride, vinyl fluoride, and vinylidene fluoride have been reported to be explosive at concentrations of 3.6-33.0, 7-16.0, 2.6-21.7, and 5.5-21.3% by volume in air, respectively [302,303]. A producer of vinyl bromide reported that vinyl bromide at concentrations of 6.0-15% by volume in air may ignite in the presence of high-energy ignition sources and suggested that vinyl bromide be handled as a moderately flammable material [304].

Since the vinyl halides are so readily flammable, it is important to prohibit smoking, carrying of uncovered smoking materials such as matches and lighters, open flames, and use of materials that can cause sparks in areas where vinyls are present. Smoking if allowed at all on the plant site should be restricted to designated areas. Signs warning of a danger of fire or explosion should be posted in areas where vinyls are produced, handled, or stored, and transport containers should have warning labels. Warning signs should also be prominently posted in areas where spills and leaks are likely to occur. Process equipment, such as tanks, pipelines, pumps, and compressors, should be grounded to prevent the build up of static electricity [299]. Firefighting and respiratory protective equipment should be readily available for use in case of emergency. Employers should inform firefighting personnel of the possible combustion products of the vinyl halides. Vinyl chloride combustion products include phosgene, hydrogen chloride, carbon monoxide, carbon dioxide, and water. Hydrogen chloride is also a major combustion product of vinylidene chloride. Employers should therefore provide firefighters with protective equipment to prevent injury from inhalation or contact with the combustion products. Vandervort and Brooks [305] reported that the major thermal decomposition products of polyvinyl chloride films were di-2-ethylhexyl adipate and hydrogen chloride. The authors found no vinyl chloride emissions during hot-wire cutting of the film, but warned against inhalation of aerosol particles from di-2-ethylhexyl adipate and hydrogen chloride.

To ensure the effectiveness of recommended work practices in protecting the employees' health, employers should require that all employees participate in an orientation program when they are hired and in periodic information seminars led by personnel qualified by experience or training. During orientation, employees should be informed of the hazards associated with handling of the vinyl halides and of the precautions that should be taken to prevent injury or illness. Employers should also inform employees that vinyl chloride is a known human carcinogen and that the other vinyls are potential human carcinogens. Employees should be made thoroughly familiar with emergency and evacuation procedures.

Periodic training of employees should include opportunities for employees to meet with management personnel to discuss or review safety procedures and new toxicologic findings. New information on the vinyl halides should be posted in designated areas accessible to employees. It is essential to stress the importance of the employees' cooperation with management in preventing adverse effects of exposure to vinyls, and employees should be encouraged to report all circumstances that might create the potential for such exposure.

VI. DEVELOPMENT OF STANDARD

Basis for Previous Standards

(a) Vinyl Chloride

Standards for regulation of exposure to vinyl chloride in the United States were first reported in 1945 in Cook's review [306] of maximum allowable concentrations (MAC's) of industrial atmospheric contaminants. A Utah State Department of Health recommendation of 500 ppm (1,280 mg/cu m) was cited. A 1930 report by Patty et al [16] indicated that guinea pigs exposed to vinyl chloride at 5,000 or 10,000 ppm (12,800 or 25,600 mg/cu m) for as long as 500 minutes "showed no symptoms." Cook [306] recommended an MAC of 1,000 ppm for prolonged exposure. Citing the lack of long-term animal experimentation data and of data on industrial exposure at known concentrations, Cook recommended medical observation of workers exposed to vinyl chloride at concentrations near the suggested limit.

In 1946, the American Conference of Governmental Industrial Hygienists (ACGIH) [307] recommended an MAC of 500 ppm (1,280 mg/cu m) for vinyl chloride. When the ACGIH changed its terminology in 1949 [308], this limit became the Threshold Limit Value (TLV) for vinyl chloride. According to the 1962 Documentation of Threshold Limit Values [309], the ACGIH TLV was also based on the study by Patty et al [16]. The 1962 documentation [309] noted that narcosis was the most important effect of exposure to vinyl chloride, and that the TLV of 500 ppm (approximately 1,300 mg/cu m) "appears to be sufficiently low to prevent significant narcosis."

In the Threshold Limit Values for 1963 [310], it was noted that a TLV in the form of a time-weighted average (TWA) concentration limit might not provide a sufficient safety factor for acutely acting substances. Consequently, a "C" or "ceiling" designation was appended to the value for vinyl chloride, indicating that the TLV, which remained at 500 ppm, was a limit that should not be exceeded.

Although the TLV had not changed, the 1966 Documentation of Threshold Limit Values [311] cited several studies that presented conflicting data. Torkelson et al [113] found liver damage in rabbits exposed repeatedly for 7 hours to vinyl chloride at 200 ppm (512 mg/cu m) and slight increases in liver weights of rats exposed at 100 ppm. Other animals were unaffected at 100 ppm. The authors suggested that worker exposure be controlled so that results for practically all analytical measurements were less than 100 ppm (256 mg/cu m) and that the TWA concentration for all exposures be limited to 50 ppm (128 mg/cu m). Lester et al [18] found some increase in the relative weights of the liver and spleen in rats exposed repeatedly to vinyl chloride at concentrations of 20,000 ppm (51,200 mg/cu m) for 92 days and 50,000 ppm (128,000 mg/cu m) for 19 days. They did not consider these changes

significantly pathologic, and they concluded that the accepted TLV for vinyl chloride of 500 ppm (1,300 mg/cu m) was adequate to protect workers. The 1966 documentation [311] concluded that, "although the available data are conflicting, the preponderance indicates a compound of relatively low toxicity with which a threshold limit of 500 ppm is consistent."

In 1970, the ACGIH [312] announced its intention to reduce the TLV for vinyl chloride to 200 ppm. In 1972, the ACGIH [313] reduced the TLV for vinyl chloride to 200 ppm (770 mg/cu m [sic], actually equivalent to 512 mg/cu m) as an 8-hour TWA concentration. Several studies supporting this action were cited in the 1971 Documentation of Threshold Limit Values for Substances in Workroom Air [314], including the 1961 study by Torkelson et al [113] and the 1963 study by Lester et al [18]. The documentation also cited a study, conducted between 1950 and 1967 and presented in 1968 by Mutchler and Kramer [315], of exposure of chemical plant workers. Workers exposed to vinyl chloride (with about 5 ppm of vinylidene chloride) at a mean concentration of 160 ppm (410 mg/cu m) did not have significant changes in blood pressure, concentration of hemoglobin in the blood, or ECG's, and acroosteolysis was not found. However, changes of possible physiologic significance were noted in serum beta-lipoprotein, icteric index, and sulfobromophthalein retention. Based on analysis of these data, the authors suggested that some liver dysfunction might result from exposure to vinyl chloride (combined with 5 ppm of vinylidene chloride) at a TWA concentration of 300 ppm (768 mg/cu m) over a working lifetime. The 1971 documentation [314] concluded that a TWA environmental limit of 200 ppm (770 mg/cu m) for vinyl chloride (with a few ppm of vinylidene chloride) "seems appropriate to prevent adverse systemic effects from long-continued daily exposure."

In 1974, the ACGIH [316] published a notice that the TLV for vinyl chloride would be reassigned as a result of its newly discovered carcinogenic potential. No specific studies were cited in support of this action. As of 1977, the TLV for vinyl chloride still awaited reassignment pending the acquisition of more definitive data [317].

According to a 1968 joint report of the International Labour Office and the World Health Organization [318], permissible limits set by foreign countries for vinyl chloride in the working environment include 30 mg/cu m for Bulgaria and 1 mg/cu m for the United Arab Republic and the Syrian Arab Republic. The German Democratic Republic has a limit of 500 mg/cu m for vinyl chloride in the work environment [319].

Limits adopted in foreign countries since 1974 reflect the accumulating evidence of the carcinogenic potential of vinyl chloride. The United Kingdom has set 25 ppm (64 mg/cu m) as a TWA limit, with a 50 ppm (128 mg/cu m) ceiling limit [305], until more definitive information is available. In 1976, the Federal Republic of Germany established Technical Guideline Concentrations for vinyl chloride of 10 ppm (26 mg/cu m) in existing polymerization plants and 5 ppm (13 mg/cu m) elsewhere until such time as an MAC value could be assigned [320]. Sweden established an 8-hour TWA limit of 1 ppm (2.5 mg/cu m)

and a ceiling limit of 5 ppm (13 mg/cu m) for exposure to vinyl chloride [321]. The Swedish document noted that vinyl chloride has carcinogenic properties and that it may be absorbed to a considerable extent through the skin.

The International Labour Office [322] recently published the following national occupational exposure limits for vinyl chloride: Yugloslavia, 75 ppm (300 mg/cu m [sic], actually equivalent to 195 mg/cu m); Rumania, 100 mg/cu m as a TWA limit and 200 mg/cu m as a ceiling limit; Australia, 25 ppm (95 mg/cu m [sic], actually equivalent to 64 mg/cu m); Hungary, 50 mg/cu m; Poland and USSR, 30 mg/cu m; Netherlands, 10 ppm (26 mg/cu m) as a ceiling limit; Finland, 10 ppm (26 mg/cu m); and Japan, 2.5 mg/cu m. In Italy, vinyl chloride is regarded as a human carcinogen, and an exposure limit of 5 ppm (13 mg/cu m) has been recommended. However, the exposure limit is intended as a guideline, as are those of Australia, Japan, and the Netherlands, and is not legally binding. In Switzerland, vinyl chloride is regarded as a probable human carcinogen also, and a provisional exposure limit of 10 ppm (26.5 mg/cu m) has been established. Switzerland also requires that the best available technical and medical protective measures be applied to ensure maximum reduction of risk from exposure to vinyl chloride.

The 1971 US Federal standard for workplace exposure to vinyl chloride (29 CFR 1910.93) was a ceiling limit of 500 ppm (1,280 mg/cu m), based on the 1968 TLV [323]. On January 22, 1974, NIOSH informed the Occupational Safety and Health Administration (OSHA) that the BF Goodrich Chemical Company had reported the deaths of several of its employees from angiosarcoma of the liver, and that the deaths may have been occupationally related. A fact-finding hearing began on February 15, 1974 (reported in the Federal Register 39:35890, October 4, 1974), after consultation with NIOSH and a joint inspection of the BF Goodrich plant by OSHA, NIOSH, and Kentucky Department of Labor personnel. Preliminary reports of experiments conducted by Cesare Maltoni of the Instituto di Oncologia, Bologna, Italy, and other information disclosed at this hearing indicated that vinyl chloride could induce angiosarcoma in the liver of rats at exposure concentrations as low as 250 ppm (640 mg/cu m). OSHA concluded from the information presented at the hearing and in posthearing comments that occupational exposure to vinyl chloride was probably the cause of angiosarcoma of the livers observed in workers in the industry. An Emergency Temporary Standard (ETS) was promulgated on April 5, 1974 (Federal Register 39:12342), as 29 CFR 1910.93(q). This standard reduced the permissible exposure level to 50 ppm (128 mg/cu m), as a ceiling limit, and established other requirements, including monitoring and respiratory protection.

OSHA published a proposed permanent standard (Federal Register 39:16896, May 10, 1974) for the regulation of exposure to vinyl chloride. The proposed standard specified that employee exposure be limited to "no detectable level" as determined by a sampling and analytical method sensitive to 1 ppm with an accuracy of 1 ppm ±50%. The proposal also called for monitoring employee exposures and implementing engineering control and work practice programs when

necessary. Hearings on this proposal were conducted from June 25 through June 28 and from July 8 through July 11, 1974. The carcinogenicity of vinyl chloride in three animal species was documented in the record of this proceeding by the studies of Maltoni and of Industrial Bio-Test Laboratories (Federal Register 39:35891, October 4, 1974). These studies demonstrated the induction of angiosarcoma of the liver in rats and mice exposed to vinyl chloride at concentrations as low as 50 ppm (128 mg/cu m) and in hamsters exposed at higher concentrations. Evidence presented by these and other investigators also indicated additional tumorigenic and toxicologic properties of vinyl chloride. OSHA concluded from these findings of angiosarcoma of the liver in experimental animals and employees exposed to vinyl chloride that vinyl chloride "must be regarded as a human carcinogen, and the probable causal agent of angiosarcoma of the liver, and that exposure of employees to vinyl chloride must be controlled."

The current permanent standard for worker exposure to vinyl chloride was promulgated on October 4, 1974 (Federal Register 39:35896) and became effective January 1, 1975. The standard (29 CFR 1910.1017), presented as Appendix I of this document, includes an 8-hour TWA exposure limit of 1 ppm and a ceiling limit of 5 ppm, averaged over any period not exceeding 15 minutes. The standard specifies that no employee may be exposed to direct contact with liquid vinyl chloride. The standard also establishes requirements for monitoring employee exposure, providing respiratory protection, and instituting medical surveillance programs. A TWA action level of 0.5 ppm (1.3 mg/cu m) also is specified in the standard. Where the results of monitoring show that no employee is exposed in excess of the action level, employers are exempted from certain provisions of the standard.

(b) Vinylidene Chloride

In 1975, the ACGIH adopted a TLV of 10 ppm (40 mg/cu m) for vinylidene chloride [324]. Several studies were cited in the 1971 Documentation of Threshold Limit Values for Substances in Workroom Air [314] in support of this limit. Increased mortality in rats, rabbits, guinea pigs, and monkeys exposed to vinylidene chloride at concentrations as low as 61 mg/cu m (15.4 ppm) for 90 days was reported by Prendergast et al [122]. Gage [120] found that after vinylidene chloride inhalation 6 hours/day for 20 days at 500 ppm (1,985 mg/cu m) there was nasal irritation, retarded weight gain, and liver cell degeneration in rats. At 200 ppm (794 mg/cu m), there was only slight nasal irritation, and no liver cell abnormalities were observed. Irish [114] reported liver and kidney damage in rats, rabbits, guinea pigs, and dogs exposed to vinylidene chloride for 6 months at concentrations as low as 25 ppm (99 mg/cu m), and he suggested that concentrations in workplaces be maintained below 25 ppm.

In 1976, the ACGIH [325] adopted a tentative Threshold Limit Value-Short Term Exposure Limit (TLV-STEL) of 20 ppm (79 mg/cu m) for vinylidene chloride. The TLV-STEL was described as the maximum concentration at which employees could be exposed continuously for up to 15 minutes without suffering

from intolerable irritation, chronic or irreversible tissue change, or narcosis sufficient to increase accident proneness, impair self-rescue, or reduce work efficiency. It should be noted that the 1976 STEL's were not determined on the basis of occupational or experimental data; rather, they were set empirically. A provision limiting the number of 20-ppm excursions to no more than four each day, with at least 60 minutes between exposure periods, was also included.

According to the 1968 joint report of the International Labour Office and the World Health Organization [318], national permissible limits for vinylidene chloride in the working environment include the following: Yugoslavia, 200 ppm (794 mg/cu m), listed as "dichloroethylene," and Bulgaria and Hungary, 50 mg/cu m, listed as "dichloroethylene." A 1977 publication of the International Labour Office [322] lists the following occupational exposure limits for vinylidene chloride in foreign countries: Rumania, 500 mg/cu m as a TWA limit and 700 mg/cu m as a ceiling limit; Poland and USSR, 50 mg/cu m as a ceiling limit; and Belgium, Federal Republic of Germany, Netherlands, and Switzerland, 10 ppm (40 mg/cu m). Australia has established a provisional exposure limit of 10 ppm (40 mg/cu m) for vinylidene chloride. The exposure limits shown for Australia and the Netherlands are intended as guidelines and are not legally binding.

No US Federal standard for workplace exposure to vinylidene chloride currently exists.

(c) Vinyl Bromide

In 1971, the ACGIH [326] recommended a TLV for vinyl bromide of 250 ppm (1,095 mg/cu m). This TLV was adopted in 1972 [313].

Two studies were included in the 1971 Documentation of Threshold Limit Values for Substances in Workroom Air [314] as bases for this TLV. In an unpublished study cited by ACGIH, Torkelson determined an oral LD50 of 500 mg/kg in male rats. In acute inhalation studies, Torkelson observed no tissue changes in rats exposed to vinyl bromide at concentrations as high as 25,000 ppm (109,500 mg/cu m). Leong and Torkelson [127] reported no significant pathologic changes in rats exposed for 20 days to vinyl bromide at 10,000 ppm (43,800 mg/cu m). In a chronic inhalation study, they found no significant changes in growth rate, hematology, organ-to-body weight ratio, or gross and microscopic tissue findings as a result of exposure to vinyl bromide at 250 or 500 ppm (1,095 or 2,190 mg/cu m). The ACGIH concluded that "a TLV of 250 ppm should protect against bromide intoxication and organic injury, and...excursions even to 500 ppm would be acceptable provided the time-weighted average does not exceed 250 ppm."

In 1976, in addition to the TWA exposure limit of 250 ppm (1,095 mg/cu m) for vinyl bromide, the ACGIH [325] adopted a tentative TLV-STEL of 250 ppm (1,100 mg/cu m). In 1977, the ACGIH [317] proposed a reduction of the TLV to 5 ppm (22 mg/cu m).

According to a 1977 publication of the International Labour Office [322], exposure limits of 250 ppm (1,095 mg/cu m) for vinyl bromide have been set by Australia, Belgium, Finland, and the Netherlands. The Australian and Dutch limits are intended as guidelines and are not legally binding.

No US Federal standard for workplace exposure to vinyl bromide currently exists.

(d) Vinyl Fluoride

The ACGIH has not adopted a TLV for vinyl fluoride. No US Federal standard for exposure to vinyl fluoride currently exists. No foreign standards have been located.

(e) Vinylidene Fluoride

The ACGIH has not adopted a TLV for vinylidene fluoride. No US Federal standard for exposure to vinylidene fluoride currently exists. No foreign standards have been located.

Basis for the Recommended Standard

(a) Permissible Exposure Limits

Among the vinyl halides discussed in this document, only vinyl chloride is regarded as a known human carcinogen that can induce a characteristic tumor, angiosarcoma of the liver [31,32,34,36,37,40,41]. Animal studies have shown that vinyl chloride [134,135,140], vinyl bromide [327], and vinylidene chloride [140] are capable of inducing angiosarcoma of the liver and other tumors. In these experiments, exposure to vinyl chloride at 50 ppm for 4 hours/day, 5 days/week, for 52 weeks induced angiosarcoma of the liver in 1/59 rats after 135 weeks [135]; vinyl bromide at 250 ppm caused angiosarcoma of the liver in 2/30 rats after 52 weeks [327]; vinylidene chloride at 55 ppm for 6 hours/day, 5 days/week, for up to 12 months caused angiosarcoma of the liver in 3/72 mice [140]. Exposure at higher concentrations induced a greater incidence of tumors and shortened the latency for their development, indicating that there was a dose-response relationship for tumor induction.

No reports in regard to the carcinogenicity of vinyl fluoride or vinylidene fluoride have been located. However, this lack of information cannot be construed as an indication that these compounds have no carcinogenic potential. Each of the vinyl halides may form reactive intermediates that can bind to cellular macromolecules [1-3,210]. Putative metabolic pathways and reactive intermediates are shown in Figure XVII-3. The metabolic studies referenced with the figure, along with information from reports on structure-activity relationships [229, RL Schowen, written communication, September 1977], indicate that both vinyl fluoride and vinylidene fluoride may have the capacity to form intermediates capable of alkylating DNA, RNA, or proteins.

The hazard potential of these compounds in a biologic system is difficult to determine, however, because of detoxication mechanisms (reduction, hydrolysis, and conjugation) that compete with alkylation, as well as repair, mechanisms.

Each of the vinyl halides has been found to be mutagenic in some test system. Vinyl chloride has been shown to have a direct mutagenic effect on Salmonella [146,149,150,162,163]; metabolic activation by microsomal enzyme systems has been shown to increase its mutagenic activity [146,145]. Vinylidene chloride [151,162,173], vinyl bromide (VF Simmon and R Nangham, written communication, August 1977), and vinyl and vinylidene fluorides [174] have also been shown to be mutagenic in bacterial test systems. Since many mutagenic compounds are known to also be carcinogenic, these findings suggest that all the vinyl halides might be potential carcinogens.

No studies have demonstrated teratogenic or other effects on human reproduction from exposure to any of the vinyl halides. Structural abnormalities, including increased numbers of unfused sternebrae, delayed ossification of skull bones, and an increase in the number of lumbar spurs in mice whose dams were exposed to vinyl chloride at 500 ppm during days 6-15 of gestation [132] and in rats exposed in utero to vinylidene chloride at 80 ppm during the same period [133], have been observed. Other reproductive effects included increased resorptions/implants, decreased numbers of live fetuses/litter, and increased fetal crown-rump length [132,133]. The authors of these studies suggested that the abnormalities observed were secondary to the maternal toxicity of the compounds. Although these changes are not generally considered to be evidence of teratogenicity, they do indicate fetotoxic effects from maternal exposure to vinyl chloride.

Other adverse health effects attributed to exposure to vinyl halides include CNS [18-20,33,78,114,127,129], cardiovascular [19,20,32,33,78,107, 110,121], respiratory [19,32,106,120,122,140], skin [19-21,32,111,112], and skeletal effects [20,21,32,35,74,78,111,112], as well as liver and spleen abnormalities [18-20,30-32,36-39,78,113].

The risk to the health of employees exposed to the vinyl halides is a combination of the risks of neoplastic and other systemic effects from their inhalation or ingestion and of their subsequent metabolism to reactive intermediates.

The observation of neoplasms in humans and animals exposed to vinyl chloride and in animals exposed to vinylidene chloride and vinyl bromide, the similarities in the excreted metabolic products of the vinyl halides, and the calculations of relative reactivity of these compounds on the basis of their physical and chemical properties suggest that each of the five may have a neoplastic potential.

Concern for employee health requires that risk of carcinogenesis as a result of workplace exposure to these compounds be minimized. NIOSH believes that sufficient information does not exist to warrant changing the present Federal Standard for vinyl chloride as stated in 29 CFR 1910.1017. Further,

NIOSH believes that the available information on vinylidene chloride and vinyl bromide indicates that they are at least as toxic as vinyl chloride. Although sufficient biologic information is not available concerning vinyl fluoride and vinylidene fluoride, chemical information suggests that these compounds may also exhibit toxicities similar to that of vinyl chloride, ie, until better animal toxicity and metabolism data are available, there appears to be no reason to treat the fluorides differently from the other vinyl halides. Therefore, NIOSH recommends that workplace exposure to each of the five vinyl halides be controlled by adherence to the provisions of 29 CFR 1910.1017, and on the basis of animal carcinogenicity data, NIOSH suggests that employers make every effort to limit employee exposures to the lowest feasible levels with an eventual goal of zero exposure. As pointed out in Chapter IV there has been a steady decline in workplace environmental concentrations of vinyl chloride since 1974. The lower limits of reliable detectability (see Appendices II-III) are 0.003 ppm for vinyl chloride and 0.5 ppm for vinylidene chloride. Workplace concentrations of vinyl bromide have been measured as low as 0.01 ppm [249]. Vinyl fluoride and vinylidene fluoride in air samples have been measured at concentrations as low as 1 ppm and 2 ppm respectively (see Appendices V-VI).

Since the promulgation of the vinyl chloride standard in 29 CFR 1910.1017 in October, 1974, several advances in respirator technology have taken place. Table I-1 reflects the latest developments in respiratory protection, and NIOSH recommends the substitution of these provisions and requirements for those contained in 29 CFR 1910.1017, paragraph (g).

VII. COMPATIBILITY WITH OTHER STANDARDS

The Environmental Protection Agency (EPA), the Department of Transportation (DOT), the Food and Drug Administration (FDA), and other Federal agencies have proposed or enacted standards regulating the use or release of several vinyl compounds. The standard recommended by NIOSH in this document for the vinyl halides is compatible with the standards promulgated and proposed by other Federal agencies. Standards proposed by other government agencies that are directly applicable to the standard proposed by NIOSH are reviewed below.

(a) Vinyl Chloride

In 1976, EPA established a national emission standard for vinyl chloride (40 CFR 61.60-71) because vinyl chloride had been implicated in the development of angiosarcoma and other serious disorders in occupationally exposed persons and in experimentally exposed animals. Vinyl chloride emissions from ethylene dichloride and vinyl chloride production and purification processes were thereby limited to 10 ppm. For the oxychlorination process, vinyl chloride emissions were restricted to 0.2 g/kg of ethylene dichloride product. Vinyl chloride emissions from polymerization plants were limited to 10 ppm through the stripping stage and to 0.02 g/kg of polyvinyl chloride product when reactors were opened. Emissions of vinyl chloride were required to be controlled after stripping operations by reduction of residual monomer in the polymer to below 400 ppm (2,000 ppm for dispersion resins). Where control devices rather than stripping technology were used to limit emissions, dispersion resins were required to be controlled to 2 g/kg of polyvinyl chloride product and all other resins to 0.1 g/kg of polyvinyl chloride product. EPA assumed that adherence to these limits would reduce hazards to the health of the estimated 4.6 million people who live within 5 miles of controlled plants so that the incidence of new primary cancers as a result of exposure to vinyl chloride in this group of people would not exceed 1/year of exposure (Federal Register 41:46560, October 21, 1976). EPA stated that a complete ban on vinyl chloride emissions was not desirable because (1) vinyl chloride has beneficial uses for which substitutes are not available, (2) potential substitutes may have unknown health effects, (3) unemployment would result, and (4) control technology is available to greatly reduce vinyl chloride emissions.

On June 2, 1977, EPA proposed amendments to the national emission standard (Federal Register 42:28154-28159). Sources currently subject to a 10-ppm emission limit and new sources of this type would be required to limit emissions to 5 ppm. Emissions from oxychlorination reactors in ethylene dichloride-vinyl chloride plants would also be limited to 5 ppm. The amendments would direct that residual monomer in the polymer after stripping be limited to 500 ppm in new dispersion resins and 100 ppm in all other new resins. Where control devices rather than stripping technology would be used

to limit emissions, new dispersion resins would have to be controlled to 0.5 g/kg of polyvinyl chloride product and all other new resins to 0.1 g/kg of polyvinyl chloride product. The proposed amendments also would prohibit any increase in emissions due to the construction of new sources within 8 km of existing sources. EPA proposed these amendments in an effort to continue to approach the zero-emissions level for vinyl chloride with available technology because of its determination that this is the only level absolutely protective of health. These limits and proposed amendments are not directly comparable with those proposed by NIOSH, since they do not specify breathing zone sampling. They do, however, reflect the same philosophy espoused by NIOSH; that is, that the final goal is zero exposure.

Aerosol drug products containing vinyl chloride as an ingredient or propellant are considered to be new drugs by FDA and are regulated as such (21 CFR 310.506). EPA (Federal Register 39:14753, April 26, 1974), FDA (21 CFR 700.14), and the Consumer Product Safety Commission (16 CFR 1500.17(a)(10)) have banned the use of vinyl chloride as an ingredient or propellant in aerosol products, including pesticides, cosmetics, and foods, intended for consumer use. These standards are more conservative than that proposed by NIOSH; however, they relate primarily to use of the product and only secondarily to occupational exposure.

FDA proposed rules for regulating the use of vinyl chloride polymers in contact with food on September 3, 1975 (Federal Register 40:40529-37). FDA stated that the use of vinyl chloride polymers and copolymers should be prohibited where there was a reasonable expectation of migration of vinyl chloride monomer into food. FDA proposed a ban on the use of vinyl chloride polymers and copolymers in food-contact articles except where specifically permitted in the FDA regulations. Exceptions to this ban included coatings, gaskets, cap liners, flexible tubing, and plasticized films. Use of polyvinyl chloride in water pipe was also permitted on an interim basis pending the outcome of studies to determine whether vinyl chloride could be extracted by water passing through such pipes. FDA has subsequently published regulations concerning the formulations and amounts of extractable monomer allowable in vinyl chloride copolymer components of paper and paperboard in contact with foods (21 CFR 176). Similar regulations for vinyl chloride copolymers used as basic components of single and repeated use food contact surfaces have also been promulgated (21 CFR 177). These are compatible, although not directly comparable, with the provisions of the NIOSH standard specifying that no food shall be stored, dispensed, prepared, or consumed in vinyl halide exposure areas.

The Materials Transportation Bureau of DOT has designated vinyl chloride as a hazardous material for purposes of transportation in commerce and has established requirements pertaining to its labeling, packaging, and transportation (49 CFR 172.101). Regulations for the bulk transport of vinyl chloride by water have been established by the US Coast Guard (46 CFR 40.15-1, 46 CFR 151.50-34). These regulations also set an exposure limit of 1 ppm (3 mg/cu m), averaged over any 8-hour period, or 5 ppm (13 mg/cu m), averaged

over any 8-hour period, or 5 ppm (13 mg/cu m), averaged over any period not exceeding 15 minutes, for personnel involved in vinyl chloride transfer operations. Continuous monitoring must be conducted during such operations, using a method with an accuracy of not less than ±50% from 0.25 through 0.5 ppm, ±35% from 0.5 ppm through 1 ppm, and ±25% over 1.0 ppm. The US Coast Guard [328] has also developed a cargo compatibility guide for bulk liquid chemicals indicating combinations of chemicals that result in dangerous chemical reactions when accidentally mixed inside a cargo tank or pipe. Vinyl chloride is listed as incompatible with nitric acid and caprolactam solution. Regulations for unmanned barges carrying certain dangerous bulk cargoes, including vinyl chloride, also have been established by the US Coast Guard (46 CFR 151). The Coast Guard standard for occupational exposure is less stringent than that proposed by NIOSH.

(b) Vinylidene Chloride

FDA has published regulations concerning the formulations and amounts of extractable monomer allowable in vinylidene chloride copolymer components of paper and paperboard that come into contact with foods (21 CFR 176). Similar regulations for vinylidene chloride copolymers used as basic components of single and repeated use food contact surfaces have also been established (21 CFR 177).

The Materials Transportation Bureau of DOT has designated vinylidene chloride as a hazardous material for purposes of transportation in commerce and has established requirements pertaining to its labeling, packaging, and transportation (49 CFR 172.101). In its cargo compatibility guide for bulk liquid chemicals, the US Coast Guard [328] has listed vinylidine chloride as incompatible with nitric acid and caprolactam solution. Regulations for unmanned barges carrying certain dangerous bulk cargoes, including vinylidene chloride, have been established by the US Coast Guard (46 CFR 151).

NFPA [329] provides a compilation of information on the hazardous properties and firefighting aspects of vinylidene chloride. This compound is very flammable and readily forms explosive mixtures in air. Polymerization may occur at elevated temperatures, possibly rupturing containers. A readily explosive peroxide may be formed during long-term storage. In the 1975 Manual of Hazardous Reactions [330], NFPA notes that vinylidene chloride polymer is self-reactive and may explode under appropriate conditions. It also reports that mixtures of vinylidene chloride and chlorosulfonic acid, nitric acid, or oleum (fuming sulfuric acid) in closed containers cause increased temperature and pressure. In firefighting operations, NFPA recommended that the gas flow be stopped and that dry chemical, foam, or carbon dioxide be used to extinguish flames. Water may be ineffective in putting out fires, but it should be used to cool containers, protect personnel in the area, flush spills away from flames, and disperse vapors if appropriate. The provisions of the National Electrical Code [331] and those of the Sections of the National Fire Codes dealing with flammable and combustible liquids [335] and static electricity [333] should be complied with where applicable.

(c) Vinyl Fluoride

The Materials Transportation Bureau of DOT has designated vinyl fluoride as a hazardous material for purposes of transportation in commerce and has established requirements pertaining to its labeling, packaging, and transportation (49 CFR 172.101).

(d) Vinylidene Fluoride

FDA has published regulations concerning the formulations and amount of extractable monomer allowable in polyvinylidene fluoride resin components of articles intended for repeated food-contact use (21 CFR 177.2510).

(e) Vinyl Bromide

No other standards were located for this compound.

VIII. RESEARCH NEEDS

The current information on biologic effects of exposure to the vinyl halides is incomplete. Vinyl chloride has been studied more extensively than the other vinyl halides; however, the exact mechanism of its toxic action is not known. Further studies are needed to obtain additional information.

(a) Epidemiology

Since one study [101] has suggested that vinyl chloride causes increased fetal mortality in the wives of exposed workers, studies should be performed to investigate this potential for each of the vinyl halides.

Epidemiologic studies should be conducted to compare cohorts from the same plant having various magnitudes of exposure. This can be done relatively easily for the vinyl halides since these compounds are generally produced and used in specific units of large chemical plants. The epidemiologic studies should include precautions to minimize the "healthy worker" and "survivor" effects usually apparent in any worker population.

(b) Toxic Effects

Exposure to vinyl chloride has been shown to induce a wide variety of toxic effects including central nervous, respiratory, cardiovascular, digestive, skin, and skeletal system effects. Studies should be designed to determine which of these systems are affected directly by vinyl chloride or its metabolites and which effects if any are secondary to the primary systemic effects. Studies should also be conducted to determine the range of toxic effects of exposure to the other vinyl halides. These studies should be designed so that comparison of primary toxic effects can be made between the compounds, ie, the same species, strains, and protocols should be used for each study.

Studies should be conducted to determine the long-term effects of inhaled and ingested vinyl fluorides. Because of the increasing latency of tumor induction with decreasing exposure concentrations reported in studies of animals exposed to vinyl chloride [135], future experiments should not be terminated until the animals become moribund or die.

(c) Sampling and Analysis

Experiments are needed to validate the lower range of the sampling and analytical methods proposed for vinyl bromide, vinyl fluoride and vinylidene fluoride. Procedures and equipment should be improved to further minimize interferences and standardize the measurement of these compounds.

Although continuous monitoring devices are commercially available for vinyl chloride and vinylidene chloride, such devices are needed for the other

vinyl halides. Research should also be conducted to increase the sensitivity and accuracy of the existing equipment so that reliable, continuous records of exposure for all work areas can be obtained.

Research is also necessary to develop techniques for biologic monitoring. At present, because of the rapid metabolism of the vinyl halides, blood analyses have only indicated adverse effects rather than determining exposures, and urinalysis has not been developed to the extent necessary to define exposures. Further studies of metabolism and excretion may develop the information necessary to calculate the body burden from the excretion products, so that an accurate assessment of the total accumulated dose can be made.

In addition, resources should be expended to assess the current state of control technology and the feasibility of implementing advances in this area. Thought should be given to the feasibility of using less toxic substitutes. Finally, respirators with end-of-service-life indicators should be developed for the vinyl halides for which they are not available.

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X. APPENDIX I

FEDERAL STANDARD FOR VINYL CHLORIDE (29 CFR 1910.1017)

§ 1910.1017 Vinyl chloride.

(a) *Scope and application.* (1) This section includes requirements for the control of employee exposure to vinyl chloride (chloroethene), Chemical Abstracts Service Registry No. 75014.

(2) This section applies to the manufacture, reaction, packaging, repackaging, storage, handling or use of vinyl chloride or polyvinyl chloride, but does not apply to the handling or use of fabricated products made of polyvinyl chloride.

(3) This section applies to the transportation of vinyl chloride or polyvinyl chloride except to the extent that the Department of Transportation may regulate the hazards covered by this section.

(b) *Definitions.* (1) "Action level" means a concentration of vinyl chloride of 0.5 ppm averaged over an 8-hour work day.

(2) "Assistant Secretary" means the Assistant Secretary of Labor for Occupational Safety and Health, U.S. Department of Labor, or his designee.

(3) "Authorized person" means any person specifically authorized by the employer whose duties require him to enter a regulated area or any person entering such an area as a designated representative of employees for the purpose of exercising an opportunity to observe monitoring and measuring procedures.

(4) "Director" means the Director, National Institute for Occupational Safety and Health, U.S. Department of Health, Education, and Welfare, or his designee.

(5) "Emergency" means any occurrence such as, but not limited to, equipment failure, or operation of a relief device which is likely to, or does, result in massive release of vinyl chloride.

(6) "Fabricated product" means a product made wholly or partly from polyvinyl chloride, and which does not require further processing at temperatures, and for times, sufficient to cause mass melting of the polyvinyl chloride resulting in the release of vinyl chloride.

(7) "Hazardous operation" means any operation, procedure, or activity where a release of either vinyl chloride liquid or gas might be expected as a consequence of the operation or because of an accident in the operation, which would result in an employee exposure in excess of the permissible exposure limit.

(8) "OSHA Area Director" means the Director for the Occupational Safety and Health Administration Area Office having jurisdiction over the geographic area in which the employer's establishment is located.

(9) "Polyvinyl chloride" means polyvinyl chloride homopolymer or copolymer before such is converted to a fabricated product.

(10) "Vinyl chloride" means vinyl chloride monomer.

(c) *Permissible exposure limit.* (1) No employee may be exposed to vinyl chloride at concentrations greater than 1 ppm averaged over any 8-hour period, and

(2) No employee may be exposed to vinyl chloride at concentrations greater than 5 ppm averaged over any period not exceeding 15 minutes.

(3) No employee may be exposed to vinyl chloride by direct contact with liquid vinyl chloride.

(d) *Monitoring.* (1) A program of initial monitoring and measurement shall be undertaken in each establishment to determine if there is any employee exposed, without regard to the use of respirators, in excess of the action level.

(2) Where a determination conducted under paragraph (d)(1) of this section shows any employee exposures, without regard to the use of respirators, in excess of the action level, a program for determining exposures for each such employee shall be established. Such a program:

(i) Shall be repeated at least monthly where any employee is exposed, without regard to the use of respirators, in excess of the permissible exposure limit.

(ii) Shall be repeated not less than quarterly where any employee is exposed, without regard to the use of respirators, in excess of the action level.

(iii) May be discontinued for any employee only when at least two consecutive monitoring determinations, made not less than 5 working days apart, show exposures for that employee at or below the action level.

(3) Whenever there has been a production, process or control change which may result in an increase in the release of vinyl chloride, or the employer has any other reason to suspect that any employee may be exposed in excess of the action level, a determination of employee exposure under paragraph (d)(1) of this section shall be performed.

(4) The method of monitoring and measurement shall have an accuracy (with a confidence level of 95 percent) of not less than plus or minus 50 percent from 0.25 through 0.5 ppm, plus or minus 35 percent from over 0.5 ppm through 1.0 ppm, and plus or minus 25 percent over 1.0 ppm. (Methods meeting these accuracy requirements are available in the "NIOSH Manual of Analytical Methods").

(5) Employees or their designated representatives shall be afforded reasonable opportunity to observe the monitoring and measuring required by this paragraph.

(e) *Regulated area.* (1) A regulated area shall be established where:

(i) Vinyl chloride or polyvinyl chloride is manufactured, reacted, repackaged, stored, handled or used; and

(ii) Vinyl chloride concentrations are in excess of the permissible exposure limit.

(2) Access to regulated areas shall be limited to authorized persons. A daily roster shall be made of authorized persons who enter.

(f) *Methods of compliance.* Employee exposures to vinyl chloride shall be controlled to at or below the permissible exposure limit provided in paragraph (c) of this section by engineering, work practice, and personal protective controls as follows:

(1) Feasible engineering and work practice controls shall immediately be used to reduce exposures to at or below the permissible exposure limit.

(2) Wherever feasible engineering and work practice controls which can be instituted immediately are not sufficient to reduce exposures to at or below the permissible exposure limit, they shall nonetheless be used to reduce exposures to the lowest practicable level, and shall be supplemented by respiratory protection in accordance with paragraph (g) of this section. A program shall be established and implemented to reduce exposures to at or below the permissible exposure limit, or to the greatest extent feasible, solely by means of engineering and work practice controls, as soon as feasible.

(3) Written plans for such a program shall be developed and furnished upon request for examination and copying to authorized representatives of the Assistant Secretary and the Director. Such plans shall be updated at least every six months.

(g) *Respiratory protection.* Where respiratory protection is required under this section:

(1) The employer shall provide a respirator which meets the requirements of this paragraph and shall assure that the employee uses such respirator, except that until April 1, 1976, wearing of respirators shall be at the discretion of each employee for exposures not in excess of 25 ppm, measured over any 15-minute period. Until April 1, 1976, each employee who chooses not to wear an appropriate respirator shall be informed at least quarterly of the hazards of vinyl chloride and the purpose, proper use, and limitations of respiratory devices.

Atmospheric concentration of vinyl chloride	*Required apparatus*
(i) Unknown, or above 36,000 ppm	Open-circuit, self-contained breathing apparatus, pressure demand type, with full facepiece.
(ii) Not over 36,000 ppm	(A) Combination type C supplied air respirator, pressure demand type, with full or half facepiece, and auxiliary self-contained air supply; or
(iii) Not over 1,000 ppm	(B) Combination type, supplied air respirator continuous flow type, with full or half facepiece, and auxiliary self-contained air supply. Type C supplied air respirator, continuous flow type, with full or half facepiece, helmet or hood.
(iv) Not over 100 ppm	(A) Combination type C supplied air respirator demand type, with full facepiece, and auxiliary self-contained air supply; or (B) Open-circuit self-contained breathing apparatus with full facepiece, in demand mode; or (C) Type C supplied air respirator, demand type, with full facepiece.
(v) Not over 25 ppm	(A) A powered air-purifying respirator with hood, helmet, full or half facepiece, and a canister which provides a service life of at least 4 hours for concentrations of vinyl chloride up to 25 ppm, or (B) Gas mask, front- or back-mounted canister which provides a service life of at least 4 hours for concentrations of vinyl chloride up to 25 ppm.
(vi) Not over 10 ppm	(A) Combination type C supplied-air respirator, demand type, with half facepiece, and auxiliary self-contained air supply; or (B) Type C supplied-air respirator, demand type, with half facepiece; or (C) Any chemical cartridge respirator with an organic vapor cartridge which provides a service life of at least 1 hour for concentrations of vinyl chloride up to 10 ppm.

(2) Respirators shall be selected from among those jointly approved by the Mining Enforcement and Safety Administration, Department of the Interior, and the National Institute for Occupational Safety and Health under the provisions of 30 CFR Part 11.

(3) A respiratory protection program meeting the requirements of § 1910.134 shall be established and maintained.

(4) Selection of respirators for vinyl chloride shall be as follows:

(5) (i) Entry into unkown concentrations or concentrations greater than 36,000 ppm (lower explosive limit) may be made only for purposes of life rescue; and

(ii) Entry into concentrations of less than 36,000 ppm, but greater than 3,600 ppm may be made only for purposes of life rescue, firefighting, or securing equipment so as to prevent a greater hazard from release of vinyl chloride.

(6) Where air-purifying respirators are used:

(I) Air-purifying cannisters or cartridges shall be replaced prior to the expiration of their service life or the end of the shift in which they are first used, whichever occurs first, and

(ii) A continuous monitoring and alarm system shall be provided where concentrations of vinyl chloride could reasonably exceed the allowable concentrations for the devices in use. Such system shall be used to alert employees when vinyl chloride concentrations exceed the allowable concentrations for the devices in use.

(7) Apparatus prescribed for higher concentrations may be used for any lower concentration.

(h) *Hazardous operations.* (1) Employees engaged in hazardous operations, including entry of vessels to clean polyvinyl chloride residue from vessel walls, shall be provided and required to wear and use:

(i) Respiratory protection in accordance with paragraphs (c) and (g) of this section; and

(ii) Protective garments to prevent skin contact with liquid vinyl chloride or with polyvinyl chloride residue from vessel walls. The protective garments shall be selected for the operation and its possible exposure conditions.

(2) Protective garments shall be provided clean and dry for each use.

(i) *Emergency situations.* A written operational plan for emergency situations shall be developed for each facility storing, handling, or otherwise using vinyl chloride as a liquid or compressed gas. Appropriate portions of the plan shall be implemented in the event of an emergency. The plan shall specifically provide that:

(1) Employees engaged in hazardous operations or correcting situations of existing hazardous releases shall be equipped as required in paragraph (h) of this section;

(2) Other employees not so equipped shall evacuate the area and not return until conditions are controlled by the methods required in paragraph (f) of this section and the emergency is abated.

(j) *Training.* Each employee engaged in vinyl chloride or polyvinyl chloride operations shall be provided training in a program relating to the hazards of vinyl chloride and precautions for its safe use.

(1) The program shall include:

(i) The nature of the health hazard from chronic exposure to vinyl chloride including specifically the carcinogenic hazard;

(ii) The specific nature of operations which could result in exposure to vinyl chloride in excess of the permissible limit and necessary protective steps;

(iii) The purpose for, proper use, and limitations of respiratory protective devices;

(iv) The fire hazard and acute toxicity of vinyl chloride, and the necessary protective steps;

(v) The purpose for and a description of the monitoring program;

(vi) The purpose for, and a description of, the medical surveillance program;

(vii) Emergency procedures;

(viii) Specific information to aid the employee in recognition of conditions which may result in the release of vinyl chloride; and

(ix) A review of this standard at the employee's first training and indoctrination program, and annually thereafter.

(2) All materials relating to the program shall be provided upon request to the Assistant Secretary and the Director.

(k) *Medical surveillance.* A program of medical surveillance shall be instituted for each employee exposed, without regard to the use of respirators, to vinyl chloride in excess of the action level. The program shall provide each such employee with an opportunity for examinations and tests in accordance with this paragraph. All medical examinations and procedures shall be performed by or under the supervision of a licensed physician, and shall be provided without cost to the employee.

(1) At the time of initial assignment, or upon institution of medical surveillance;

(i) A general physical examination shall be performed, with specific attention to detecting enlargement of liver, spleen or kidneys, or dysfunction in these organs, and for abnormalties in skin, connective tissues and the pulmonary system (See Appendix A).

(ii) A medical history shall be taken, including the following topics:

(A) Alcohol intake;

(B) Past history of hepatitis;

(C) Work history and past exposure to potential hepatotoxic agents, including drugs and chemicals;

(D) Past history of blood transfusions; and

(E) Past history of hospitalizations.

(iii) A serum specimen shall be obtained and determinations made of:

(A) Total bilirubin;

(B) Alkaline phosphatase;

(C) Serum glutamic oxalacetic transaminase (SGOT);

(D) Serum glutamic pyruvic transaminase (SGPT); and

(E) Gamma glustamyl transpeptidase.

(2) Examinations provided in accordance with this paragraph shall be performed at least:

(i) Every 6 months for each employee who has been employed in vinyl chloride or polyvinyl chloride manufacturing for 10 years or longer; and

(ii) Annually for all other employees.

(3) Each employee exposed to an emergency shall be afforded appropriate medical surveillance.

(4) A statement of each employee's suitability for continued exposure to vinyl chloride including use of protective equipment and respirators, shall be obtained from the examining physician promptly after any examination. A copy of the physician's statement shall be provided each employee.

(5) If any employee's health would be materially impaired by continued exposure, such employee shall be withdrawn from possible contact with vinyl chloride.

(6) Laboratory analyses for all biological specimens included in medical examinations shall be performed in laboratories licensed under 42 CFR Part 74.

(7) If the examining physician determines that alternative medical examinations to those required by paragraph (k)(1) of this section will provide at least equal assurance of detecting medical conditions pertinent to the exposure to vinyl chloride, the employer may accept such alternative examinations as meeting the requirements of paragraph (k)(1) of this section, if the employer obtains a statement from the examining physician setting forth the alternative examinations and the rationale for substitution. This statement shall be available upon request for examination and copying to authorized representatives of the Assistant Secretary and the Director.

(l) *Signs and labels.* (1) Entrances to regulated areas shall be posted with legible signs bearing the legend:

CANCER-SUSPECT AGENT AREA AUTHORIZED PERSONNEL ONLY

(2) Areas containing hazardous operations or where an emergency currently exists shall be posted with legible signs bearing the legend:

CANCER-SUSPECT AGENT IN THIS AREA PROTECTIVE EQUIPMENT REQUIRED AUTHORIZED PERSONNEL ONLY

(3) Containers of polyvinyl chloride resin waste from reactors or other waste contaminated with vinyl chloride shall be legibly labeled:

CONTAMINATED WITH VINYL CHLORIDE CANCER-SUSPECT AGENT

(4) Containers of polyvinyl chloride shall be legibly labeled:

POLYVINYL CHLORIDE (OR TRADE NAME)
Contains
VINYL CHLORIDE
VINYL CHLORIDE IS A CANCER-SUSPECT AGENT

(5) Containers of vinyl chloride shall be legibly labeled either:

(i)

VINYL CHLORIDE
EXTREMELY FLAMMABLE GAS UNDER PRESSURE
CANCER-SUSPECT AGENT

or (ii) In accordance with 49 CFR Parts 170–189, with the additional legend:

CANCER-SUSPECT AGENT

applied near the label or placard.

(6) No statement shall appear on or near any required sign, label or instruction which contradicts or detracts from the effect of, any required warning, information or instruction.

(m) *Records.* (1) All records maintained in accordance with this section shall include the name and social security number of each employee where relevant.

(2) Records of required monitoring and measuring, medical records, and authorized personnel rosters, shall be made and shall be available upon request for examination and copying to authorized representatives of the Assistant Secretary and the Director.

(i) Monitoring and measuring records shall:

(A) State the date of such monitoring and measuring and the concentrations determined and identify the instruments and methods used;

(B) Include any additional information necessary to determine individual

employee exposures where such exposures are determined by means other than individual monitoring of employees; and

(C) Be maintained for not less than 30 years.

(ii) Authorized personnel rosters shall be maintained for not less than 30 years.

(iii) Medical records shall be maintained for the duration of the employment of each employee plus 20 years, or 30 years, whichever is longer.

(3) In the event that the employer ceases to do business and there is no successor to receive and retain his records for the prescribed period, these records shall be transmitted by registered mail to the Director, and each employee individually notified in writing of this transfer.

(4) Employees or their designated representatives shall be provided access to examine and copy records of required monitoring and measuring.

(5) Former employees shall be provided access to examine and copy required monitoring and measuring records reflecting their own exposures.

(6) Upon written request of any employee, a copy of the medical record of that employee shall be furnished to any physician designated by the employee.

(n) *Reports.* (1) Not later than 1 month after the establishment of a regulated area, the following information shall be reported to the OSHA Area Director. Any changes to such information shall be reported within 15 days.

(i) The address and location of each establishment which has one or more regulated areas; and

(ii) The number of employees in each regulated area during normal operations, including maintenance.

(2) Emergencies, and the facts obtainable at that time, shall be reported within 24 hours to the OSHA Area Director. Upon request of the Area Director, the employer shall submit additional information in writing relevant to the nature and extent of employee exposures and measures taken to prevent future emergencies of similar nature.

(3) Within 10 working days following any monitoring and measuring which discloses that any employee has been exposed, without regard to the use of respirators, in excess of the permissible exposure limit, each such employee shall be notified in writing of the results of the exposure measurement and the steps being taken to reduce the exposure to within the permissible exposure limit.

(o) *Effective dates.* (1) Until April 1, 1975, the provisions currently set forth in § 1910.93q of this Part shall apply.

(2) Effective April 1, 1975, the provisions set forth in § 1910.93q of this Part shall apply.

Appendix A—Supplementary Medical Information

When required tests under paragraph (k)(1) of this section show abnormalities, the tests should be repeated as soon as practicable, preferably within 3 to 4 weeks. If tests remain abnormal, consideration should be given to withdrawal of the employee from contact with vinyl chloride, while a more comprehensive examination is made.

Additional tests which may be useful:

A. For kidney dysfunction: urine examination for albumin, red blood cells, and exfoliative abnormal cells.

B. Pulmonary system: Forced vital capacity, Forced expiratory volume at 1 second, and chest roentgenogram (posterior-anterior, 14 x 17 inches).

C. Additional serum tests: Lactic acid dehydrogenase, lactic acid dehydrogenase isoenzyme, protein determination, and protein electrophoresis.

D. For a more comprehensive examination on repeated abnormal serum tests: Hepatitis B antigen, and liver scanning.

(Secs. 6 and 8, 84 Stat. 1596, 1599 (29 U.S.C. 655, 657); Secretary of Labor's Order No. 12-71, 36 FR 8754) [39 FR 35896, Oct. 4, 1974; 39 FR 41848, Dec. 3, 1974, as amended at 40 FR 13211, Mar. 25, 1975. Redesignated at 40 FR 23073, May 28, 1975]

XI. APPENDIX II

SAMPLING AND ANALYTICAL METHOD FOR VINYL CHLORIDE IN AIR

This is NIOSH-accepted (Classification B) analytical method No. P&CAM 178 for determination of vinyl chloride in air, issued September 3, 1974 and revised January 29, 1976 [245]. This method involves adsorption on activated carbon, desorption with carbon disulfide, and gas chromatography. The range for determination of vinyl chloride using this method is 0.008-5.2 mg/cu m (0.003-2.03 ppm) in a 5-liter air sample. The precision (coefficient of variation-CV(T)) is approximately 0.08 at levels of 7 and 71 mg/cu m (2.73 and 27.7 ppm).

Principle of the Method

A known volume of air is drawn through two sorbent tubes in series containing activated carbon (made from coconut shells), which adsorbs the vinyl chloride present in the air sample. The collected vinyl chloride is then desorbed with carbon disulfide, and the resulting solutions are analyzed by gas chromatography with a flame-ionization detector. The areas under the resulting peaks are compared with areas obtained from the injection of standards.

Range and Sensitivity

(a) The minimum detectable amount of vinyl chloride was found to be 0.2 ng/injection at a 1 x 1 attenuation of a gas chromatograph. This corresponds to an estimated concentration of 0.008 mg/cu m in a 5-liter air sample analyzed by this method. However, the desorption efficiency from activated carbon of amounts of vinyl chloride as small as 40 ng (0.008 µg/liter x 5 liters) has not been determined. Therefore, the detection limit of the overall method may be somewhat higher than 0.008 mg/cu m.

(b) At a sampling flowrate of 50 ml/minute, the total volume to be sampled should not exceed 5 liters. This value is based on data indicating that more than 10 liters of air containing 2.6 µg/liter (1 ppm) of vinyl chloride could be sampled on activated carbon before 5% breakthrough was observed. This would indicate that 5 liters of air containing no more than 5.2 mg/cu m may be sampled without significant breakthrough. If a particular atmosphere is suspected of containing a high concentration of contaminants or a high humidity is suspected, the sampling volume should be reduced by 50%. A safety factor has been included in the 5-liter volume, and the capacity of the first tube should be adequate within these limits except under the most extreme conditions.

Interferences

(a) When the amount of water in the air is so great that condensation actually occurs in the tube, organic vapors will not be trapped effectively. Experiments indicate that high humidity severely decreases the capacity of activated carbon for organic vapors.

(b) When two or more substances are known or suspected to be present in the air, this information, including their suspected identities, should be transmitted with the sample, since these compounds may interfere with the analysis for vinyl chloride.

(c) Any compound that has the same retention time as vinyl chloride under the operating conditions described in this method is an interference. Hence, retention time data on a single column, or even on a number of columns, may not provide proof of chemical identity. Often, operating conditions can be modified to eliminate interferences. Samples should be analyzed by an independent method when overlapping gas-chromatographic peaks cannot be resolved.

Precision and Accuracy

(a) A coefficient of variation of 0.076 was obtained from analysis of each of two sets of sorbent tubes, one set of 27 tubes exposed to vinyl chloride at a concentration of 7.2 mg/cu m in air and another set of 29 tubes exposed at a concentration of 71.3 mg/cu m. These values reflect total sampling and analytical error as well as desorption efficiency correction errors.

(b) Experiments were performed to obtain some indication of the accuracy of this method, although accuracy was difficult to evaluate. These experiments generally involved six sorbent tube samples exposed to a synthetic atmosphere. The calculated value was the concentration expected based on the measured amounts of vinyl chloride and air mixed to prepare the synthetic atmosphere. The calculated value was not the true value, since it was subject to experimental error. The value found from analysis of each sorbent tube, after correction for desorption efficiency, was also compared with that found by the direct injection of gas samples from the same synthetic atmosphere used in loading the tubes. The results of these experiments are shown in Table XI-1. It should be noted that average concentrations determined by analysis of sorbent tubes were within 6% of the average concentrations determined by analysis of gas samples.

TABLE XI-1

ACCURACY OF THE RECOMMENDED SAMPLING METHOD FOR VINYL CHLORIDE

Experiment Number	Samples	Calculated Concentration (mg/cu m)	Experimental Concentration* (mg/cu m)	Estimated Error** (1%)
I	Gas samples	64	71.2 ±0.7	-2
	Solvent tubes	64	69.8 ±1.5	
II	"	13	14.5 ±0.5	
		13	13.6 ±0.4	-6
III	"	2.6	2.88 ±0.07	
		2.6	2.91 ±0.13	+1
IV	"	1.3	-	
		1.3	1.27 ±0.09	-

*Average of concentrations determined from sorbent tubes minus average of concentrations determined from gas samples, divided by average of concentrations determined from gas samples, x 100
**Mean value ±95% confidence level (standard deviation x Student's t at 0.05 significance level, divided by square root of number of samples)

Advantages and Disadvantages of the Method

(a) The sampling device is small, portable, and involves no liquids. Interferences are minimal, and most of those that do occur can be eliminated by altering chromatographic conditions. The tubes are analyzed by a rapid instrumental method. The method can also be used for the simultaneous determination of two or more components suspected to be present in the same sample by changing gas-chromatographic conditions from isothermal to a temperature-programmed mode of operation.

(b) One disadvantage of the method is that the amount of sample that can be taken is limited by the amount of vinyl chloride that the tube will hold before it becomes overloaded. When the value obtained for the backup section of the sorbent tube exceeds 20% of that found on the front section, there is a possibility of sample loss. During storage, volatile compounds such as vinyl chloride will migrate throughout the tube until equilibrium is reached. At this time, 33% of these compounds will be found in the backup section. This

may lead to some confusion as to whether sample loss has occurred. This migration effect can be considerably decreased by shipping and storing the tubes at -20 C or by using two separately capped tubes for the front and backup sections.

(c) The precision of the method is limited by the reproducibility of the pressure drop and, therefore, by the flowrates across the tubes. Because the pump is usually calibrated for one particular tube, differences in flowrates from tube to tube can cause sample volumes to vary.

Apparatus

(a) Personal sampling pump: The pump should be a properly calibrated personal sampling pump for personal and area samples. The pump should also be capable of accurate performance at the recommended flowrates. It should be calibrated with a representative sorbent tube in the sampling line. A dry or wet test meter or a glass rotameter that will determine the flowrate to within ±5% may be used for the calibration.

(b) Sorbent tubes: The glass tubes are flame sealed at both ends. Each is 7 cm long, 6-mm outer diameter, 4-mm inner diameter, and contains two sections of 20/40-mesh activated carbon separated by a 3-mm portion of urethane foam. The activated carbon is prepared from coconut shells and is fired at 600 C prior to packing to remove adsorbed materials. The primary adsorbing section contains 100 mg of sorbent, the backup section 50 mg. A plug of silanized glass wool is placed in front of the adsorbing section. The pressure drop across the tube must be less than 2 inches of water at a flowrate of 0.2 liters/minute.

(c) Gas chromatograph equipped with a flame-ionization detector.

(d) Stainless steel column (20 feet x 0.125 inch) packed with 10% SE-30 on 80/100 mesh Chromosorb W (acid washed, silanized with dimethyldichlorosilane). Other columns capable of performing the required separations may be used.

(e) A mechanical or electronic integrator and a recorder or some method for determining peak area.

(f) Vials (2 ml) that can be sealed with caps containing Teflon-lined silicone rubber septa.

(g) Microliter syringes (10 µl and other convenient sizes for making standards).

(h) Gastight syringe (1 ml, with a gastight valve).

(i) Pipets (0.5-ml delivery pipets or 1.0-ml pipets graduated in 0.1-ml increments).

(j) Volumetric flasks (10 ml or convenient sizes for making solutions), preferably with plastic stoppers.

(k) Gas bags, Tedlar or equivalent.

Reagents

(a) Carbon disulfide, "spectroquality" or better grade.

(b) Vinyl chloride, lecture bottle, 99.9% minimum purity.

(c) Toluene, chromatographic quality.

(d) Helium, Bureau of Mines grade A.

(e) Prepurified hydrogen.

(f) Filtered, compressed air.

Procedure

(a) Collection and Shipping of Samples

(1) Immediately before sampling, break the ends of the two tubes to provide an opening of at least 2 mm, one-half the internal diameter of the tube.

(2) Position the second sorbent tube next to the sampling pump in tandem with the first tube, to serve as a backup. If one tube is used, position the smaller section of tube nearest the sampling pump.

(3) Place the sorbent tubes in a vertical position with the larger section of sorbent pointing up during sampling to minimize channeling of the vinyl chloride through the sorbent.

(4) Do not allow air being sampled to pass through any hose or tubing before entering the sorbent tubes.

(5) Measure the flowrate and time, or the sampling volume, as accurately as possible. Take the sample at a flowrate of 50 ml/minute. The maximum volume to be sampled should not exceed 5 liters.

(6) Sample relatively large volumes (10-20 liters) of air through other sorbent tubes at the same time personal samples are taken. These bulk air samples will be used by the analyst to identify possible interferences before the personal samples are analyzed.

(7) Measure and record the temperature and pressure of the atmosphere being sampled if they are significantly different from 25 C or 760 mmHg.

(8) Cap the sorbent tubes with the supplied plastic caps immediately after sampling. Under no circumstances should rubber caps be used.

(9) Treat one tube in the same manner as a sample tube (break, seal, and transport), but do not sample any air through the tube. This tube is labeled as a blank.

(10) Pack capped tubes tightly to minimize tube breakage during transport to the laboratory. The use of two tubes in series during sampling eliminates the need for cooling during shipping. However, if only one tube is used, and if the samples will spend a day or more in transit, then cool the tubes, eg, with dry ice, to minimize migration of the vinyl chloride to the backup section.

(11) Samples received at the laboratory are logged in and immediately stored in a freezer (around -20 C) until time for analysis. Samples may be stored in this manner for long periods of time with no appreciable loss of vinyl chloride (2 months). Even around -20 C, vinyl chloride will equilibrate between the two sections of activated carbon in one tube, ie, it will migrate to the backup section. This phenomenon is observable after 2 weeks and may be confused with sample loss after 1-2 months.

(b) Analysis of Samples

(1) Cleaning of Equipment. All glassware used for the laboratory analysis should be washed with detergent and thoroughly rinsed with tapwater and distilled water.

(2) Preparation and Desorption of Samples. The two tubes used in the collection of a single sample are analyzed separately. If only one tube is used for sampling, then each section of activated carbon should be analyzed separately. Discard the glass wool from each tube. Transfer both sections of each tube to a small vial containing 1 ml of the precooled carbon disulfide. It is important to add the sorbent to carbon disulfide and not the carbon disulfide to the sorbent. Top vial with a septum cap. Discard the separating section in each tube. Tests indicate that desorption is complete in 30 minutes if the sample is agitated occasionally during this period. The samples should be analyzed within 60 minutes after addition to carbon disulfide.

(3) Gas-Chromatographic Conditions. The typical operating conditions for the gas chromatograph are:

(A) Helium carrier gas flow, 40 ml/minute (80 psig).

(B) Hydrogen gas flow to detector, 65 ml/minute (20 psig).

(C) Airflow to detector, 500 ml/minute (50 psig).

(D) Injector temperature, 230 C.

(E) Detector temperature, 230 C.

(F) Column temperature, 60 C.

(4) Injection: The first step in the analysis is the injection of the sample into the gas chromatograph. To eliminate difficulties arising from blowback or distillation within the syringe needle, use the solvent flush injection technqiue. Flush a 10-μl syringe with solvent several times to wet the barrel and plunger. Draw 2 μl of solvent into the syringe to increase the accuracy and reproducibility of the injected sample volume. Remove the needle from the solvent and pull the plunger back about 0.4 μl to separate the solvent flush from the sample with a pocket of air to be used as a marker. Then immerse the needle in the sample and withdraw a 5-μl aliquot to the 7.4-μl mark (2 μl of solvent + 0.4 μl of air + 5 μl of sample = 7.4 μl). After the needle is removed from the sample and prior to injection, the plunger is pulled back a short distance to minimize evaporation of the sample from the tip of the needle. Make duplicate injections of each sample and standard. No more than a 3% difference in area from repeated injections is to be expected. Automatic sampling devices may also be used. A syringe equipped with a Chaney adapter may also be used in lieu of the solvent flush technique.

(5) Measurement of Area: Measure the area under the sample peak using an electronic integrator or some other suitable form of area measurement. Area measurements are compared with a standard curve prepared as discussed in Preparation of Standards. Preliminary results are read from a standard curve prepared as discussed below.

(c) Determination of Desorption Efficiency

(1) Importance of Determination. The efficiency of desorption of a particular compound can vary from one laboratory to another and also from one batch of sorbent to another. Thus, it is necessary to determine at least once the percentage of vinyl chloride that is removed in the desorption process. Desorption efficiency should be determined on the same batch of sorbent tubes used in sampling. Results indicate that desorption efficiency varies with loading (total vinyl chloride on the tube), particularly at lower values, eg, 2.5 μg.

(2) Procedure for Determining Desorption Efficiency. Sorbent tubes from the same batch as that used in obtaining samples are used in this determination. Inject a measured volume of vinyl chloride gas into a bag containing a measured volume of air. The concentration in the bag may be calculated if room temperature and pressure are known. The bag is made of Tedlar (or other material that will retain the vinyl chloride and not absorb it) and should have a gas sampling valve and a septum injection port. Sample a measured volume from the bag through a sorbent tube using a calibrated sampling pump. Prepare at least five tubes in this manner. These tubes are desorbed and analyzed in the same manner as the samples. Samples taken with a gastight syringe from the bag are also injected into the gas chromatograph. The concentration in the bag (standard) is compared with the concentration obtained from the tube (sample).

The desorption efficiency equals the amount of vinyl chloride desorbed from the charcoal divided by the product of the vinyl chloride concentration in the bag times the volume of synthetic atmosphere sampled, or:

$$\frac{\text{(amount of vinyl chloride desorbed from sorbent)}}{\text{(vinyl chloride concentration in bag) x (volume of atmosphere sampled)}}$$

Preparations of Standards

Caution: These laboratory operations involve carcinogens.

Vinyl chloride has been identified as a human carcinogen and appropriate precautions must be taken in handling this compound.

A series of standards, varying in concentration over the range of interest, is prepared and analyzed under the same gas-chromatographic conditions and during the same time period as the unknown samples. Curves are established by plotting concentration in µg/ml vs peak area or peak height. There are two methods of preparing standards, and they are comparable if highly purified vinyl chloride is used. If no internal standard is used in the method, standard solutions must be analyzed at the same time as the sample. This will minimize the effect of day-to-day variations of the flame-ionization response.

(a) Gravimetric Method. Slowly bubble vinyl chloride into a weighed 10-ml volumetric flask containing approximately 5 ml of toluene. After 3 minutes, weigh the flask again. A weight change of 100-300 mg will usually be observed. Dilute the solution to exactly 10 ml with carbon disulfide and use to prepare other standards by removing aliquots with syringes of various sizes. Subsequent dilution of these aliquots with carbon disulfide results in a series of standards that have linear values from the range of 0.2 ng/injection, the minimum detectable amount of vinyl chloride, to 1.5 µg/injection.

(b) Volumetric Method. Draw a 1-ml gas sample of pure vinyl chloride into a gastight syringe and close the syringe valve. Insert the tip of the needle into a 10-ml volumetric flask containing approximately 5 ml of carbon disulfide. Open the syringe valve and withdraw the plunger slightly to allow the carbon disulfide to enter the syringe. Return the solution in the syringe to the flask and rinse the syringe with clean carbon disulfide, adding the washings to the volumetric flask. Fill the volumetric flask to the mark with carbon disulfide. Other standards are then prepared from this stock solution.

Standards are stored in a freezer at -20 C and have been found to be stable at this temperature for 3 days. Tight-fitting plastic tops on the volumetric flasks seem to retain the vinyl chloride better than ground-glass stoppers.

Calculations

(a) The weight, in μg, corresponding to the area under each peak is read from the standard curve for vinyl chloride. No liquid volume corrections are needed because both the standards and the samples are based on the number of μg in 1.0 ml of carbon disulfide and the volume injected in both cases is identical.

(b) Corrections for the blank are made for each sample:

$$\mu g = \mu g(\text{sample}) - \mu g(\text{blank})$$

A similar procedure is followed for the backup sections.

(c) Add the amounts present in the front and backup sections of the same sample tube to determine the total amount of vinyl chloride in the sample.

(d) The total amount is corrected for the desorption efficiency at the level of vinyl chloride measured:

$$\text{Corrected amount (in } \mu g) = \frac{\text{amount (in } \mu g)}{\text{desorption efficiency}}$$

(e) The concentration of vinyl chloride in air may be expressed in mg/cu m:

$$\text{mg/cu m} = \frac{\text{corrected weight (in } \mu g)}{\text{volume of air sampled (in liters)}}$$

(f) The concentration may also be expressed in terms of ppm by volume:

$$\text{ppm} = \text{mg/cu m} \times \frac{24.45}{MW} \times \frac{760}{P} \times \frac{T+273}{298}$$

where:

24.45 = molar volume (liters/mole) at 25 C and 760 mmHg
MW = molecular weight
P = pressure (mmHg) of air sampled
T = temperature (C) of air sampled

XII. APPENDIX III

SAMPLING AND ANALYTICAL METHOD FOR VINYLIDENE CHLORIDE IN AIR

This is the NIOSH-proposed (Classification E) analytical method No. P&CAM 266 for determination of vinylidene chloride in air issued November 21, 1977 [259]. This method involves adsorption on charcoal, desorption with carbon disulfide, and gas chromatography. The range for determination of vinylidene chloride using this method is 2-12 mg/cu m (0.5-3.02 ppm) in 7 liters of air. The precision (pooled relative standard deviation) is approximately 5% for analysis of samples containing 12-85 μg of vinylidene chloride/sample.

Synopsis

(a) A known volume of air is drawn through a charcoal tube to trap the vinylidene chloride present.

(b) The charcoal in the tube is transferred to a small vial where the vinylidene chloride is desorbed with carbon disulfide.

(c) An aliquot of the desorbed sample is injected into a gas chromatograph.

(d) The area or the height of the resulting peak is determined and compared with either the peak areas or heights obtained from injection of standards.

Working Range, Sensitivity, and Detection Limit

(a) The method was tested with sample loading between 12 and 85 μg of vinylidene chloride/charcoal tube. The samples were collected from atmospheres containing vinylidene chloride in the range of 7.6-10.0 mg/cu m and having a relative humidity of greater than 80%.

(b) The slope of the calibration curve (response vs weight/sample) was 0.0322 area count/μg when analysis was done by electronic integration. When analysis was done using peak height, the slope of the calibration curve was 4.75×10^{-12} amps/μg.

(c) The lowest quantifiable limit for this method was determined to be 7 μg of vinylidene chloride/sample. At this level the relative standard deviation of replicate samples was found to be less than 10% and the

desorption efficiency was greater than 80%. This limit could be lower if the charcoal used is shown to give better desorption characteristics at the lower level.

Interferences

(a) When two or more substances are known or suspected to be present in the air, this information, including their suspected identities, should be transmitted with the sample, since these compounds may interfere with the analysis for vinylidene chloride.

(b) Any compound that has the same retention time as vinylidene chloride under the operating conditions described in this method is an interference. Therefore, retention time data on single or multiple columns cannot be considered proof of chemical identity.

(c) If the possibility of interference exists, separation conditions, eg, column packing, temperature, carrier flow, and detector, must be changed to circumvent the problem.

Precision and Accuracy

(a) The pooled relative standard deviation of the analytical method was 4.8% for the analysis of 36 samples over the range of 12-85 μg vinylidene chloride/sample.

(b) The concentration of the sampled air was also determined using a gas phase infrared analyzer. The gas-chromatographic determinations averaged 5% lower when compared with the results of the infrared analyzer. No desorption efficiency corrections were used.

(c) The breakthrough volume and, therefore, the capacity of charcoal for vinylidene chloride decreased with increasing relative humidity. At 87% relative humidity the breakthrough volume was 10% of the breakthrough volume at 10% relative humidity. The breakthrough volume was also found to be a function of concentration of vinylidene chloride. When high relative humidity air containing 144 mg/cu m of vinylidene chloride was sampled at 0.2 liter/minute the breakthrough volume was 3.7 liters. At a vinylidene chloride concentration of 10 mg/cu m and high relative humidity the breakthrough volume was 7.3 liters.

(d) Samples of vinylidene chloride on charcoal were found to be stable at 25 C for 7 days and for 21 days if stored at 5 C for the remainder of the period.

Advantages and Disadvantages of the Method

(a) The sampling device is small, portable, and involves no liquids. Many of the interferences can be eliminated by altering chromatographic conditions. The tubes are analyzed by means of a quick instrumental method.

(b) One disadvantage of the method is that the amount of sample that can be taken is limited by the capacity of the charcoal tube. When the sample value obtained for the backup section of the charcoal tube exceeds 20% of that found on the front section, the possibility of sample loss exists. During sample storage the volatile compounds may migrate throughout the tube until equilibrium is reached (33% of the sample on the backup section). This can be minimized by storing the samples in a refrigerator until the analysis is performed.

(c) The precision of the method is limited by the reproducibility of the pressure drop across the tubes. Variation in pressure drop will affect the flowrate. The reported sample volume will then be imprecise because the pump is usually calibrated for one tube only.

(d) The recommended gas-chromatographic packing will not separate vinyl chloride and carbon disulfide. Other gas-chromatographic packings that separate vinyl chloride and carbon disulfide do not separate vinylidene chloride and carbon disulfide. If analysis for each of these monomers is to be performed, it is necessary to use different columns to analyze the samples.

Apparatus

(a) Personal sampling pump capable of accurate performance at 0.2 liter/minute and calibrated with a representative charcoal tube in the line.

(b) Charcoal tubes: Glass tubes with both ends flame-sealed, 7 cm long with a 6-mm outer diameter, and a 4-mm inner diameter, containing two sections of 20/40-mesh activated carbon separated by a 2-mm portion of urethane foam. The activated charcoal is prepared from coconut shells and is fired at 600 C prior to packing. The adsorbing section contains 100 mg of charcoal, the backup section 50 mg. A plug of silylated glass wool is placed in front of the adsorbing section. The pressure drop across the tube must be less than 1 inch of mercury at a flowrate of 0.2 liter/minute.

(c) Gas chromatograph equipped with a flame-ionization detector. Optional: electronic integrator.

(d) Silanized glass gas-chromatographic column (10 feet x 1/4-inch outer diameter) packed with Durapak OPN 100/120 mesh. Any gas-chromatographic column capable of separating carbon disulfide and vinylidene chloride may be used.

(e) Vials (2 ml) that can be sealed with caps containing Teflon-lined silicone rubber septa.

(f) Microliter syringes, 10 µl, and convenient sizes for making standards.

(g) Pipet, 1.0 ml.

Reagents

All reagents used should be ACS Reagent Grade or better.

(a) Carbon disulfide, "spectroquality" or better.

(b) Vinylidene chloride, 99%.

(c) Cyclohexane.

(d) Helium, Bureau of Mines grade A.

(e) Prepurified hydrogen.

(f) Filtered, compressed air.

Procedure

(a) Cleaning of Equipment. All nondisposable glassware used for the laboratory analysis should be washed with detergent and rinsed thoroughly with tap water and distilled water.

(b) Collection and Shipping of Samples

(1) Immediately before sampling, the ends of the tube are broken to provide an opening (2 mm) at least one-half the internal diameter of the tube.

(2) The tube is connected to the sampling pump via rubber tubing. The smaller section of charcoal is the backup and is positioned nearest the sampling pump.

(3) The charcoal tube should be vertical during sampling to prevent channeling through the tube.

(4) Air being sampled should not be passed through any hose or tubing before entering the charcoal tubes.

(5) Measure and report the flowrate and time, or the sampling volume, as accurately as possible. The sample is taken at 0.2 liter/minute or less. The maximum volume sampled should not exceed 7.0 liters.

(6) Measure and record the temperature and pressure of the atmosphere being sampled.

(7) Cap the charcoal tubes with the plastic caps supplied immediately after sampling. Under no circumstances should rubber caps be used.

(8) For every 10 samples taken, one charcoal tube should be handled in the same manner as the samples (break, seal, and transport), except that no air is sampled through this tube. This should be labeled as a blank.

(9) If samples are shipped to a laboratory, they should be packed tightly to minimize tube breakage during shipping.

(10) Six to twelve unopened charcoal tubes should also be shipped so desorption efficiency studies can be performed on the same type and lot of charcoal used for sampling.

(11) Samples received at the laboratory are logged in and immediately stored in a refrigerator.

(c) Analysis of Samples

(1) Preparation of Samples. The charcoal tubes are removed from the refrigerator and permitted to equilibrate to room temperature to prevent water condensation on the cold charcoal. Each charcoal tube is scored with a file in front of the first section of charcoal and broken open. The glass wool is removed and discarded. The front section (larger) is transferred to a small vial. The separating foam is removed from the tube and discarded. The backup section is also transferred to a small vial. The contents of each individual tube are desorbed before the next sample tube is opened.

(2) Desorption of Samples. After the two sections of a charcoal tube are transferred to small vials, 1.00 ml of carbon disulfide is pipetted into each of the two vials. A serum cap is then crimped into place immediately after the carbon disulfide has been added. (All work with carbon disulfide should be performed in a hood because of the high toxicity of carbon disulfide). The capped samples are kept at room temperature with occasional agitation. Desorption is complete in 30 minutes. The samples should be analyzed the same day they are desorbed.

(3) Gas-Chromatographic Conditions:

(A) 70 ml/minute helium carrier flow.

(B) 50 ml/minute hydrogen flow to detector.

(C) 500 ml/minute air flow to detector.

(D) 150 C injector temperature.

(E) 200 C manifold (detector) temperature.

(F) 65 C (isothermal) oven temperature.

Under these conditions the capacity ratio for vinylidene chloride was 5.2.

(4) Injection. Inject a 5-µl aliquot into the gas chromatograph. A syringe equipped with a Chaney adapter may be used in lieu of the solvent flush technique.

(5) Measurement of Area: Measure the area under the sample peak using an electronic integrator or another suitable form of area measurement. Area measurements are compared with a standard curve prepared as discussed in Preparation of Standards.

(6) Measurement of Peak Height. The product of peak height and attenuator setting is linear over the analytical range. The peak height is multiplied by the attenuator setting necessary to keep the peak on scale. Preliminary results are read from a standard curve prepared as discussed below.

(d) Determination of Desorption Efficiency

(1) Importance of Determination. The desorption efficiency of a particular compound can vary between laboratories and batches of charcoal. Also, for a given batch of charcoal the desorption efficiency can vary with the weight of contaminant adsorbed. The charcoal used for the study of this method gave a desorption efficiency of 80% for a loading of 7 µg of vinylidene chloride/100 mg bed of charcoal.

(2) Procedure for Determining Desorption Efficiency. The desorption efficiency should be determined at three levels with a minimum of three samples at each level. Vinylidene chloride can be dissolved in cyclohexane to give stock solutions. The concentrations should be such that no more than 8 µl of a stock solution will be injected onto the charcoal. Activated charcoal in an amount equivalent to that found in the larger section of the charcoal tube (100 mg) is placed in a small vial and capped. An aliquot of the stock solution is injected into the charcoal tube. Two of the levels should reflect the extremes of the analytical range while the third level is inbetween the high and low levels. Each vial is allowed to stand overnight to assure complete adsorption of vinylidene chloride onto the charcoal. Standards are

prepared by injecting an identical amount of cyclohexane stock solution into 1.0 ml of carbon disulfide. The samples and standards are analyzed as described in Analysis of Samples.

The desorption efficiency at each level is the ratio of the average amount found to the amount taken. A blank correction is not expected to be necessary. The desorption efficiency curve is constructed by plotting the amount of vinylidene chloride found in a sample vs the desorption efficiency.

Calibration and Standardization

CAUTION: Vinylidene chloride has been tentatively identified as a carcinogen. Precautions must be taken while handling this compound to prevent contamination of personnel and the working area.

It is convenient to express the concentration of standards in terms of μg/1.0 ml of carbon disulfide or μg/sample. The density of vinylidene chloride is used to convert the volume taken to the mass taken (1.218 mg/μl). A series of standards varying in concentration over the range of interest is prepared and analyzed under the same gas-chromatographic conditions and during the same time period as the samples. It is best to alternate standard then sample, during the analysis. Curves are established by plotting the concentration of the standards in μg/1.0 ml of carbon disulfide vs peak area or peak height.

Calculations

(a) The sample weight in μg is read from the standard curve.

(b) Blank corrections are not expected but, if the analysis shows a blank correction is needed, the correction is:

$$WF = Ws - Wb$$

where:

WF = corrected amount (μg) on the front section of the charcoal tube
Ws = amount found on the front section of the charcoal tube
Wb = amount (μg) found on the front section of the blank charcoal tube

A similar procedure is followed for the backup sections.

(c) A correction for desorption efficiency is made:

$$MF = \frac{WF}{D}$$

where:

MF = corrected amount (μg)
WF = amount (μg) after blank correction
D = desorption efficiency corresponding to the weight WF

The corrected amount of the backup section, MB, is similarly calculated.

(d) The concentration, C, of vinylidene chloride in the air sampled is expressed in mg/cu m, which is numerically equal to μg/liter:

$$C = \frac{MF + MB}{V}$$

where:

MF = amount of vinylidene chloride found on front section in μg
MB = amount of vinylidene chloride found on backup section in μg
V = volume of air sampled in liters

(e) If desired the results may be expressed in ppm at 25 C (298 K) and 760 mmHg:

$$C(ppm) = C(\mu g/liter) \times \frac{24.45}{96.6} \times \frac{760}{P} \times \frac{T + 273}{298}$$

where:

P = pressure of air sampled in mmHg
T = temperature of air sampled in C
24.45 = molar volume at 25 C and 760 mmHg in liters/mol
96.9 = molecular weight of vinylidene chloride in g/mol

XIII. APPENDIX IV

SAMPLING AND ANALYTICAL METHOD FOR VINYL BROMIDE IN AIR

The data presented in this proposed sampling and analytical method for vinyl bromide were adapted from NIOSH method No. P&CAM 127 for Organic Solvents in Air [336] and from information provided by Bales [249] and DW Yeager (written communication, February 1978). This proposed method, as outlined below, has not been tested by NIOSH but should allow routine analyses in the 1-ppm range.

Principle of the Method

(a) A known volume of air is drawn through a charcoal tube to trap the vinyl bromide present.

(b) The charcoal in the tube is transferred to a small, graduated test tube and desorbed with carbon disulfide.

(c) An aliquot of the desorbed sample is injected into a gas chromatograph.

(d) The area of the resulting peak is determined and compared with areas obtained from the injection of standards.

Range and Sensitivity

No data are currently available. However, Bales [249] reported measurement of vinyl bromide concentrations down to 0.01 ppm using this general method.

Interferences

(a) When the amount of water in the air is so great that condensation actually occurs in the tube, vinyl bromide will not be trapped. Preliminary experiments indicate that high humidity severely decreases the breakthrough volume.

(b) It must be emphasized that any compound which has the same retention time as vinyl bromide at the operating conditions described in this method is an interference. Hence, retention time data on a single column, or even on a number of columns, cannot be considered as proof of chemical identity. For this reason it is important that a sample of the solvent(s) be submitted at the same time so that identity(ies) can be established by other means.

(c) If the possibility of interference exists, separation conditions (column packing, temperatures, etc) must be changed to circumvent the problem.

Precision and Accuracy

No data are currently available.

Advantages and Disadvantages of the Method

(a) The sampling device is small, portable, and involves no liquids. Interferences are minimal, and most of those which do occur can be eliminated by altering chromatographic conditions. The charcoal tubes are analyzed by means of a quick, instrumental method.

(b) One disadvantage of the method is that the amount of sample which can be taken is limited by the number of mg that the tube will hold before overloading. When the sample value obtained for the backup section of the charcoal trap exceeds approximately 20% of that found on the front section, the possibility of sample loss exists. During sample storage the more volatile compounds will migrate throughout the tube until equilibrium is reached.

(c) Furthermore, the precision of the method is limited by the reproducibility of the pressure drop across the two sections of the sampling tube. This drop will affect the flowrate and cause the volume to be imprecise, because the pump is usually calibrated for one tube only. This disadvantage could be eliminated by calibrating the pump with a representative charcoal tube.

Apparatus

(a) An approved and calibrated personal sampling pump for personal samples. For an area sample any vacuum pump whose flow can be determined accurately at 1 liter/minute or less.

(b) Charcoal tubes: glass tube with both ends flame-sealed, 7 cm long with a 6-mm outer diameter and a 4-mm inner diameter, containing two sections of 20/40-mesh activated charcoal separated by a 2-mm portion of urethane foam. The activated charcoal is prepared from coconut shells and is fired at 600 C prior to packing. The absorbing section contains 100 mg of charcoal, the backup section 50 mg. A 3-mm portion of urethane foam is placed between the outlet end of the tube and the backup section. A plug of silylated glass wool is placed in front of the absorbing section. The pressure drop across the tube must be less than 1 inch of mercury at a flowrate of 1 liter/minute.

(c) Gas chromatograph equipped with a flame-ionization detector.

(d) Column, 20 feet, SE-30. Other columns capable of performing the required separations may be used.

(e) A mechanical or electronic integrator or a recorder and some method for determining peak area.

(f) Glass stoppered micro tubes. The 2.5-ml graduated microcentrifuge tubes are recommended.

(g) Hamilton syringes: 10 µl, and convenient sizes for making standards.

(h) Pipets: 0.5-ml delivery pipets or 1.0-ml type graduated in 0.1-ml increments.

(i) Volumetric flasks: 10 ml, or convenient sizes for making standard solutions.

Reagents

(a) Carbon disulfide, "spectroquality" or better.

(b) Sample of the specific compound under study, preferably "chromatoquality" grade.

(c) Helium, Bureau of Mines grade A.

(d) Prepurified hydrogen.

(e) Filtered, compressed air.

Procedure

(a) Calibration of Personal Pumps. Each personal pump must be calibrated with a representative charcoal tube in the line. This will minimize errors associated with uncertainties in the sample volume collected.

(b) Collection and Shipping of Samples

(1) Immediately before sampling, the ends of the charcoal tube should be broken to provide an opening at least one-half the internal diameter of the tube (2 mm).

(2) The smaller section of charcoal is used as a backup and should be positioned nearest the sampling pump.

(3) The charcoal tube should be vertical during sampling.

(4) Air being sampled should not be passed through any hose or tubing before entering the charcoal tube.

(5) The flowrate, time, and/or volume must be measured as accurately as possible. The sample should be taken at a flowrate of 1 liter/minute or less to attain the total sample volume required.

(6) The temperature and pressure of the atmosphere being sampled should be measured and recorded.

(7) The charcoal tubes should be capped with the supplied plastic caps immediately after sampling. Under no circumstances should rubber caps be used.

(8) One tube should be handled in the same manner as the sample tube (break, seal, and transport), except that no air is sampled through this tube. This tube should be labeled as a blank.

(9) Capped tubes should be packed tightly before they are shipped to minimize tube breakage during shipping.

(10) Samples received at the laboratory are logged in and immediately stored in a refrigerator.

(c) Cleaning of Equipment. All glassware used for the laboratory analysis should be detergent washed and thoroughly rinsed with tap water and distilled water.

(d) Analysis of Samples

(1) Preparation of Samples. In preparation for analysis, each charcoal tube is scored with a file in front of the first section of charcoal and broken open. The glass wool is removed and discarded. The charcoal in the first (larger) section is transferred to a small stoppered test tube. The separating section of foam is removed and discarded; the second section is transferred to another test tube. These two sections are analyzed separately.

(2) Desorption of Samples. Prior to analysis, 0.5 ml of carbon disulfide is pipetted into each test tube and the glass stopper is inserted. (All work with carbon disulfide should be performed in a hood because of its high toxicity.) Tests indicate that desorption is complete in 30 minutes if the sample is agitated occasionally during this period. The use of graduated glass-stoppered, microcentrifuge tubes is recommended so that one can observe any change in volume during the desorption process. Carbon disulfide is a very volatile solvent, so volume changes can occur during the desorption process depending on the surrounding temperature. The initial volume occupied

by the charcoal plus the 0.5 ml of carbon disulfide should be noted and corresponding volume adjustments should be made whenever necessary just before gas chromatographic analysis.

(3) Gas-Chromatographic Conditions. The typical operating conditions for the gas chromatograph are:

(A) 30 cc/minute helium carrier gas flow.

(B) 65 cc/minute (24 psig) hydrogen gas flow to detector.

(C) 500 cc/minute (50 psig) air flow to detector.

(D) 200 C injector temperature.

(E) 200 C manifold temperature (detector)

(F) Column temperature, 70 C, door on instrument closed.

(4) Injection. The first step in the analysis is the injection of the sample into the gas chromatograph. To eliminate difficulties arising from blowback or distillation within the syringe needle, one should employ the solvent flush injection technique. The 10-µl syringe is first flushed with solvent several times to wet the barrel and plunger. Three microliters of solvent are drawn into the syringe to increase the accuracy and reproducibility of the injected sample volume. The needle is removed from the solvent, and the plunger is pulled back about 0.2 µl to separate the solvent flush from the sample with a pocket of air to be used as a marker. The needle is then immersed in the sample, and a 5-µl aliquot is withdrawn, taking into consideration the volume of the needle, since the sample in the needle will be completely injected. After the needle is removed from the sample and prior to injection, the plunger is pulled back a short distance to minimize evaporation of the sample from the tip of the needle. Duplicate injections of each sample and standard should be made. No more than a 3% difference in area is to be expected.

(5) Measurement of Area. The area of the sample peak is measured by an electronic integrator or some other suitable form of area measurement, and preliminary results are read from a standard curve prepared as discussed below.

(e) Determination of Desorption Efficiency

(1) Importance of Dtermination. The desorption efficiency of a particular compound can vary from one laboratory to another and also from one batch of charcoal to another. Thus, it is necessary to determine at least once the percentage of the specific compound that is removed in the desorption process for a given compound, provided the same batch of charcoal is used.

(2) Procedure for Determining Desorption Efficiency. Activated charcoal equivalent to the amount in the first section of the sampling tube (100 mg) is measured into a 5-cm, 4-mm inner diameter glass tube, flame-sealed at one end (similar to commercially available culture tubes). This charcoal must be from the same batch as that used in obtaining the samples and can be obtained from unused charcoal tubes. The open end is capped with Parafilm. A known amount of the vinyl bromide is injected directly into the activated charcoal with a microliter syringe, and the tube is capped with more Parafilm.

At least five tubes are prepared in this manner and allowed to stand for at least overnight to assure complete absorption of the vinyl bromide onto the charcoal. These five tubes are referred to as the samples. A parallel blank tube should be treated in the same manner except that no sample is added to it. The sample and blank tubes are desorbed and analyzed in exactly the same manner as the sampling tube described in Analysis of Samples.

Two or three standards are prepared by injecting the same volume of vinyl bromide into 0.5 ml of carbon disulfide with the same syringe used in the preparation of the sample. These are anal Samplingyzed with the samples.

The desorption efficiency equals the difference between the average peak area of the samples and the peak area of the blank divided by the average peak area of the standards, or:

$$\text{Desorption Efficiency} = \frac{\text{Area sample} - \text{Area blank}}{\text{Area standard}}$$

Calibration and Standards

It is convenient to express concentration of standards in terms of mg/0.5 ml of carbon disulfide because samples are desorbed in this amount of carbon disulfide. To minimize error due to the volatility of carbon disulfide, one can inject 20 times the volume of vinyl bromide into 10 ml of carbon disulfide. For example, to prepare a 0.3 mg/0.5 ml of standard, one would inject 6.0 mg into exactly 10 ml of carbon disulfide in a glass-stoppered flask. The density of the specific compound is used to convert 6.0 mg into µl for easy measurement with a microliter syringe. A series of standards, varying in concentration over the range of interest, is prepared and analyzed under the same gas-chromatographic conditions and during the same time period as the unknown samples. Curves are established by plotting concentration in mg/0.5 ml vs peak area.

NOTE: Since no internal standard is used in the method, standard solutions must be analyzed at the same time that the sample analysis is done. This will minimize the effect of known day-to-day variations and variations during the same day of the flame-ionization detector response.

Calculations

(a) The weight, in mg, corresponding to each peak area is read from the standard curve. No volume corrections are needed, because the standard curve is based on mg/0.5 ml of carbon disulfide and the volume of sample injected is identical to the volume of the standards injected.

(b) Corrections for the blank must be made for each sample.

$$\text{Correct mg} = \text{mg(s)} - \text{mg(b)}$$

where:

mg(s) = mg found in front section of sample tube
mg(b) = mg found in front section of blank tube

A similar procedure is followed for the backup sections.

(c) The corrected amounts present in the front and backup sections of the same sample tube are added to determine the total measured amount in the sample.

(d) This total weight is divided by the determined desorption efficiency to obtain the total mg/sample.

(e) The volume of air sampled is converted to standard conditions of 25 C and 760 mmHg:

$$Vs = V \times \frac{P}{760} \times \frac{298}{T+273}$$

where:

Vs = volume of air in liters at 25 C and 760 mmHg
V = volume of air in liters as measured
P = barometric pressure in mmHg
T = temperature of air in degrees C

(f) The concentration of the vinyl bromide in the air sampled can be expressed in mg/cu m, which is numerically equal to µg/liter of air:

$$\text{mg/cu m} = \mu\text{g/liter} = \frac{\text{total mg} \times 1{,}000\ (\mu\text{g/liter})}{Vs}$$

(g) Another method of expressing concentration is ppm:

$$ppm = \mu l \text{ of vinyl bromide}/Vs$$

$$ppm = \frac{\mu g \text{ of vinyl bromide}}{Vs} \times \frac{24.45}{MW}$$

where:

24.45 = molar volume at 25 C and 760 mmHg
MW = molecular weight of vinyl bromide

XIV. APPENDIX V

SAMPLING AND ANALYTICAL METHOD FOR VINYL FLUORIDE IN AIR

The data presented in this proposed sampling and analytical method for vinyl fluoride were adapted from NIOSH method No. P&CAM 127 for Organic Solvents in Air [336] and information provided by Bales [250] and DW Yeager (written communications, August 1977 and February 1978). The proposed method, as outlined below, has not been tested by NIOSH, but should allow routine analyses in the 1-ppm range.

Principle of the Method

(a) A known volume of air is pumped into a Teflon bag.

(b) An aliquot of the air sample in the bag is injected into a gas chromatograph.

(c) The area of the resulting peak is determined and compared with areas obtained from the injection of standards.

Range and Sensitivity

The limit of detection has been reported as 1 ppm (1.88 mg/cu m) (DW Yeager, written communication, February 1978).

Interferences

(a) It must be emphasized that any compound which has the same retention time as vinyl fluoride at the operating conditions described in this method is an interference. Hence, retention time data on a single column, or even on a number of columns, cannot be considered as proof of chemical identity. For this reason it is important that a sample of the bulk solvent(s) be submitted at the same time so that identity(ies) can be established by other means.

(b) If the possibility of interference exists, separation conditions (column packing, temperatures, etc) must be changed to circumvent the problem.

(c) If samples are not analyzed within 3-4 days, significant sample leakage may occur (DW Yeager, written communication, August 1977).

Precision and Accuracy

No data on precision and accuracy are available at this time.

Advantages and Disadvantages of the Method

(a) The sampling device is portable and involves no liquids. Interferences are minimal, and most of those which do occur can be eliminated by altering chromatographic conditions. The samples are analyzed by means of a quick, instrumental method. No solvent desorption is necessary.

(b) One disadvantage of the method is that the amount of sample which can be taken is limited by the volume capacity of the bag. Full sample bags may interfere with the free movement of the worker.

(c) Furthermore, the precision of the method is limited by the reproducibility of the sampling rate of the pump.

Apparatus

(a) An approved and calibrated peristaltic sampling pump, diaphragm-pump, or vacuum pump, with filtered outlet to remove oil, for personal samples. For an area sample any vacuum pump whose flow can be determined accurately at 1 liter/minute or less.

(b) Teflon bag.

(c) Gas chromatograph equipped with a flame-ionization detector.

(d) Column, 20 feet, SE-30. Other columns capable of performing the required separations may be used.

(e) A mechanical or electronic integrator or a recorder and some method for determining peak area.

(f) Syringes: 5 ml.

Reagents

(a) Vinyl fluoride, 99%.

(b) Helium, Bureau of Mines grade A.

(c) Prepurified hydrogen.

(d) Filtered, compressed air.

Procedure

(a) Calibration of Personal Sampling Pumps. Each personal smapling pump must be calibrated with a representative bag in the line. This will minimize errors associated with uncertainties in the sample volume collected.

(b) Collection and Shipment of Samples

(1) The flowrate, time, and/or volume must be measured as accurately as possible. The sampling bags should be flushed before use. The sample should be taken at a flowrate of 1 liter/minute or less to attain the total sample volume required.

(2) The temperature and pressure of the atmosphere being sampled should be measured and recorded.

(3) Air samples are shipped to the laboratory for analysis in the Teflon bags. Appropriate precautions should be taken to prevent damage of the bags while in transit.

(c) Analysis of Samples

(1) Gas-Chromatographic Conditions. The typical operating conditions for the gas chromatograph are:

(A) 30 cc/minute helium carrier gas flow.

(B) 65 cc/minute (24 psig) hydrogen gas flow to detector.

(C) 500 cc/minute (50 psig) air flow to detector.

(D) 200 C injector temperature.

(E) 200 C manifold tempertaure (detector).

(F) Column temperature, 33 C, door of oven open and blower left on.

(2) Injection

Five milliliters of air from the Teflon bag is withdrawn with a syringe. Two milliliters are injected directly into the gas chromatograph.

(3) Measurement of Area. The area of the sample peak is measured by an electronic integrator or some other suitable form of area measurement, and preliminary results are read from a standard curve prepared as discussed below.

Calibration and Standards

Standards are prepared by filling several Teflon bags with known concentrations of vinyl fluoride which cover the range of interest. Five milliliters of air from each standard bag are withdrawn and 2 ml are injected directly into the instrument.

Calibration curves are prepared by plotting the concentration (mg of vinyl fluoride/2 ml) vs peak area.

Calculations

(a) The weight, in mg, corresponding to each peak area is read from the standard curve for the particular compound. No volume corrections are needed, because the standard curve is based on mg/2 ml and the volume of sample injected is identical to the volume of the standards injected.

(b) The volume of air sampled (collected in bag) is converted to standard conditions of 25 C and 760 mmHg:

$$Vs = V \times \frac{P}{760} \times \frac{298}{T+273}$$

where:

Vs = volume of air in liters at 25 C and 760 mmHg
V = volume of air in liters as measured
P = barometric pressure in mmHg
T = temperature of air in degrees centigrade

(c) The concentration of vinyl fluoride in the air sampled can be expressed in mg/cu m, which is numerically equal to μg/liter of air:

$$\text{mg/cu m} = \mu\text{g/liter} = \frac{\text{total mg} \times 1{,}000\ (\mu\text{g/mg})}{Vs}$$

XV. APPENDIX VI

SAMPLING AND ANALYTICAL METHOD FOR VINYLIDENE FLUORIDE IN AIR

The data presented in this proposed sampling and analytical method for vinylidene fluoride were adapted from NIOSH method No. P&CAM 127 for Organic Solvents in Air [336] and from information provided by the Pennwalt Corporation [251] and JL Sadenwasser (written communication, March 1978). This proposed method, as outlined below, has not been tested by NIOSH, but it should allow routine analyses in the 1-ppm range.

Principle of the Method

(a) A known volume of air is drawn through two charcoal tubes in series to trap the vinylidene fluoride present.

(b) The charcoal in the tubes is transferred to a small, graduated test tube and desorbed with carbon disulfide.

(c) An aliquot of the desorbed sample is injected into a gas chromatograph.

(d) The area of the resulting peak is determined and compared with areas obtained from the injection of standards

Range and Sensitivity

No data are currently available. However, Sadenwasser (written communication, March 1978) reported measuring vinylidene fluoride concentrations down to about 2 ppm using this general method.

Interferences

(a) When the amount of water in the air is so great that condensation actually occurs in the tube, vinylidene fluoride will not be trapped. Preliminary experiments indicate that high humidity severely decreases the breakthrough volume.

(b) It must be emphasized that any compound which has the same retention time as vinylidene fluoride at the operating conditions described in this method is an interference. Hence, retention time data on a single column, or even on a number of columns, cannot be considered as proof of chemical

identity. For this reason it is important that a sample of the solvent(s) be submitted at the same time so that identity(ies) can be established by other means.

(c) If the possibility of interference exists, separation conditions (column packing, temperatures, etc) must be changed to circumvent the problem.

(d) If samples are not analyzed within 5 days, significant sample loss may occur. Although no specific data were provided, JL Sadenwasser (written communication, March 1978) stated that vinylidene fluoride was retained by the charcoal for at least 5 days with little loss.

Precision and Accuracy

No data are currently available.

Advantages and Disadvantages of the Method

(a) The sampling device is small, portable, and involves no liquids. Interferences are minimal, and most of those that do occur can be eliminated by altering chromatographic conditions. The charcoal tubes are analyzed by means of a quick, instrumental method.

(b) One disadvantage of the method is that the amount of sample which can be taken is limited by the number of mg that the tubes will hold before overloading. When the sample value obtained for the backup section of the charcoal trap exceeds approximately 20% of that found on the front section, the possibility of sample loss exists. Sampling at 1 liter/minute caused a significant breakthrough after collection of 3 liters. During sample storage, volatile compounds such as vinylidene fluoride will migrate throughout the tube until equilibrium is reached.

(c) Furthermore, the precision of the method is limited by the reproducibility of the pressure drop across the two sections of the sampling tubes. This drop will affect the flowrate and cause the volume to be imprecise, because the pump is usually calibrated for one particular tube only. This disadvantage could be eliminated by calibrating the pump with representative charcoal tubes.

Apparatus

(a) An approved and calibrated personal-sampling pump for personal samples. For an area sample any vacuum pump whose flow can be determined accurately at 0.5 liter/minute or less.

(b) Charcoal tubes: glass tube with both ends flame-sealed, 7 cm long with a 6-mm outer diameter and a 4-mm inner diameter, containing two sections of 20/40-mesh activated charcoal separated by a 2-mm portion of urethane foam. The activated charcoal is prepared from coconut shells and is fired at 600 C prior to packing. The absorbing section contains 100 mg of charcoal, the backup section 50 mg. A 3-mm portion of urethane foam is placed between the outlet end of the tube and the backup section. A plug of silylated glass wool is placed in front of the absorbing section. The pressure drop across the tube must be less than 1 inch of mercury at a flowrate of 1 liter/minute.

(c) Gas chromatograph equipped with a flame-ionization detector.

(d) Column, stainless steel, 6-feet x 1/8-inch outer diameter, packed with Chromosorb 102, 80/100 mesh. Other columns capable of performing the required separations may be used.

(e) A mechanical or electronic integrator or a recorder and some method for determining peak area.

(f) Glass stoppered micro tubes. The 2.5-ml graduated microcentrifuge tubes are recommended.

(g) Hamilton syringes: 10 µl, and convenient sizes for making standards.

(h) Pipets: 0.5-ml delivery pipets or 1.0-ml type graduated in 0.1 ml increments.

(i) Volumetric flasks: 10 ml or convenient sizes for making standard solutions.

Reagents

(a) Carbon disulfide, "spectroquality" or better.

(b) Sample of the specific compound under study, preferably "chromatoquality" grade.

(c) Helium, Bureau of Mines grade A.

(d) Prepurified hydrogen.

(e) Filtered, compressed air.

Procedure

(a) Calibration of Personal Sampling Pumps. Each personal sampling pump

must be calibrated with representative charcoal tubes in the line. This will minimize errors associated with uncertainties in the sample volume collected.

(b) Collection and Shipping of Samples

(1) Immediately before sampling, the ends of the tube should be broken to provide an opening at least one-half the internal diameter of the tube (2 mm).

(2) Position the second charcoal tube next to the sampling pump in tandem with the first tube, to serve as a backup. If one tube is used the smaller section of charcoal is used as a backup and should be positioned nearest the sampling pump.

(3) The charcoal tube should be vertical during sampling.

(4) Air being sampled should not be passed through any hose or tubing before entering the charcoal tube.

(5) The flowrate, time, and/or volume must be measured as accurately as possible. The sample should be taken at a flowrate of 0.5 liter/minute or less to attain the total sample volume required. The sensitivity of the method is increased by using lower flowrates to increase the amount of sample collected (JL Sademwasser, written communication, March 1978).

(6) The temperature and pressure of the atmosphere being sampled should be measured and recorded.

(7) The charcoal tubes should be capped with the supplied plastic caps immediately after sampling. Under no circumstances should rubber caps be used.

(8) One tube should be handled in the same manner as a sample tube (break, seal, and transport), except that no air is sampled through this tube. This tube should be labeled as a blank.

(9) Capped tubes should be packed tightly before they are shipped to minimize tube breakage during shipping.

(10) Samples received at the laboratory are logged in and immediately stored in a refrigerator.

(c) Cleaning of Equipment. All glassware used for the laboratory analysis should be detergent washed and thoroughly rinsed with tap water and distilled water.

(d) Analysis of Samples

(1) Preparation of Samples. The two tubes used in the collection of

a single sample are analyzed separately. If only one tube is used for sampling, then each section of activated carbon should be analyzed separately. In preparation for analysis, each charcoal tube is scored with a file in front of the first section of charcoal and broken open. The glass wool is removed and discarded. The charcoal in the first (larger) section is transferred to a small stoppered test tube. The separating section of foam is removed and discarded; the second section is transferred to another test tube. These two sections are analyzed separately.

(2) Desorption of Samples. Prior to analysis, 2 ml of carbon disulfide is pipetted into each test tube and the glass stopper is inserted. (All work with carbon disulfide should be performed in a hood because of its high toxicity.) Tests indicate that desorption is complete in 15 minutes if the sample is agitated occasionally during this period. The use of graduated glass-stoppered, microcentrifuge tubes is recommended so that one can observe any change in volume during the desorption process. Carbon disulfide is a very volatile solvent, so volume changes can occur during the desorption process depending on the surrounding temperature. The initial volume occupied by the charcoal plus the 2 ml of carbon disulfide should be noted and corresponding volume adjustments should be made whenever necessary just before gas-chromatographic analysis.

(3) Gas-Chromatographic Conditions. The typical operating conditions for the gas chromatograph are:

(A) 30 cc/minute helium carrier gas flow.

(B) 50 cc/minute (24 psig) hydrogen gas flow to detector.

(C) 500 cc/minute (50 psig) air flow to detector.

(D) 150 C injector temperature.

(E) 200 C manifold temperature (detector)

(F) Column temperature, 100 C, door on instrument closed.

(4) Injection. The first step in the analysis is the injection of the sample into the gas chromatograph. To eliminate difficulties arising from blowback or distillation within the syringe needle, one should employ the solvent flush injection technique. The 10-μl syringe is first flushed with solvent several times to wet the barrel and plunger. Three microliters of solvent is drawn into the syringe to increase the accuracy and reproducibility of the injected sample volume. The needle is removed from the solvent, and the plunger is pulled back about 0.2 μl to separate the solvent flush from the sample with a pocket of air to be used as a marker. The needle is then immersed in the sample, and a 1-μl aliquot is withdrawn, taking into consideration the volume of the needle, since the sample in the needle will be completely injected. After the needle is removed from the sample and prior to

injection, the plunger is pulled back a short distance to minimize evaporation of the sample from the tip of the needle. Duplicate injections of each sample and standard should be made. No more than a 3% difference in area is to be expected. A larger sample injection may be used to increase the sensitivity of the method (JL Sadenwasser, written communication, March 1978).

(5) Measurement of Area. The area of the sample peak is measured by an electronic integrator or some other suitable form of area measurement, and preliminary results are read from a standard curve prepared as discussed below.

(e) Determination of Desorption Efficiency

(1) Importance of Determination. The desorption efficiency of a particular compound can vary from one laboratory to another and also from one batch of charcoal to another. Thus, it is necessary to determine at least once the percentage of the specific compound that is removed in the desorption process for a given compound, provided the same batch of charcoal is used.

(2) Procedure for Determining Desorption Efficiency. Activated charcoal equivalent to the amount in the first section of the sampling tube (100 mg) is measured into a 5-cm, 4-mm inner diameter glass tube, flame-sealed at one end (similar to commercially available culture tubes). This charcoal must be from the same batch as that used in obtaining the samples and can be obtained from unused charcoal tubes. The open end is capped with Parafilm. A known amount of the vinylidene fluoride is injected directly into the activated charcoal with a microliter syringe, and the tube is capped with more Parafilm.

At least five tubes are prepared in this manner and allowed to stand for at least overnight to assure complete absorption of the vinylidene fluoride onto the charcoal. These five tubes are referred to as the samples. A parallel blank tube should be treated in the same manner except that no sample is added to it. The sample and blank tubes are desorbed and analyzed in exactly the same manner as the sampling tube described in Analysis of Samples.

Two or three standards are prepared by injecting the same volume of vinylidene fluoride into 2 ml of carbon disulfide with the same syringe used in the preparation of the sample. These are analyzed with the samples.

The desorption efficiency equals the difference between the average peak area of the samples and the peak area of the blank divided by the average peak area of the standards, or:

$$\text{Desorption Efficiency} = \frac{\text{Area sample} - \text{Area blank}}{\text{Area standard}}$$

Calibration and Standards

It is convenient to express concentration of standards in terms of mg/2 ml of carbon disulfide because samples are desorbed in this amount of carbon disulfide. To minimize error due to the volatility of carbon disulfide, one can inject five times the volume of vinylidene fluoride into 10 ml of carbon disulfide. For example, to prepare 0.3 mg/2 ml of standard, one would inject 1.5 mg into exactly 10 ml of carbon disulfide in a glass-stoppered flask. The density of the specific compound is used to convert 1.5 mg into µl for easy measurement with a microliter syringe. A series of standards, varying in concentration over the range of interest, is prepared and analyzed under the same gas-chromatographic conditions and during the same time period as the unknown samples. Curves are established by plotting concentration in mg/2 ml vs peak area.

NOTE: Since no internal standard is used in the method, standard solutions must be analyzed at the same time that the sample analysis is done. This will minimize the effect of known day-to-day variations and variations during the same day of the flame-ionization detector response.

Calculations

(a) The weight, in mg, corresponding to each peak area is read from the standard curve. No volume corrections are needed, because the standard curve is based on mg/2 ml of carbon disulfide and the volume of sample injected is identical to the volume of the standards injected.

(b) Corrections for the blank must be made for each sample:

$$\text{Correct mg} = \text{mg(s)} - \text{mg(b)}$$

where:

mg(s) = mg found in front section of sample tube
mg(b) = mg found in front section of blank tube

A similar procedure is followed for the backup sections.

(c) The corrected amounts present in the front and backup sections of the same sample tube are added to determine the total measured amount in the sample.

(d) This total weight is divided by the determined desorption efficiency to obtain the total mg/sample.

(e) The volume of air sampled is converted to standard conditions of 25 C and 760 mmHg:

$$Vs = V \times \frac{P}{760} \times \frac{298}{T+273}$$

where:

Vs = volume of air in liters at 25 C and 760 mmHg
V = volume of air in liters as measured
P = barometric pressure in mmHg
T = temperature of air in degrees C

(f) The concentration of the vinylidene fluoride in the air sampled can be expressed in mg/cu m, which is numerically equal to µg/liter of air:

$$\text{mg/cu m} = \mu\text{g/liter} = \frac{\text{total mg} \times 1{,}000\ (\mu\text{g/mg})}{Vs}$$

(g) Another method of expressing concentration is ppm:

$$\text{ppm} = \mu\text{l of vinylidene fluoride/Vs}$$

$$\text{ppm} = \frac{\mu\text{g of vinylidene fluoride}}{Vs} \times \frac{24.45}{MW}$$

where:

24.45 = molar volume at 25 C and 760 mmHg
MW = molecular weight of vinylidene fluoride

XVI. APPENDIX VII

MATERIAL SAFETY DATA SHEET

The following items of information which are applicable to a specific product or material shall be provided in the appropriate block of the Material Safety Data Sheet (MSDS).

The product designation is inserted in the block in the upper left corner of the first page to facilitate filing and retrieval. Print in upper case letters as large as possible. It should be printed to read upright with the sheet turned sideways. The product designation is that name or code designation which appears on the label, or by which the product is sold or known by employees. The relative numerical hazard ratings and key statements are those determined by the rules in Chapter V, Part B, of the NIOSH publication, An Identification System for Occupationally Hazardous Materials. The company identification may be printed in the upper right corner if desired.

(a) Section I. Product Identification

The manufacturer's name, address, and regular and emergency telephone numbers (including area code) are inserted in the appropriate blocks of Section I. The company listed should be a source of detailed backup information on the hazards of the material(s) covered by the MSDS. The listing of suppliers or wholesale distributors is discouraged. The trade name should be the product designation or common name associated with the material. The synonyms are those commonly used for the product, especially formal chemical nomenclature. Every known chemical designation or competitor's trade name need not be listed.

(b) Section II. Hazardous Ingredients

The "materials" listed in Section II shall be those substances which are part of the hazardous product covered by the MSDS and individually meet any of the criteria defining a hazardous material. Thus, one component of a multicomponent product might be listed because of its toxicity, another component because of its flammability, while a third component could be included both for its toxicity and its reactivity. Note that a MSDS for a single component product must have the name of the material repeated in this section to avoid giving the impression that there are no hazardous ingredients.

Chemical substances should be listed according to their complete name derived from a recognized system of nomenclature. Where possible, avoid using

common names and general class names such as "aromatic amine," "safety solvent," or "aliphatic hydrocarbon" when the specific name is known.

The "%" may be the approximate percentage by weight or volume (indicate basis) which each hazardous ingredient of the mixture bears to the whole mixture. This may be indicated as a range or maximum amount, ie, "10-40% vol" or "10% max wt" to avoid disclosure of trade secrets.

Toxic hazard data shall be stated in terms of concentration, mode of exposure or test, and animal used, eg, "100 ppm LC50-rat," "25 mg/kg LD50-skin-rabbit," "75 ppm LC man," or "permissible exposure from 29 CFR 1910.1000," or, if not available, from other sources of publications such as the American Conference of Governmental Industrial Hygienists or the American National Standards Institute Inc. Flashpoint, shock sensitivity, or similar descriptive data may be used to indicate flammability, reactivity, or similar hazardous properties of the material.

(c) Section III. Physical Data

The data in Section III should be for the total mixture and should include the boiling point and melting point in degrees Fahrenheit (Celsius in parentheses); vapor pressure, in conventional millimeters of mercury (mmHg); vapor density of gas or vapor (air = 1); solubility in water, in parts/hundred parts of water by weight; specific gravity (water = 1); percent volatiles (indicated if by weight or volume) at 70 F (21.1 C); evaporation rate for liquids or sublimable solids, relative to butyl acetate; and appearance and odor. These data are useful for the control of toxic substances. Boiling point, vapor density, percent volatiles, vapor pressure, and evaporation are useful for designing proper ventilation equipment. This information is also useful for design and deployment of adequate fire and spill containment equipment. The appearance and odor may facilitate identification of substances stored in improperly marked containers, or when spilled.

(d) Section IV. Fire and Explosion Data

Section IV should contain complete fire and explosion data for the product, including flashpoint and autoignition temperature in degrees Fahrenheit (Celsius in parentheses); flammable limits, in percent by volume in air; suitable extinguishing media or materials; special firefighting procedures; and unusual fire and explosion hazard information. If the product presents no fire hazard, insert "NO FIRE HAZARD" on the line labeled "Extinguishing Media."

(e) Section V. Health Hazard Information

The "Health Hazard Data" should be a combined estimate of the hazard of the total product. This can be expressed as a TWA concentration, as a

permissible exposure, or by some other indication of an acceptable standard. Other data are acceptable, such as lowest LD50 if multiple components are involved.

Under "Routes of Exposure," comments in each category should reflect the potential hazard from absorption by the route in question. Comments should indicate the severity of the effect and the basis for the statement if possible. The basis might be animal studies, analogy with similar products, or human experiences. Comments such as "yes" or "possible" are not helpful. Typical comments might be:

Skin Contact--single short contact, no adverse effects likely; prolonged or repeated contact, possibly mild irritation.

Eye Contact--some pain and mild transient irritation; no corneal scarring.

"Emergency and First Aid Procedures" should be written in lay language and should primarily represent first-aid treatment that could be provided by paramedical personnel or individuals trained in first aid.

Information in the "Notes to Physician" section should include any special medical information which would be of assistance to an attending physician including required or recommended preplacement and periodic medical examinations, diagnostic procedures, and medical management of overexposed employees.

(f) Section VI. Reactivity Data

The comments in Section VI relate to safe storage and handling of hazardous, unstable substances. It is particularly important to highlight instability or incompatibility to common substances or circumstances, such as water, direct sunlight, steel or copper piping, acids, alkalies, etc. "Hazardous Decomposition Products" shall include those products released under fire conditions. It must also include dangerous products produced by aging, such as peroxides in the case of some ethers. Where applicable, shelf life should also be indicated.

(g) Section VII. Spill or Leak Procedures

Detailed procedures for cleanup and disposal should be listed with emphasis on precautions to be taken to protect employees assigned to cleanup detail. Specific neutralizing chemicals or procedures should be described in detail. Disposal methods should be explicit including proper labeling of containers holding residues and ultimate disposal methods such as "sanitary landfill" or "incineration." Warnings such as "comply with local, state, and Federal antipollution ordinances" are proper but not sufficient. Specific procedures shall be identified.

(h) Section VIII. Special Protection Information

Section VIII requires specific information. Statements such as "Yes," "No," or "If necessary" are not informative. Ventilation requirements should be specific as to type and preferred methods. Respirators shall be specified as to type and NIOSH or MSHA approval class, ie, "Supplied air," "Organic vapor canister," etc. Protective equipment must be specified as to type and materials of construction.

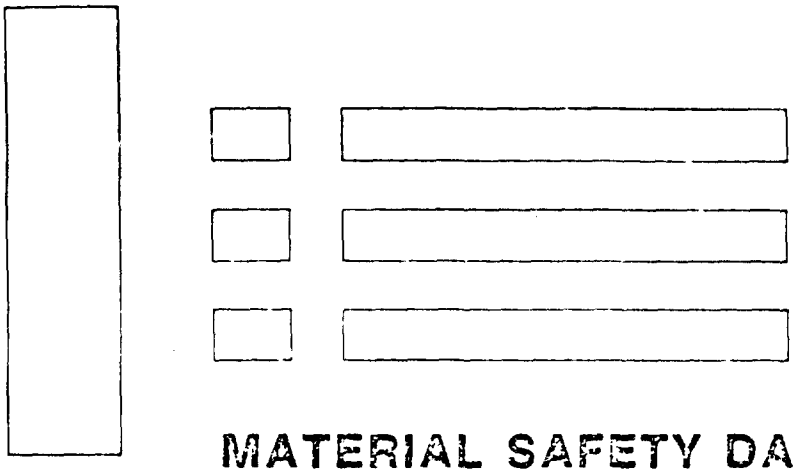
(i) Section IX. Special Precautions

"Precautionary Statements" shall consist of the label statements selected for use on the container or placard. Additional information on any aspect of safety or health not covered in other sections should be inserted in Section IX. The lower block can contain references to published guides or in-house procedures for handling and storage. Department of Transportation markings and classifications and other freight, handling, or storage requirements and environmental controls can be noted.

(j) Signature and Filing

Finally, the name and address of the responsible person who completed the MSDS and the date of completion are entered. This will facilitate correction of errors and identify a source of additional information.

The MSDS shall be filed in a location readily accessible to employees exposed to the hazardous substance. The MSDS can be used as a training aid and basis for discussion during safety meetings and training of new employees. It should assist management by directing attention to the need for specific control engineering, work practices, and protective measures to ensure safe handling and use of the material. It will aid the safety and health staff in planning a safe and healthful work environment and in suggesting appropriate emergency procedures and sources of help in the event of harmful exposure of employees.



MATERIAL SAFETY DATA SHEET

I PRODUCT IDENTIFICATION	
MANUFACTURER'S NAME	REGULAR TELEPHONE NO EMERGENCY TELEPHONE NO
ADDRESS	
TRADE NAME	
SYNONYMS	

II HAZARDOUS INGREDIENTS		
MATERIAL OR COMPONENT	%	HAZARD DATA

III PHYSICAL DATA			
BOILING POINT 760 MM HG		MELTING POINT	
SPECIFIC GRAVITY (H_2O=1)		VAPOR PRESSURE	
VAPOR DENSITY (AIR=1)		SOLUBILITY IN H_2O, % BY WT	
% VOLATILES BY VOL		EVAPORATION RATE (BUTYL ACETATE=1)	
APPEARANCE AND ODOR			

IV FIRE AND EXPLOSION DATA

FLASH POINT (TEST METHOD)		AUTOIGNITION TEMPERATURE	
FLAMMABLE LIMITS IN AIR, % BY VOL	LOWER		UPPER
EXTINGUISHING MEDIA			
SPECIAL FIRE FIGHTING PROCEDURES			
UNUSUAL FIRE AND EXPLOSION HAZARD			

V HEALTH HAZARD INFORMATION

HEALTH HAZARD DATA

ROUTES OF EXPOSURE

INHALATION

SKIN CONTACT

SKIN ABSORPTION

EYE CONTACT

INGESTION

EFFECTS OF OVEREXPOSURE

ACUTE OVEREXPOSURE

CHRONIC OVEREXPOSURE

EMERGENCY AND FIRST AID PROCEDURES

EYES

SKIN

INHALATION

INGESTION

NOTES TO PHYSICIAN

VI REACTIVITY DATA

CONDITIONS CONTRIBUTING TO INSTABILITY

INCOMPATIBILITY

HAZARDOUS DECOMPOSITION PRODUCTS

CONDITIONS CONTRIBUTING TO HAZARDOUS POLYMERIZATION

VII SPILL OR LEAK PROCEDURES

STEPS TO BE TAKEN IF MATERIAL IS RELEASED OR SPILLED

NEUTRALIZING CHEMICALS

WASTE DISPOSAL METHOD

VIII SPECIAL PROTECTION INFORMATION

VENTILATION REQUIREMENTS

SPECIFIC PERSONAL PROTECTIVE EQUIPMENT

RESPIRATORY (SPECIFY IN DETAIL)

EYE

GLOVES

OTHER CLOTHING AND EQUIPMENT

IX SPECIAL PRECAUTIONS

PRECAUTIONARY STATEMENTS

OTHER HANDLING AND STORAGE REQUIREMENTS

PREPARED BY

ADDRESS

DATE

TABLE XVII-1

PHYSICAL AND CHEMICAL PROPERTIES OF VINYL HALIDE COMPOUNDS

Property	Vinyl Chloride	Ref	Vinylidene Chloride	Ref	Vinyl Bromide	Ref	Vinyl Fluoride	Ref	Vinylidene Fluoride	Ref
Molecular formula	CH_2:CHCl	287	CH_2:CCl2	301	CH_2:CHBr	337	CH_2:CHF	130	CH_2:CF_2	130
Formula weight	62.50	338	96.95	301	106.96	304	46.046	130	64.038	130
Appearance	Colorless gas	287	Clear, colorless liquid	114	Colorless gas	337	Colorless gas	114	Colorless gas	114
Odor/Threshold (ppm)	Sweet	339	Sweet/500-1,000	114	Pungent	304	Faint, ethereal	340	Faint, ethereal	8
Boiling point	-13.9 C	287	31.56 C	301	15.85 C	300	-72.0 C	130	-85.7 C	130
Melting point	-153.7 C	287	-122.5 C	301	-137.8 C	127	-160 C	130	-144 C	129
Specific gravity	0.99 at -25 C	338	1.218 at 20 C	114	1.529 at 11 C	341	0.853 at -26 C	341	-	
Density liquid (g/ml)	0.9121 at 20 C	287	1.2132 at 20 C	301	1.522 at 20 C	304	0.636 at 21 C	130	0.659 at 21 C	251
Vapor pressure (mmHg)	2,580 at 20 C	114	495 at 20 C	339	1,000 at 20 C	342	19,129 at 21 C**	130 343	27,763 at 21 C**	130 343
Vapor density (air = 1)	2.15	339	3.34	301	3.7	304	1.56	114	2.2	114
Density of saturated air	-		2.8	301					-	
Refractive index	1.4066 at 10 C	287	1.42468 at 20 C	301	1.4410 at 20 C	343	1.35 at 20 C	340	-	
Molar refractivity*	15.66	229 344	20.44	229 344	18.58	229 344	10.65	229 344	10.43	229 344
Viscosity	0.2734 centipoise at -20 C	10	0.3302 centipoise at 20 C	301	0.376 centipoise at 0 C	360	0.15 centipoise at 15.6 C (liquid)	130	-	
Specific heat (cal/g)	Liquid, 0.38 at 20 C; gas at 1 atm and 25 C, 0.205	10	0.275	345	Gas at 1 atm and 25 C, 0.1241	337	-		Gas at 25 C, 14.37 cal/mole	251
Heat of vaporization (at boiling point)	79.84 cal/g	10	6,257 cal/mole	301	54.9 cal/g	304	3.97 Kcal/mole	340	980 cal/mole	251
Heat of combustion	286.2 Kcal/mole	339	261.93 Kcal/mole	301					-	
Heat of polymerization	22.9 Kcal/mole	339	18 Kcal/mole	301	18 Kcal/mole	300	-		-	
Heat of fusion	18.14 cal/g at melting point	10	1,557 cal/mole	301	12.3 cal/g	304			-	
Flashpoint (open cup)	-78 C	287	15 C	114	None	304	-		-	
Flammable limits (in air)	3.6 -33.0%	339	7 - 16% at 28 C	301	9 - 15%	300	2.6 - 21.7%	130	5.5 - 21.3%	130
Dielectric constant	6.26 at 17.2 C	10	4.67 at 16 C	301	Liquid at 5 C, 5.83, gas at 100 C, 1.01	342	20.2 at -81 C, 100,000cHz	130	-	
Dipole moment (μ)	1.45	343	1.34	343	1.42	343	1.43	343	1.38	343
Solubility										
Water (g/100 ml)	0.11 at 24 C	10	0.25 at 25 C	345	0.565 at 25 C	300	Insoluble	340	0.018 at 25 C	130
Organic solvents	-		Soluble	114	Soluble in most	300	-		-	
Alcohol	Soluble	287	Soluble	301	Soluble	300	Soluble	340	Soluble	343
Ether	Very soluble	287			"	300	"	340	Very soluble	343
CCl4	"	287	Very soluble	301	"	300	-		-	
Benzene	"	287	Soluble	301	"	343	-		-	
Acetone	-		"	301	"	343	Soluble	343	-	

TABLE XVII-1 (CONTINUED)

PHYSICAL AND CHEMICAL PROPERTIES OF VINYL HALIDE COMPOUNDS

Property	Vinyl Chloride	Ref	Vinylidene Chloride	Ref	Vinyl Bromide	Ref	Vinyl Fluoride	Ref	Vinylidene Fluoride	Ref
Σ electronegativity of substituents	9.3	346	10.2	346	9.1	346	10.3	346	12.2	346
Log P (calculated octanol/water partition coefficient) †	0.60	229, 347	0.73	229, 347	0.74	229, 347	0.16	229, 347	-0.15	229, 347
Σσ * (substituent on vinyl) ††	1.05	229, 232, 346	2.10	229, 232, 346	1.02	229, 232, 346	1.10	229, 232, 346	2.20	229, 232, 346
Σσ I (substituent on vinyl) ††	0.47	229, 232, 346	0.94	229, 232, 346	0.45	229, 232, 346	0.52	229, 232, 346	1.04	229, 232, 346
ΣσR (substituent on vinyl) £	-0.24	229, 346	-0.48	229, 346	-0.22	229, 346	0.44	229, 346	-0.88	229, 346
IR C = C stretch cm^{-1}	1,620	348	1,560	348	1,610	348				
Symmetry of epoxide (1=y,0=N) ‡‡	0	1,229	0	1,229	0	1,229	0	1,229	0	1,229
Chi # *	0.99	229, 349, 350, 351	1.35	229, 349, 350, 351	0.99	229, 349, 350, 351	.99	229, 349, 350, 351	1.35	229, 349, 350, 351
Conversion Factors (760 mm Hg and 25 C)										
1.00 mg/cu m *	0.391	114	0.252 ppm	114	0.2285 ppm	127	0.532 ppm	114	0.382 ppm	114
1 ppm *	2.56 mg/cu m		3.97 mg/cu m		4.38 mg/cu m		1.88 mg/cu m		2.62 mg/cu m	

** Calculated using lbs/sq in multiplied by 51.7 to obtain values in mm Hg [130,343]

* Calculated [229] using additivity rules for structural fragments as described by Hansch [349]

† Calculated [229] using fragment constants and rules for additivity developed by Leo et al. [351] These values may express the duration and relative order of the lipid water solubility ratios better than the absolute magnitude of the ratios

†† Chemical substituent constant measuring electronic inductive effects. Values were calculated [229] directly from data in references [348] and [232] and represent the sum of the effects of all halo substituents on the ethylene bond. Relevance of these values in evaluating reactivity of vinyl compounds has not been established empirically

£ Chemical substituent constant measuring resonance effects. Values represent the sum of the effects of the halo substituents on the ethylene bond and were calculated [229] directly from data in reference [348] Relevance evaluating reactivity of vinyl compounds has not been empirically established

‡‡ 1 indicates symmetry, 0 indicates asymmetry [229]. Bunse and Henschler [1] hypothesized that asymmetrical intermediates would be less stable and more reactive than symmetrical ones

Calculated value [229] describing bonding state of the molecule. Chi increases with increased branching of the carbon chain. Chi values presented here consider all atoms to be carbon, thus, they differentiate between multiple and single substituents rather than between effects of different types of substituents

TABLE XVII-2

SYNONYMS FOR VINYL HALIDES

Vinyl Chloride	Vinyl Bromide
Chloroethene	Bromoethene
Chloroethylene	Bromoethylene
Chlorethene	VBr
Chlorethylene	
Ethylene monochloride	
Monochloroethene	Vinyl Fluoride
Monochloroethylene	
Vinyl chloride monomer	Fluoroethylene
Vinyl C monomer	Fluoroethene
VC	VF
VCM	
Triclene	

Vinylidene Chloride	Vinylidene Fluoride
as-Dichloroethylene	1,1-Difluoroethylene
asym-Dichloroethylene	1,1-Difluoroethene
uns-Dichloroethylene	alpha,alpha-Difluoroethylene
1,1-Dichloroethene	VDF
1,1-Dichloroethylene	Isotron 1132A
Vinylidene dichloride	Genetron 1132A
alpha,alpha-Dichloroethylene	
Vinylidene chloride monomer	
VDC	
Sconatex	

Adapted from references 8,251,287,298,301,341,343,352-354

TABLE XVII-3

OCCUPATIONS WITH POTENTIAL EXPOSURE TO VINYL HALIDES

Chemical-synthesis workers
Equipment cleaners
Equipment repairers
Maintenance workers
Monomer-containing aerosol producers
Monomer-containing aerosol users
Monomer loaders and unloaders
Monomer production workers
Monomer samplers and gagers
Monomer transport workers
Polymer compounders
Polymer fabricators
Polymer loaders and unloaders
Polymer packagers
Polymer processors
Polymer production workers
Polymer transport workers
Polymer control-laboratory workers
Warehouse workers

Adapted from references 130,279,284,287,294,300,301,355,356

TABLE XVII-4

REPORTED CASES OF ANGIOSARCOMA OF THE LIVER IN VINYL CHLORIDE POLYMERIZATION WORKERS*

Country	Case No.	Birth Date	First VC or PVC Exposure	Diagnosis of Angio-sarcoma	Age at Diag-nosis	Years from First Ex-posure to Diagnosis	Total Years Expo-sure	Date of Death
Belgium	01	00-00-00	00-00-00	00-00-00	00	00	00	06-29-76
Canada	01**	12-15-13	00-00-44	00-00-55	41	10	11	09-02-55
"	02**	03-06-14	00-00-43	00-00-57	43	14	14	12-21-57
"	03**	08-26-19	00-00-41	00-00-62	42	21	20	03-22-62
"	04**	04-05-19	00-00-45	00-00-67	48	22	22	01-21-68
"	05**	05-07-11	00-00-44	00-00-68	57	24	05	07-05-68
"	06**	12-15-19	00-00-47	00-00-71	51	24	23	04-10-71
"	07**	11-09-19	00-00-46	00-00-72	53	26	25	12-24-72
"	08	05-13-20	00-00-61	00-00-73	53	12	05	06-12-73
"	09	07-19-21	00-00-46	00-00-74	53	28	26	09-04-74
"	10	05-16-15	00-00-53	00-00-76	61	23	14	04-00-77
Czechoslovakia	01**	00-00-28	00-00-57	00-00-73	46	16	16	00-00-74
"	02**	00-00-26	00-00-51	00-00-66	40	15	15	00-00-66
Federal Republic of Germany	01**	06-04-30	10-01-56	09-19-68	38	12	12	01-25-69
"	02**	07-26-31	10-14-57	09-25-70	39	13	12	12-14-71
"	04	09-04-30	04-16-57	00-00-74	44	17	17	11-25-74
"	05**	01-01-32	12-16-62	00-00-75	43	13	12	01-09-75
"	07**	09-29-26	04-15-54	00-00-75	49	21	12	11-13-75
"	08**	10-19-17	04-19-54	00-00-75	58	22	21	12-25-75
"	09**	12-13-34	12-02-59	06-16-76	42	17	15	Alive

TABLE XVII-4 (CONTINUED)

REPORTED CASES OF ANGIOSARCOMA OF THE LIVER IN VINYL CHLORIDE POLYMERIZATION WORKERS*

Country	Case No.	Birth Date	First VC or PVC Exposure	Diagnosis of Angiosarcoma	Age at Diagnosis	Years from First Exposure to Diagnosis	Total Years Exposure	Date of Death
Federal Republic of Germany	11	Awaiting Details						
France	01**	04-15-24	01-00-46	02-18-67	43	21	19	02-19-67
"	02	06-03-11	07-06-59	01-08-75	63	15	12	01-24-75
"	03**	00-00-19	00-00-46	01-00-75	55	29	29	06-29-75
"	04**	01-27-27	10-19-49	01-04-76	49	26	26	01-04-76
"	05**	01-29-38	00-00-65	04-00-76	38	11	10	05-13-76
"	06**	04-14-34	00-00-58	09-00-76	42	18	17	09-12-76
"	07	00-00-27	07-01-50	07-00-76	49	26	23	07-02-76
"	08	00-00-00	00-00-00	00-00-00	00	00	00	01-30-77
Great Britain	01**	00-00-01	00-00-46	12-00-72	71	26	20	12-00-72
"	03	06-02-37	02-00-66	00-00-74	37	09	04	12-24-74
Italy	02**	11-13-29	00-00-57	12-13-72	43	15	06	12-00-72
"	03**	03-14-20	00-00-53	07-10-75	55	22	21	07-10-75
Japan	01	08-01-22	04-00-53	08-21-74	52	22	22	10-24-75
Norway	01**	12-23-15	03-00-50	12-20-71	56	22	21	01-04-72
Sweden	01**	06-23-27	08-14-51	02-00-70	43	19	18	10-20-70
"	03	Awaiting Details						
"	04	"	"					
United States	01**	10-17-23	12-09-48	03-03-73	49	22	16	03-03-73
"	02**	08-19-33	11-15-55	05-00-70	37	14	13	09-28-71

TABLE XVII-4 (CONTINUED)

REPORTED CASES OF ANGIOSARCOMA OF THE LIVER IN VINYL CHLORIDE POLYMERIZATION WORKERS*

Country	Case No.	Birth Date	First VC or PVC Exposure	Diagnosis of Angio-sarcoma	Age at Diag-nosis	Years from First Ex-posure to Diagnosis	Total Years Expo-sure	Date of Death
United States	03**	05-25-15	11-28-45	12-19-73	58	28	28	12-19-73
"	04**	01-15-24	07-06-52	08-13-67	43	15	15	01-07-68
"	05**	01-25-12	06-13-44	04-09-64	52	20	18	04-09-64
"	06**	00-00-29	01-17-62	02-00-74	45	12	12	07-24-75
"	07**	05-03-22	08-27-44	00-00-68	45	24	18	03-23-68
"	08**	05-06-20	10-07-46	08-00-61	41	15	15	08-29-61
"	09**	11-08-31	09-09-54	03-01-74	43	17	17	03-00-75
"	10**	08-16-13	06-12-51	05-00-68	55	17	17	05-10-68
"	11**	05-27-09	10-14-46	03-00-70	61	23	23	03-16-70
"	12**	11-17-18	09-13-49	05-02-69	50	20	15	05-02-69
"	13**	12-01-21	08-19-44	05-00-74	52	30	30	07-04-74
"	16**	11-04-27	05-08-50	00-00-69	41	17	4	03-27-69
"	17**	05-06-31	06-23-55	10-11-74	43	19	19	Alive
"	18**	04-22-28	09-15-54	00-00-75	46	21	13	11-02-75
"	19**	00-00-15	00-00-43	06-19-75	60	32	32	Alive
"	20**	08-31-17	00-00-55	01-30-76	58	21	18	01-30-76
"	21**	00-00-10	12-00-46	00-00-77	67	30	22	01-02-77
"	22**	10-02-23	00-00-49	01-00-76	52	27	27	12-04-76
"	23**	00-00-23	09-08-58	00-00-00	50	00	14	04-06-73
"	24**	00-00-17	00-00-39	05-27-77	60	38	26	05-27-77
"	25**	08-07-10	09-00-47	03-10-77	67	30	20	03-10-77
Yugoslavia	01**	04-05-14	00-00-53	04-08-73	59	20	20	04-08-73
"	02**	11-15-31	00-00-50	07-12-73	42	23	18	07-12-73

*"00" indicates unknown data.
**Diagnosis was microscopically confirmed.

Adapted from reference 61

TABLE XVII-5

BREAKTHROUGH VOLUMES FOR VINYL CHLORIDE ON VARIOUS SORBENTS

	Mesh	Concentration of Vinyl Chloride (μg/liter)	Sampling Rate (liter/min)	Breakthrough Volume* (liter)
Chromosorb 101-103	60/80	500	1.00	<0.1
Chromosorb 106-107	60/80	500	0.20	<0.1
Tenax GC	35/60	500	0.20	<0.1
Silica gel	20/40	130	0.20	<0.1
Silica gel with 1% AgNO3	20/40	130	0.20	<0.1
Molecular Sieve, 5A	30/40	500	0.20	2.0**
Carbopak A	45/60	500	0.20	<0.1
Carbopak B	45/60	500	0.20	<0.1
Carbosieve B	45/60	500	0.20	2.8
Dow Carbon XF4175L	20/40	6.5	0.20	5.7**
"	20/40	6.5	0.15	11.1
"	20/40	6.5	0.10	15.0
"	20/40	6.5	0.05	21.2**
Petroleum Charcoal, SKC-104	20/40	6.5	0.10	7.7***
Coal Charcoal, BPL	20/40	6.5	0.10	8.2**
Coconut Shell Charcoal:				
MSA-6	20/40	500	1.00	0.9
"	20/40	500	0.20	2.4**
"	20/40	500	0.05	5.2
"	20/40	130	0.20	3.4
"	20/40	6.5	0.20	5.7
"	20/40	6.5	0.10	10.3****
"	20/40	6.5	0.05	10.7
SKC-105	20/40	6.5	0.10	10.6
PCB	20/40	6.5	0.10	8.1**

*Values from a single experiment unless otherwise indicated
**Average of values from two experiments
***Average of values from three experiments
****Average of values from four experiments

Adapted from reference 244

TABLE XVII-6

RETENTION DATA FOR VINYL CHLORIDE ON CHARCOAL TUBES*

Concentration of Vinyl Chloride (ppm)	Sample Rate (ml/min)	Mass VCM Flowrate (μg/min)	Retention Volume** (liter)	Retention Time** (min)	Total Mass** (μg)
5	50	0.639	10.0	200	127.9
5	100	1.278	9.8	98	125.2
5	150	1.916	29.3	195	373.6
25	50	3.19	7.9	158	504
25	100	6.38	22.8	228	1,456
25	150	9.58	20.5	137	1,312
50	50	6.38	9.0	180	1,285
50	100	12.78	18.1	181	2,311
50	150	19.16	14.8	98.7	1,891

*Standard (150-mg charcoal) tubes from MSA
**At 10% breakthrough from front section of tube

Adapted from reference 254

TABLE XVII-7

RELATIVE RETENTION TIMES FOR COMPOUNDS POTENTIALLY INTERFERING WITH GAS CHROMATOGRAPHIC ANALYSIS OF VINYL CHLORIDE*

Compound	Chromosorb 102**		Porapak Q**	0.4% Carbowax 1500 on Carbopak A***
	100 C	145 C	100 C	Ambient Temperature
Methane	0.15	-	0.05	0.20
Ethane	0.21	-	-	0.29
Ethene	0.21	0.33	-	0.26
1,1-Difluoroethylene	-	0.33	-	0.63
Propene	-	0.62	0.46	0.63
Propane	0.54	-	0.52	0.63
Methylacetylene	-	-	0.56	-
Methyl chloride	0.63	-	0.57	0.45
1,1-Difluoroethane	-	0.51	-	-
Chlorodifluoromethane	-	0.53	-	-
Cyclopropane	-	-	0.59	-
Formaldehyde	-	-	0.62	-
1-Chloro-1,1-difluoroethane	-	0.92	-	-
Acetaldehyde	0.93	-	0.95	0.77
Freon 114	-	1.21	-	-
Isobutane	1.22	-	-	-
Isobutylene	1.37	1.25	-	-

TABLE XVII-7 (CONTINUED)

RELATIVE RETENTION TIMES FOR COMPOUNDS POTENTIALLY INTERFERING WITH GAS CHROMATOGRAPHIC ANALYSIS OF VINYL CHLORIDE*

Compound	Chromosorb 101**		Porapak Q**	0.4% Carbowax 1500 on Carbopak A***
	100 C	145 C	100 C	Ambient Temperature
Methanol	-	-	-	1.38
1,3-Butadiene	1.57	1.27	-	-
1-Butene	1.43	1.30	-	1.83
Vinyl methyl ether	-	1.36	-	-
Trans-2-butene	1.57	1.38	-	2.92
Ethyl chloride	1.70	-	-	1.54
Cis-2-butene	1.73	1.43	-	-
Vinyl bromide	-	1.85	-	-
1,1-Dichloroethylene	2.00	-	-	-

*Retention of vinyl chloride = 1.0
**6 feet x 1/8 inch, 80/100 mesh
***6 feet x 1/8 inch

Adapted from reference 264

TABLE XVII-8

COMPARISON OF GAS CHROMATOGRAPHY DETECTORS
FOR VINYL CHLORIDE ANALYSIS

Detector	Specificity	Approximate Detection Limit (g)
Flame ionization	Organic compounds	1.0×10^{-10}
Electron capture	Halides	2.0×10^{-9}
Electroconductivity (Hall detector)	"	7.0×10^{-11}
Chemiluminescence	Olefins	2.0×10^{-9}
Mass spectroscopy (specific ion monitoring)	M/e 62 and 64 ions	$1\text{-}2.0 \times 10^{-11}$

Adapted from reference 264

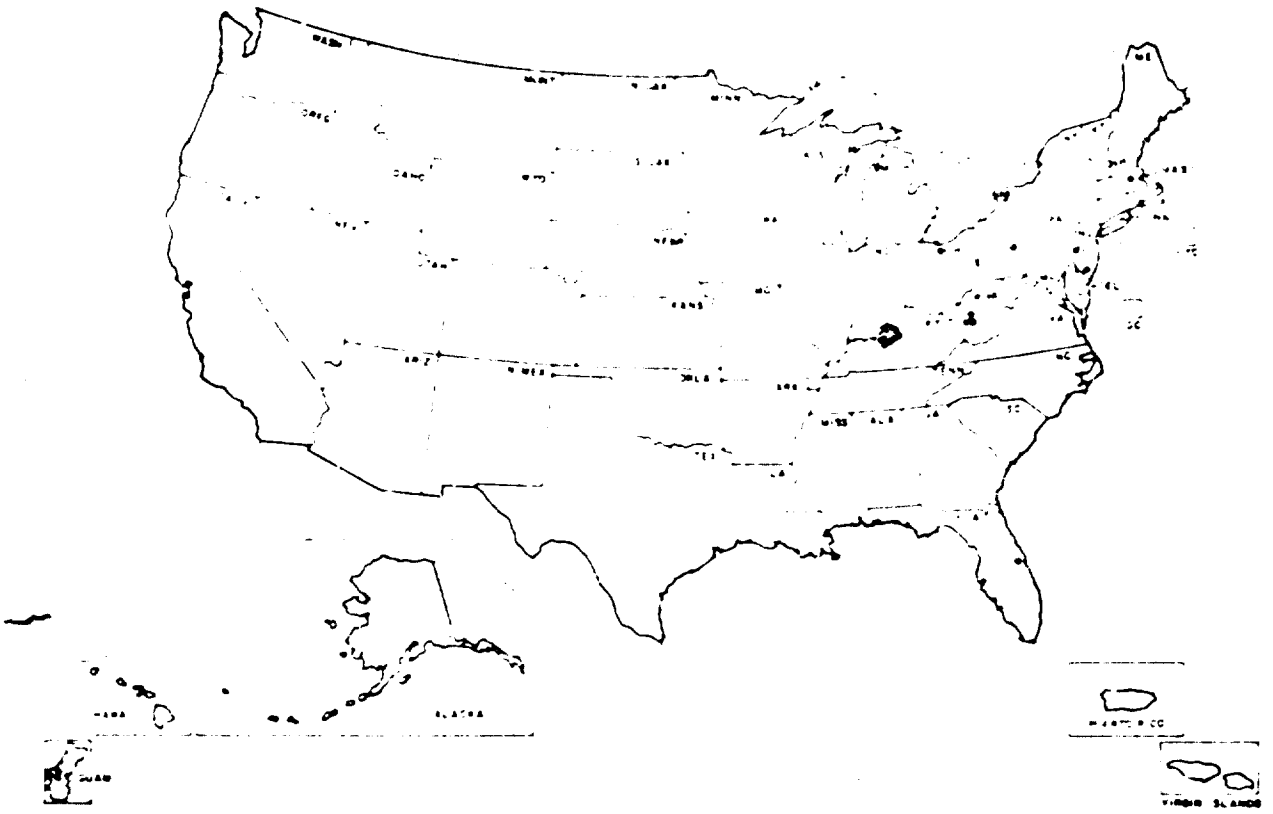


FIGURE XVII-1

GEOGRAPHIC DISTRIBUTION* OF 22 CASES OF ANGIOSARCOMA OF THE LIVER IN US VINYL CHLORIDE POLYMERIZATION WORKERS, 1961-1977**

* By place of residence at time of death or on date of diagnosis, if still alive

** Preliminary results; includes only pathologically confirmed cases in Center for Disease Control review; 1 additional case is pending

Adapted from reference 63

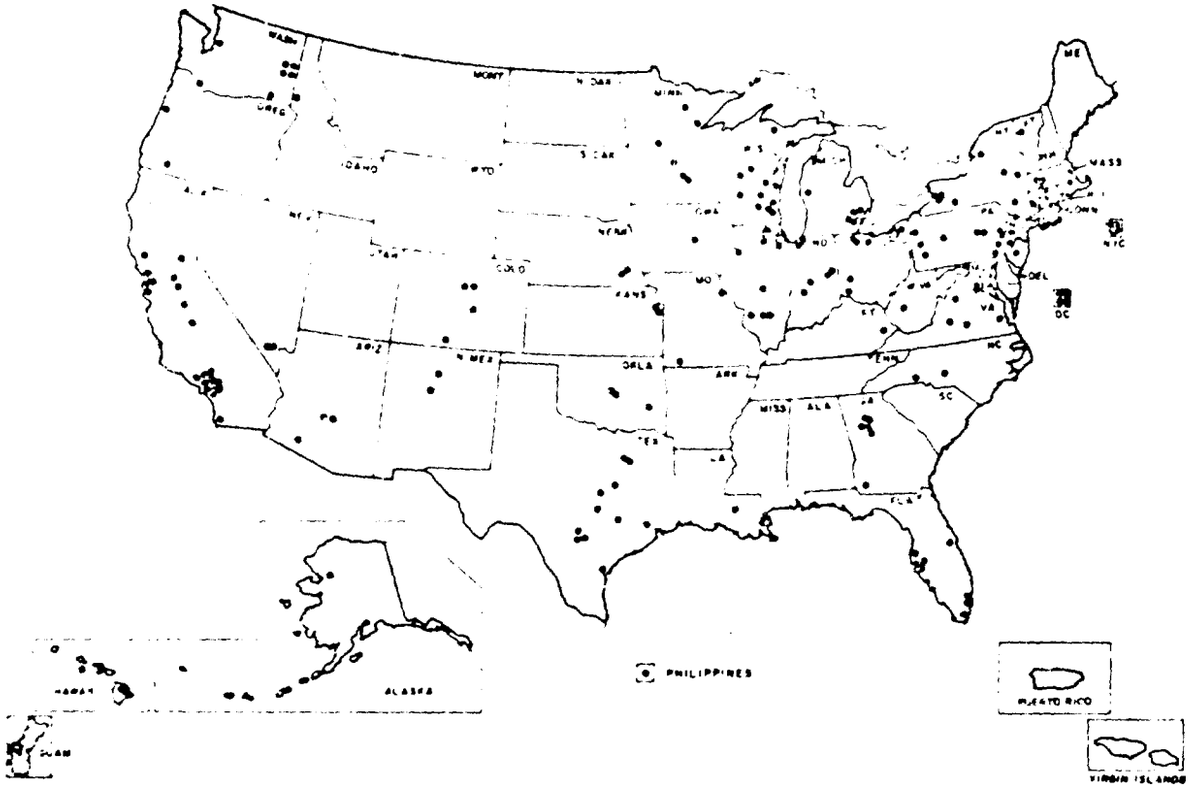


FIGURE XVII-2

GEOGRAPHIC DISTRIBUTION* OF 200 CASES OF ANGIOSARCOMA OF THE LIVER IN US RESIDENTS NOT OCCUPATIONALLY EXPOSED TO VINYL CHLORIDE, 1943-1977**

* By place of residence at time of death or on date of diagnosis, if still alive

** Preliminary results; includes only pathologically confirmed cases in Center for Disease Control review; evaluation of additional cases is pending

Adapted from reference 53

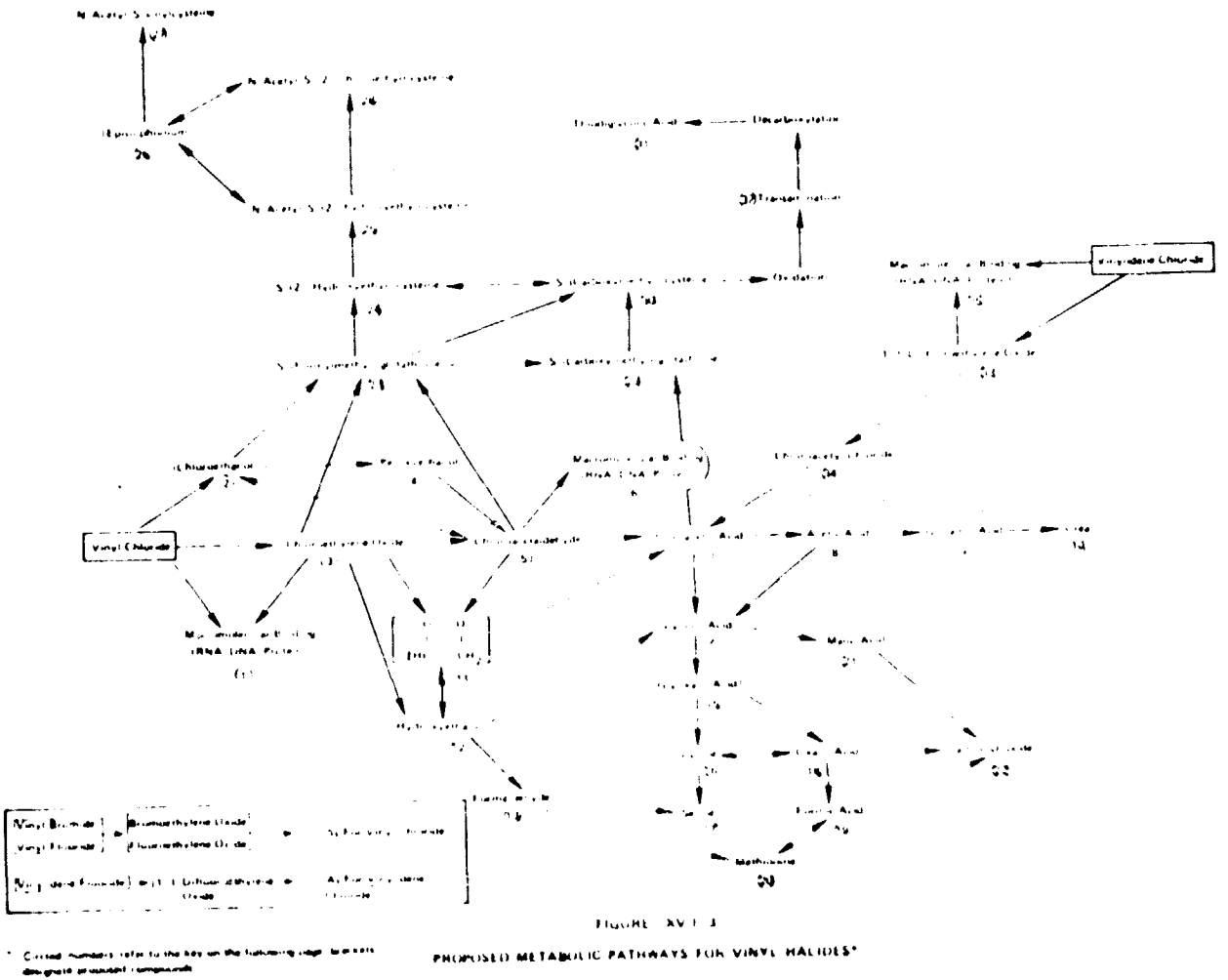


FIGURE XVI.3

PROPOSED METABOLIC PATHWAYS FOR VINYL HALIDES*

* Circled numbers refer to the key on the following page. Brackets designate proposed compounds.

KEY TO FIGURE XVII-3

Compound Process*	Identification	Species	Exposure	Reference
1	In vivo	Rat	Inhalation	280
	"			215
	In vitro		Liver homogenate	212
				204
				205
		-	Aqueous solution	[illegible]
		-		[illegible]
2	Proposed	Rat	[illegible]	-
			Liver [illegible]	-
3	In vitro			3
		Mouse		-
	Proposed		-	-
		-	-	-
		-	-	-
		-	-	145
		-	-	146
		-	-	[illegible]
4		-	-	-
5	In vivo	Rat	Oral	193
	In vitro		Liver homogenate	3
	Proposed	-	-	1
		-	-	4
		-	-	145
		-	-	146
		-	-	[illegible]
		-	-	-
6	In vitro		Aqueous solution	[illegible]
				214
	Proposed	-	-	158
7	In vivo	Rat	Oral, ip, iv	5
			Inhalation	-
		Mouse	ip	19
	In vitro	Rat	Liver perfusion	19[illegible]
(Vinylidene chloride)	Proposed	-	-	219
		-	-	1
8		-	-	196
9	In vivo	Rat	Oral, ip, iv	5
	In vitro		Liver extract**	193
10	In vivo		Oral, ip, iv	1
11	Proposed	-	-	1
12	"	-	-	196
13	"	-	-	5
	"	-	-	195
14	In vivo	Mouse	ip	198
15	Proposed	-	-	196
16	In vivo	Rat	Oral, ip, iv	5
	In vitro		Liver extract**	193
17	In vivo	"	Oral, ip, iv	5
18	"	Mouse	ip	198
19	Proposed	-	-	196

Compound Process*	Identification	Species	Exposure	Reference
20.	In vivo	Rat	Oral, ip, iv	5
21.	Proposed	-	-	196
22.	In vivo	Rat	Oral, ip, iv	5
			Inhalation	-
			Oral	177
(Vinylidene chloride)			Inhalation	216
			Oral	217
23.	"	"		193
24.			Inhalation	-
25.	"	"	Oral	177
			Inhalation	175
(Vinylidene chloride)		"	"	216
	"		Inhalation, oral	218
	"	"	Oral	217
26.	Proposed	-	-	195
27.	In vivo	Rat	Oral	195
28.		"	Oral, ip, iv	5
		"	Oral	195
29.	"	"	"	193
	In vitro	"	Liver homogenate	193
30.	In vivo	"	Inhalation	185
	"	Mouse	ip	198
	In vitro	Rat	Liver extract**	193
31.	In vivo	"	Oral, ip, iv	5
	"	"	Oral	177
	"	"	Inhalation	185
	"	"	"	175
	"	Mouse	ip	198
(Vinylidene chloride)	"	Rat	Inhalation	216
	"	"	Inhalation, oral	218
	"	"	Oral	217
32. (Mechanism)	Proposed	-	-	195
33. (Vinylidene chloride)	"	-	-	219
"	"	-	-	1
34. (Vinylidene chloride)	"	-	-	219
"	"	-	-	1
35. (Vinylidene chloride)	In vivo	Rat	Inhalation	216
"	"	"	"	219
"	"	"	Oral	217
"	"	Mouse	ip	117

*Numbers refer to circled numbers in Figure XVIII-1, on preceding page.
**Incubated with kidney homogenate

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