

Carcinogenicity and Epidemiological Profile Analysis of Vinyl Chloride and Polyvinyl Chloride

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The carcinogenicity of vinyl chloride and polyvinyl chloride (VC/PVC) is reviewed with specific attention to the gaps in knowledge for risk estimation and epidemiological presentation of the available data. Although experimental studies have demonstrated the carcinogenicity and mutagenicity of VC/PVC in general, the epidemiologic studies available for review do not include an assessment of carcinogenic risk among humans exposed to these chemicals. This conclusion is based on the observation that the majority of cohort studies reviewed lacked sufficient statistical power because of small sample sizes. Further, in epidemiological studies, individuals were not followed over an adequate period of time during which cancer could become clinically manifest.

INTRODUCTION

Vinyl chloride (VC) and/or polyvinyl chloride (PVC) are among the most widely used synthetic organic chemicals. This multiplicity of usage has led to the distribution of these compounds throughout the environment. PVC appears in wire insulation, clothing, food containers, flooring, upholstery, phonograph records, and a variety of other items.

PVC is produced by most industrialized countries. Commercially prepared PVC exists as polyvinyl chloride resins, polyvinyl chloride latexes, polyvinyl chloride compounds and polyvinyl chloride film.

Preparation of these synthetic resins from vinyl chloride and other monomers involves reacting the monomers in agitated pressure vessels in the presence of catalysts and then converting these liquids and gases into solid resins. This reaction generates excess heat which is removed by cooling processes. During the reaction, as the monomer is converted to polymer, the rate of reaction slows down significantly. Thus, after a certain period of reaction time, the unreacted and/or unconverted monomer is removed from the reacting system by heat and/or vacuum and the product resin is recovered

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as a liquid latex or solution or dried white powder. The polymerization reaction usually takes place in pure monomer, in a water-monomer emulsion, or in a water suspension of monomer. The characteristics of the product depends primarily on the polymerization process used. Basically, the four polymerization processes employed include (a) bulk polymerization, (b) emulsion polymerization, (c) suspension polymerization, and (d) solution polymerization. The bulk process produces porous resins. Emulsion resins are small particle powders containing very little free monomer. Suspension resins are relatively dust free and are granular with varying degrees of particle porosity. PVC resins are smaller in particle size than suspension PVC with porosity particles containing essentially no free monomer. Most VC monomer plants utilize the acetylene-hydrogen chloride process (the older process for making VC); another process employed utilizes ethylene dichloride pyrolysis.

Generally, VC polymerization involves suspension resin operations, dispersion resin operations, and solvent resin operations. Recent studies show that the suspension and dispersion resin operations have the highest exposure level (1).

In PVC fabrication plants, the calendaring, compounding, extrusion, molding, and plastisol operations are considered to have low exposure levels. Studies by Jones (1) show that polymerization had the highest and fabrication the lowest exposure among the segments of VC/PVC facilities.

In the workplace, the production processes, product, and other materials involved must be considered before valid toxicological and health effects can be assessed. Exposure in the occupational setting is usually at higher levels than those that occur in the general environment. Since higher levels of exposure are often associated with greater risks, studies of the occupationally exposed population may facilitate the detection of statistically significant effects. A limitation of workplace exposure studies is that, frequently, the number of exposed subjects is too small to draw statistical inferences. This problem of small numbers of exposed subjects might have a significant effect on the validity of a statistical test since the results could infer no exposure association when, in fact, one does exist. In a statistical analysis, when the number of exposed subjects is small, the chance is greater that an association between an exposure and a health effect will not be statistically significant. Thus, false negative study results can lead to erroneous conclusions as to the possible harmful effects of VC/PVC on the population in the workplace. In a statistical evaluation of the workplace, exposure to VC/PVC must be examined in relation to the possible adverse effects that occur before considering whether any negative results found are sufficient evidence to justify a "no association." It is also necessary to evaluate whether or not the results reported as demonstrating a harmful association truly support such a conclusion.

CARCINOGENICITY OF VINYL CHLORIDE AND/OR POLYVINYL CHLORIDE

Vinyl chloride toxicity and/or polyvinyl chloride toxicity were reported shortly after they were introduced into the market in 1930. In the same year, Patty and associates (2) reported toxicity of VC in experimental animals. Throughout the years, the studies indicated that workers in the VC/PVC industry were associated with a range of toxicity and carcinogenicity of these chemicals.

In 1970, experimental bioassays demonstrated that VC/PVC induced cancer in multiple organs, including the lung, liver, brain, and lymphatic system. These carcinogenic responses were observed in several experimental animal species which had been given a wide range of doses by various routes of administration (3, 4). Recent results presented by Maltoni (5) and Infante (6) confirm an excess cancer risk involving multiple sites among individuals employed in operations using VC/PVC. Maltoni (5) demonstrated the carcinogenicity of VC for rats, mice, and hamsters over a wide range of doses. His early study results indicated that, on inhalation of VC by adult rats, tumors are induced in dose-dependent fashion in the liver, nasal cavity, kidneys, and Zymbol's gland, and in the blood vessels, especially those of the liver.

The strongest evidence of the carcinogenicity of VC/PVC was uncovered in a study involving Swiss mice (7, 8). In this study, 24/150 dosed male mice had kidney tumors as compared to 0/190 in the controls. Other studies by Lee and associates (9, 10) showed liver angiosarcomas in mice and rats.

Transplacental exposure for a period of 1 week, between the 12th and 18th days of pregnancy, generated tumors in the blood vessels, Zymbol's gland, and kidneys of the offspring. The tissues and organs affected in offspring exposed transplacentally to VC included some but not all of those tissues in which tumors developed in adults enduring prolonged exposure periods. In the transplacental study, significant numbers of tumors were also induced in the offspring.

Salmon (11) has demonstrated that VC is basically a metabolism-dependent carcinogen and that its carcinogenicity depends on the function of oxidases which convert VC to chloroethylene oxide. Chloroethylene oxide proved to be an effective carcinogen, resulting in both papillomas and carcinomas of the skin and giving rise to sarcomas upon injection (12). The endoplasmic reticulum of the hepatic cells has been suggested as being the site where VC is metabolized for transformation into a chemically reactive metabolite which is ultimately the carcinogen. Hepatic hemangiosarcoma has been found by several investigators to be associated with vinyl chloride exposure among VC plant workers (13-16).

The results of recent studies in experimental animals have shown that various organs (such as the liver, lung, brain, breast, and skin, including sebaceous glands) were involved in the induction of primary neoplasia by VC (17). Lilis and associates (18) reported, on the basis of chest x rays, the occurrence of nonneoplastic pulmonary abnormalities among VC polymerization workers. Abnormalities also have been reported by others (13, 19) on the basis of pulmonary function (signs of loss of lung recoil pressure and small airway obstruction), smear cytology, and sputum. A high incidence of pulmonary tumors in mice exposed to VC was uncovered in studies by Holmberg and associates (20) and Suzuki (21). A detailed characterization of the neoplastic and nonneoplastic pulmonary effects of vinyl chloride was reported by Suzuki (17), who studied the neoplastic effects of VC in the lungs of 27 mice exposed to VC monomer at 2500 and 6000 mg/m³ for 5 and 6 months. He observed pulmonary tumors arranged in either tubulopapillary or adenomatous formations. Although mitotic divisions and invaginations into the bronchiolar lumen were observed, no metastases were seen. Electron microscopic studies showed short microvilli, tight junctions between two adjacent cells, large mitochondria of irregular shape, well-developed Golgi complexes, continuous or discontinuous basement membranes and crystalloids, and a lack of both cilia and mucous secretory granules which are char-

acteristic features of neoplastic cells. The pulmonary tumors corresponded to alveologenic tumors.

Nonneoplastic effects were also studied in the 27 mice by Suzuki (17). Light microscopy showed alterations, proliferations, and hypertrophy of the terminal bronchiolar cells, consisting of ciliated and Clara cells, hypersecretion of the epithelial mucin in the goblet cells of the bronchiolar epithelium, the mobilization of alveolar macrophages, and the occasional presence of peribronchial. Major electron microscopic changes were seen in the Clara cells of the terminal bronchiole, epithelium proliferation, and with the appearance of large and abnormally shaped mitochondria. Submicroscopic studies (17) showed changes in the pulmonary alveoli and focal thickening of the basement membrane, multiple foci of hyperplastic type II cell (precursors of the alveologenic tumor), active discharge of osmiophilic lamellar bodies from the type II cell, phagocytosis of the bodies by macrophages, the appearance of cholesterol crystalloids in the macrophages, and degeneration of alveolar septal cells. These observations demonstrated a dose-response relation in the incidence of alveologenic tumor production, the sensitivity of mouse lung, and the oncogenicity of VC. In previous studies, Suzuki (17) also demonstrated that mice exposed to VC at doses of 2500 and 6000 mg/m³ over 5 and 6 months showed bronchioloalveolar changes. Alterations were observed in almost all of the experimental animals.

Consideration of the potential risk factor of VC/PVC to human reproduction came from a study of birth defects in three Ohio communities housing VC plants (22). In this study, the malformation rate found was compared in the index communities with the statewide rates. The results showed a significant excess of central nervous system malformations, especially in one of the cities where the risk of neural tube defects, relative to the state as a whole, was 5.8.

Edmonds and associates (23) reported a study examining the relation of neural tube defects to parental exposure to VC/PVC. Hehir and associates (24) studied 150 colony rats divided into three groups, each with equal numbers of males and females. These specific pathogen-free, random-bred rats were 12 weeks old when initially exposed to VC. One hundred rats were exposed and the remaining 50 were carried as controls. The parental generations of rats were maintained 24 months postexposure for carcinogenic evaluation. Complete gross and microscopic pathological studies of all tissues were done on each of the control and exposed animals. Neoplastic and nonneoplastic lesions in equal frequency were observed in both the control and the parent generation rats exposed to VC in different dose levels. The results of this study demonstrated a strong dose-time relationship for carcinogenesis related to the VC exposure. These investigators concluded that cancer production is dependent on the dose of VC, especially in lifetime exposure studies. In short-term exposure, the results showed that concentration was the most critical factor.

Exposure to VC has also been shown to produce chromosome breaks in exposed workers (25) and to cause mutation in *Salmonella typhimurium* (26). Anderson and associates (27) studied the mutagenic activity of VC at three exposure levels in fertile male mice via the dominant lethal test. They demonstrated mutagenic effects of VC in laboratory tests and in exposed workers. No mutational effect in the germ cells was observed.

Mutagenicity studies in both man and test organisms show the positive mutagenic activity of VC. Fabricant and Legetor (28) found that a concentration of VC as low as 2% increased revertant colonies when compared to the nontreated controls (7 versus 33). Several other investigators (29-31) also reported an increase in the total

number of revertant colonies in *Salmonella*. Griem and associates (32) reported a positive response in *Escherichia coli*, and Shahin (33) showed mutagenicity in yeast via both gene conversion and gene mutation assays.

Vogel and Sorbels (34) had positive results from the recessive lethal assay in *Drosophila*. They also showed, following pretreatment of phenobarbital for 24 hr, an even greater mutagenic effect from VC. One study showed an increase in metabolites in Chinese hamsters (35). Anderson and associates (27) reported decreased fertility in male mice which had received a high dosage of vinyl chloride (50 mg/m³ for 6 hr/day) for 5 days. Increased frequencies of both chromatid and chromosomal damage have been reported by several investigators (36-38). A correlation was found between the length of exposure and excursion levels of VC during the year prior to sampling (39). Another study (36) has shown an increase in chromosomal aberrations in 20 workers exposed to vinyl chloride. Although all types of chromosomal and chromatid damage were found, the most common type was cytogenetic damage (40). Recently, Downs and associates (41) prepared a report about the birth defects and fetal wastage caused by VC for the Society of the Plastic Industries, Inc., which had questioned the results of studies with human subjects. In some cases, investigative results were questionable in terms of analysis, sample size, and experimental design. However, the evidence taken as a whole was strong enough to indicate the mutagenic activity of VC.

Hansteen and associates (40) did a follow-up study on VC workers who had initially shown increased frequencies of chromosomal aberrations and who were later removed from their plant working site to other areas where VC concentrations were low. Reexamined 2½ years later, these workers showed no significant difference in chromosomal aberration frequencies when compared to controls. Although most mutagenicity studies have been shown positive VC results, some have demonstrated no response (27, 42-44).

A cytogenic study in men showed negative results following a single 5-min acute exposure to VC (40). Sufficient data exist to demonstrate the positive mutagenic activity of VC in test organisms (38, 41, 45). Other study results demonstrate somatic mutations in man which are seen as increased frequencies of chromosomal aberrations in the lymphocytes of workers. Increased spontaneous abortions in the wives of VC workers could be a result of mutations occurring in the germ cells of the husband.

Hatch and associates (46) reviewed the evidence by examining the relation of reproductive function and exposure to VC and analogs. None of their data could point unambiguously to a relation between VC or analogs and reproductive outcome. However, in other studies reporting no association, the statistical power employed to detect a modest association between exposure and outcome, if it should be present, was either insufficient or could not be calculated from the existing data. At present, no data indicate that the fetus is at greater risk because of maternal exposure than because of paternal exposure. Carefully designed and executed investigations, where the association of vinyl chloride with reproductive outcome can be accurately examined, are needed.

Liver Cancer in Humans

Recent studies in the United States were conducted among workers who had been exposed to VC for 5 years or more and who had lived for a period of 10 or more

years since their initial exposure (47). The studies demonstrated up to a 16-fold excessive risk of death from cancer among VC-exposed workers.

Cohort study results of workers exposed to VC in 33 US plants were reported by Tabershaw and Gaffey (48). These investigators did not separately analyze the data for liver and biliary cancers. There were 19 deaths from digestive organ cancer for the total cohort versus 21.7 expected and 11 digestive organ cancer deaths observed versus 7.5 expected for the highest exposure cohort with more than 5 years of exposure. The analysis results, however, were not statistically significant. They indicated that individuals in the group with no vital status determination (15% of the population) began their exposure 10 years before those in the group for whom follow-up was completed; some individuals with longer latency periods were omitted from the study. Recent studies by Buffer and associates (49) and Ott and associates (50) showed no cancer death among 20 deaths reported during their investigations.

The cohort study, conducted by Byren and associates (51) on all Swedish workers employed in positions where exposure to VC could have occurred, combined the deaths from cancer of the liver and pancreas because these investigators believed that there was a strong overlap of these causes. They observed four liver and pancreatic cancer deaths as compared to 0.77 expected ($P < 0.02$). An additional death from liver angiosarcoma occurred after the study cutoff date and thus was not included in their report.

Proportional mortality studies of 161 deceased workers from two plants showed 8 deaths from liver and biliary tract cancer versus 0.7 expected; the risk ratio was 11.0 (47, 52). In England, Fox and Collier (53) studied workers exposed to VC and found a total of 4 deaths from liver cancer as compared to 1.64 expected. In that study the deaths occurred in a workplace where 0.13 would have been expected ($P < 0.01$). These investigators found it difficult to identify angiosarcoma of the liver from death certificate notations since some of these deaths were classified as primary and some as secondary liver cancer, and others were not certified as being cancer deaths.

Clinical and epidemiological studies suggest that the occurrence of angiosarcoma of the liver (ASL) in VC-exposed workers might be greater than initially appreciated. In recent studies, a gradual increase in the frequency of ASL that may have occurred during the past two decades was indicated (54). This gradual increase may be a reflection of a long latency period or an increased recognition of the entity. Most cases of ASL have appeared in people living in close proximity to VC production plants. In the United States, a total of 68 deaths (males 46, females 22) due to this tumor were identified for the period 1966 through 1973 (55). In England ASL adult deaths numbered 32 (males 21, females 11) 1963 through 1973 (56). It has been suggested that the age of diagnosis and the latency period for ASL might be increasing in recent years (54). It is also suggested that these observations could be very important in evaluating the possibility that lower doses of VC might be associated with ASL after a prolonged latency period. Studies of Hammond and Selikoff (57) found one case of ASL identified among 52,000 autopsies at Los Angeles County Hospital, thus proving the rarity of ASL. Block (13) suggested that chronic low-level exposure to VC has a significant role in the development of ASL. At present, no conclusive evidence associates this tumor with nonoccupational exposure to VC. However, a correlation of ASL and chronic low-level dose exposure requires further examination. In such an evaluation process, residential proximity to VC plants and other sources of public exposure must be considered. One recent study showed that 4.6 million people live within 5 miles of U. S. monomer and polymer production plants (58).

Brain Cancer in Humans

Results of epidemiological studies by several investigators have shown an association of brain cancer with exposure to VC/PVC. Studies involving a small number of cohorts exposed to VC have revealed significant excesses of brain cancer (47, 51). These investigators contrasted that observed high proportion with that of the Yale autopsy series in which 33% of intracranial neoplasms were glioblastoma multiforme. Fox and Collier (53) reported two brain cancer deaths compared to 3.7 expected in a cohort. They observed 1 brain cancer death versus 0.4 expected among cohort members categorized as having high exposure to VC. Other investigators observed an even higher (fourfold) risk of brain cancer in VC-exposed cohort members (52). These investigators categorized brain cancer death to identify brain cancer risk in this group of subjects (48). Final observations of the overall investigation showed 6 brain cancer deaths among individuals exposed to VC compared to 2.4 expected (48).

In other small cohort studies, the investigators did not identify deaths from brain cancer from those from all sites other than the digestive and respiratory tracts. A study showed 2 brain cancer deaths compared to an estimated 0.7 deaths expected. Other studies also have demonstrated a significant excess of brain cancer occurring among workers exposed to VC (39, 42).

Lung Cancer and Other Complications in Humans

It is known that the lungs have the capacity to metabolize VC to produce a carcinogen by the utilization of bronchiolar and Clara cells. According to Wolff (59), VC has a great tendency to form lipid-soluble substances, especially type II cells, and alveolar septal cells may bind to VC. Both Clara and type II cells have been shown to be surfactant factor-producing cells (60). Other investigators (61, 62) suggest the hyperproduction of surfactant factor. They concluded that the osmiophilic lamellar bodies and cholesterol crystalloids seen in alveolar macrophages may represent lipid substances bound to VC. They also indicated that mesenchymal elements such as bone, connective tissue, and blood vessels are involved in the response of various organs to VC. A risk of lung cancer among VC workers was discerned on the basis of epidemiological studies (47, 48). These results showed an unusual distribution in histologic types of lung cancer. Of 8 histologically confirmed lung cancers observed, 5 were classified as large cell undifferentiated and 3 were categorized as adenocarcinoma. Waxweiler and associates (47) observed 11 lung cancer deaths as compared to 5.7 expected ($P < 0.005$) among cohort members who had had a 15-year latency period.

Other studies (47, 48, 59) show an excess risk of lung cancer ranging from 7 to 200% with the exception of the study by Fox and Collier (53); the short period of follow-up significantly limited the statistical interpretation of their results. Buffer and associates (49) observed a fourfold risk of lung cancer within a small cohort of 464 workers exposed to VC. Their studies suggested a qualitative dose-response relationship between VC exposure and lung cancer risk. When these authors also examined the effects of smoking, the data still demonstrated a significant excess of lung cancer.

Recently Groth and associates (63) exposed experimental animals, by inhalation for 6 hr/day, 5 day/week, and for up to 22 months, to a 13 mg/m³ concentration of PVC dust. Autopsies were performed after 12 and 22 months of exposure. Lung function tests were also performed after 9, 14, and 22 months of exposure. Aggregates

containing PVC particles were found in the lungs of all experimental animals. No fibrosis and/or significant cellular infiltrates were present in these cellular aggregates. These authors also were not able to demonstrate a significant effect on pulmonary function in animals exposed to PVC. They did demonstrate a benign pneumoconiosis in animals exposed to PVC, and were able to show that PVC dust generated under controlled experimental conditions is respirable and was deposited in cell aggregates in the lungs of the experimental animals and that the PVC particles identified within macrophages (confirmed via microprobe analysis) were unique in appearance.

Mastrangelo and associates (64) examined the working population of plants producing PVC in Porto Marghera, Italy. None of the 1216 workers had been previously exposed to dust. Of these workers, 731 were exposed to PVC dust polymer while 485 were exposed to VC. In the drying, sacking, and blending departments, PVC dust concentration was over 10 mg/m^3 of total dust in about 60% of the samples whereas, in the polymerization departments, no concentration over 10 mg/m^3 was detected. In the samples taken, particles with diameters of 1 to $6 \mu\text{m}$ constituted 4.5 to 30.9% of total dust weight. All chest x-ray films were read by two independent physicians and the consensus reading was used for statistical analysis.

Among the 1216 workers, 20 cases of pneumoconiosis were observed. X-Ray abnormalities were characterized by limited profusion, irregular type, and low gravity; in a small percentage of cases, these were associated with restrictive respiratory function impairments. All 20 workers with PVC-induced pneumoconiosis had been exposed to high levels of PVC dust for 5 years. Mild nonspecific alterations were observed in workers exposed to both PVC dust and VC alone. The changes observed were related mainly to age and smoking habits, and the overall effects of exposure to PVC were found to be rather minimal. The investigators concluded that the lung changes were directly related to PVC dust exposure whereas VC exposure alone failed to produce changes.

Wagner and Johnson (65) studied inhalation on experimental animals exposed to PVC in inhalation chambers. The animals were exposed to dispersion polymer at a concentration of 12 mg/m^3 for 7 hr/day, 5 days/week, over a period of 5 months. Nonexposed animals were used as controls. The cumulative dose of the exposed animals was 8552 mg/m^3 . A group of experimental animals was killed at the end of the exposure period and the remaining animals were allowed to survive until they died of natural causes. PVC particles were observed in the macrophages within the alveoli and dust particles in sections from the bronchopulmonary lymph glands and the Kupffer cells in the liver and spleen. At the end of a year, dust particles, found in the spleen and around some foci of macrophages, caused proliferation of the reticulin fibers.

Molina and associates (66) studied the mortality and cancer rates of the workers of Swedish PVC processing plants. The lists of workers from PVC plants were collected at 3 months of employment at the beginning of 1945 and on the last day of employment December 31, 1974. The cohort of 1970 individuals was analyzed and compared with the national population with respect to mortality from various diseases and cancer morbidity. The death risk from myocardial infarction was found to be elevated in the cohort as was also the risk of morbidity and mortality from tumors in the digestive organs (although the latter was not confirmed statistically). The results of this study demonstrated the occurrence of tumors after a long latency period.

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Cancer of the Lymphatic and Hematopoietic System in Humans

The relative risks of cancer of the lymphatic and hematopoietic systems among workers exposed to VC/PVC ranged from 1.0 to 2.2 and did not demonstrate statistical significance (47, 48, 52, 53). None of these investigators made separate analyses of the data from lymphatic cancers and leukemia. In addition, their statistical analyses did not include the exposure level and latency period.

Recent investigation results show an increase in pulmonary disease in VC- and PVC-exposed workers (67, 68). Most of the studies associated the pulmonary effects of PVC and VC with the occurrence of radiological abnormalities and functional impairment (19, 69-72). Lillis and associates (18) observed reticularlinear and nodular opacities in the lower zones of both lungs.

PVC dust as the etiological agent in a peculiar type of pulmonary fibrosis has been associated with a granulomatous reaction (67, 68). Arnaud and associates (67) identified diffused micronodular chest radiographic abnormalities, exertional dyspnea, and restrictive pulmonary dysfunction in PVC pulmonary fibrosis associated with granulomatous lesions. They observed a similar radiologic pattern by incubating human macrophages, obtained by bronchial lavage, with PVC powder. Similar histologic lesions have been found in humans (69) and experimental animals (73). Mastrangelo and associates (68) detected 20 cases of typical pneumoconiosis, irregular opacities, and micronodular shadows among PVC-exposed workers. Ward and associates (74) studied the immunologic status of 58 workers from a VC polymerization plant. Their observations included cryoglobulinemia, hyperimmunoglobulinemia, cryofibrinogenemia, *in vivo* complement activation via the classic pathway with C₄ and C₃ conversion, and an increase in the B-cell lymphocyte population. The results of immunological studies suggest that VC metabolic cyclic chloroethylene epoxide, an alkylating agent with high biological activity, binds to IgG to produce structural conformational changes that promote the aggregation of IgG molecules (75). Langauer-Lewowicka and associates (76) observed immunological abnormalities in 22 workers exposed to VC. Latent cryoglobulinemia was detected in 18 cases with increased immunoglobulins. Increased IgG levels have also been shown by Crystal and associates (77) to be characteristic of bronchoalveolar lavage fluid in VC-exposed workers. The majority of experimental studies has demonstrated a dose-response relation in the incidence of tumor production of VC.

Breast Cancer Mortality

Early reports included the results of a cross-sectional mortality study of deaths occurring among workers of 17 PVC fabricators during the years 1964-1973 (78). A total of 44 deaths among white women was caused by cancer of the breast. In the proportional mortality ratio analysis, the observed number of deaths from breast cancer was found to exceed the number expected based on the distribution of deaths by cause and age among U. S. white women in 1968. Recent statistical analysis also reveals a significant relative risk of breast cancer among VC/PVC workers (79).

SUMMARY

The VC/PVC industry has several thousand workers who are exposed to VC/PVC on an average in the range of 0.1 mg/m³ (80). In spite of all current available techniques

to reduce exposure in the order-of-magnitude range, VC/PVC industries may still place a substantial number of people at risk in situations where some of the new technical measures to reduce exposure have not been fully implemented. Generally, the carcinogenicity of VC/PVC is conclusive and, therefore, the likely untapped opportunities to control exposure suggest that these industries should be kept on Environmental Protection Agency (EPA) priority lists. The clinical and epidemiological investigations on work groups with previous exposure to VC/PVC should be pursued in future years. However, in the future, to assess more disaggregated data different statistical analysis approaches for assessing the duration of exposure, age at which exposure occurred, level of exposure, and the years of follow-up relative to the years of exposure should be used. Because of the conclusive results of VC/PVC carcinogenicity in experimental animals, it should not be assumed in the epidemiological data that high-level short-term exposures will have the same effects as low-level long-term exposures that deliver the same dosage. Epidemiological observations on large worker groups exposed to VC/PVC should not be considered to be complete. Further ongoing epidemiological studies on these populations is clearly of major importance. Further, investigations in experimental animal models should be aimed at developing reliable quantitative animal-to-human extrapolations to advance the understanding of the dynamics of metabolism of precursor substances to active carcinogenic intermediates, and to provide a set of technical expectations relevant to future risk assessments. Laboratory studies also should seek biochemical explanations for the ways in which the VC/PVC carcinogenic response changes with the dosage, animal strain, and tissue affected.

In general, the effects of VC/PVC exposure on the respiratory system of exposed workers indicate two basic patterns of nonmalignant effects: (1) the granulomatous reaction to PVC dust with inclusion of PVC particles in macrophages and histocytes and the associated interstitial pulmonary fibrosis due to VC monomer effects on protein molecules, and (2) the immunologic mechanisms triggered by the altered protein. The studies and case reports of investigators indicate that long-term exposure to PVC dust (less than 5–10 μm in diameter) can lead to chronic declines in standard measures of normal lung function (80). Among all the processes and products, the PVC preparations with predominantly small particle sizes are produced by the relatively small portion of the industry that utilizes the emulsion polymerization process. The problem of exposure to low-level dust in general is common in PVC preparation processes (80). A general reappraisal of policies and standards with regard to particulates in respirable size ranges might lead to significant long-term benefits in the prevention of chronic pulmonary impairment. If a broad data base is to be developed for evaluating pulmonary impairment among PVC workers, a cross-sectional analysis must be made of lung function among workers exposed for many years to PVC particulates (including the consideration of smoking habits and other relevant factors). In these epidemiological studies, it is important that the data be presented not only in terms of average losses of lung function among populations as related to exposure and age factors but also in terms which allow the full reconstruction of the population distribution of lung function values as related to exposure and age. Hattis (80) has suggested that the significant changes at the tails of the population distributions of lung function may be obscured unless the statistical analysis (which determines average effects) is supplemented by presentations revealing what is happening to subgroups which, for other reasons, have better or worse lung function than is considered to be average.

Based on the available data (4)—an assumption of linear dose-response kinetics at low doses and four alternative sets of rules for translating the animal VC/PVC dosage to equivalents to human, 1 mg/m^3 (81)—the current VC standard may still pose a carcinogenic risk to workers. The four alternative animal/human extrapolation choices between expressing dosage as milligrams per unit body weight versus milligrams per unit body surface area, and the choice of dividing the animal dosage by 35 to adjust for the 35-fold difference between the experimental animal and the human life span projections may suggest that a year of worker exposure to VC at the current 8-hr limit of 1 mg/m^3 might be expected to have some risk for all tumors of between 1×10^4 and 3×10^{-2} for the four different extrapolation rules (80).

CONCLUSIONS

In cases of mortality and morbidity from tumors, most results at present are uncertain. In some cases, there are certain levels of indications of an elevation but the differences are not statistically confirmed. Two major trends of thought may be contributing to these differences: (1) in reality, there is no increase in the rate of tumors, and (2) there is indeed a true increase of risk of tumors. Some statistical analyses neither confirm nor refute these conjectures. In general, tumors do not occur until after a long latency period. In some cases, the subjects included in studies have not been exposed to VC/PVC for a sufficient amount of time. For this kind of incomplete study, an accurate follow-up of the present cohort during the coming 5- to 10-year period should bring greater clarity into some of the current study results. Also, it is necessary to hypothesize the statistical tests for VC/PVC in these cohort studies by using the one-sided *t* test of the observed minus the expected cumulative doses over all years before death or for 10 or more years before death.

The information that has become available over the last several years suggests the necessity for the scientists to make two important conclusions about VC/PVC: (1) that there is a substantial chance that long-term exposure to VC/PVC at current standard levels poses a considerable risk, and (2) that a new standard and enforcement would lead to substantial reduction in worker exposure to VC/PVC.

The risk of tumor production is related to the length of exposure and the total dose. In fact, it appears from the results of most studies that concentration is the dominant factor for acute or low-level intermittent exposures. These results may be explained on the basis of a number of factors such as detoxification, metabolism, genetic material repair, or time for tumor development for low level exposure beyond the animals' life span.

The regulatory bodies of most industrialized nations attempt to establish safe exposure levels, and industry, in turn, works to control exposures in production facilities. Such control measures may be of the practical value in the home and general environments. Another complication associated with making valid judgements about potential risks of population exposure is that traditional cancer bioassays involve daily exposure to the chemical over the animal's remaining lifetime. There are not enough short-term comparable studies on short-term exposure to a carcinogen like VC/PVC which are followed by lifetime monitoring for toxicological symptoms with complete histopathological examination at death. Therefore, an approach to follow may be to explore what happens to experimental animals following brief or intermittent exposure to the known carcinogen VC/PVC. VC and PVC are ideal chemicals to use

in dose-related experiments because of their widespread use in industrial and consumer products.

The preliminary epidemiological results available to date do not seem to indicate as large a risk among workers exposed to VC in the past as might be expected under the current extrapolation rules from animal data.

Recent study results clearly demonstrate that German chemical industry workers show elevated mortality rates from different kinds of tumors which reach as high as 6% of the total deaths that have occurred in the cohort to date. Because of the long latency period for the development of cancer, it is very likely that the final percentage of past VC-exposed workers who develop cancers will be higher than the level observed up to present time.

Epidemiological studies on VC/PVC need to be pursued in future years. There is also need for future study of VC/PVC in terms of their potential to produce generalized quantitative animal-to-human extrapolations, precursor formation and/or conversion to active carcinogenic intermediates, and the development of more sensitive methods for future risk assessments. To analyze the data, different approaches should be utilized for separate assessments of the effects of duration of exposure, level of exposure, age at which exposure occurred, years of follow-up as related to years of exposure, and the calendar year of exposure. Further studies in experimental animal models could be aimed at uncovering biochemical explanations for the ways in which the VC/PVC carcinogenic and mutagenic responses change with dosage, animal sex, animal strain, and age since it is known that these factors have an effect on the modification of the neoplastic responses both qualitatively and quantitatively. The choice of experimental animal type has to be made with the intention of having an integrated system of complementary biological models which can express as wide a range as is possible of the various neoplastic responses. Long-term carcinogenicity bioassays on VC/PVC are crucial to the field of environmental and occupational carcinogenesis, a most important area of public health concerns. These studies, especially long-term carcinogenicity bioassays, may predict carcinogenic risk of humans, may give an indication of the level of risk in relation to dose, may provide information on possible target organs, and, in general terms, may represent a tool for obtaining information on the risk represented by VC/PVC.

REFERENCES

1. JONES, J. H. (1981). Workers exposure to vinyl chloride and poly(vinyl) chloride. *Environ. Health Perspect.* 41, 129-136.
2. PATTY, F. A., YANT, W. P., AND WAITE, C. P. (1930). Acute response of guinea pigs to vapors of some new commercial organic compounds. *Publ. Health Rep.* 45, 1963.
3. VIOLA, P. L., BIOGOTTI, A., AND CAPUTO, A. (1971). Oncogenic responses of rat skin, lungs, and bones to vinyl chloride. *Cancer Res.* 31, 516-522.
4. MALTONI, C. (1976). The value of predictive experimental bioassay in occupational and environmental carcinogenesis: An example: Vinyl chloride. *Ambio* 4, 18-23.
5. MALTONI, C. (1976). Predictive value of carcinogenesis bioassays. *Ann. N. Y. Acad. Sci.* 271, 431-443.
6. INFANTE, P. F. (1981). Observations of the site-specific carcinogenicity of vinyl chloride to humans. *Environ. Health Perspect.* 41, 89-94.
7. MALTONI, C., COTTI, G., MORISI, L., AND CHIECO, P. (1977). Carcinogenicity bioassays of vinylidene chloride. Research plan and early results. *Med. Lav.* 68, 241-262.

8. MALTONI, C. (1977). Recent findings on the carcinogenicity of chlorinated olefins. *Environ. Health Perspect.* 21, 1-5.
9. LEE, C. C., BHARDARI, J. C., WINSTON, J. M., HOUSE, W. B., PETERS, P. J., DIXON, R. L., AND WOODS, J. S. (1977). Inhalation toxicity of vinyl chloride. *Environ. Health Perspect.* 21, 2532-2534.
10. LEE, C. C., BHARDARI, J. C., WINSTON, J. M., AND HOUSE, W. B. (1978). Carcinogenicity of vinyl chloride and vinylidene chloride. *J. Toxicol. Environ. Health* 4, 15-30.
11. SALMON, A. G. (1976). Cytochrome P-450 and the metabolism of vinyl chloride. *Cancer Lett.* 2, 109-114.
12. ZAJDELA, F., CROISY, A., BARBIN, A., MALAVEILLE, C., TOMATIS, L., AND BARTSCH, H. (1980). Carcinogenicity of chloroethylene oxide, an ultimate reactive metabolite of vinyl chloride, and bis(chloromethyl) ether after subcutaneous administration and initiation-promotion experiments in mice. *Cancer Res.* 40, 352-356.
13. BLOCK, J. B. (1974). Angiosarcoma of the liver following vinyl chloride exposure. *J. Amer. Med. Assoc.* 229, 53-54.
14. FALK, H., CREECH, J. L., HEATH, C. W., JOHNSON, M. N., AND KEY, M. M. (1974). Hepatic diseases among workers at a vinyl chloride polymerization plant. *J. Amer. Med. Assoc.* 230, 59-63.
15. LANGE, C. E., JUHE, S., AND VELTMAN, G. (1974). Über das auftreten von angiosarkomen der leber von zwei arbeitern der PVC-herstellender industrie. *Dtsch. Med. Wochenschr.* 31, 1598-1599.
16. LEE, F. I., AND HARRY, D. S. (1974). Angiosarcoma of the liver in a vinyl chloride worker. *Lancet* 1, 1316-1319.
17. SUZUKI, Y. (1981). Neoplastic and nonneoplastic effects of vinyl chloride in mouse lung. *Environ. Health Perspect.* 41, 31-52.
18. LILIS, R., ANDERSON, H. A., NICHOLSON, W. J., DAUM, S., FISCHBEIN, A., AND SELIKOFF, I. J. (1975). Prevalence of disease among vinyl chloride and poly-vinyl chloride workers. *Ann. N. Y. Acad. Sci.* 246, 22-24.
19. MILLER, A., TEIRSTEIN, A. S., CHUANG, M., AND SELIKOFF, I. J. (1975). Changes in pulmonary function in workers exposed to vinyl chloride and poly-vinyl chloride. *Ann. N. Y. Acad. Sci.* 246, 42-52.
20. HOLMBERG, B., TRONEVI, T., AND WINELL, M. (1976). The pathology of vinyl chloride exposed mice. *Acta. Vet. Scand.* 17, 328-342.
21. SUZUKI, Y. (1978). Pulmonary tumors induced in mice by vinyl chloride monomer. *Environ. Res.* 16, 285-301.
22. INFANTE, P. F. (1976). Oncogenic mutagenic risks in communities with polyvinyl chloride production facilities. *Ann. N. Y. Acad. Sci.* 271, 49-57.
23. EDMONDS, L. D., ANDERSON, C. E., FLYNT, J. W., JR., AND JAMES, L. M. (1978). Congenital central nervous system malformations and vinyl chloride monomer exposure: A community study. *Teratology* 17, 137.
24. HEHIR, R. M., MCNAMARA, B. P., MCLAUGHLIN, J., WILLIGAN, D. A., BIERHOWER, G., AND HARDISTY, J. F. (1981). Cancer induction following single and multiple exposures to a constant amount of vinyl chloride monomer. *Environ. Health Perspect.* 41, 63-72.
25. DUCATMAN, A., HIRSCHHORN, K., AND SELIKOFF, I. J. (1975). Vinyl chloride exposure and human chromosome aberrations. *Mutat. Res.* 31, 163-168.
26. BARTSCH, H., MALAVEILLE, C. M., BARBIN, A., BRESIL, H., TOMATIS, L., AND MONTESANO, R. (1976). Mutagenicity and metabolism of vinyl chloride and chloride and related compounds. *Environ. Health Perspect.* 16, 193-198.
27. ANDERSON, D., HODGE, M. C. E., AND PURCHASE, I. F. H. (1977). Dominant lethal studies with halogenated olefins vinyl chloride and vinylidene dichloride in male CD-1 mice. *Environ. Health Perspect.* 21, 71-74.
28. FABRICANT, J. D., AND LEGATOR, M. S. (1981). Mutagenicity study of vinyl chloride. *Environ. Health Perspect.* 41, 189-198.
29. MCCANN, J., SIMMON, V., STREITWIESER, D., AND AMES, B. N. (1975). Mutagenicity of chloroacetaldehyde, a possible metabolic product of 1,2-dichloroethane (ethylene dichloride), chloroethane (ethylene chlorohydrin), vinyl chloride and cyclophosphamide. *Proc. Natl. Acad. Sci. USA* 72, 3190.
30. BARBIN, A., BRESIE, H., CROISY, A., JACQUIGNON, P., MALAVEILLE, C., MONTESANO, R., AND BARTSCH, H. (1975). Liver-microsome-mediated formation of alkylating agents from vinyl bromide. *Biochem. Biophys. Res. Commun.* 67, 596.
31. RANNUG, V., GOTHE, R., AND WACHTMEISTER, C. A. (1976). The mutagenicity of chloroethylene

- oxide, chloroacetaldehyde, 2-chloroethanol and chloroacetic acid, conceivable metabolites of vinyl chloride. *Chem. Biol. Interact.* 12, 251-256.
32. GRIEM, H., BONSE, G., RADWAN, Z., REICHERT, D., AND HENSCHLER, D. (1975). Mutagenicity *in vitro* and potential carcinogenicity of chlorinated ethylenes as a function of metabolic oxirane formation. *Biochem. Pharmacol.* 24, 2013-2015.
 33. SHAHIN, M. M. (1976). Nonmutagenicity and recombinogenicity of vinyl chloride in the absence of metabolic activation. *Mutat. Res.* 40, 269-272.
 34. VOGEL, E., AND SOBELS, F. H. (1976). The function of *Drosophila* in genetic toxicology testing. In *Chemical Mutagens* (A. Hallaender, Ed.), pp. 93-142. Plenum, New York.
 35. DREVON, C., KUROKI, T., AND MONTESANO, R. (1977). Microsome mediated mutagenesis of a Chinese hamster cell line by various chemicals. *Dev. Toxicol. Environ. Sci.* 2, 207-211.
 36. BARTSCH, H., AND MONTESANO, R. (1975). Mutagenic and carcinogenic effects of vinyl chloride. *Mutat. Res.* 31, 93.
 37. PURCHASE, I. F. H., RICHARDSON, C. R., ANDERSON, D., AND ADAMS, W. G. E. (1978). Chromosomal analysis in vinyl chloride exposed workers. *Mutat. Res.* 57, 325-334.
 38. HEATH, C. W., JR., AND DUMONT, C. R. (1977). Chromosomal damage in men occupationally exposed to vinyl chloride monomer and other chemicals. *Environ. Res.* 14, 68-72.
 39. FUNES-CRAVIOTO, F., LAMBERT, B., LINDSTEN, J., EHRENBURG, L., NATARAJAN, A. T., AND OSTERMAN-GOLKAR, S. (1975). Chromosome aberrations in workers exposed to vinyl chloride. *Lancet* 1, 459.
 40. HANSTEEN, I., HILLESTAD, L., THIS-EVERSON, E., AND HELDAAS, S. S. (1978). Effects of vinyl chloride in man: A cytogenic follow-up study. *Mutat. Res.* 51, 271-278.
 41. DOWNS, T. D., STALLONES, R. A., FRANKOWSKI, R. F., AND LABARTHE, D. R. (1977). *Vinyl Chloride, Birth Defects and Fetal Wastage: A Critical Review*. The Society of Plastics Industries, Inc.
 42. DROZDOWICZ, B. Z., AND HUANG, P. C. (1977). Lack of mutagenicity of vinyl chloride in two strains of *Neurospora crassa*. *Mutat. Res.* 48, 43-50.
 43. SPECK, W. T., SANTELLA, R. M., AND ROSENKRANZ, H. S. (1978). Evaluation of the prophage lambda induction (Inductest) for the detection of potential carcinogens. *Mutat. Res.* 54, 101-104.
 44. SHORT, R. D., MINOR, J. L., WINSTON, J. M., AND LEE, C. C. (1977). A dominant lethal study in male rats after repeated exposures to vinyl chloride or vinylidene chloride. *J. Toxicol. Environ. Health* 3, 965-967.
 45. SZENTESI, I., HORNYAK, E., UNGUARY, G., CZEIZEL, A., BOGNAR, Z., AND TIMAR, M. (1976). High rate of chromosomal aberration in V/C workers. *Mutat. Res.* 37, 313-316.
 46. HATCH, M., KLINE, J., AND STEIN, Z. (1981). Power considerations in studies of reproductive effects of vinyl chloride and some structural analogs. *Environ. Health Perspect.* 41, 195-202.
 47. WAXWEILLER, R. J., STRINGER, W., JONES, J., WAGONER, K. J., FALK, H., AND CARTER, C. (1976). Neoplastic risk among workers exposed to vinyl chloride. *Ann. N. Y. Acad. Sci.* 271, 39-48.
 48. TABERSHAM, I. R., AND GAFFEY, W. R. (1974). Mortality study of workers in the manufacture of vinyl chloride and its monomers. *J. Occup. Med.* 16, 509-518.
 49. BUFFER, A., WOOD, S., EIFTER, C., SUAREZ, L., AND KILIAN, D. J. (1979). Mortality experience of workers in a vinyl chloride monomer production plant. *J. Occup. Med.* 21, 195-203.
 50. OTT, M. G., LANGNER, R. R., AND HOLDER, B. B. (1975). Vinyl chloride exposure in a controlled industrial environment. *Arch. Environ. Health* 30, 333-339.
 51. BYREN, D., ENGHOLM, G., ENGLUND, A., AND WESTERHOLM, P. (1976). Mortality and cancer morbidity in a group of Swedish VCM and PVC production workers. *Environ. Health Perspect.* 17, 167-170.
 52. MONSON, R. R., PETERS, J. M., AND JOHNSON, M. N. (1974). Proportional mortality among vinyl-chloride workers. *Lancet* 17, 397-398.
 53. FOX, A. J., AND COLLIER, P. R. (1977). Mortality experience of workers exposed to vinyl chloride monomer in the manufacture of polyvinyl chloride in Great Britain. *Brit. J. Ind. Med.* 34, 1-10.
 54. SPIRTAS, R., AND KAMINSKI, R. (1978). Angiosarcoma of the liver in vinyl chloride/polyvinyl chloride workers. *J. Occup. Med.* 20, 427-429.
 55. FALK, H., AND WAXWEILLER, R. J. (1976). Epidemiological studies of vinyl chloride health effects in the United States. *Proc. Roy. Soc. Med.* 69, 303-305.
 56. BAXTER, P. J., AND FOX, A. J. (1975). Angiosarcoma of the liver as the certified cause of death 1963-1973. *Lancet* 2, 27-28.
 57. HAMMOND, E. C., AND SELIKOFF, I. J. (1974). Two deaths of a rare cancer. *Occup. Health Nursing* 22, 17-19.
 58. NICHOLSON, W. J. (1977). Cancer following occupational exposure to asbestos and vinyl chloride. *Cancer* 39, 1792-1801.

59. WOLFF, M. S. (1976). Evidence for existence in human tissues of monomers for plastics and rubber manufacture. *Environ. Health Perspect.* 17, 183-187.
60. SMITH, P., HEATH, D., AND MOOSAVI, H. (1974). The clara cell. *Thorax* 29, 147-163.
61. COOK, W. A., GIEVER, P. M., DINMAN, B. D., AND MAGNUSON, H. J. (1971). Occupational acroosteolysis II: An industrial hygiene study. *Arch. Environ. Health* 22, 74-82.
62. VELTMAN, G., LANGE, C. E., JUHE, S., STEIN, G., AND BACHNER, U. (1975). Chemical manifestation and course of vinyl chloride disease: Toxicity of vinyl chloride-polyvinyl chloride. *Ann. N. Y. Acad. Sci.* 246, 6-21.
63. GROTH, D. H., LYNCH, D. W., MOORMAN, W. J., STETTLER, L. E., LEWIS, T. R., WAGNER, W. D., AND KOMMINENI, C. (1981). Pneumoconiosis in animals exposed to poly(vinyl chloride) dust. *Environ. Health Perspect.* 41, 73-81.
64. MASTRANGELO, G., SAIA, B., MARCER, G., AND PIAZZA, G. (1981). Epidemiological study of pneumoconiosis in the Italian poly(vinyl chloride) industry. *Environ. Health Perspect.* 41, 153-157.
65. WAGNER, J. C., AND JOHNSON, N. F. (1981). Preliminary observations of the effect of inhalation of PVC in man and experimental animals. *Environ. Health Perspect.* 41, 83-84.
66. MOLINA, G., HOLMBERG, B., ELOFSSON, S., HOLMLUND, L., MOOSING, R., AND WESTERHOLM, P. (1981). Mortality and cancer rates among workers in the Swedish PVC processing industry. *Environ. Health Perspect.* 41, 145-151.
67. ARNAUD, A., POMMIER DE SANTI, GARBE, L., PAYAN, H., AND CHARPIN, J. (1978). Poly vinyl chloride pneumoconiosis. *Thorax* 33, 19-25.
68. MASTRANGELO, G., MANNO, M., MARCER, G., BARTOLUCCI, G., GEMIGNANI, C., SALADINO, G., SIMONALO, L., AND SAIA, B. (1979). Poly vinyl chloride pneumoconiosis: Epidemiological study of exposed workers. *J. Occup. Med.* 21, 540-545.
69. SZENDE, B., LAPID, K., NEMES, A., AND PINTER, A. (1970). A pneumoconiosis caused by the inhalation of polyvinyl chloride dust. *Med. Lav.* 61, 433-436.
70. WEGMEN, D. (1975). Further results in polyvinyl chloride production workers. *Ann. N. Y. Acad. Sci.* 246, 18-21.
71. WALKER, A. E. (1975). A preliminary report on a vascular abnormality occurring in men engaged in the manufacture of polyvinyl chloride. *Brit. J. Dermatol.* 93, 22-23.
72. WALKER, A. E. (1976). Clinical aspects of vinyl chloride disease: Skin. *Proc. Roy. Soc. Med.* 69, 286-290.
73. FRONGIA, N., SPINAZZOLA, A., AND BUCARELLI, A. (1974). Lesioni polmonari sperimentali da inalazione prolungata di PVC in ambiente di lavoro. *Med. Lav.* 65, 321-342.
74. WARD, A. M., UDNOON, S., WATKINS, J., WALKER, A. E., AND DARKE, C. S. (1976). Immunological mechanisms in the pathogenesis of vinyl chloride disease. *Brit. Med. J.* 1, 936-938.
75. GRAINGER, R. G., WALKER, A. E., AND WARD, A. M. (1980). Vinyl chloride monomer induced disease: Clinical radiological and immunological aspects. In *Induced Disease, Drug, Irradiation, Occupation* (L. Preger, Ed.), pp. 191-214. Grune & Stratton, New York.
76. LANGAUER-LEWOWICKA, H., DUDZIAK, Z., BYCZKOWSKA, Z., AND MARKS, J. (1976). Cryoglobulinemia in Raynaud's phenomenon due to vinyl chloride. *Int. Arch. Occup. Environ. Health* 36, 197-207.
77. CRYSTAL, R. G., FULMER, J. D., ROBERTS, W. C., MOSS, M., LINE, B. R., AND REYNOLDS, H. Y. (1976). Idiopathic pulmonary fibrosis: Clinical histologic, radiographic, physiologic, scintigraphic, cytologic and biochemical aspects. *Ann. Intern. Med.* 85, 769-788.
78. CHIAZZE, L., JR., NICHOLS, W. E., AND WONG, O. (1977). Mortality among employees of PVC fabricators. *J. Occup. Med.* 19, 623-628.
79. CHIAZZE, L., JR., WONG, O., NICHOLS, W. E., AND FERENCE, L. (1980). Breast cancer mortality among PVC fabricators. *J. Occup. Med.* 22, 677-679.
80. HATTIS, D. (1981). Needs for public health intervention and needs for new research on vinyl halides and their polymers: A public policy perspectives. *Environ. Health Perspect.* 41, 227-231.
81. HADZIMA, J., HATTIS, D., MESROBIAN, A., HAZEN, S., KATZ, J. J., AND ASHFORD, N. (1976). *A Case Study on the Regulation of Vinyl Chloride Emission in the Workplace*. Center for Policy Alternatives, Massachusetts Institute of Technology, Cambridge.

Pesticides: The Good and the Bad¹

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Pesticides have been used for many years. In earlier times they were a protection against fungi and insect pests. The great increase in the use of pesticides occurred with the development of new organic chemicals following World Wars I and II. In addition to chemicals for the control of fungi and insects, new developments were nematocides, herbicides, rodenticides, avicides, defoliants, wood preservatives, etc.

The use of chemicals helped increase productivity, but caused great concern about their effect on human health and safety. On the other hand, chemicals did help tremendously from the standpoint of protecting against diseases that were carried by insects, especially mosquitoes.

Adverse publicity has caused great concern about pesticides and this is especially so since our society has undergone great changes from an agricultural society to an industrial society and finally to a communications society. Unfortunately, publicity relating to the use of pesticides has seldom been balanced from the standpoint of the good and the bad. In fact, the communications media has and does usually stress the potential adverse effects of pesticides without reference to the good. This has caused concern on the part of advocates and the average person to the extent that it has placed heavy constraints on agriculture. There is a need for the dissemination of balanced information on the good as well as the bad of pesticides.

The title "Pesticides: The Good and the Bad" means to me the good and the bad things about pesticides and not necessarily that there are good and bad pesticides.

Pesticides have been used for a good many years and, strange as it may seem, one of the earliest uses was to discourage boys from stealing grapes to be used in the production of prize wines. The deterrent was a blue copper compound which discouraged the stealing of grapes. Eventually, it was found to be a good pesticide to control certain fungi.

The early uses of pesticides were mostly for the control of fungi and insects. The great increase and extended use of these materials occurred with the development of new organic chemicals, particularly after World War II. For example, in addition to insecticides and fungicides, came nematocides to control nematodes, herbicides to control weeds, rodenticides to combat rodents, avicides for birds, chemicals to control coyotes, defoliants to remove leaves, agents to control, stimulate, or retard growth, and even wood preservatives.

¹ Dedicated to Prof. Dr. F. Korte in celebration of his 60th birthday.