HAZARD EVALUATION AND RISK ASSESSMENT

FOR

VINYL CHLORIDE

Prepared for the American Industrial
Health Council Risk Assessment Subcommittee

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I. INTRODUCTION AND BACKGROUND

Vinyl chloride (VC) is a classical carcinogen, in that it exhibits dose response effects in humans and several species of mammals, shows binding to DNA, and is mutagenic with activation in bacteria. Its industrial importance has led to one of the larger bodies of scientific data available on toxicity and metabolism, and several attempts at risk asssessments have been made. There have been a number of reviews of the literature on specific aspects of vinyl chloride, but none that has attempted a complete view of all of its toxic aspects so that their relative hazards can be evaluated. That is the purpose of this effort.

A. Occurrence and Use

Vinyl chloride was first prepared about 1833 (Herrle, 1963). The French chemist Regnault first observed its polymerization in 1838, and his work was extended by the German scientist Baumann in 1872, and further developed by Ostromislensky, Staudinger, and others during the first two decades of this century. Plastisol and organosol applications were the first industrial uses. See, e.g., German patent 281,877, in 1915 to Klatte and Rolette and U.S. Patent 1,721,034 to Ostromislensky (Whittington, 1962). Its industrial use in this country dates from the late 1930s (Semon, 1933, Brous and Semon, 1935). Production and use of vinyl chloride, primarily for conversion to polyvinyl chloride polymers, has grown steadily at rates of 6-8% annually until the present manufacturing capacity in the United States is about 8 billion pounds per year (C&EN, 1980, Cameron, Lundeen and McCulley 1980), and the worldwide capacity is about four times that.

There are minor uses of the material as a manufacturing intermediate for other chlorinated products. It was used as a propellant in aerosol containers until the early 1970s, when this application was withdrawn by the suppliers, and later officially banned (FDA, 1974, CPSC, 1974).

Consideration has been given to the use of VC as an anesthetic, but it was considered unsatisfactory because of possible cardiac effects (Peoples and Leake, 1933, Oster, et al., 1947).

It now appears that vinyl chloride may have been a minor constituent of the environment from natural causes. Hoffman and coworkers (1976) reported finding vinyl chloride in cigarette smoke, and therefore by inference in the combustion products of other chlorine-containing organic matter, such as from forest fires.

B. Health Concerns

Vinyl chloride has been recognized for several decades as an anesthetic, and as being toxic to the liver of mammals. (See later sections for a fuller discussion of these points.) During the early 1960s a health problem was recognized in polymerization reactor cleaners termed acroosteolysis (AOL) (Dinman, 1971). Industry efforts to reproduce this effect in rodents were partially successful (Viola,

1970) and also disclosed that very high exposures of about 3% for 12 months led to cancers of the skin, bones, and lungs (Viola, 1971). More extensive studies sponsored by a European producer group led to the finding in 1973 that angiosarcoma of the liver (ASL) and tumors at other sites were developed at lower concentrations and longer exposures (Torgelson, 1974) and late in 1973 this same rare disease was discovered in polymerization workers (Creech and Johnson, 1974). There have now been a total of 81 cases of ASL reported worldwide and 25 cases in the U.S. (Stafford, 1980). Concern for this usually fatal disease has prompted an enormous amount of animal experimentation and human epidemiology relating to vinyl chloride health effects, and this will be summarized in the following sections. Many of the steps which industry has taken to protect the employee are discussed in the proceedings of a recent NIOSH Symposium (Enviro Controls, 1980).

II. ENVIRONMENTAL EFFECTS

As the physical properties in Table I indicate, vinyl chloride has low water solubility, and is easily lost to the atmosphere from streams and discharges (Hill, et al., 1976). Unpublished reports cited by EPA (1974) state that a stirred beaker lost 96% of its original 16 ppm in two hours, while an unstirred beaker lost 25%, at 22°C. Plots of log concentrations versus time gave straight lines, indicating volatility to be the only important loss mechanism. There was no difference in loss rates between distilled water, river water, or industrial effluent. It is photochemically reactive, with a half-life in sunlight of about six hours (EPA, 1975). The reaction rates are slightly less than those of ethylene (Cox, Eggleton, and Sandalls, 1974, Gay, Noonan and Bufalini, 1976) in the reaction with NO_x, and considerably less in the reactions with ozone. The residence time in the atmosphere was estimated as 1.8 days by Singh, et al., (1980), with a 43% loss per 12 hours of sunlight, based on the rate of reaction with hydroxyl radical only. It does not appear to be absorbed by microorganisms, as shown by tests with five mixed bacteria populations, three mixed fungal populations, two axenic bacterial cultures, and one algae. The mixed bacteria did not degrade the VC, nor was it toxic to the bacteria at concentrations up to 900 mg/l (Hill, 1976). It does not bioaccumulate in the food chain (Lu, et al., 1977).

Brown, et al., (1977) reported on the acute toxicity of VC to northern pike, but the data are inadequate for evaluation of the results.

The EPA has reported (EPA, 1975) finding VC in the water supplies of some cities in the ppb range. The concentration was higher in the finished than in the raw water, indicating that it may be produced in the chlorination step. Dressman and McFarren (1978) have found VC in the ppb range in water from distribution systems using PVC pipe. Banzer (1979) states that no extraction of VC occurs from pipe containing less than 1 ppm residual by a test sensitive to 2 ppb. It is also present in the discharge of some VC handling plants in the low ppm range (EPA, 1974). The EPA has since imposed stripping requirements on industrial effluents (EPA, 1976).

The EPA has conducted three ambient monitoring programs around VC handling plants (EPA, 1975). The first, in 1974, found measurable quantities at distances up to 0.5 km from a PVC plant. The third program failed to find significant quantities at the fence line of five large fabricating plants. The results of the second program have not been released, but analysis of the data has shown (Air Products, 1976) that the average concentration in early 1975 at the plant tested was about 40 ppb at 500 meters for the plant center, 10 ppb at 1 km, and 2 ppb at 2 km. The EPA has calculated (EPA, 1975b) an average exposure of 17 ppb to persons residing within five miles of a typical PVC plant, using emission data and modeling techniques which were strongly disputed by industry. The estimated 95% reduction of emissions by the current standard (EPA, 1976) presumably gives a current exposure to those within five miles of 0.4 ppb. The generally accepted field monitoring method for VC has a lower sensitivity of 10 ppb (EPA, 1976), so that these estimates cannot be verified.

Gruinard, Taft, and Wiberg (1976) calculated that the steady state, worldwide ambient concentration in 1973 was about 0.0014 ppb (3.6 nanograms/m^3). Hoffman, et al., (1976) found VC in tobacco smoke and speculated that it might be present in combustion gases from all chloride-contaminated materials, and therefore ubiquitous. Current industry estimates are that emissions have been reduced about two orders of magnitude from VC handling plants and three orders of magnitude in the residual VC in products, and thus in the emissions from fabrication operations.

Kuebler (1964) reports that the thermal decomposition of VC in air at 1000°C produces phosgene, carbon monoxide, and hydrogen chloride, as do other chlorinated substances. The complete combustion of vinyl chloride produces stoichiometric amounts of hydrogen chloride. Heating of the polymer does not cause it to revert to the monomer, except in negligible amounts at temperatures well above the normal processing temperature (Wakeman and Johnson, 1978).

The use of PVC for liquor bottles was stopped in 1973 when low concentrations of VC were found in the contents. The FDA still permits the use of PVC as packaging for foods, and the use is much more widespread in Europe than in the U.S. There, a limit of 50 ppb of VC in the foodstuff is imposed (Council of Europe, 1979).

Both Feron et al., (1975) and Witney and Collins (1976) have shown that the retention of VC from drinking water by rats is inefficient. The latter authors calculated that 20 ppm in total drinking water (45 g/day) would produce VC levels in the blood equal to a constant exposure to 2 ppm in the air. Schaumann (1934) had reported earlier that cats lost 82% of their blood levels of VC within 10 minutes after cessation of exposure by inhalation. Buchter, et al., (1978) gave the figure as 70-74% after 10 minutes in humans.

Hefner, et al., (1975) have shown that skin absorption in monkeys is only 0.1% as rapid as absorption through the lungs.

III. ANIMAL METABOLISM

Clapp and coworkers (Clapp, 1969) identified cystiene derivatives in the urine of rats treated with vinyl chloride (VC) or vinyl acetate, and postulated that intermediates were formed in the metabolism of these compounds which were reactive with glutathione. Vazin and Plokhova (1969) reported an increase in adrenaline derivatives in the blood of chinchilla rabbits exposed to VC.

Hefner and coworkers (Hefner, 1975) proposed a saturable metabolic pathway in rats via alcohol dehydrogenase which gives rise to chloroethylene oxide or chloroacetaldehyde as the first active intermediate, and which is the primary metabolic route at concentrations below 100 ppm. The final excretion products appeared to be the result of binding with glutathione and/or cysteine at the sulfhydryl group. Higher concentrations, or the addition of alcohol, were believed to result in an alternate pathway via chloroethanol. Gothe, et al. (1974) found support for this primary metabolic route by trapping metabolic products from rat liver homogonates exposed to VC. (See also Muller, Norpath, and Ouzanski, 1978.) Van Duuren (1975) also postulated that the epoxide route was active. Kappus et al. (1975) reported that the addition of glutathione reduces the binding of VC-products to protein in rat liver microsomes, and Jaeger (1975) found that chronic exposure to VC reduced the glutathione concentration in the liver of rats, and that pretreatment of the rats with phenobarbitol, an alcohol metabolism suppressor, increased the liver toxicity of VC (Jaeger, 1974). Watanabe, et al., (1976) found, however, that the suppression of hepatic nonprotein sulfhydryl was not seen at exposures below 50 ppm. Bolt, et al., (1975) found that the presence of NADPH was required for binding of VC metabolites to protein in either rat or human liver microsomes.

These workers also found (Bolt, 1976) that respiratory uptake of VC by rats was completely blocked by cytochrome P-450 inhibitors.

Green and Hathaway (1975) isolated and identified the cystiene-containing metabolic products of VC, but postulated a free-radical initiated direct addition of VC to the -SH group, rather than an epoxide intermediate. However, these workers concluded later that the epoxide route was compatible with experimental data. (Green and Hathaway, 1977, 1978, Hathaway, 1977.) Guengerich and Strictland (1977) disputed both the epoxide and free-radical mechanisms in a study which found that both NADPH and cytochrome P-450, together with molecular oxygen, were necessary for the metabolism of VC, and proposed a mixed-function oxidation route.

Ottenwalder and Bolt (1980) found that the metabolism of VC occurs primarily in the hepatocytes of rat livers, and not in the sinusoidal cells, which have very low oxidative metabolic capacity, but are the site of tumor induction.

Buchter and coworkers (1978) concluded that rodents and humans have similar metabolic pathways, but that the human metabolic rate is much lower than that for rodents.

The postulated metabolic intermediate chloroethylene oxide has been shown to cause tumors in mice at the site of injection or after phorbol-promoted skin application while the other intermediate chloroacetaldehyde did not (Zajdela, et al., 1980)

The metabolic rate for VC in rats has been found to be 1000 times as fast as that of vinylidene fluoride, which is a much weaker inducer than VC of pre-neoplastic hepatic foci in newborn rats (Stockle, et al., 1979). Vinyl bromide also has a much lower rate than VC (Filser and Bolt, 1979). Metabolites of VC have a higher binding affinity for rat microsomal protein than do those of trichloroethylene, a related compound for which the demonstration of carcinomicity is dubious (Saib, 1979). Vinylidene chloride appears to be metabolized by a very different pathway (Hathaway, 1977), although see also Watanabe, et al., (1980) who feels that rate is important. Andersen, et al., (1979) have recently reported that the pathway for this compound also is saturable. Styrene is also postulated to metabolize via a reactive oxide intermediate (Vainio, 1978) but it has not proven carcinogenic to rodents; thus, rate of metabolism, and not only route, may also be a key to the carcinogenicity of similar substances.

Gehring (1977) has reviewed several studies of his coworkers and concluded that there is a dose-dependence for the fate of inhaled VC, with a threshold for the ability of the test animal to provide sufficient sulfhydryl groups to prevent covalent binding to protein. They, and several other workers (Schauman, 1934, Feron, 1975, Green and Hathaway, 1975, Withey, 1976, and Buchter, et al., 1978) found that an equilibrium is established very quickly between the VC content of the blood and the ambient concentration, and that the expiration levels drop very quickly after cessation of exposure in both humans and animals. This indicates that there is little or no storage of VC in the body.

In summary, it appears that vinyl chloride is metabolized in most mammals tested by a mixed-function oxidase route. The metabolic intermediates are excreted after reaction with the sulfhydryl groups of glutathione or similar substances. Excess depletion of the available sulfhydryl groups in the microsomes may lead to a localized surplus of the active product, which could eventually cause genotoxic effects. Ottenwalder and Bolt (1980) suggest that, in rats at least, the active metabolite must leave the hepatocytes to act on the sinusoidal cells, the site of neoplastic development.

IV. ACUTE TOXICITY

A. Plants and Lower Organisms

There are few published data on the effect of VC on flora. Hill, et al. (1976) reported that VC does not appear to be absorbed by bacteria, fungi, or algae, nor was the VC degraded by the bacteria. No toxic effects were seen. Heck and Pines (1962) found no effect on several plant species from seven days' exposure at 10 ppm, with moderate damage at 100 and 1000 ppm, an effect very similar to that of ethylene. The EPA states (1975) that vegetational damage around VC-handling plants has not been documented. See Section VI for further discussion of effects on lower organisms.

B. Animals

The principal acute dangers from VC are anesthesia, which can cause death from respiratory paralysis, reversible liver damage, and cardiac arrhythmia.

A summary of the early literature was prepared by von Oettinger in 1955, and an exerpt is reproduced below:

> "Like other chlorinated hydrocarbons, vinyl chloride has narcotic properties. According to Peoples and Leake (1933) the narcotic range for mice is between 3.5 and 5 mM per liter of air. Concentrations of 7 mM per liter of air will cause narcosis in rabbits and dogs after 1 minute, and the recovery is prompt and not followed by untoward effects even after prolonged exposure. Schaumann (1934) determined the vinyl chloride level in the blood of cats anesthetized with 10 to 13 vol. percent as 15 to 17 mg. percent. Oster, Carr, Krantz, Jr., and Sauerwald (1947) used vinyl chloride stabilized with 0.5 percent of p-tert-butyl-catechol for narcosis of dogs, starting with concentrations of 50 vol. percent and reducing the concentration gradually to 7 vol. percent. They found that the induction was rapid, but that "crowing" continued even during deep anesthesia and that there was profuse salivation. During narcosis the relaxation of the abdominal muscles was good but the legs remained rigid showing, throughout the anesthesia, incoordinated movements. The recovery was rapid but associated with violent excitation.
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> As to the effect of vinyl chloride on the circulation, Schaumann (1934) studied its effects in the Starling heart-lung preparation of cats judging the action by the effect on the intra-auricular pressure. He found that similar effects were produced by 1.3 percent of solaesthin (dichloroethylene), 3 vol. percent of ether, and 18 vol. percent of vinyl chloride. Higher concentrations (20 vol. percent) of vinyl chloride caused a more or less marked relative insufficiency and even 25 to 30 vol. percent were unable to produce complete cardiac failure. Oster, Carr, Krantz, Jr., and Sauerwald (1947) studied the circulatory response in dogs anesthetized with 10 vol. percent

of vinyl chloride. They noted a moderate fall of the blood pressure and definite evidence of cardiac irregularities as indicated by intermittent tachycardia, extraventricular systoles and vagal beats. Electrocardiographic studies revealed marked changes of the cardiac rhythm such as tachycardia followed by bradycardia, inversion of the R spike, and in one instance incipient ventricular fibrillation. All records showed abnormalities of the QRS interval varying from sinus arrhythmia and transitory extreme left axis deviation to very serious conditions such as auricular-ventricular block, ventricular tachycardia, ventricular multiform extrasystoles, and inversion of the T wave with elevated ST segment in lead II. As the anesthesia progressed towards respiratory failure most of the QRS abnormalities disappeared but the R amplitude was generally reduced.

As to the toxicity of vinyl chloride, Patty, Yant, and Waite (1930) studied this in guinea pigs. They found that exposure to 20 to 40 vol. percent kills the animals in a very short time, that concentrations of 10 vol. percent are dangerous to life with exposures for 30 to 60 minutes, and that 0.5 vol. percent is the maximum allowable concentration for several hours' exposure without causing acute disturbances of severe nature. Animals exposed in this way showed some edema of the lungs and hyperemia of liver and kidneys. They considered vinyl chloride less harmful than chloroform or carbon tetrachloride and of a similar order of toxicity as ethyl chloride. Schaumann (1938) found that mice and rats tolerate repeated light narcosis for 4 hours daily on 5 to 8 consecutive days and for 1 hour daily for 4 weeks without showing kidney or liver injuries. Dogs which had been narcotized for 3 hours with 10 vol. percent on 7 occasions in the course of several weeks showed no considerable changes in kidney and liver. Higher concentrations (20 vol. percent) caused in dogs marked salivation, respiratory arrest, and vomiting after narcosis. Peoples and Leake (1933) determined the lethal range for mice with 10 minutes' exposure as 10 to 12 mM per liter, and Schaumann (1934) determined the vinyl chloride level in the blood at the time of cardiac arrest as $<$ 40 mg. percent and at the time of respiratory arrest as 27 to 30 mg. percent, the same value for chloroform being 60 to 70 mg. percent."

Lehman and Flury (1943) also discuss the work of Schaumann, including some unpublished studies, and, as did several other reviewers, reach the conclusion that "vinyl chloride is one of the least dangerous of the chlorinated hydrocarbons." Schaumann's published reports (1934, 1936) demonstrate that VC is a safer anesthetic for cats than is ether or chloroform because it cannot induce cardiac insufficiency at concentrations up to 30 vol.%, and because of very rapid clearing after the end of administration. There was 82% expired after 10 minutes at blood levels of 15-17 mg. percent. He reported that the VC in the blood was distributed 85% in the corpuscles and 15% in the plasma. He found no harmful effects on the heart, and recommended its use as an anesthetic, especially in combination

with nitrous oxide. However, Oster (1947) and Carr (1949) reported that with dogs, at an anesthetic level of 8-12%, they found serious cardiac arrhythmias and there was development of sensitization. Peoples and Leake (1933) had commented on this effect earlier.

Mastromatteo, et al., (1960) exposed mice, rats, and guinea pigs to 10, 20, 30, and 40% VC in air for 30 minutes and found 1 of 5 mice died at 20%, all mice and rats and one guinea pig died at 30%, and 2 of 5 guinea pigs died at 40%. Deaths were due to narcosis and some pulmonary edema was reported. Kuebler (1964) reported "no histological damage" to several species exposed to as much as 5% for 100 days.

Prodan (1975) studied the two-hour lethal dose of VC in mice, rabbits, guinea pigs and rats, and found a rather sharp boundary between lethal and non-lethal doses for this time period. Sensitivity to VC was found to be: rabbits, guinea pigs < rats < mice. Surviving animals exhibited general congestion of all internal organs. Pulmonary edema, marmorated liver, and kidney tumefaction were observed. A three-month exposure of guinea pigs at 10,000 ppm for 2 hours daily over 3 months produced lung fibrosis. This has not been reported for other rodents.

Torgelson, Ogen, and Rowe (1961) found that repeated 7-hour exposures to 100 ppm for six months resulted in increase in rat liver weights, but no observable effect in guinea pigs, rabbits or dogs. Similar exposure to 200 ppm resulted in micropathological changes in rabbit livers and weight increases in rat livers. Exposure to 500 ppm for 4.5 months caused micropathological changes in rat livers. There was no observable effect from 50 ppm at six months in either species, nor from daily 100 and 200 ppm doses for one hour, but longer daily exposure times caused slight increases in liver weights. They then suggested that a 50 ppm time-weighted average (TWA) be used as a limit for human exposure.

Lester, Greenberg, and Adams (1963) proposed a 500 ppm TWA as the result of their work at much higher concentrations, and this was accepted by the American Conference of Governmental and Industrial Hygiene first as a TWA, then as a ceiling concentration (ACGIH, 1963). This was adopted by the Occupational Safety and Health Administration in May, 1971 as a formal regulation. The ACGIH recommended a reduction to 200 ppm TWA in its Third Edition in 1971. Rowe and Torgelson (1977) have since commented: "Had our recommendations based upon relatively simple toxicology been followed then, the difficulties of today may never have occurred."

Feron, et al., (1975) administered VC in soya oil to rats by gavage for 13 weeks. They reported a no-effect level for liver damage of at least 30 mg/kg, and doubtful toxic effects at 100 and 300 mg/kg. Over 92% of the administered VC was expired in four hours after treatment.

One part of a bioassay (Hehir, 1980) on rodents conducted for the Consumer Product Safety Commission consisted of high, short exposures to VC in the air. These included one-hour exposures to rats and mice at 50, 500, 5000, and 50,000 ppm, 10 and 40 one-hour exposures at 500 ppm, and 49 and 100 exposures at 50 ppm. There were no external signs of toxic response during the exposure period except for the mice at 50,000 ppm, during which time the males exhibited hyperventilation, twitching, atoxia, and tremors, and the females showed hyperactivity, atoxia, and respiratory difficulty. During the lifetime holding period following exposure, all mice exposed to 500 ppm or more showed high levels of pneumonitis. Male rats exposed at 50,000 ppm developed bronchopneumonia at a higher rate than did other groups. Mortality of two strains of mice exposed at 50,000 ppm, and one strain exposed at 50 ppm was higher than the controls. Rats showed sublethal cytoplasmic liver damage from which they recovered.

Jaeger, et al., (1974) also exposed rats to 50,000 ppm VC, for up to five consecutive days at six hr/day. Those animals not pretreated with phenobarbitone showed no abnormality, while pretreated rats did have acute biochemical and histological changes after the first treatment. Subsequent treatments caused no further effects, which led the author to hypothesize that the first treatment caused the development of some protection against further damage.

C. Humans

Humans appear to respond to the acute effects of VC much as do the lower mammals. The odor threshold of VC is about 1200-2000 ppm (Union Carbide, 1974). Deaths have been reported (see, for example, Damziger, 1960) of workers exposed to unknown, but high occupational concentrations, and there are numerous anecdotal reports of workers suffering temporary loss of consciousness in the industry. (Spiritas, et al., 1975, Cole, 1975, Klein, 1976). Schaumann (1936) reports that the human narcotic range is 7-10% with 12% being dangerous. Lester, 1963, reported the range as 8-10%. There are no immediate effects of exposure in the 50-500 ppm range (Baretta, 1969). Dublin and Vane (1935) give confusion, intoxication, burning of the soles of the feet, and subsequent headaches as the results of exposure.

V. CHRONIC TOXICITY

A. Animals

Few animal studies extending more than six months have been reported apart from bioassays for carcinogenicity. Viola's attempt (1970) to reproduce AOL in rats used exposure of 25 rats at 3% for four hrs/day, five days/week for 12 months. He reported that the animals were slightly soporific, and began to show a decrease in weight and reaction to external stimuli. Half of the animals died of cardio-respiratory complications and two of hematoperitoneum. Most showed pathological involvement of the brain, liver, kidney and thyroid. Six showed pathological alterations of the skeleton, bone metaplasia and changes in the cartilage. There were, in addition, tumors at various sites.

Basalaev, et al., (1972) reported a study with rats and rabbits in which they claimed to have reproduced AOL in these species at 0.03-0.04 mg/l. Few details were given, and these results have not been duplicated.

Feron and Krees (1979) exposed rats to 5,000 ppm, 7 hr/day, 5 day/week for up to one year and found tubular nephrosis, focal degeneration of the myocardium, and spleen damage, in addition to various primary tumors.

B. Humans

An article which has been cited frequently as supplying an early warning of the toxicity of VC is that by Tribukh (1949) which discusses health conditions in a PVC processing plant in Russia. The author actually does not ascribe the health problems to any specific material, but mentions diphenyl chloride, hydrogen chloride, and other toxic materials as being present. No measurements were made for VC, but it is extremely unlikely that any significant quantities could have been present in the workplace.

Several articles appeared before 1974 describing what has come to be called "VC poisoning" or "VC disease", although the latter has become more closely associated with AOL than gastro-neural problems. Many of these are not particularly useful because there are no exposure data and there often is known exposure to other recognized toxic materials. It does appear, however, in light of subsequent information, that the exposures must have been quite high for these symptoms to have appeared so quickly. Suciu (1975) reported a decrease in symptoms as the exposure was reduced. Some of these reports are listed briefly below:

Filatova, et al., (1958) reported spastic angioneurosis in workers that had been exposed to 20-315 ppm VC in a PVC process.

Gabor, et al., (1962) observed a decrease in catalase and an increase in peroxidase activities and glutathione levels for VC and other exposures.

Gabor, et al., (1964) reported that PVC workers had a decrease of albumin and increase of beta- and gamma- globulins and other blood serum changes.

Grigorescu and Toba (1966) found chloroacetic acid in the urine of VC-exposed workers and changes in the alpha/gamma globulin ratio.

Antonyuzhenko (1968) found that early clinical signs were reversible, but that the majority of "poisoning" manifestations were progressive.

Smirnova and Granik (1970) reported residual central nervous system effects in persons exposed to a variety of chemicals, including VC in some instances.

Kudryantseva (1970) found that severe cases had cardiac disturbances, including changes in rhythm, conductance, and polarization.

Juhe and Lange (1972) found liver disfunction in 2 of 7 patients with serious AOL, another with respiratory disease, and three with scleradoma. Several subsequent papers by the same group reported similar findings. (Stein, Juhe, Lange and Viltoman, 1973, Juhe, et al., 1973, Lange, et al., 1974).

Kramer and Mutchler (1972) made a statistical analysis of the difference between a group who had been exposed to VC for up to 25 years work history at up to 300 ppm versus other chemical workers, and found minor changes in certain blood chemistry and liver functions.

Portal fibrosis and portal hypertension, frequently combined with spleenomegaly, are found in both workers with ASL and other workers with extensive history of high VC exposure (Suciu, et al., 1967, Marsteller, et al., 1973, Falk, et al., 1974, Thomas, et al., 1975, Waxweiler, 1977). Abnormal sinusoidal lining cell development also is frequently associated with these symptoms. It has been postulated that these are early stages of ASL, but there have not been enough observations to confirm this hypothesis. Taylor (1977) has suggested the use of grey-scale ultrasound as a diagnostic tool for measuring portal vein involvement.

Voltman (1975), Lillis (1975), and Lange (1975) discussed this problem, and added thrombocytopenia and esophogeal varices to the list of symptoms. Suciu (1963) and Lange (1975) report lowered thyroid activity and production of 17-ketosteroids. Czermielewski, et al., (1979) emphasized the skin changes seen on long exposure.

Neither Waxweiler, et al., (1977), nor Gamble, et al., (1976), found any indication of loss of respiratory function associated with VC exposure although Mapp, et al., (1978) and Miller (1975) did believe that there were some functional lung disorders in PVC workers which could not be explained totally by smoking, age, dust exposure, or bronchitis. A recent review (Joint Conference, 1980) of data relating to the respiratory functionality of VC/PVC workers supplied no significant data associating VC exposure with lung abnormalities.

A second area of concern for humans exposed to VC over long periods is a degenerative disease of the bone tufts, accompanied by Raynouds syndrome, and, frequently, scleradoma. Suciu (1963) first reported this disease, then Cordier (1966). These were followed by Harris and Adams (1967), Wilson, et al., (1967), and Basalaev (1970). One industry-sponsored survey (Dinman, 1971) identified 25 definitive cases and 16 suspect cases in the U.S. No certain eiteological agent was found, but the cases were clearly associated with hand cleaning of reactors, (Cook, 1971), where there is a combination of physical joint insult and VC exposure. The disease is most often seen in the hands and fingers, but occasionally in the feet or back (Harris, 1967). Dodson (1971) could find no obvious medical reason for predeliction to the disease in the four cases which he studied. It appears to be reversible after cessation of exposure (Graniger, Walker and Ward (1980).

Maricq (1976) found a strong association of capillary abnormalities in the hands with workers suffering from AOL. Lillis (1975) reported that an abnormal Allen test for circulatory efficiency was found in many affected workers, as well as many other organic symptoms related to the liver and circulatory systems.

This disease (AOL) is seen occasionally in patients not exposed to VC, Cheney (1965), Wilson (1967) Meyerson (1972), but there is no question that VC exposure is responsible for the cases seen in the industry. It appears to be a result of circulatory deficiencies brought on by VC exposure, possibly aggravated by physical insult. Bretza and Goldman (1979) have discussed non-occupational cases of scleradoma and AOL.

Bertozzi, et al., (1979) studied the status as of 1975 of a group of 4,777 workers, some of whom had been employed since 1952 in VC/PVC production facilities. No control or comparison data are given, and many different laboratories performed the analyses so only relative trends within the cohort can be identified. They stated that the highest exposures were "above 800 ppm." Confirmed and suspected cases of AOL increased with the degree of exposure and the age of the worker, but not with the length of exposure. "Abnormal" liver test results increased with length of exposure but not the degree. Heavy drinking appeared to act synergistically with duration of exposure in affecting hepatomegaly and elevated GGT.

Graniger, Walker, and Ward (1980) reviewed the literature on symptoms associated with VC exposure, and discussed the symptoms of 88 workers from a factory, 9 of whom were stated to have definite vinyl chloride disease. They report a gradiation of findings from those with the symptoms to those without, but do not make comparisons with unexposed controls. They postulate that vascular and/or immunological changes are responsible for the observed effects, and state that they expect no new cases to develop at current exposures below 5 ppm.

Thus, these are two major areas of concern in the noncarcinogenic chronic effects of VC exposure: AOL and liver damage. These two problems are sometimes associated in workers with long histories of high exposure. Various liver symptoms have been considered precursors in the progression to ASL, but it is curious that, although there are roughly the same number of AOL and ASL cases recorded, only one person has yet been diagnosed as suffering from both diseases.

Knowledge of the exact exposures of these cases would be of great assistance in evaluating the concern for exposures experienced at present, but there have been no definitive estimates made. Suciu (1975) reported values associated with clinical symptoms that appear to be far too low, in light of industry experiences since 1974. OSHA (1975) estimated that reactor cleaners had been exposed to 1,600 ppm in their work. A CEFIC publication (1976) has estimated the average exposure for all European PVC workers in the 1945-1960 era as "up to and beyond 1000 ppm", and there is no reason to believe that the U.S. conditions were much different, but even this is an average for all workers, and the symptoms, AOL, chronic liver damage, and ASL, are more closely associated with reactor entry and cleaning than with other jobs. The National Toxicology Program (1980) quotes IARC data which also cites very high potential exposures, and Fishbein (1979) quotes several other sources.

The EPA requires (EPA, 1976) all PVC processes to displace the vapor from reactors with water before opening for entry. This is based on a study (EPA, 1975, page 4-71) which showed that this reduced the residual content of the reactor vapor to 8,000 ppm. This is a new procedure, which had not been in general use before 1975. It had been the practice of some companies to force air through an opened reactor before entry, but this was generally an unmonitored procedure. Cook et al., (1971) reported that unventilated reactors were often over 3,000 ppm, and Filatova and Gronsberg (1957) stated that excursions were seen up to 34,000 ppm. This, coupled with the anecdotal reports of anesthesia of workers (Spiritas, 1975, Cole, 1975, Klein, 1975), supports the conclusion that reactor cleaners certainly were exposed to recurring concentrations in the several thousand ppm range. This fact must be considered in any attempt to evaluate the hazard to workers at the present time, or to the population at large.

VI. MUTAGENICITY

Vinyl chloride has been shown to cause various types of chromosomal changes in single-celled life forms. This is generally termed "mutagenesis", and is in common use as a screening test for possible carcinogenicity, and bears no necessary relationship to its ability to cause heridable changes in higher forms of life. That subject will be considered in the next section.

Hopkins (1979) has published a review of the mutagenicity data on VC. Although it is clear that VC is mutagenic in several strains of Salmonella where activated by rat liver cells (Rannung, et al., 1974, Bantsch, 1975, Grein, et al., 1975), some studies have shown it to be effective without activation (McCann, et al., 1975, Andrews, et al., 1976) and some have not (Rannung, 1974, Bartsch, 1975, Elmore, 1976). This may be explained by the direct metabolism of VC by the bacteria microsomes; Kappus, et al . (1975) found that rat liver microsomes are effective in this, and thus bacteria may be also. Garro, et al., (1976) suggested a free radical mechanism for the activity of the rat liver fraction, but Bartsch and Montesano (1975) and Kappus, et al., (1975) favored the mixed-function oxidase as the mediator.

Both of the suspected metabolic intermediates for VC, chloroethylene oxide and chloroacetaldehyde, are also mutagenic to Salmonella (Malavielle, 1975, Rannung, 1976).

These metabolites also were effective in transforming Bacillus subtillis (Elmore, et al., 1976) and Chinese hampster cells in vitro (Huberman, et al., 1975). Laumbach, et al. (1978) studied the effect of VC and its metabolites on Salmonella and B. subtillis strains, and concluded that recombination repair is the mechanism for correcting VC-metabolite damage.

Mouse-liver microsomes were necessary for VC to have an effect on various Saccharomyces varieties (Soprieno, et al., 1976) while chloroethylene oxide was active directly (Soprieno, et al., 1977). Chloroacetaldehyde was only weakly active and chloroethanol was inactive. The mouse-mediated assay with Saccharomyces was positive with VC, also (Soprieno, 1976).

Mattern, et al., (1977) were not successful in obtaining positive results in Salmonella with urine from either exposed men or rats, even in the presence of Arochlor-treated rat liver cell preparation and glucuronidase. Therefore, the final metabolites do not appear active in this test.

Drozdowicz and Huang (1977) did not find VC, with or without S-9 rat liver fraction, to cause a detectable change in two species of Neurospora crassa.

Verburgt and Vogel (1977) found only recessive lethal effects with VC in Drosophila. Magnusson and Romel (1978) found that pretreatment of the Drosophila with barbiturate enhanced the activity of VC, but did not eliminate the threshold limit on activity seen by them and Verburgt. They agreed with Bartsch and Montesano (1975) that the mixed-function oxidase system was employed in the activation of VC.

The EPA has announced (J. Commerce, 1980) that a hybrid spiderwort changes the color of its blooms in the presence of VC and may thus be useful as a detection device for VC emissions. This announcement appears to be based on a paper by Schainer (1979), who reported that vinyl chloride was a "weak mutagen," with a lowest effective concentration of 75 ppm for a 6-hour exposure.

In summary, the conversion of VC into metabolites serves to affect chromosomal damage on several varieties of bacteria and plants. Repair mechanism deficiency is believed to be the cause of transmittable hereditary defects.

Fleig (1978) has reviewed the literature on chromosomal damage to humans exposed to VC and concluded that damage is seen only in those persons exhibiting "VC illness," that is, overt clinical symptoms ascribed to high exposures.

The first reports discussed here are based on small cohorts, presumably selected for some special interest in this type of test. Not all studies had controls, and neither radiography, age, other occupational exposures nor smoking were accounted for in some studies. Positive results, that is, an apparent excess of chromosomal abnormalities versus controls (in most cases), were found by Ducetman, et al. (1975) in 11 U.S. workers, Funes-Cravioto et al., (1975) in 7 workers in Sweden compared to 3 controls, Puchase, et al., (1975) in 56 British workers, and Fleig (1977) in 20 German workers suffering from severe clinical symptoms. It is possible that the severe breaks found by Leonard, et al., (1977) may be due to X-ray treatments, and those found by Kucerova (1979) to smoking or the use of alcohol. Hansteen et al., (1978) restudied 37 of 39 Norwegian workers after 2.5 years with only minimal VC exposure and found that the originally reported excess of abnormalities was not seen. No excess of abnormalities was reported by Fleig and Thiess (1974) for 10 German workers, by Picciano, et al., (1977) on 203 workers with up to 30 years exposure but probably less than average exposure, and by Lange, Swinger, and Veltman (1975) on 20 German workers with some symptoms. Kilian et al., (1975) found changes only in those workers directly involved in the polymerization process.

Fleig and Thiess (1978) reported chromosome aberrations in Chinese hamster bone marrow cells after exposure to high VC concentrations. Johnson, et al., (1976) did not find such an effect in the bone marrow cells of rats exposed at lower concentrations, but sufficient to cause a significant incidence of AOL-like symptoms.

Picciano, et al., (1977) concluded that any cytogenic observations were probably related to length and degree of exposure, and that any genetic risks were avoidable by adequate control of exposure. Basler and Rohrborn (1980) found that this was true for the bone marrow cells of Chinese hampsters exposed to high levels of VC *in vivo*.

VII. REPRODUCTIVE EFFECTS

Purchase, et al., (1975) evaluated the significance of their findings of chromosomal damage to possible genetic risks by performing a dominant lethal study (Anderson, et al., 1976) in male mice, which were mated with two untreated females for 8 successive weeks after exposure to 3-30,000 ppm of VC per 6 hrs/day for 5 days. There was no increase in the number of early deaths per implantation, and they concluded that any expression of harm to the chromosomes of somatic cells was not carried over to stem cells. Short, et al., (1979) performed a similar experiment with longer exposures to lower concentrations, and also found no effect on reproduction or survival.

Hehir, et al., (1980) included an F_3-generation study in their program. Parent rats were exposed to 50 or 500 ppm VC one hr/day, 5 days/week for 10 weeks before mating and the subsequent three generations were examined for litter size, percent stillborn, growth, viability, and reproductive anomalies. No effect of F_0 generation exposure was seen.

A study by John, et al., (1977) found no excess fetal wastage in mice, rats or rabbits at VC exposures sufficient to cause maternal toxicity. The authors also found that VC, either alone or in combination with ethanol, was not teratogenic when dams were exposed on days 6-15 at 50-2500 ppm VC. The combination of alcohol and VC did cause higher incidences of some skeletal variations.

Mirkova, et al., (1978) reported skeletal ossification effects, increased embryo resorption and other effects in rats, at exposures considerably below those used by other workers, but adequate details of the study are not available for thorough evaluation of the report.

One portion of the Maltoni (1977) program was an examination of the second generation rats whose dams were exposed. Experiment BT-5 found zymbal gland carcinomas, angiosarcomas at sites other than the liver, and subcutaneous tumors in the adult offspring of dams exposed to 6,000 and 10,000 ppm VC from the 12th to the 18th day of pregnancy. There were no specific controls for these experiments, and relatively little detail is reported. There is no mention of other effects to the offspring. The total number of tumors, both in the exposed and offspring, are substantially less than for the controls used in his other experiments. There was no ASL in either.

Infante (1976) has reported finding an excess of congenital birth malformations in three communities in Ohio that are near VC processing plants. The Center for Disease Control performed a follow-up study and stated (CDC, 1975) that "it could not establish any association between cases and vinyl chloride exposure." (Subsequently, it has reported [CDC, 1979] that the recent trend in birth defects in the U.S. has been downward.) Edmonds (1976) has discussed the methodology of the follow-up study which was of the case-control type, and stated that no relationship was found between the cases and their parents' employment or place of residence relative to the VC plants.

The CDC performed two other birth-defect studies in areas possibly associated with vinyl chloride. In one (Edmonds, et al., 1975) the hospital records for a city in Pennsylvania where a PVC plant is located were reviewed, and no increase in birth defects was seen. In another (Edmonds, 1976) hospital records for Kanawha County, West Virginia were reviewed for 1970-74 and all cases of birth defects were compared for residence and employment by case-control methodology. The study concluded that "no relationship between infants with malformations and parents' exposure to VC could be established."

Theriault and Goulet (1977) reported a comparison of two cities in Canada, and found an increase in birth defects in the city which contained a VC processing plant. The increase was spread over a wide variety of types of defects, and only raw statistics were used. There was no attempt to compare exposures of the parents, nor were there controls for any other environmental factors. Thus, the significance of this finding cannot be evaluated.

Infante, et al., (1976) have reported an increase in fetal wastage among the wives of workers in a PVC plant. This study has been criticized by Paddle (1976), MacMahon, (1977) and by Downes, Stallone, and Frankowski (1977), on the grounds of improper data gathering techniques, incorrect statistical treatment, and incomplete reporting. Also, the statistical significance of the reported excess of fetal wastage of exposed workers' wives disappears if those women subject to chronic spontaneous abortion are omitted. Hass and Schottenfeld (1979) concluded that the inferences by Infante could not be sustained by the data.

Hatch (1980) explored the statistical power of the various studies on reproductive effects. She found that the Ohio birth defect study (Infante, 1976) was deficient in power, but that the negative CDC recheck (CDC, 1975, Edmonds, 1976) of this report had adequate power to detect a significant effect, as did the CDC (1976) study in West Virginia, which also was negative. Similarly, the worker study (Infante, et al., 1976) on abortions and miscarriages had design deficiencies that prevented its results from being accurate.

In summary, VC does not appear to be teratogenic, nor to cause excess fetal wastage in animals or humans. It can cause reversible chromosome damage in somatic cells, but apparently not in stem cells. It may be a transplacental carcinogen at high exposures in rats, but the data are not conclusive.

VIII. CARCINOGENICITY

A. Animal

Viola (1970, 1971) was the first to report the carcinogenicity of VC, as the result of an attempt to reproduce AOL in rats. (See Sections I and IV above.) His experiments were at such high exposures that life-shortening of the animals was evident, so a second series of experiments by Maltoni (1977) was sponsored. Several other studies by industrial and governmental groups were also undertaken at about the same period.

Caputo, et al., (1974) exposed Wistar rats to 50-20,000 ppm of VC for 4 hrs/day, 5 days/wk for 12 months, and found ASL and skin carcinomas in those exposed at 500 ppm and above, and lung adenocarcinomas in those exposed to 2,000 ppm and above. Rabbits exposed to 10,000 ppm VC for 15 months had lung and skin tumors.

Keplinger, et al., (1975) reported the preliminary results of tests with mice, rats, and hamsters which confirmed the carcinogenicity of VC. It appeared that mice were much more sensitive to VC than were rats and hamsters less so. However, the study contained procedural flaws which precludes its use in quantitative risk assessment (Torkelson, 1974).

It has been shown (Radike, et al., 1977, Radike, 1980) that a combination of VC and ethanol enhances the number of malignant and benign tumors in rats over that found in with VC alone, or ethanol alone.

Feron, et al., (1978, 1979) administered VC to rats which was absorbed into PVC so as to constitute dosages of 1.7, 5.0 and 14.1 mg/kg/day, and by gavage in soya oil at 300 mg/kg/day. This assured a 24 hr/day exposure as the VC desorbed (Feron, et al., 1975). An increase in tumors was found at all levels of dosage, with ASL being elevated at 5.0 mg/kg and above, and other liver tumors being found at 1.7 mg/kg. Fibrosis was not seen as a precursor to tumors. There was some decrease in the incidence of normal age-related tumors as the dose increased, and there was a decrease in the latency period for ASL as the dose increased. No brain or primary lung tumors were seen.

Lee, et al., (1978) also reported that mice were much more responsive to VC exposure than were rats, finding tumors at many sites in mice at 50 ppm and above, but only primary ASL in rats at 250 and 1,000 ppm. Feron and Krees (1979) found tumors at multiple sites in rats at 5,000 ppm exposure for one year.

Hong, et al., (1979) saw no effect on rats, after 12 months, from exposures of one or three months at 50-1,000 ppm VC, while exposure times of six or 10 months did induce tumor formation during the one-year observation period. Mice did respond to exposure periods of as little as one month. Simultaneous treatment with disulfiram reduced the incidence of angiosarcoma in the animals, and extended

the average life span. The authors theorize that this could have been due either to reduced metabolic conversion of VC or to increased availability of sulfhydryl groups.

Maltoni (1977) found that day-old rats were more susceptible to exposure to VC than normal young adults. He also found that Wistar rats and hamsters were less responsive than the Sprague-Dawley rats used in the bulk of his experiments, and confirmed that mice were more susceptible. Stockel et al., (1979) theorized that the relatively higher rate of metabolism of VC compared to other halogenated olefins was responsible for its greater carcinogenicity in newborn rats. Groth (1980) reported that the time-to-tumor decreased and the incidence of ASL increased in rats exposed at 948 ppm VC as the age at the beginning of exposure increased from that of the normal weanling.

Maltoni summarized (1979) his extensive series of experiments with rats exposed to VC by inhalation and gavage by stating that tumors at various sites followed different dose response curves. The lowest doses at which statistically significant elevations of various tumors were seen were:

Forestomach papillomas:	30,000 ppm
Neuroblastomas:	10,000 ppm
Zymbal gland carcinomas:	10,000 ppm
Nephroblastomas:	250 ppm
Liver angiosarcoma male:	200 ppm, 50 mg/kg
female:	50 ppm, 16.7 mg/kg
Mammary adenocarcinoma:	5 ppm

The finding of an increase in mammary adenoma at very low exposures led to concern for female workers, particularly when a study of fabricator employees found an excess of breast cancer among females (Chiazze, Nichols, and Wong, 1977). However, a case-control follow-up (Chiazze, 1980) found no relationship to VC exposure in the cases found in those workers. In any case, the very high and variable incidence of such tumors in the controls, about which Maltoni has often commented in his oral presentations, makes it very difficult to support a conclusion that the test animals did respond at such doses. Tomatis, et al., (1978) have noted that "the target organs in animals are more often multiple than in humans." Early unpublished analyses of the two very large animal studies by the NCTR similarly show that the no-response levels of various organs are substantially different in each of these studies, as was found by Maltoni.

No final report can be found for the injection experiments of Maltoni, his numbers BT-12 and 13. Preliminary results were presented at the GECOM symposium on VC at the Fondation Curie, Paris, on 2 March 1976. After 105-106 weeks he had found no ASL in the S-D rats, with about 20% of the animals still surviving.

Much emphasis has been placed on the fact that ASL is a rare tumor, and Maltoni found none among his 465 controls. He did report four cases among 4,200 historical controls in his colony, for an incidence

of 0.0952%. (Summing his seven lifetime experiments yields a total of 881 Sprague-Dawley controls for a total of 2,534 exposed animals, so some groups may have served as controls for more than one experiment.)

The control groups were not given the same housing treatment as the exposed animals, but experienced more stress. This also may help explain the question of mammary tumor incidence (Tassignon, personal communication).

It is interesting to note that in Sprague-Dawley rats from a different colony (FDA, 1980) a crude spontaneous incidence of 12/573, or 2.1% was reported in the five control groups, with an adjusted incidence, after allowing for competing risks, of 7.15%. The actual incidences recorded were 0-4.9% in the 65-70 animal groups, with males running about 50% higher than females. Thus, the spontaneous incidence of LAS appears to vary considerably among colonies in this strain. These experiments will be discussed in more detail in Section XB.

Maltoni's experiments BT-12 and 13 used subcutaneous or endoperitoneal injection of S-D rats with VC in olive oil, 4.25 mg per dose, for 1-4 months. Final results never were reported. A preliminary summary after 105-106 weeks (Maltoni, 1976) reported no ASL at the site of injection. No conclusions can be drawn from this work without the complete data. Maltoni (1977, 1979) and Feron (1979) reported the average time to observed tumor (death) for ASL decreased as the dose increased. It can be speculated that the rapid course of the disease in humans would support the conclusion that the onset of the tumor was only shortly before observation, but we have no confirmation of this, nor of the distribution of the observed times. Tassignon (1979) states that the survival is independent of the type of tumor in the Maltoni studies, and ascribes the early deaths to a systemic toxicity of VC. Thus, a serial sacrifice study will be necessary to determine the shape of the time-to-tumor curve.

In summary, VC exposure can cause tumors at several different sites in various species of rodents. The dose response is quite different for the different sites and species. Age at time of exposure can also affect the sensitivity of the animal. One experiment suggests that VC may be a transplacental carcinogen, also.

B. Human Carcinogenicity

The first connection between VC and cancer in humans was made in 1973 when physicians at the Louisville, KY plant of B. F. Goodrich, Inc. recognized the association between three deaths of workers from ASL (Creech and Johnson, 1974). A review of company records (Block, 1974) revealed several other cases at that site.

This tumor is rare. A review (Popper, et al., 1978) of all cases reported in the United States for the period from 1964 to 1974 revealed 167 cases, of which 19 were ascribed at that time to occupational VC exposure, 26 to Thorotrast given medically, and 9 to arsenic in Fowler's solution, also used medically. The remainder

were of unknown etiology, with no connection to VC. The high level of interest in this specific tumor is such that any subsequent cases would most certainly have been reported, and none have. For a time, NIOSH published (see, for example, NIOSH, 1974) a summary of VC-related cases, but this task now has been taken over by John Stafford of ICI, England (Stafford, 1980). His most recent compilation shows a total of 24 cases in the U.S., one of which is alive, and 81 worldwide. One additional death occurred in the United States in January of 1981. A summary of the number of cases by countries, and of the U.S. cases by company and by date of death, are given in Tables 2-4, respectively. The average latency period in the U.S. has been 23.2 years, but with a mode of about 17 years. There is an unusual clustering of cases in relatively few plants (Table 3). All of the U.S. cases, and almost all of the cases in the rest of the world, are closely associated with the job of reactor cleaning, which was once done manually at the end of the polymerization cycle. It may be speculated that differing work programs and job progression has had some effect here.

Ten cases of ASL have been reported in one plant in Canada, the last in 1976, with no new cases since that time (Delorme and Theriault, 1978). These cases are completely typical, both as to the clustering and the medical symptoms.

It is also worthy of note that there is, at most, one case of both AOL and ASL in the same person (Stafford, 1980) although both of these diseases are associated with VC exposure as a reactor cleaner.

An industry-sponsored epidemiological survey of workers in the VC/PVC industry covered 8,384 men (Tabershaw and Gaffey, 1974) with at least one year exposure before 1973. The expected excess of ASL was found. There were also suggestions of an excess of cancers in the brain, respiratory, and at unknown sites, and of lymphoma. This study was expanded to 10,173 workers (Equitable Environmental Health, 1978, Cooper, 1980), where the excess of brain and respiratory cancers continued to be seen without, however, an association between the brain cancer and exposure. Plans are being made for a follow-up study of this cohort to determine the status of the workers as of the end of 1979.

Several studies have been conducted on smaller groups of workers which are also subsets of the larger study discussed above. Monson, Peters and Johnson (1974) found an excess of brain and lung cancers as well in the Goodrich plant which developed the most ASL cases in the United States. Waxweiler, et al., (1976) studied 1,151 workers who had at least five years exposure in four older PVC plants, and found an excess of brain, respiratory, and lymphatic cancer, as well as the known cases of ASL. A later study (Waxweiler, et al., 1978) expressed the opinion that it was not VC exposure that was responsible for the excess of respiratory cancer, and speculated that it may be due to PVC-dust (see also Waxweiler, 1980). However, preliminary results on a study of subsequent lung cancer cases in that same plant (Greenberg, 1980) do not show an association with PVC dust.

Ott, Langner, and Holder (1975) studied 594 workers at one location and found no excess of cancer deaths in workers who had been exposed to less than 200 ppm VC in their work. There was an excess of malignancies among workers with extended experience in what was rated as a high exposure group. There were no ASL cases in this cohort.

Nicholson, et al., (1975) reported a study on 257 workers employed for at least five years since 1946 in a PVC plant, and found an excess of deaths from cancer, nine as opposed to 3.9 expected. Much of the excess can be explained by three cases of ASL; there also were two lymphatic cancers and one brain cancer. Among the other 15 deaths was one from bleeding esophageal varicies, which is thought to be associated with liver damage from VC exposure, and a possible precursor to ASL. The statistical significance of these excess cases was not reported.

Duck, Carter, and Coombes (1975) found no excess of mortality, including cancer, in British workers for 1948-1973, while following 2,120 workers. Wagoner, Infante, and Saracci (1976) criticized the mathematical treatment of the data and stated that there was an excess mortality in the longer-exposed group. Duck and Carter (1976) then made corrections to the numerical results, but did not change the conclusion. Berry and Rossiter (1976) criticized both the original calculations and the changes proposed by Wagoner and Infante, as did Fox (1976) but neither found any evidence of excess mortality in the group. Fox and Collier (1977) studied 7,000 men who had worked with VC in Great Britain between 1940 and 1974 and found no evidence that cancers other than that of the liver are associated with VC exposure.

Frentzel-Beyme, Schmitz, and Thiess (1978) reported on 1,618 VC-PVC workers in Germany, and could not confirm the U.S. reports that tumors at other sites than the liver were in excess, and suggested that this may be because of the consistently low exposures at the plant studied. A paper by Reinl, et al., (1978) reported excess deaths in German workers, but the authors have since found calculation errors in the processing of the data.

Workers who fabricated PVC were of interest as a group whose exposure to VC was significantly less than the workers in the VC/PVC industry, but much higher than any expected exposure to the general population. Chiazze, Nichols, and Wong (1977) studied 4,341 deaths from employees of 17 PVC fabricators, and found no ASL. There was an excess of deaths from intestinal cancer in both sexes, and breast and urinary system cancer in females, using proportionate mortality ratios based on an external standard. A case-study follow-up on the breast cancer deaths showed (Chiazze, 1980) no relationship to VC exposure. Baxter and Fox (1976) found very similar results in a study of 707 deaths of male fabrication workers in Great Britain. There was no excess of lung or brain cancers in either cohort.

Several studies have been made of the general population using ASL as the marker disease in an effort to detect an association with possible environmental exposure to VC. There was no association with living near a VC handling plant in the general U.S. survey conducted by the Center for Disease Control (Popper, et al., 1978). Brady, et al., (1977) surveyed 26 ASL deaths in New York State between 1970 and 1975, and found five who lived nearer VC handling plants than did their matched controls, but could not establish a direct connection with the disease to exposure. Ten cases of ASL in Wisconsin were examined for possible connection with VC exposure, and none was found (Fiechtner, et al., 1976). Baxter, et al., (1977) found no relationship between distance of residence from VC emitters and the 47 cases of ASL in the general population of Great Britain reported in 1963-1973. A later update (Baxter, et al., 1980) found one case which had lived the last six years of his life near a PVC plant and three cases where the man had worked in the plastics fabricating industry, but for whom there were no records to indicate exposure to VC. The lack of relationship between residence and cases of unknown etiology was confirmed. Saric, et al., (1976) studied the deaths during the years 1968-1971 in an area surrounding a PVC plant that had been in operation since 1949 and in which three workers had died of ASL. No relationship was found for liver or lung/bronchial cancer and place of residence. A similar study for communities near a Swedish plant which had operated since 1945 and had found four ASL cases showed (Elinder and Pershager, 1978) no unexpected elevation of fetal mortality, deaths from all cancers, or cancer of the liver or lungs during the years 1961-1974. Pancreatic cancer in males was elevated in the age group over 60. All ASL cases in Holland since 1950 (27 cases) were studied, and none had any traceable contact with VC (Dalerup, et al., 1976).

Iturra (1976) observed an excess of cancer deaths in a city in Canada with a PVC plant as compared to a similar nearby city. This difference was principally found in males aged 20-64, which is not indicative of a general pollution effect. The author drew no conclusion as to why the condition existed.

The Environmental Protection Agency has stated (Kusmack and McGaughy, 1975, Marcus, 1976) that it has been unable to establish a link between living near VC handling plants and ASL. It awarded a contract in 1978 (Contract 68-02-2986 to Science Application Incorporated) to examine the present health of a cohort which was presumed to have been exposed to VC as children, but no results have been published.

The disease ASL is difficult to diagnose (Heath, Falk and Creech, 1975), is almost invariably fatal within a short time, and presents a variety of symptoms including portal fibrosis and hypertension with splenomegaly and varicies, proliferation of the sinusoidal lining, megalocytosia, and thrombocytopenia (Thomas and Popper, 1975, Gedligk, Muller and Bechtelsheimar, 1975). Metastasis is frequently involved. These symptoms are very similar to those seen in the mouse (Schaffner, 1978) and rat (Feron, et al., 1979) and the pathology also is similar (Gordon, 1975). No really adequate

early warning tests have been devised (Waxweiler, Falk, et al., 1977, Tamburro, 1980), although the gammaglutamyl transpepsidase test is promising, along with ICG clearance and SGOT.

Bentozzi, et al., (1979) performed sputum cytology tests on 2,558 workers. They found 41% of these to be in the international classification groups 04-08. Thirty-one percent were grade 04 and 0.3% in grade 08; none were in grades 09 and 10. Overall mortality rates for the larger group of 4,777 workers were well below expected, perhaps because of only 86% follow-up of the potential cohort. Elevated SMR's were seen in tumor deaths, although quite variable from plant to plant. They state that the sites most frequently involved were liver, lung, and GI-tract, but no comparison with unexposed populations is given. No excess of brain tumors was reported. Maltoni (1980b) has reported an ongoing study which will make further attempts to relate sputum cytology findings to possible lung pathology.

In summary, VC is clearly a human carcinogen, causing ASL in a small percentage of highly exposed workers. There is suggestive evidence that it may be a weak general carcinogen at high concentrations, perhaps through an immunosuppressive mechanism, but more data are required to confirm this suspicion. Several studies of large populations have not shown a connection between general ambient exposure and increased incidence of cancer.

IX. HAZARD EVALUATION

The hazards to humans from exposure to vinyl chloride may be summarized as follows:

Acute

1. Frostbite from skin contact with liquid VC.
2. Fire and explosion from ignition of spills above 3.5% concentration
3. Anesthesia and cardiac arrythmia from exposure to concentrations around 1%.

These hazards are abated by conventional safety practices in equipment design and operating procedures which are beyond the scope of this discussion. The potential seriousness of the effect of these hazards should not be overlooked in the concern for chronic effects.

Chronic

1. Damage to liver, spleen, and circulatory system.
2. AOL and associated symptoms.
3. ASL, and possibly cancer at other sites.

No precise threshold for time or concentration can be given for the onset of these effects. Apparently they are not seen at lifetime occupational exposure of a few hundred ppm, and possibly higher. It also is apparent that a direct extrapolation of animal experience cannot be made. A whole generation of the entire industry experienced exposures at least an order of magnitude above those which elicited chronic response in rats, and harmful effects were seen in only a few of the higher exposed members of the group. Even larger populations have been exposed to trace concentrations with no detected effect. The number of persons exposed to substantial concentrations in the VC-PVC industry certainly is well above 20,000 and about 0.1% of that number have developed either AOL or ASL. If humans were as sensitive to VC as are rats, the expected number of cases would be above 10% (NCAB, 1979, Reitz, et al., 1979). Even 0.1% is an unacceptable hazard to permit to continue, and substantial steps have been taken to abate the risks, but it is of importance to understand the degree of abatement which has been achieved by these steps, and to determine if it has been adequate, and if a significant risk exists for the non-occupationally exposed population.

The metabolism of vinyl chloride seems to be carried out in the microsomes of the hepatocyte liver cells by a mixed oxidase function process which is thought to proceed via an epoxide intermediate. This intermediate is detoxified by interaction with sulfhydryl groups of amino acids. If the intermediate is generated in quantities too large for detoxification, or if there is a depletion of sulfhydryl groups by competing reactions, or for some other reason, then there is a greater probability that some of the active intermediate may escape the microsome, and eventually, some of it may cause damage to the genetic material of the chromosomes. Ottenwalder and Bolt (1980) suggest that the active metabolite must leave the hepatocytes to act on the sinusoidal cells. It is conceivable

that, in the case of massive doses, some of the reactive intermediate could escape the liver cells, and attack other cells at remote sites. If this damaged chromosome is not repaired by the various mechanisms available for that purpose, and if the resulting altered chromosome is a viable entity, then subsequent replication may produce a cancerous cell, which could lead to a tumor.

Consideration of this sequence of events leads to the conclusion that the dose response to very low levels of VC could not be linear, with the several consecutive steps and competing reactions that are involved (Reitz, et al., 1979, Watanabe, et al., 1980). Of the various conventional extrapolation models, it would appear that the linear quadratic, multi-hit model may be more appropriate than the others. It may also be that a unique model must be devised for each substance, and that no general model will be adequate. Bioassays of sufficient sensitivity have not been performed to answer this question.

Scientists of the EPA Cancer Advisory Group have stated (Albert, 1980) that their use of the linear extrapolation method in risk assessment is not intended to represent biological processes, but merely to assure that the risk assessment result is the maximum likely probability of harm. Several analyses have shown that the data do not fit a linear-through-zero curve, and thus this model is inappropriate for accurate risk estimation.

Another question of interest is whether a single massive dose or a series of smaller doses is likely to be more harmful. Development of cancer from single doses is a familiar event to experimentalists, and should not be confused with the "one-hit" theory, or the no-threshold concept.

It would appear that a limit is placed on the rate of formation of the active intermediate by the amount of enzyme available, and by the rapid exhalation of surplus VC in the body. However, if enzyme availability were the limiting factor, then suppression of that enzyme by a competing substrate should lessen the toxic effect of VC, and it is seen that alcohol and phenobarbitol, which are thought to utilize the same metabolic route, actually enhance its toxicity. Thus, it may be that the detoxification is the limiting step, as was found by Laumback et al., (1978) for bacteria. This would lead to the conclusion that both high doses and chronic exposure are harmful, although the latter would be more effective for equal dosage because of the inability of the body to store VC in excess of the metabolic capacity. No long-term effect of a single high dose was seen in the CPSC study, (Hehir, 1980) which leads to the further conclusion that the repair capacity of the target is important, and that so long as that procedure can be effective, the mode of application of the dose is not of primary importance.

It is known that humans have more competent repair systems than do shorter-lived rodents (Hart and Setlaw, 1974) which may account in part for their relative longevity.

There have been no new cases of AOL reported in recent years, and the current medical surveillance on workers is such that chronic organ damage is being prevented. Concern for exposure to single doses high enough to cause acute or chronic effects is unnecessary in the general population, and very unlikely in workers under present conditions. Therefore, we conclude that the only reasonable possibility of harm to humans today is from long-term exposure to low doses, and the remainder of the discussion will be devoted to evaluating that risk.

In regard to tumors at sites other than the liver, the Maltoni data (1977, 1979) show that rats do develop tumors at other sites, but that the observed no-effect level is considerably above that for ASL (see data in Section VII above). Watanabe, et al., (1976) show that the metabolic products of VC are distributed in many organs of test animals, but there is no information as to whether these are the final detoxified products, or the potentially carcinogenic intermediates. Human epidemiology may show a suggestive increase in brain and lung tumors at past high exposures; the data are inconclusive. But, if present, the risk is at least an order of magnitude less than that for ASL. Therefore, the risks for ASL will be taken as representing all potential risks for tumors from VC exposure.

In summary, the risk for development of ASL is thought to be the most likely chronic hazard facing the working or general population from exposure at the present time, if, indeed, there is any risk. Other chronic hazards are low in comparison. A consideration of the metabolic data suggests that the immune and repair mechanism may be the limiting factor in controlling the onset of the disease, and that the dose response curve at either very low or very high exposures is unlikely to be linear, but probably is "S" shaped.

X. RISK ASSESSMENT

Any effort at risk assessment assumes a probabalistic relationship between dose and effect; no other approach is possible. However, it must be remembered that the probability distribution for the observed population may not be the same as that of the population of interest. The patterns in the past have been selected strains of laboratory animals and adult white males. These may well not be representative of the general population. Certainly, direct extrapolation of rodent data to humans is tentative, at best.

A. Previous Risk Assessments

1. Schneiderman, 1975

One of the first attempts to utilize animal data to estimate risks at very low exposures was that of Schneiderman, Mantell and Brown (1975). They used early Maltoni results to compare the estimates obtained from three possible mathematical models. The 99% assurance level of a "safe" dose at a lifetime risk of 10^{-6} was as follows:

Log Probit (slope = 1)	73 ppb
Logit (slope = 3.45)	119 ppb
Logit (slope = 2.3, one-hit)	2.1 ppb

The authors discussed the recognized difficulties of extending these rat data to humans and of providing animal experiments that could answer satisfactorily the question of risk at very low doses.

2. Kusmack and McGaughy, 1975

The EPA was the first group to attempt a human risk assessment for vinyl chloride (Kusmack and McGaughy, 1975). This pioneering effort attempted to use both animal and human data, and to show comparative results from both the linear and log-probit models. It concluded that there was an individual risk of 71 x 10^{-6} per ppm of lifetime exposure to VC by the linear method, and that the log-probit results were one-tenth to one-hundredth of that.

This effort is subject to several serious criticisms. The exposure data used for human experience was that from a group with less than average exposure, while the ASL rate was chosen from only those plants which did report cases, and ignored the remainder of the population. Thus, their incidence rate of 7.5% compares to an actual figure of about 0.1%.

They used as their primary method a linear extrapolation of rat data, which has been seen to overestimate the human rates by two orders of magnitude above that which actually exists, and they assumed the total cancer rate to be twice that found for ASL.

This same estimate was used by the EPA (1979) to estimate the concentration of VC in drinking water which would produce various levels of risk. These estimates are, of course, subject to the same criticisms.

Nisbet (1978) challenged the estimate of Kusmack and McGaughy (1975) when it was used by Wilson in testimony before the OSHA hearing on its generic cancer policy. Nisbet stated that his calculations showed the risk to be 10-30 times greater, by the same calculation method. Wilson (1979) suggested several flaws in the Nisbet procedure, including the fact that he chose for his extrapolation one point at 25 ppm from Maltoni experiment BT-15, and that this point is not in good agreement with the whole body of data. Further, he chose to use total cancer incidence in the rats, including those at zymbal glands, which have no counterpart in humans. Both Wilson and Kusmack and McGaughy had used a factor of two times LAS to account for possible cancer at other sites. Wilson did acknowledge a mathematical error which made his results half the proper number.

Albert (1978) applied this same general procedure to other potentially carcinogenic air pollutants in the United States and calculated the expected annual cancer deaths as follows:

Arsenic	15.6
Benzene	77.8
Cadmium	26.2
Coke Ovens	149.5
VC after regulation	1.0

3. Gehring, 1979

Gehring, et al., (1979) applied an experimentally derived biotransformation correction (Gehring, et al., 1978) to rat data and estimated the incidence in humans at two different exposures by means of four different extrapolation models. Their estimates at 500 and 200 ppm TWA bracket the observed (Cooper, 1980) experience for humans when derived from the probit and the unconstrained linear models. The linear-through-zero and one-hit models consistently overestimated the incidence. Although not considered by the authors, the linear and probit models match rather closely the total U.S. experience of occupational ASL at an assumed 500 ppm exposure. The linear model predicts no incidence below 99 ppm in humans. The probit model predicts a human risk of 1.5×10^{-8} at 1 ppm. Thus, a mechanism for adjusting for the difference in metabolism between animals and humans is shown to be useful.

4. Food Safety Council 1978, 1980

The Food Safety Council has recommended (FSC, 1978) the use of the gamma multi-hit model because of its flexibility in handling dose response data of varying curvealinity at low doses. It

has calculated (FSC, 1980) the maximum likely and lower 97.5% limit doses for substances at various risk levels and with different models. For VC, at 10^{-6} risk, these results are as follows (based on early Maltoni data):

One-hit	2.0×10^{-2} ppm
Armitage-Doll	2.0×10^{-2}
Weibull	2.1×10^{-9}
Multi-hit	3.9×10^{-10}

For this substance, the goodness of fit of the Weibull model (0.56) was superior to that of the multi-hit (0.32). Neither of the other two models gave acceptable fits. This was in part because of the concave shape of the curve, which included all of the high doses in the dose response data.

It has been stated by OSHA (1980) that the wide range of values obtained from various models is an indication of the unsuitability of the concept. In reality, it is the result of improper manipulation of the data, which data may not always be satisfactory for the intended purpose. However, subjective use of data can, and does, sometime affect the results. The Food Safety Council recommends (FSC, 1980) that appropriate biological and other considerations be used in the choice of models.

5. Dow, 1979

A Dow Heath Team performed a relative risk estimation for several compounds (Langer, et al., 1979) which considered probable exposure, the consequence of exposure, the physical state of the substance during processing, and the current exposure standards. This resulted in a value of 480 for VC in a "closed system but with employees in the vicinity." The same procedure assigned hazard rating values to some other substances as follows: benzene, 10; phosgene, 410; hydrogen sulfide, 5; arsine, 9,700; and bis-chloromethyl ether, 69,700. In a batch operation with occasional manual handling, the hazard rating for VC increased to 9,700 by this method.

6. Hehir, 1980

Hehir, et al., (1980) considered the published data on animal exposures and concluded that there was a lifetime dose below which no oncogenic response is seen. This was estimated to be 5,000 ppm-hrs for mice and greater than 50,000 ppm for rats, regardless of whether the dose was administered over a short or long period. This concept of equality of effectiveness for all modes of exposure does not have general acceptance, and would not appear to be correct, based on the earlier discussion of this point. Dose-rate effects are, of course, well known. See, e.g., Laskin, et al., (1980). However, the degree to which this can be extended is not known. See Section XB for further discussion.

These authors also used the Crump-Griess model (Crump, Griess and Deal, 1977) to evaluate their data on mouse pulmonary cancer, and estimated that exposure to 5,000 ppm VC doubles the probability of cancer, while 50,000 ppm increased the risk nine-fold. In view of the fact that pneumonitis was present in all animals exposed above 500 ppm, it is questionable if this was a direct oncogenic response, or the result of an epigenetic event because of severe lung damage. Maltoni (1977) also reports an increase in lung tumors in mice, but not in rats or hamsters. Thus, the significance of this finding to risk in humans is questionable.

7. Anderson, 1980

Anderson, et al., (1980) extended the work of Gehring, et al., (1978 and 1979) to incorporate the amount of metabolic products from VC which was bound to the DNA of exposed rats, (Gehring and Blau, 1977) rather than the total amount metabolized. They assigned various values to the parameters in a Michaelis-Menten equation depicting the kinetics of the metabolic process, and compared the results from extrapolation to low doses by log-probit and multihit models. They found that the two extrapolation models responded quite differently to these variations at very low doses, and that it was not possible to select one model as the more appropriate form from the high-dose data. Use of the values of Gehring for the primary parameters gave estimates of the dose equivalent to lifetime risks of 10^{-7} of less than 1 ppm for the probit model and less than 2 ppm for the multistage model, a correspondence which the authors pointed out was better than the precision of interspecies comparisons.

8. EPA, 1980

The final version of the water quality criteria document for VC (EPA, 1980) used a different approach for risk estimation. The slope of the incidence of all tumors at the lowest doses of Maltoni experiment BT-1 was adjusted for the fraction of exposure, the equivalent feeding level to give the same blood concentration of VC as by inhalation (see Withey and Collins, 1976), and the ratio of the surface area of humans vs. rats, to produce an estimate that a lifetime risk of 10^{-5} would be caused by drinking 2 l/day of water containing 20 µg/l. There is some confusion over the mathematics given in the report, and the assumptions on which the adjustments are made are far from having general acceptance, although generally following NAS recommendations. It appears that this procedure overstates the risk by several orders of magnitude.

9. NAS, 1980

The National Academy of Science (1977) calculated the upper 95% confidence limit for risk from drinking water containing vinyl chloride from the probabilistic multistage model and

early Maltoni rat data. They report (NAS, 1980) a lifetime risk of 10^{-6} as being equivalent to $3.08 10^{-5}$ mg/kg/day. For a 70 kg person consuming 2 l/day, this would calculate to 1 µg/l. The difference between the EPA and NAS numbers comes from the different curve-fitting methods for the animal data.

In summary, prior risk assessments, most of them based on the same early Maltoni experiment, have given a wide range of calculated risks depending on the model used and the treatment of the data. A reasonable fit with experience was obtained when suitably biotransformed rat data were fitted by the probit model.

B. Further Calculations

Almost all of the risk assessments to date have been based on experiment BT-1 of Maltoni (Maltoni, 1977). Tassignon (1979) analyzed the results of some of Maltoni's work, and commented on a systemic toxicity of VC which caused a general dose-related life shortening in these experiments. After correcting for these effects he agreed generally with the statistical evaluation by Maltoni of malignant tumors, and found the extent of specific organ response to vary greatly with dose. He suggested that the gastric tumors could appear significant because of genetic drift in the animal colony during the two-year interval between comparable experiments. The equality of fit between several mathematical models was illustrated. A factorial analysis was suggested which identifies the relative potency of VC for each type of organ response in rats.

Final results have now been reported (Maltoni, 1979) for several more bioassay programs. There are several differences between the data in the early and late Maltoni reports which are due to updating of the tables as old material was reviewed by him. Those of interest here are listed in Table 5. Among these are four more experiments in which rat data comparable to BT-1 were obtained, containing results from one-year inhalation exposures with the animals held for a normal lifetime, BT-2,7,9 and 15. In addition, there are two ingestion studies with comparable time periods, BT-11 and 27. The exposures and percent incidence of LAS for the rats in these two series are given in Tables 6 and 7. The inhalation data have been converted from ppm to g/kg/yr by the CEFIC method (CEFIC, 1976) in order that they may be combined with the ingestion data. This method tends to give an overestimate of the actual metabolized dose from inhalation because of the equilibrium blood concentration which is established (Withey, 1976). All of these experiments are with Sprague-Dawley rats except BT-7, which used the Wistar strain. The data of Tables 6 and 7 are displayed in a log dose vs percentage of incidence plot on log-probit paper in Figure 1. Points for exposures above 2,500 ppm were excluded because the high rate of competing causes of death actually give a decrease in incidence at those exposures. It can be seen that the grouped data generally follow a similar trend, and thus the combined points should permit a more reliable application of mathematical extrapolation models.

However, this graph also illustrates the problems involved in extrapolation from a single experiment. The slopes of BT-1, the first inhalation experiment, and also the one with the greatest number of points, and experiments BT-11 and 27, the two ingestion experiments, generally are similar. Experiments BT-15, and especially BT-2, both done at lower exposures and with fewer points, have substantially different slopes. BT-9 has only a single point, but is in general concordance with the remaining experiments.

Confidence ranges were not calculated for the individuals points. This may reduce the disparity between experiments to some degree, but it will not eliminate the problem entirely. (See Wilson (1978).)

Equations were fitted to these results, using the Hewlett-Packard HP-67 calculator and the manufacturer's program SD-03A (Hewlett-Packard, 1977). Linear curves were not constrained to pass through 0,0. Zero results were included when there was no observed incidence at finite exposures, but very small values, approximately 10^{-5}, were used rather than zero with the logarithmic and expotential programs to avoid machine error. These result are presented in Table 8.

Various combinations of studies were used for the calculations. The vertical line in Figure 1 is the historical control incidence of 0.09, and when that point (0 exposure, 0.09% incidence) was used in the calculations, the experiment column contains the notation "plus controls".

The results of several individual experiments fit various types of curves with high reliability. For example, BT-1 yields r values of 0.95-0.99 for linear, power, and log-probit curves, and BT-2 does also for linear, logarithmic, and power curves. Thus, mathematical manipulations are not helpful in evaluating the biochemical aspects of low dose response.

Inclusion of the historical controls usually lower the goodness of fit, although not always to a significant degree. The combination of the inhalation studies is an exception. However, no confidence should be placed in good fits for three- (or fewer) point curves (BT-2); these fits are to be expected.

The apparent difference in slopes that is seen in Figure 1 is reflected here in the greatly different values for the calculated constants from experiment to experiment.

The combined ingestion experiments, BT-11 and 27, were tested with the origin as an included point for the linear equation. This reduced significantly the goodness of fit.

Selection of data points also had a large effect on the resulting equation. Omission of points above 15 g/kg/yr (about 500 ppm) significantly altered the slope and intercept of the lines (last few lines of Table 8). These data points are shown on a log-log plot in Figure 2, and the low dose points are given on a linear plot in Figure 3.

The intuitive (and mathematical) conclusion is that a poorer goodness of fit with more data points is more reliable than a higher degree of fit for fewer points, if the data are for the same substance by the same procedure, but are independent and of equal degree of precision. Thus, it appears appropriate in this case to use the equation derived from the combined low dose experiments for further discussion for the limited value which it may have.

BT-1, the combined ingestion studies, the combined inhalation studies, and the combined injestion and inhalation studies, with and without the controls all showed a positive y-intercept. That is, the data do not extrapolate to predict a no-observed-effect exposure, as was reported by Maltoni. The inhalation experiments BT-2, 7, and 15 do predict this.

Some of the other Maltoni experiments not shown in Table 6 or Figure 1 employed variable lengths of exposure times. In BT-3, the animals were exposed for 17 weeks, rather than the 52 weeks of experiment BT-1, which used the same exposure levels. After 155 weeks, only one animal each in three of the higher exposure groups (500, 2,500, and 6,000 ppm) had developed ASL, while a total of 33 animals in these three exposure groups did so in BT-1, with 52 weeks of exposure. In BT-5, pregnant dams were exposed to 6,000 or 10,000 ppm, 4 hr/day for one week. There were no cases of ASL in the dams or offspring. These results were confirmed by the work of Hehir (1980). See Section VIII A, above.

Similarly, the CIVO ingestion studies (Feron, 1978, 1979) extended exposure by a lifetime feeding, and gave 24-hour exposure to VC, rather than the 52 weeks at 4 hr/day used by Maltoni, and resulted in a higher incidence of ASL at equal daily dose rates. See Table 9. CIVO used Wistar rats, while Maltoni performed this experiment with the S-D strain. However, the two strains do not appear to be greatly different in their response to VC (see Table 6). Thus, the extended exposure time, and the more uniform daily exposure, produced a higher yield of ASL.

Therefore, it can be concluded that equal doses, if sufficient to produce cancer, are more effective in a series of small doses than as fewer high doses, and that the use of total ppm-hrs by Hehir is not appropriate over the entire range of possible exposures. The inability of the body to retain or metabolize large doses, and organ damage from continued insult, appear to be some of the causes of this effect.

This is reassuring, in that it lessens the concern for harmful results from one or a few high exposures, but emphasizes the need for concern over extended exposures great enough to elicit chronic organ response.

The only difficulty with the Gerig procedure is that it uses partial Maltoni data, and tests the results against the CMA epidemiology study. That study was not the "end of the experiment"; it stopped at the end of 1973, and several deaths have occurred since then.

Neither did it cover the entire population, but only the employees of those plants which met certain criteria for data retention and length of operation. The Stafford (1980) data does cover the entire population and extends the history for seven years. The size of the population is not known, but a reasonable estimate, based on normal worker turnover rates and the number of plants not included in the CMA study, is certainly not less than 25,000 (Heath, 1975). This would give a gross incidence of about 0.1%. Of these, the number actually exposed to substantial exposures would be about 25-30 per plant at any one time. Multiplication by 25 plants, and a factor of three for the turnover during this period, would give about 2,000 highly exposed persons, for an effective incidence of just over 1%. Personal experience would indicate that, for the period prior to 1962, when all of the first exposures of the fatal 23 cases had occurred, the average exposures of this highly exposed group certainly was in excess of 1,000 ppm for the working day. Reference to Figure 1 and Tables 6 and 7 indicate that Maltoni found a 1% incidence at about 1-10 ppm. Calculation of the dose equivalent to a 1% incidence in rats gives 0 ppm by the linear equations in Table 8, and 7.5 ppm from the log-probit equation for the combined inhalation experiments. This crude and subjective estimate would then say that man is about 100 times as resistant as the rat to VC inhalation, a figure generally in agreement with other estimates.

Attempts to calculate the incidence for rats (or man) at low doses by the linear extrapolation method fail because the derived equations yield a positive y-intercept. That is, they predict a spontaneous response at zero dose.

One further evaluation of human risk can be made from the experience of persons residing near VC-PVC plants. The EPA estimated (Kusmock and McGaughy, 1975) that five million persons lived within five miles of these plants, and were exposed to an annual average concentration of 17 ppb. The present distribution of plants was generally well-established by 1959, thus we have 22 years of history, or about 110 million person-years. About five or six of these plants, with 1-2 million neighbors, go back another 20 years, but these data are not firm enough for inclusion.

The fact that no case of ASL has been confirmed as arising from these exposures places the upper bound of risk at less than 2.7×10^{-7} per ppm-yr. It is believed that the exposure data were over-estimated by EPA, and thus this result may be too low, but it is in the same general range as that arrived at by Gehring (1979) and Anderson (1980) after making corrections for pharmacokinetics.

Extending this crude calculation, these five million persons are now supposed by EPA to be exposed to 0.2 ppb (probably a high figure), which would predict no more than 0.0003 deaths per year, or one per 3,700 years in that whole population.

In the absence of new data or evaluation methods, it appears that the Gehring-Anderson results will stand as the most appropriate estimates of human risk at ambient exposures.

C. Suggestions for Additional Work

The Gehring (1979)-Anderson (1980) approach of incorporating adjustments for the metabolized VC at various exposures appears to be the most appropriate methodology for attempting to estimate human risks from animal data. Suggestions are made below for additional work in this direction which should be useful for further delineation of the risks faced by humans from exposure to VC.

1. Extend the Gehring-Anderson procedures to the total available rat data from the Maltoni (1979) series and compare it to the currently available human data from the Cooper (1980)-Stafford (1980) reports.

2. Apply the Food Safety Council (1980) methodology to the full Maltoni (1979) report, in an effort to see if the extended data range can help elucidate the form of the curve at lower doses. Data at very high exposures should not be included because of the confounding effect of competing risks.

3. Examine the original Maltoni data for time-to-tumor records. The rapid course of the disease in humans suggests that time-to-observed-tumor in rats should correspond well to time-to-onset, but serial sacrifice may be necessary to determine this. The shape of this curve would be very valuable in further development of the risk evaluation.

4. Explore further the applicability of Tassignon's (1979) factorial analysis to the evaluation of actual human risks.

5. Perform the proposed update of the epidemiological study sponsored by the CMA. An additional five- or six-year history will be valuable in estimating the risk from tumors at other sites.

TABLE 1

Selected Physical Properties of Vinyl Chloride

Formula Weight	62.50
Heat of Formation, 25°C, gas Kcal/mol	7.5
Free Energy of Formation BTU/lb.	-3310
Density, liquid, g/ml	
32°F, 0°C	0.9471
50°F, 10°C	0.9293
68°F, 20°C	0.9109
86°F, 30°C	0.8918
104°F, 40°C	0.8721
Refractive Index, d^{15}	1.398
Freezing Point, °C/°F	-153.7/-244.7
Boiling Point, 760 mm °C/°F	-13.37/7.9
Liquid Viscosity, absolute, CP	
32°F	0.225
50°F	0.207
68°F	0.193
86°F	0.181
Heat of Fusion, cal/g	18.14
Heat of Vaporization @ 57°F, BTU/lb.	158.4
Specific Heat	
Liquid, 25°C K cal/kg	0.38
Vapor 25°C, constant pressure, Kcal/Kg-mol	12.83
Vapor, constant volume	10.84
Heat of Polymerization, BTU/lb	-720
Explosive Limits in Air	
Lower, wt, %	8.3
vol.%	3.6
Upper wt.%	37.8
vol.%	33.0
Flash Point, open cup	-78°C
Autoignition temperature	472°C
Critical Temperature °K	431.4
Critical Pressure, atm	52.7
Critical Density g/cc	0.370
Vapor cloud explosion yield, lbs. to yield the equivalent of 1 ton of TNT	24,305

TABLE 1 (cont'd)

Vapor Pressure, psia	
-10°C	18
0°C	26
10°C	35
30°C	48
50°C	115
70°C	180
Heat of Combustion, Kcal/mol	2826
Latent Heat, BTU/lb.	
0°C	147
50°C	126
Solubility in Water, 30°C, % by wt.	
Partial Pressure 0.5 atm	0.5%
1.0 atm	1%
autogenous	2%
Solubility of Water in VC, %	0.11
CAS Registry Number	75-01-4

TABLE 2

Angiosarcoma Cases in the VC/PVC Industry
by Country
as of January, 1980

United States	24
West Germany	15
France	13
Canada	10
United Kingdom	4
Sweden	4
Yugoslavia	3
Italy	2
Czechoslovakia	2
Japan	2
Norway	1
Belgium	1
Total	81

TABLE 3

Angiosarcoma Cases in the U.S.
by Company
as of January, 1980

Goodrich, Louisville	10
Union Carbide, S. Charleston	6
Goodyear, Niagara	4
3 Others	4
Total	24

TABLE 4

Chronology of U.S. Deaths From Angiosarcoma

	Deaths	Year of First Exposure
1961	1	1946
1962	0	
1963	0	
1964	1	1944
1965	0	
1966	0	
1967	0	
1968	3	1944, 1951, 1952
1969	2	1949, 1950
1970	1	1946
1971	1	1955
1972	0	
1973	2	1945, 1948
1974	1	1942
1975	4	1945, 1947, 1954, 1962
1976	4	1943, 1947, 1955, 1958
1977	1	1946
1978	2	1941, 1944
1979	0	
1980	0	
1981 (as of February)	1	1964
Total	24	

One Case Living (First Exposure 1955)

Data From Stafford (1980), except last case.

TABLE 5

Listing of Fully-Reported Maltoni Experiments

Experiment	Route	Exposure Period	Exposure Term, wks	Length of Experiment, wks	Range of Doses, ppm	No. of Animals*	Remarks
RATS							
1	Inhalation	4 hr/5 day	52	135	50-10,000	60	
2	Inhalation	4 hr/5 day	52	143	100-200	120	
3	Inhalation	4 hr/5 day	17	135	50-10,000	60	
5	Inhalation	4 hr.	1	143	6,000-10,000	30	F_1 study
6	Inhalation	4 hr/5 day	52	68	30,000	60	
7	Inhalation	4 hr/5 day	52	136	50-10,000	30	Wistar rats (all others S-D)
9	Inhalation	4 hr/5 day	52	142	50	294	
10	Inhalation	4 hr/5 day	5	136	6,000-10,000	120	
11	Ingestion	once, 4-5 days	52	136	3.3-50 mg/kg	80	
14	Inhalation	4 hr/5 day	52	104	6,000-10,000	45	Day-old rats
15	Inhalation	4 hr/5 day	52	147	1-25	120	
27	Ingestion	once, 4-5 day	59	136	0.03-1.0 m/kg	150	
MICE							
4	Inhalation	4 hr/5 day	30	81	50-10,000	60	
HAMSTERS							
8	Inhalation	4 hr/5 day	30	109			

*Number of animals at each dose level, usually counted as the number alive at time of first tumor, about equally male and female.

TABLE 6

LAS Incidence (%) In Rats, Inhalation

52 Weeks Exposure, Lifetime Study

Exposure, ppm	10,000	6,000	2,500	500	250	200	150	100	50	25	10	5	1
Equivalent dose, g./kg./yr.	300	180	75	15	7.5	6.0	4.6	3.0	1.5	0.8	0.3	0.15	0.03
Experiment No.													
1	12	22	22	10	5				1.7				
2						10	5	0.8					
7*	27	6.6	10	13	3.3				0				
9									4.8				
15										4.2	0.8	0	0

*Wistar Rats, All Others S-D.

TABLE 7

LAS Incidence in Rats, Ingestion

52 Weeks Exposure, Lifetime Study

Dose, mg/day	50	17	3.3	1.0	0.3	0.03
g/kg/yr	12.5	4.2	0.8	0.26	0.07	0.007
Experiment						
BT-11	21	12.5	0			
BT-27				2	0.7	

TABLE 8
Equations For Curves Fitted to Various Single and Combined Maltoni Experiments

Experiment	Linear y = ax+b			Log Probit P = a ln dose + b		
	a	b	r	a	b	r
BT-1	0.26	3.36	0.97	0.35	2.76	0.99
plus controls	0.27	2.47	0.97			
BT-2	3.05	-8.59	1.0	1.60	0.88	1.0
plus controls	1.52	-1.13	0.88			
BT-15	6.5	-1.06	1.0	0.69	3.46	1.0
plus controls	5.28	-0.30	0.95			
All inhalation studies (4)	0.26	3.07	0.91	0.27	2.98	0.82
plus controls	0.27	2.80	0.91			
All ingestion studies (2)	1.75	0.15	0.95	0.30	3.22	0.88
plus controls	1.74	0.20	0.95			
All studies (6)	0.29	3.60	0.73	0.27	3.05	0.82
plus controls	0.29	3.41	0.72			
All studies; low doses only,				0.51	2.53	0.75
plus controls	1.03	0.97	0.79	0.17	2.71	0.49

TABLE 9

LAS Incidence in Wistar Rats, Ingestion
Lifetime Exposure, Lifetime Study

Dose mg/kg/day	300	14.1	5.0	1.7	0
g/kg/yr	110	5.2	1.8	0.6	0
Incidence ASL, %	58	31	7.1	0	0

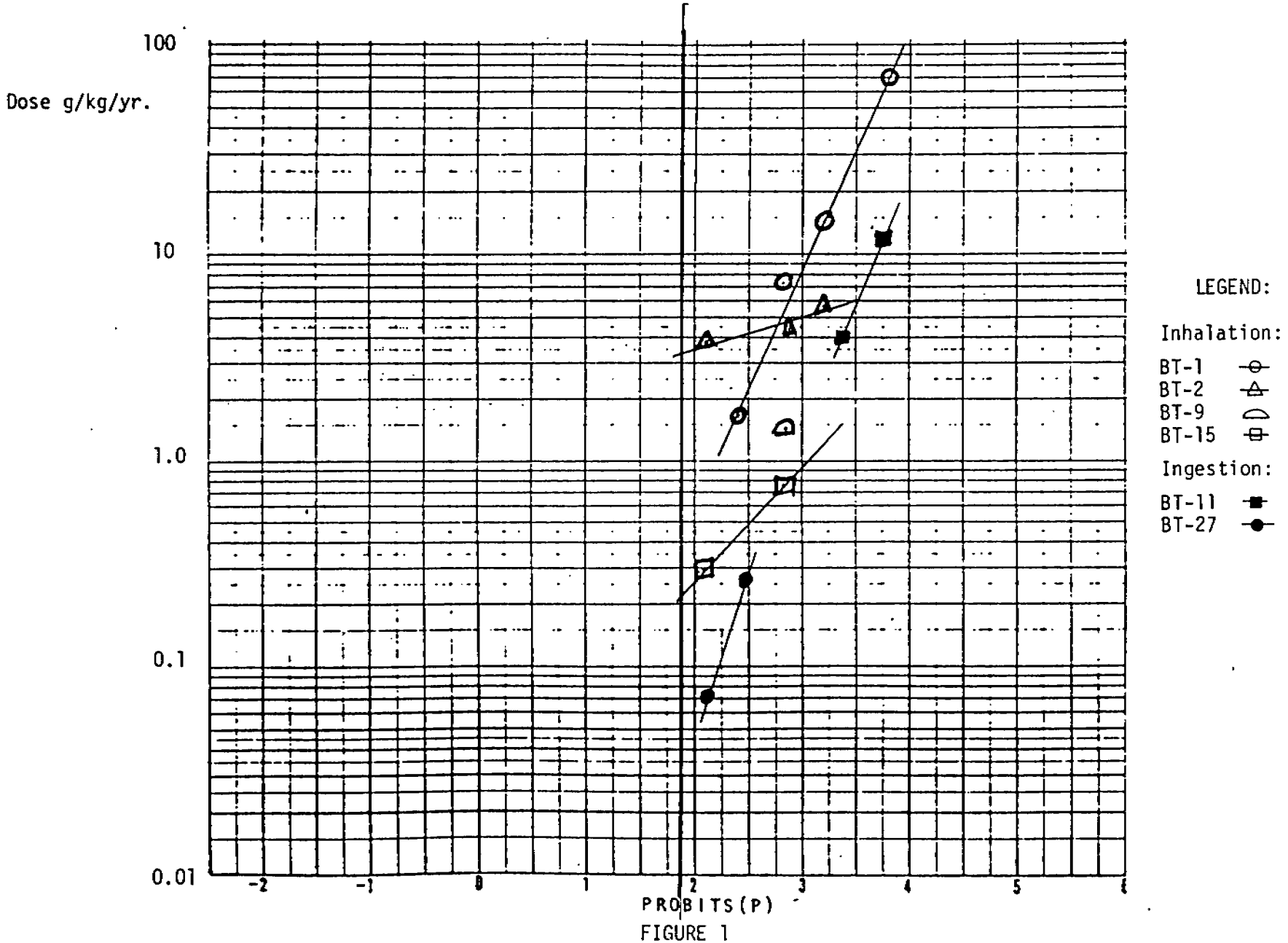

FIGURE 1

Graphical Representation of
Tables 6 and 7

Log-Probit Plot

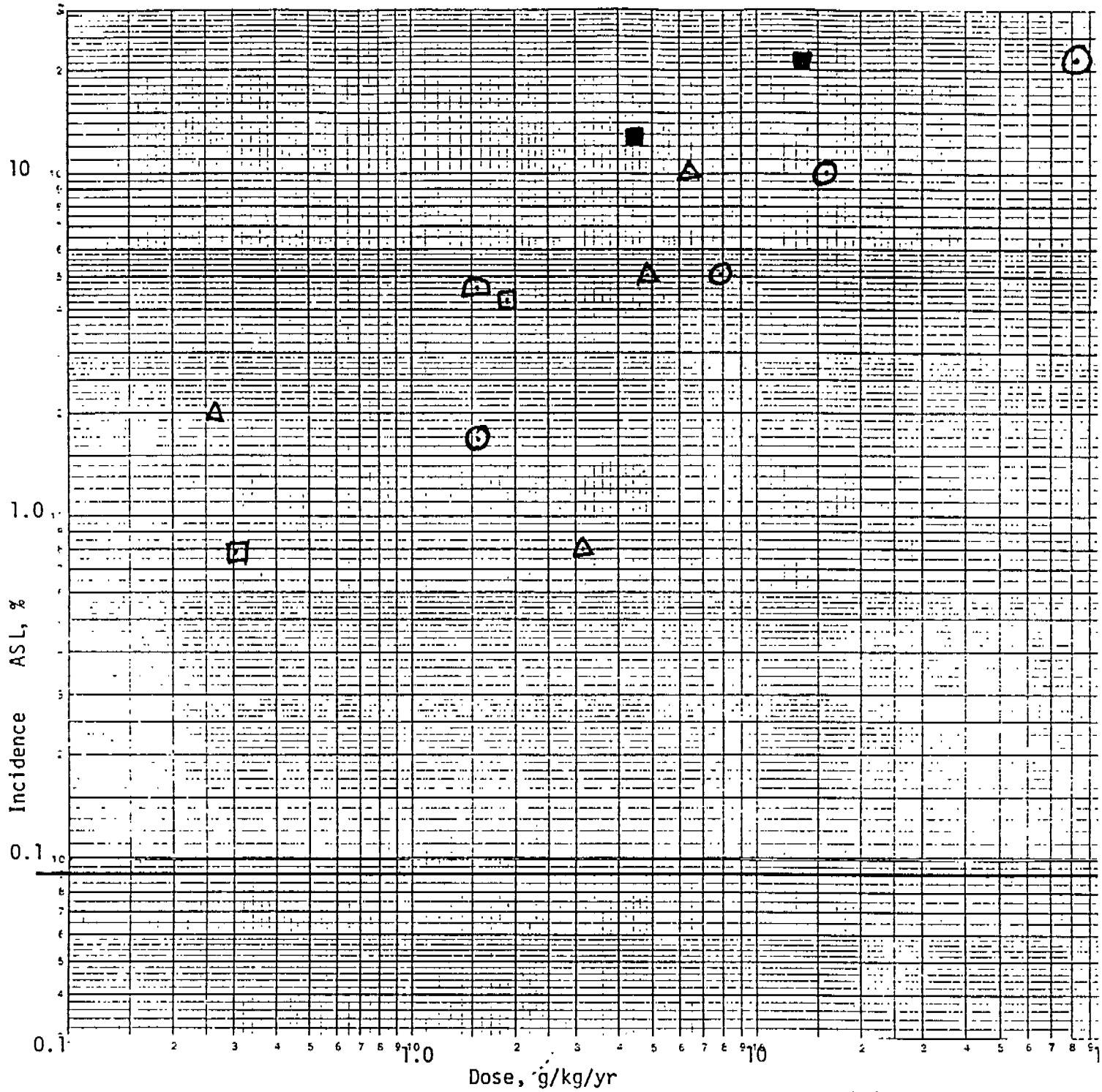

FIGURE 2

Graphical Representation of
Tables 6 and 7

Log-Log Plot

LEGEND:

Inhalation:

BT-1
BT-2
BT-9
BT-15

Ingestion:

BT-11
BT-27

GENC 015620

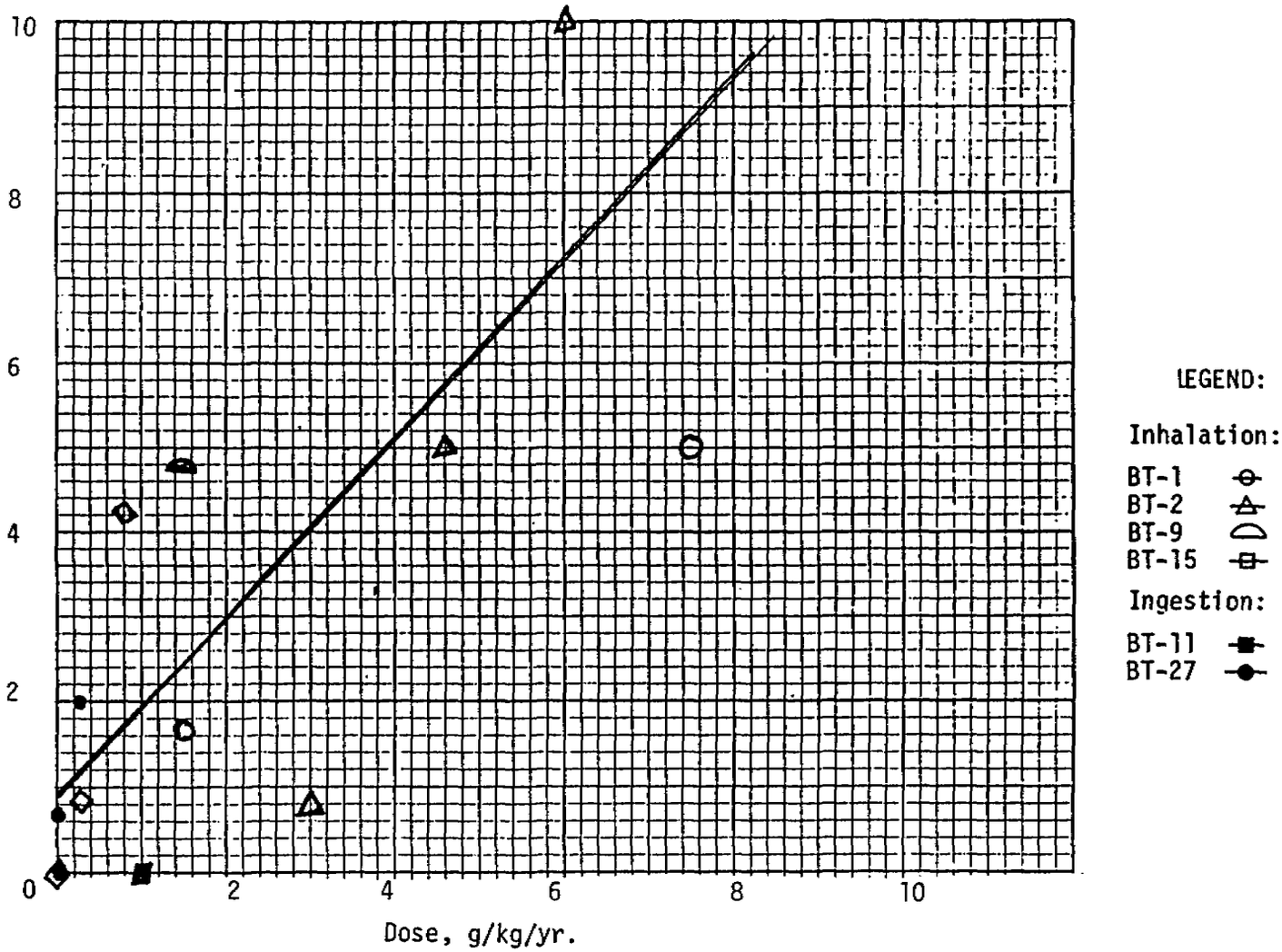

FIGURE 3

Graphical Representation of the
Low-Dose Data of Tables 6 and 7

Linear Plot

REFERENCES

Air Products and Chemicals, Inc., "Comments on the Proposed Standard for Vinyl Chloride", letter to D. R. Goodwin, EPA, 23 September 1976.

Albert, R. E., letter to R. S. Naveen, EPA, "Comparson of vinyl clhoride carcinogenic risks with risk from other pollutants", Washington, D.C., 16 June, 1978.

Albert, R. E., Statements at the 4-5 Sept. meeting of the Science Advisory Board Subcommittee on Airborne Carcinogens, transcript p. 21, 36 - 3 Sept. session. Washington, D. C., 1980.

American Conference of Governmental and Industrial Hygienists, "Documentation of the Threshold Limit Valve", 1963.

American Public Health Association, 1977.

Andersen, M. E., et al., Tox. Appl. Pharm. 47, 385 and 395 (1979).

Anderson, D., et al., Mut. Res., 40 359 (1976).

Anderson, M. W., et al., Tox. Appl. Pharm. 55, 154 (1980).

Andrews, A. W., et al., Mut. Res., 40 273 (1976).

Antonyuzhenko, V. A., Gig. Tr. Prof. Zabol 12 50 (1968).

Banzer, J. D., J. Vinyl Technol., 1 (3) 164 (1979).

Barkin, A., et al., Biochem. Biophys. Res. Comm. 67 596 (1975).

Baretta, E. D., et al., Am. Ind. Hyg. Assn. J. 30 537 (1969).

Bartsch, H., et al., Int. J. Cancer, 15 429 (1975).

Bartsch, H., and R. Montesano, Mut. Res., 32 93 (1975).

Basalaev, A. V., Gig. Tr. Prof. Zabol 14 34 (1970).

Basalaev, A. V., A. N. Vozin and A. G. Kochetkov, Gig Tr. Prof. Zabol 16 24 (1972).

Basler, A., and G. Rohrborn, Arch. Toxicol. 45 1 (1980).

Baxter, P. J., et al., Br. Med. J., 1977 919.

Baxter, P. J., et al., ibid, 1980 213.

Baxter, P. J., and A. J. Fox, Lancet, 1976 245.

Berry, G., and C. E. Rossiter, Lancet, 1976 ii, 416.

Bertozzi, P. A., et al., Arh. hig. rada toksikal, 30 suppl. 379 (1979).

Block, J. B. J.A.M.A., 229 53 (1974).

Bolt, H. M., H. Kappus, A. Buchter, and W. Bolt, The Lancet 1975 1425.

Bolt, H. M., H. Kappus, A. Buchter, and W. Bolt, Arch. Toxicol 35 153 (1976).

Brady, J., et al., J. Natl. Cancer Inst., 59 1383 (1977).

Bretza, J., and J. A. Goldman, J.Occup. Med., 21 436 (1979).

Bretza, J., and J. A. Goldman, J. Occup. Med., 21 436 (1979).

Brown, E. T., et al., Ann. N.Y. Aud. Sci. 298 535 (1977).

Brous, S. L., and W. L. Semon Ind. Eng. Chem. 27 667 (1935).

Buchter, A., H. M. Bolt, J. Filser, H. W. Goergens, R. J. Laib, and W. Bolt. Verh Deutsch Ges. Arbeitsmed 18 111 (1978).

Cameron, J. B., A. J. Lundeen, and J. H. McCulley, Jr., Hydrocarbon Proc., 59 39 (1980).

Caputo, A., et al., IRCS 2 1582 (1974) cited in EPA, op. cit., 1979.

Carr, J., R. M. Burgison, I. F. Vitcha, and J. C. Krantz, J. Pharm. Expath. Ther. 97 (1949).

CEFIC, "Vinyl Chloride Toxicity and the Use of PVC for Packaging Foodstuff." Conseil European des Federations de L'Industrie Chemique, Brussels, Feb. 1976.

Center for Disease Control Morbidity and Mortality Weekly Report 24 (29) 245, July 19, 1975.

Center for Disease Control Morbidity and Mortality Weekly Report, 28 (34) 401 (1979).

Chemical and Engineering News, July 7, 1980, page 9.

Cheney, W. D., Amer. J. Roentgeu, 94 595 (1965).

Chiazze, L., "Mortality Among Polyvinyl Chloride Fabricators", in "Joint Conference, op. cit., 1980.

Chiazze, L., Jr., W. E. Nichols, and O. Wong, J. Occup. Med., 19 623 (1977).

Clapp, J. J., C. M. Kaye and L. Young, Biochem J. 114 6P-7P (1969).

Cole, J. "Inside Story on Vinyl Chloride at B. E. Goodrich in Avon Lake", Ihe Journal, Lorain, Ohio, March 26, 1975.

Consumers Product Safety Commission, Federal Register 39 30112, Aug. 21, 1979.

Cook, W. A., et al., Arch. Envir. Health 22 74 (1971).

Cooper, C., "Epidemiological Study of Vinyl Chloride Workers", in Joint Conference, op. cit., 1980.

Cordier, J. M., et al., Cahiers Med. Travail. 4 14 (1966).

Council of Europe "Substances used in Plastics Materials Coming into Contact with Food", Strasburg, 1979.

Cox, R. A., A. G. J. Eggleton, and E. J. Sandalls, "Photochemical Reactivity of Vinyl Chloride," U.K. At. Energy Res. Establ., Publ. No. AERE-R-7820, Sept., 1974.

Creech, J. L., and M. N. Johnson, J. Occup. Med. 16 150 (1974).

Creech, J. L. Jr., and L. Makk, Ann. N.Y. Acad. Sci., 246 88 (1975).

Creech, J. L., Jr., and M. N. Johnson, J. Occup. Med. 16 150 (1974).

Crump, K. S., H. A. Griess, and K. L. Deal, Biometrics, 33 437045] (1977).

Czernielewski, et al., Derm. Beruf Umwelt 27 108 (1979).

Dalderup, L. M., et al., Lancet, 1976, 246.

Damziger, H., Can. Med. Assn. J. 82 828 (1968).

Dinman, et al., Arch. Envir. Health 22 61 (1971).

Dodson, V. N., et al., Arch Envir. Health 22 83 (1971).

Downes, I. D., R. A. Stallones, R. E. Frankowski, and D. R. Labarthe "Vinyl Chloride, Birth Defects, and Fetal Wastage - A Critical Review. Prepared for the Society of Plastic Industries, Inc., by Research Statistics Inc., Houston, Texas, September 16, 1977.

Dressman, R. C., and E. E. McEarren, Am. Water Works Assn. J. 70 29 (1978).

Drozdowicz and Huang, Mut. Res. 48 43 (1977).

Dublin and Vane, 1935, cited in K. B. Lehman and E. Flury, "Toxicology and Hygiene of Industrial Solvents", 1938.

Ducatman, A., K. Hirshman, and I. J. Selikoff, Mut. Res. 31 163 (1975).

Duck, B. W., and J. I. Carter, Lancet 1976 195.

Duck, B. W., J. I. Carter, and E. J. Coowba, Lancet 1975 ii, 1197.

Edmonds, L., "Birth Defects and Vinyl Chloride", Proc. Conference on Women and the Workplace, Washington, D. C., 1976, also Teratology, 17 137 (1978).

Edmonds, L. D., H. Ealk and J. E. Nissini, Ihe Lancet 1975 1098.

Elinder, C. G., and G. Pershagen, "Pilot Study Concerning the Mortality in Njurunda Community," Swedish Nature Conservancy Board, April, 1978.

Elmore, et al., Biochem. biophys. Acta, 442 405 (1976).

Enviro Controls, Inc., "Control Iechnology in the Plastics and Industry, Atlanta, Ga., Eeb. 27-28, 1979, 11300 Rockville Pike, Rockville, Md., 1980.

Environmental Protection Agency "National Emission Standard for Hazardous Air Pollutants. Standard for Vinyl Chloride." 41 Eederal Register 46560, Oct. 21, 1976. 40CERE61.

Environmental Protection Agency "Preliminary Assessment of the Environmental Problems Associated with Vinyl Chloride and Polyvinyl Chloride", EPA 500/4-74-001, 1974.

Environmental Protection Agency "Scientific and Iechnical Assessment Report on Vinyl Chloride and Polyvinyl Chloride "EPA 600/675-004, June 1975.

Environmental Protection Agency "Standard Support Document and Environmental Impact Statement; Emission Standard for Vinyl Chloride", EPA 450/2-75-009, September, 1975.

Environmental Protection Agency, "Standard for Vinyl Chloride," 41 ER 46560, October 21, 1976.

Environmental Protection Agency "Vinyl Chloride, Ambient Water Quality Criteria", PB-292446, Washington, D.C., 1979.

Environmental Protection Agency "Ambient Water Quality Criteria for Vinyl Chloride," EPA 440/5-80-078, October, 1980.

Equitable Environmental Health, Inc., "Epidemiological Study of Vinyl Chloride Workers, Final Report". Prepared for Manufacturing Chemists Assoc., Washington, D. C., January, 1978.

Ealk, H., J. L. Creech, Jr., C. W. Heath, M. N. Johnson, and M. M. Key, JAMA 230 59 (1975).

Eeron, et al., Ed. Cosmet. Iox. 13 633 (1975).

Eeron, V. J., et al., "Life Span Oral Ioxicity Study of Vinyl Chloride in Rats", Report No. R-5788, Centraal Instituut Voor Voedingsonderzoek (CIVO), Zeist, Neth. October 1978.

Eeron, V. J., et al., Ioxicol., 13 143 (1979).

Eeron, V. J., and R. Krees, Ioxicol. 13 131 (1979).

Fiechtner, J., et al., Center for Disease Control Morbidity and Mortality Weekly Report, 25 57 (1976).

Filatova, V. S., and Gronsberg, E. S., Gig. Sanit. 22 38 (1957).

Filatova, V. S., et al., Gig. Ir. Prof. Zabol., 1 6 (1958).

Filser, J. G., and H. M. Bolt, Arch. Toxical. 42 123 (1979).

Fishbein, L., "Potential Industrial Carcinogens and Mutogens", Elsevier, 1979.

Fleig, J., and A. M. Thiess, ASP, 9 282 (1974) Abstracts of Second Int. Conf. on Environmental Mutagens, p. 219 (1977).

Food and Drug Administration, Federal Register 39 30830, Aug. 26, 1974.

Food and Drug Administration, "Report of the Interagency Working Group on Nitrite Research," Washington, D.C., August 15, 1980.

Food Safety Council Final Report "Proposed System for Food Safety Assessment", Washington, D. C., June, 1980.

Food Safety Council, Scientific Committee "Proposed System for Food Safety Assessment." Food and Cosmet. Tox. 16 Suppl. 2, December, 1978.

Fox, A. J., Lancet, 1976 ii, 416.

Fox, A. J., and P. E. Collier, Br. J. Ind. Med. 34 1 (1977).

Frentzel-Beyrne, R., T. Schmitz, and A. M. Thiess, Arb. Socialmed. Prevent., 13 218 (1978).

Funes-Cravioto, F., Lancet 459 i (1975).

Gabor, S., et al., Igiena (Bucharest) 13 409 (1964).

Gabor, S., M. Lecea - Radu, and I. Manta. Prom. Toksikol, i Klinika Prof. Zabole Khim Etiol. 1962 221.

Gamble, J., L. Shuguey, A. J. McMichael, and R. J. Waxweiler, J. Occup. Med. 18 659 (1976).

Garro, A. J., et al., Mut. Res., 38 81 (1976).

Gay, B. W., Jr., P. L. Hanst, R. C. Noonan, and J. J. Bufalini, Environ. Sci. Tech., 10 58 (1976).

Gedigk, P., R. Muller, and H. Bechtelsheimer, Am. N.Y. Acad. Sci., 246 278 (1975).

Gehring, P. J., and G. E. Blau, J. Environ. Pathol. Toxicol, 1 163 (1977).

Gehring, P. J., P. G. Watanabe and J. D. Young, in Origins of Human Cancer, Hiatt, H. H., J. D. Watson, and J. A. Winsten, eds., Cold Spring Harbor Laboratory, 1977, Vol. A, p. 187.

Gehring, P. J., P. G. Watanbe, and C. N. Park, Tox. and Appl. Pharm. 49 15 (1979).

Gehring, P. J., et al., Tox. Appl. Pharmacol. 44 581 (1978).

Gordon, D. E., et al., "Comparison of the Morphologic Features of Hepatic Angiosarcoma in Man and Rodents Following Prolonged Exposure to Vinyl Chloride", Presented at the International Academy of Pathology Meeting, New Orleans, La., 5 March 1975, Abstracted in Laboratory Investigations 32 (3), 8 (1975).

Gothe, R., C. J. Calleman, L. Esneuberg, and C. A. Wachtmeister, Ambio 3 234 (1974).

Graniger, R. G., A. E. Walker, and A. M. Ward "Vinyl Chloride Monomer-induced Disease: Clinical, Radiological and Immunological Aspects," Chapter 11 in "Induced Disease; Drug, Irradiation, Occupation", L. Preger, ed., Grune and Stratton, London, 1980.

Green, T., and D. E. Hathaway, Chem-Biol. Interactions 11 545 (1975).

Green, T., and D. E. Hathaway, Chem-Biol. Interactions 17 137 (1977).

Green, T., and D. E. Hathaway, Chem-Biol. Interactions 22 211 (1978).

Greenberg, R., Discussion of paper by R. Waxweiler in Joint Conference, op. cit, 1980 transcript pages 337-342.

Greim, H., et al., Biochem. Pharmacol. 24 2013 (1975).

Grigorescu, I., and Gh. Toba, Rev. Chim. (Bucharest) 17 499 (1966).

Groth, D., "The Role of Aging on Cancer Induced by Vinyl Chloride Monomer" in "Joint Conference", op. cit. 1980.

Grunard, M., P. Taft, and G. S. Wiberg, "Report of Task Force on Vinyl Chloride" Environmental Health Directorate, Ottawa, Canada, June, 1976.

Guengerich, F. P., and T. W. Strickland, Mol. Pharmecol. 13 993 (1977).

Hansteene, I.-L., et al., Mut. Res. 78 211 (1978).

Harris, D. K., and W. G. F. Adams, Brit. Med. J. 5567 712 (1967).

Hart, R. W., and R. B. Setlow, Proc. Nat. Acad. Sci., 71, 2169 (1974).

Hass, J. F., and D. Schottenfeld, J. Occup. Med., 21 607 (1979).

Hatch, M., "Power Considerations in Studies of Reproductive Effects Associated with Vinyl Chloride and some Structural Analyses" in "Joint Conference", op. cit. 1980.

Hathaway, D. E., Environ. Health Persp. 21 55 (1977).

Heath, C. W., H. Falk, and S. L. Creech. Jr., Ann N.Y. Acad. Sci. 246 231 (1975). See also Environ. Res., 14 68 (1977).

Heck, W. W. and E. G. Pines, "Growth of Plants Fumigated with Saturated and Unsaturated Hydrocarbon Gases and their Derivatives", Texas Agricultural Experimental Station, Agricultural and Mechanical College of Texas, Publication No. MP603, 1962.

Hefner, R. E. Jr., P. G. Watanabe, and P. J. Gehring, Ann. N.Y. Acad. Sci. 246 135 (1975).

Hefner, R., P. Watanabe, and P. Gehring, Tox. Appl. Pharm. 34 529 (1975).

Hehir, R. M., et al., "Toxicology, Carcinogenicity and Reproductive Effects of Single and Multiple Exposures to Vinyl Chloride in Rats and Mice", Pre-publication draft, Feb. 6, 1980, U. S. Consumer Product Safety Commission, Washington, D. C.

Herrle, K. "Polyvinylchloride", In Ullmanns Encyklopadie der technischen Chemie, W. Faerst, Ed., Vol. 14, 3rd Edition, Urban S. Schwarzenberg, Munich, W. Germany, 1963.

Hewlett Packard Company, Instruction Manual for Model HP-69, "Standard Pac," revised May, 1977.

Hill, James, IV, H. P. Kollig, D. E. Paris, N. L. Wolfe, and R. G. Zepp. "Dynamic Behavior of Vinyl Chloride in Aquatic Ecostems." EPA - 600/ 3-76-001, Experimental Research Laboratory, Athens, Ga., January, 1976.

Hoffmann, D., et al., Anal. Chem. 48 47 (1976).

Hong, C-B, et al., "Additional Evaluation of the Environmental Toxicants VC and Vinylidene Chloride. Final Report", Midwest Research Institute under NIH-NIGHS contract N01-ES-2-2084, 1979.

Hopkins, J., Fd. Cosmet. Toxicol., 17 542 (1979).

Huberman, E., et al., Int. J. Cancer, 16 639 (1975).

Infante, P. F., Ann. N.Y. Acad. Sci., 271, 49 (1976), See also, Mut. Res., 41 131 (1976). Center for Disease Control Morbidity and Mortality Weekly Report, 24 (29) 245 (1975).

Infante, P. F., et al., The Lancet 1976 734.

Iturra, H., "A Community Vinyl Chloride Mortality Analysis Study". Presented at the Air Environment Specialty Conference, Pittsburg, Pa., 1976. Proceeding page 96.

Jaeger, R. J., Ann. N.Y. Acad. Sci. 246 150 (1975).

Jaeger, R. J., et al., Nature 252 724 (1974).

John, J. A., et al., Tox. and Appl. Pharmocol. 39 497 (1977).

Johnson, R. V., et al., "Cytogenetic Studies of Bone Marrow Cells from Rats Exposed to Vinyl Chloride" Report prepared for the Chemical Manufacturing Assocation by the Dow Chemical Co., April, 1976, unpublished.

Joint Conference to Reevaluate the Toxicity of Vinyl Chloride, Polyvinyl Chloride, and Structural Analogues, National Institute of Environmental Health Sciences, National Institute of Occupational Safety and Health, and Occupational Safety and Health Administrative, Bethesda, Md., March 20-21, 1980. Proceeding to be published in J. Envir. Health and Path.

Journal of Commerce, p. 5, July 3, 1980.

Juhe, S., and C.-E. Lange, Dt. med. Wschr. 97 1922 (1972).

Juhe, S., C.-E. Lange, G. Stein, and G. Veltman, Dt. med. Wschr. 98 2034 (1973).

Kappus, H., H. M. Balt, A. Buchter, and W. Balt. Nature 257 134 (1975).

Keplinger, M. L., S. W. Goode, D. E. Gordon, and J. C. Calandra, Ann. N.Y. Acad. Sci. 246 219 (1975).

Kilian, D. J., D. J. Picciano, and C. B. Jacobson, Ann. N. Y. Acad. Sci., 269 4 (1975).

Klein, J., "The Plastic Coffin of Charlie Arthur", Rolling Stone, Jan. 15, 1976.

Kucerova, et al., Mut. Res. 67 97 (1979).

Kudryavtseva, D. G., Gig. Tr. Prof. Zabol, 14 54 (1970).

Kuebler, H., Aerosol Age, 9 (14) 44 (1964).

Kuzmack, A. M., and R. E. McGaughy, "Quantitative Risk Assessment for Community Exposure to Vinyl Chloride", U.S. EPA, Washington, D.C., Dec. 5, 1975.

Laib, R. J., G. Stockle, H. M. Bolt, and W. Kunz, J. Cancer Res. Clin. Oncol. 94 139 (1979).

Lange, C.-E., S. Juhe, G. Stein and G. Veltman, Int. Arch. Arbeitsmed. 32 1 (1974).

Lange, C. E., Schwinger, E., and G. Veltman, Dt. Ges. f. Arbeitsmed., Munich, 1975.

Langer, R. R., S. K. Norwood, G. E. Socha, and H. R. Hoyle, Am. Ind. Hyg. Assn. J., 40 (12) 1039 (1979).

Laskin, S., et al., J.N.C.I., 65, 751 (1980).

Laumbach, A. D., et al., "Studies on the Mutagenicity of Vinyl Chloride Metabolites and Related Chemiclas" University of Louisville School of Medicine, Louisville, Ky. Unpublished results.

Lee, C. C., et al., J. Tox. and Envir. Health 4 15 (1978).

Lehman, L. B. and F. Flury "Toxicology and Hygiene of Industrial Solvents", Translated by E. King and H. F. Smyth, Jr., T. H. Williams, S. Wilkins Co., Baltimore, 1943.

Leonard, A., et al., J. Toxical. Environ. - Health, 2 1135 (1977).

Lester, D., L. A. Greenberg, and W. R. Adams, Ann. Ind. Hyg. Assn. J., 24 265 (1963).

Lilis, Lr., et al., Am. N.Y. Acad. Sci. 246 22 (1975).

Loprieno, N., et al., Cancer Res., 36 253 (1977).

Loprieno, N., et al., Mut. Res., 40 85 (1976).

Lu, P. 4., et al., Arch. Environ. Contan. Toxical., 6 129 (1977).

MacMahon, B., "Vinyl Chloride and Human Reproduction", Submitted by the Society of the Plastic Industry, Inc., in comments on the Proposed Amendment to the EPA Vinyl Chloride Standard, 1977.

Malavielle, et al., Biochim. biophys. Res. Commun. 63 363 (1975).

Maltoni, C., Presentation at the GEOCOM Symposium on Vinyl Chloride, Institute Curie, Paris, March 2, 1976.

Maltoni, C., in "Origins of Human Cancer", H. H. Hiatt, J. D. Wilson, and J. A. Winsten eds., Cold Spring Harbor Laboratory, 1977, Vol. A., p. 119.

Maltoni, C., "Results of Sputum Cytology Among Workers Exposed to Vinyl Chloride Monomer and to Polyvinyl Chloride", in "Joint Symposium", Op. cit., 1980 S.

Maltoni, C., G. Lefenuine, A. Ciliberti, G. Colti, and D. Carretti, "Vinyl Chloride Carcinogenecity Bioassays (B T Project) as an Experimental Model for Risk Identification and Assessment in Environmenta and Occupational Carcinogenesis" Presented at "Le Club de Cancergenese Chemique", Institute Curie, Paris, Nov. 10, 1979. See also the "Joint Conference", op., cit., 1980.

Mapp, C., et al., Med. Lavoro 69 151 (1978).

Marcus, W., Comments during hearing on the Vinyl Chloride Standard, EPA, Washington D. C., Feb. 3, 1976. transcript page 43.

Maricq, H. R., M. N. Johnson, C. L. Whetstone, and E. C. LeRoy, JAMA 236, 1368 (1976).

Markowitz, S. S., C. J. McDonald, W. Fethiere, and M. S. Kerzner, Arch. Dermatol. 106 219 (1972).

Marsteller, H. J., Dt. Med. Wschr. 98 2311 (1973).

Mastromatteo, E., A. M. Fisher, H. Christie, and H. Danziger, Am. Ind. Hyg. Ass. J. 21 394 (1960).

Mattern, I. E., W. B. Van der Zwaau, and M. J. Willems, Mut. Res., 46 230 (1977).

McCann, J., et al., Proc. Nat. Acad. Sci., 72 3190 (1975).

Meselson, M., and K. Russell, "Comparison of Carcinogenic and Mutagenic Potency", in H. H. Hiat, J. D. Watson, and J. A. Winsten, eds., "Origin of Human Cancer", Book C, p. 1473. Cold Spring Harbor, N. Y., 1977.

Meyerson, L. B., and G. C. Meier, Arch. Dermatol. 106 224 (1972).

Miller, A., et al., Ann. N. Y. Acad. Sci. 246 42 (1975).

Mirkova, E., A. Mihailova, and M. Nosko, Khig. Zdraveopaz 21 440 (1978).

Monson, R. R., J. M. Peters, and M. N. Johnson, Lancet 2 397 (1974).

Muller, G., Norpoth, K., and W. Owzarski Int. Arch. Occup. Environ. Health 42 137 (1978).

National Academy of Science, "Drinking Water and Health," National Academy Press, 1977.

National Academy of Science, "Drinking Water and Health", Vol. 3, p. 38, National Academy Press, 1980.

National Cancer Advisory Board, "The Relation of Bioassay Dose to the Assessment of the Risk of Carcinogens for Humans under Conditions of Low Exposure", Subcommittee on Environmental Carcinogenesis, Draft of 1979, Citing data from Meselson and Russell, 1979.

National Institute of Occupational Safety and Health, J. Occup. Med. 16 809 (1974).

National Toxicology Program, "First Animal Report on Carcinogens; Vol. II, p. 190. Dept. of Health and Human Services, Washington, D. C., July, 1980.
Nicholson, W. J., et al. Ann. N.Y. Acad. Sci., 246 225 (1975).

Nisbet, I.C.T., Post-hearing statement to OSHA docket 090, September 15, 1978.

Occupational Safety and Health Administration, "Vinyl Chloride", Job Health Hazard Series, OSHA, 2225, June, 1975.

Occupational Safety and Health Administration. "Identification, Classification and Regulation of Potential Occupational Carcinogens", 45 FR 5178-5200, Jan. 22, 1980.

Oster, R. H., C. J. Carr, J. C. Krantz, and M. J. Saverwald, Anesthesiology 8 358 (1947).

Ott, M. G., R. R. Langner, and B. B. Holder, Arch. Envir. Health, 30 333 (1975).

Ottenwalder, H., and H. M. Bolt, J. Envir. Path. Toxicol., 4 411 (1980).

Paddle, G. M. The Lancet 1976 May 15.

Patty, F. A., W. P. Yant, and C. F. Waite, Pub. Health Reports, 45 1963 (1930).

Peoples, S. A. and S. D. Leake, J. Pharmacol. Exptl. Theory 48 284 (1933).

Picciano, D. J., et al., J. Occup. Med. 19 527 (1977).

Popper, H., et al., Am. J. Pathol. 92 349 (1978).

Prodan, L., Ann. N.Y. Acad. Sci., 246 154 (1975).

Purchase, I. F. H., C. R. Richardson, and D. Anderson, Lancet 411 ii (1975).

Radike, M. J., "Carcinogenic Effects of Exposure to Vinylchloride Monomer and Ethyl Alcohol on Rats", in "Joint Conference", op. cit., 1980.

Radike, M. J., et al., Envir. Health Persspent. 21 (153) 1977.

Rannung, H., et al., Chemico-Biol. Ineract. 12 251 (1976).

Reinl, W., H. Weker, and E. Greiser, "Epidemiological Study of the Mortality of Workers Exposed to Vinyl Chloride in the FRG", Paper presented at the Nineteenth International Conference for Occupational Health, Dubrovnic, Yugo, Sept. 19, 1978.

Reitz, R. H., et al., Science 205 1206 (1979).

Rowe, V. K., and T. R. Torkelson, Am. Ind. Hyg. Assn. J. 38 A-25 (1977).

Saric, M., Z. Kulcar, M. Zorica, and J. Gelic., Envir. Health Persp., 17 189 (1976).

Schaffner, F., Falk Symp. 25 Primary Liver Tumors, p. 189, 1978.

Schainer, L. A., "Mutagenicity of ambient air at selected sites in the United States using Tradescantia as a Monitor," paper presented at the conference on "In vitro toxicity testing of environmental agents," Monaco, September 22-23, 1979. Brookhaven National Laboratory paper BNL-27251.

Schaumann, O., see K. B. Lehman and F. Flug, "Toxikol. u. Hyg. d. techniochem Losungs mittel", J. Springer, Berlin, 1938, p. 130-143.

Schaumann, O., Medizin u. Chemie 2 132 (1934).

Schaumann, O., Arch., f. exper Path., 181, 144 (1936).

Schneiderman, M. A., N. Mantel, and C. C. Brown "From Mouse to Man ...", Ann. N.Y. Acad. Sci., 246 237 (1975).

Semon, W. L., U. S. Patent 1, 929, 453 (Oct. 18, 1933).

Short, R. D., J. L. Minor, J. M. Winston, and C. C. Lee, J. Toxical. Environ. Health, 3 965 (1977).

Singh, H. B., et al., "Atmospheric Measurements of Selected Toxic Organic Chemicals - Interim Report 1979", EPA-600/3-80-072, July 1980, PB 80-198989.

Smirnova, N. A. and N. P. Granik, Gig. Tr. Prof. Zabol, 14 50 (1970).

Spiritas, R., et al., Am. Ind. Hyg. J. 36, 729 (1975).

Stafford, J., private communication (1980).

Stein, G., S. Juhe, C.-E. Lange and G. Veltman, Sonderdruck aus Rontgen-Blatter 26 3 (1973).

Stockle, G., R. J. Laib, J. G. Fibser, and H. M. Bolt, Toxicology Letters 3 337 (1979).

Suciu, I., et al., Ann. N.Y. Acad. Sci. 246 53 (1975).

Suciu, J., J. Drejman, and M. Valaskai, Med. Intern. 15 967 (1963).

Suciu, F., J. Drejman, and M. Valaskai, Med. Lav. 58 261 (1967).

Tabershaw, I. R., and W. R. Gaffey, J. Occup. Med. 16 509 (1974).

Tamburro, C., "Liver Screening Tests for Vinyl Chloride Exposed Workers", in "Joint Conference", op. cit. 1980.

Tassignou, J. P., Proceedings of 20th meeting of Le Club De Cancerogenese Chimique, 10 Nov. 1979, Institute du Radium, Fondation Curie, Paris.

Taylor, K. J. W., "Toxic Substances in the Air Environment" Proceedings of the Air Pollution Control Asociation, Pittsburgh Conference, 1977, p. 119.

Theriault, G. P., and L. Goulet, "Birth Defects in a Community Located Near A Vinyl Chloride Plant" Presented at the Annual Meeting of the Am. Public Health Assn., 1977.

Thomas, L. B., and H. Popper, Ann. N.Y. Acad. Sci., 246 268 (1975).

Tomatis, L., et al., Cancer Research 38 877 (1978).

Torkelson, T. R., Statement before the Senate Subcommittee on Environment, Aug. 21, 1974. Committee on Commerce Serial No. 93-110.

Torkelson, T. R., F. Oyen, and V. K. Rowe, Am. Ind. Hyg. Assn. J., 22 354 (1961).

Tribukh, S. L., N. P. Tikhomirova, S. V. Levina, and L. A. Kozlov, Gigiena i Sanit 10 38 (1949).

Union Carbide, unpublished data, (1974).

Vainio, H. Chem-Biol. Interactions 22, 117 (1978).

Van Duuren, B. L., Ann. N.Y. Acad. Sci. 246 258 (1975).

Vazin, A. N., and E. I. Plokhova, Gig. Tr. Prof. Zabol 13 46 (1969). Chem. Abstracts 71 89621q. (1969).

Veltman, G., et al., Ann. N.Y. Acad. Sci. 246 6 (1975).

Verburgt, F. G., and E. Vogel, Mut. Res., 48 327 (1977).

Viola, P. L., Medicina del Lavoro 61 174 (1970).

Viola, P. L., A. Bigotti, and A. Caputo, Cancer Research 31 516 (1971).

von Dettingen, W. F., Public Health Service Publication no. 414, U. S. Department of Health, Education and Welfare, Washington, D. C., 1955.

Wagoner, J. K., P. F. Infante, and R. Saracci, Lancet, 1976 194.

Wakeman, I. B., and H. R. Johnson, Pol. Eng. Sci., 18 404 (1978).

Watanabe, P. G., R. E. Hefner, Jr., and P. J. Gehring, Toxicol. 6 (1976).

Watanabe, P. G., G. R. McGowan, E. D. Madrid and P. J. Gehring, Toxicol. Appl. Pharmacol. 37 49 (1976).

Watanabe, P. G., G. R. McGowan and P. J. Gehring, Toxicol. Appl. Pharmacol. 36 339 (1976).

Watanabe, P. G., J. H. Zenpel, D. G. Pegg, and P. J. Gehring, Appl. Pharmacol., 44 571 (1978).

Watanabe, P. G., et al., Dev. in Tox. and Envir. Sci., 6 69 (1980).

Waxweiler, R., et al., Am. J. Epidol., 104 (3) 347 (1976).

Waxweiler, R., et al., "An Epidemiological Investigation of an Excess Lung Cancer Risk in a Synthetic Chemicals Plant", Presented at the Nineteenth International Congress for Occupational Health, Dubrovnik, Yugo., Sept., 1978.

Waxweiler, R., "A Case-controlled Study of Lung Cancer Among Vinyl Chloride-Polyvinyl Chloride Workers", in Joint Conference, op. cit., 1980.

Waxweiler, R. J., H. Falk, et al., "A Cross-sectional Epidemiologic Survey of Vinyl Chloride Workers" Center for Disease Control, Division of Surveillance, Cincinnati, OH, April, 1977.

Whittington, L. R., Plastics World (1962).

Wilson, R. "Response to comments of I. C. Nisbet," Post-hearing record OSHA Docket 090, 1978.

Wilson, R. H., W. E. McCormick, C. F. Tatum, and J. L. Creech, JAMA 201 577 (1967).

Withey, J. R., J. Tox. and Envir. Health 1 381 (1976).

Withey, J. R., and B. T. Collins, J. Tox. Envir. Health, 2 311 (1976).

Zajdela, F., et al., Cancer Research 40 352 (1980).

Published Bibliographies on VC Not Cited Directly in the Test

Office of Occupational Health Surveillance and Biometrics, and Office of Research and Standards Development National Institute of Occupational Safety and Health, "A Bibliography on Vinyl Chloride," May 7, 1974.

International Occupational Safety and Health Information Centre (CIS)
International Labor Office
CH 1211 Geneva 22 Switzerland
"CIS Bibliography no. 10, Vinyl Chloride," undated, 1975 or 1976.

Oak Ridge National Laboratory, Oak Ridge, TN, 37830 "Vinyl Chloride, A Review", H. S. Warren, J. E. Huff, and H. B. Gerstner, ORNL/TIRC-78/3, November, 1978.

National Technical Information Service, U.S. Department of Commerce, Springfield, VA 22161, "Toxicity of Vinyl Chloride," NTIS/PS-77/0365, May, 1977, updated as NTIS/PS-79/0419/6, May, 1979, PB80-807662.