

HAZARD EVALUATION AND RISK ASSESSMENT
FOR
VINYL CHLORIDE

Prepared for the American Industrial
Health Council Risk Assessment Subcommittee

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Summary

A review of the environmental and health effects of vinyl chloride (VC) was performed in order to reconfirm that the risk of angiosarcoma of the liver (ASL) from chronic exposure is the major human health concern, and is therefore the appropriate risk on which to base risk assessments.

Vinyl chloride may be found in trace amounts from the combustion of chloride-contaminated organic materials; it is not otherwise known to be produced naturally. Emissions from VC-producing and handling operations is controlled by OSHA and EPA. The FDA regulates its presence in food-contact materials.

The metabolism of VC is via the mixed - function oxidase route, primarily in the hepatocytes of mammals, and is similar in rodents and humans.

The reactive intermediate metabolates such as chloroethylene oxide are thought to be the source of chronic damage to the liver cells because of their ability to combine with sulfhydryl groups. Detoxification appears to be a saturable mechanism which depends on conjugation with glutathione.

The toxic effect on plants is reported to be similar to that of ethylene. VC is not degraded by lower species of plant, but is photochemically reactive with a half-life of a few hours.

Acute toxic effects in animals include reversible liver damage, cardiac arrhythmia, and lung edema. It is an effective anesthetic and causes respiratory failure at high concentrations. VC is very flammable, but with a relatively high ignition temperature, and forms explosive mixtures over a wide range of concentrations with air. Contact with the liquid will result in frostbite.

Extended exposure by humans is associated with acroosteolysis, a degenerative disease of the bone tufts, and causes ASL in both humans and rodents. There is an increased incidence of tumors at other sites in rodents at higher concentrations, but this has not been confirmed in humans.

Studies suggest that reversible chromosomal changes in somatic cells occur in humans at elevated concentrations. Rodent tests do not show teratogenicity or dominant lethal effects, although there are some indications of delayed development and various skeletal variations. Studies of human birth defects provide no correlation with parental exposure to VC.

A review of the quantitative risk assessments which have been published shows a wide variety of results depending on the data base chosen, the mathematical model used, and the assumptions made. The best correspondence with actual experience is found when biotransformed animal data are applied to unconstrained probit and linear models.

Suggestions are made for further calculations and experiments which may clarify the appropriate model and improve the precision of the estimates.

I. INTRODUCTION AND BACKGROUND

Vinyl chloride (VC) is a classical procarcinogen (becomes active upon metabolism by the host), 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 assessments 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 co-workers (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).

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). Conventional water treatment systems are capable of removing VC from wastewater streams (Minott, 1973, Crider, et al., 1977).

The EPA has conducted three ambient monitoring programs around VC handling plants (EPA, 1975, Dimmick, 1981). 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 from the plant center, 10 ppb at 1 km, and 2 ppb at 2 km. The EPA has calculated (EPA, 1975) 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

III. ANIMAL METABOLISM

Clapp and co-workers (Clapp, 1969) identified cysteine 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 co-workers (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 homogenates exposed to VC. (See also Muller, Norpoth, and Owzarski 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 phenobarbital, 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. Bolt, et al., (1977, 1979) reported a change in the rate of metabolism of VC by rats at 250 ppm, very nearly the same critical concentration as found by Hefner and co-workers (1975). Du, et al., (1979, 1981) Laib, Guinner and Bolt (1981) and Guengerich, et al., (1981) all have reconfirmed these findings on the importance of glutathione in the detoxification mechanism.

These workers also found (Bolt, 1976) that respiratory uptake of VC by rats was completely blocked by cytochrome P-450 inhibitors, presumably because of interference with the metabolic pathway.

Green and Hathaway (1975) isolated and identified the cysteine-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 Strickland (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.

metabolite must leave the hepatocytes to act on the sinusoidal cells, the site of neoplastic development. Tamburro (1978) had made the same proposal for human cases.

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 Oettingen in 1955, and an excerpt 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.

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 sollaesthin (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

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. Clarke and Tinston (1973) commented on the rapid reversibility of this effect.

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.

Muratov and Takhirov (1979) report that the toxic effect of VC on rats is more pronounced at 36°C than at 18°C, and recommend lower allowable exposures at higher temperatures.

Torkelson, Oyen, 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 any species, nor from daily 100 and 200 ppm doses for one hour, but longer daily exposure times caused slight increases in liver weights in rats. 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 Torkelson (1977) have since commented: "Had our recommendations based upon relatively simple toxicology been followed then, the difficulties of today (cancer) may never have occurred."

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 hemoperitoneum. 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. Suciú (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.

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 Reynauld's syndrome, and, frequently, scleraderma. 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 definite cases and 16 suspect cases in the U.S. No certain etiological 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) or jaw (Jayson, et al., 1976). Dodson (1971) could find no obvious medical reason for predilection to the disease in the four cases which he studied. It appears to be reversible after cessation of exposure (Graniger, Walker and Ward, 1980, Hess, Schneider and Roush, 1967).

Maricq (1976) found a strong association of capillary abnormalities in the hands with workers suffering from AOL. Lilis (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). There is no question that VC exposure is associated with the cases seen in the industry, but the exact cause or mechanism for development of the disease has not been determined. It appears to be a result of circulatory deficiencies perhaps brought on by VC exposure, and possibly aggravated by physical insult. Bretza and Goldman (1979) have discussed non-occupational cases of scleraderma 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.

Czernielewski, et al., (1979) described 30 cases with severe scleraderma, 3 of which had progressed to AOL, and 9 had abnormal liver scans. Twenty-five had Reynauld's syndrome. They stressed the importance of skin changes as warning signs.

VI. MUTAGENICITY

Hopkins (1979) and Montesano, et al., (1976) have published reviews of the mutagenicity data on VC. Although it is clear that VC is mutagenic in several strains of Salmonella when activated by rat liver cells (Rannung, et al., 1974, Bartsch, 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, chloro ethylene oxide and chloro acetaldehyde, are also mutagenic to Salmonella (Malavielle, 1975, Rannung, 1976).

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

Mouse liver microsomes were necessary in some tests for VC to have an effect on various Saccharomyces varieties (Loprieno, et al., 1976), but not in others (Bartsch, 1979) while chloro ethylene oxide was active directly (Loprieno, et al., 1977). Chloro acetaldehyde was only weakly active and chloro ethanol was inactive. The mouse-mediated assay with Saccharomyces was positive with VC, also (Loprieno, 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. Haellstrom, et al., (1981) called VC a "fairly weak mutagen" in a test system utilizing Drosophila microsomal fractions to activate VC when Salmonella was the indicator organism.

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 hamsters 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 F₃-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 F₀ generation exposure was seen.

Studies by Schwetz, et al (1975) and 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 delayed development and a higher incidence 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.

A recent review of animal data for the Council on Environmental Quality (1981) cites two other studies which suggest increased embryo toxicity and fetal mortality in rats exposed during the entire pregnancy. In one of these, Ungvary, et al., (1978) reported embryotoxicity and increased resorption in rats exposed to 1,500 ppm during the first third of pregnancy.

Rice (1981) concluded that there is no evidence that exposure to VC or any other carcinogen has produced increased tumors in the offspring.

One portion of the Maltoni (1977) program was an examination of the second generation rats whose dams were exposed. Experiment BT-5 found zymal 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

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. Her conclusion was that "there are no data which point unambiguously to a relation between VC and reproductive outcome."

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 by the same group of VC/PVC producers. Several other studies by industrial and governmental groups were also undertaken at about the same period.

Viola found principally tumors of the zymbal gland. This is an organ near the ear which secretes oil, and is found only in rodents. He also reported tumors of the skin, bone and lung. These are generally thought to have been metastasized zymbal tumors, and not primary cancer.

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 adeno-carcinomas in those exposed to 2,000 ppm and above. Rabbits exposed to 10,000 ppm VC for 15 months had lung and skin tumors at the end of the experiment.

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 (Garmon, 1981).

It has been shown (Radike, et al., 1977, 1981) 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, 1981) 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

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 reported 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 event, 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.

Two injection experiments were included in the Maltoni study. Mice were injected with 4.25 mg. VC in olive oil at intervals ranging from once per lifetime to two times per month for life. There was no dose-related statistically significant change in either benign or malignant tumors at the end of 144 weeks, (Maltoni, et al., 1981) and no cases of ASL.

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

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, Theriault and Allard, 1981). 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, 1982) 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, 1981), 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 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, 1981). 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. See also Theriault and Allard (1981), Falk and Waxweiler (1976). This conclusion came from the application of an elaborate method for determination of exposure indices for workers potentially exposed to several chemicals (Greenburg and Tamburro, 1981).

Beaumont and Breslow (1981) evaluated the statistical power of nine epidemiological studies dealing with possible lung cancer from VC exposure and concluded that the lack of a general trend in these results indicated that VC is not a human lung carcinogen. This was supported by the negative results in the two studies with the highest statistical power (Equitable Environmental Health, 1978, Fox and Collier, 1977). They concluded that the reported studies were compatible with a relationship between VC and brain cancer. This was based, however, on the assumption that the result of the EEH study was positive, a conclusion that is not altogether clear.

Tamburro and his associates at the University of Louisville have followed closely the histories of the ASL cases at the Goodrich plant. This work has been summarized by Dannaher, et al., (1981). Diagnostic methods, treatment, and survival are described. The

deaths in German workers, but the authors have since found calculation errors in the processing of the data. A later summary of this study (Weber, Reinl, and Greiser, 1981) found an elevation of lymphatic tumors in addition to the expected ASL cases, but no elevation of lung or brain tumors. Molina, et al., (1981) found that the Swedish work group had an elevated heart disease rate, but not tumors other than ASL.

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 (Dimmick, 1981), 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, 1981) 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., 1981) 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. Sardi, 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 Pershagen, 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 (Dalderup, et al., 1976).

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 arrhythmia 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

There has been a decreasing incidence of 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. Occupational exposures were reduced by a large factor in 1974-5 (Jones, et al., 1976, 1981, Barnhart, et al., 1975), and further reductions of workplace and environmental emissions have continued since that time. 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, these risks are at least an order of magnitude less than that for ASL (Monson, 1980). 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.

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 Kuzmack 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 Kuzmack and McGaughy had used a factor of two times ASL 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 from exposure to ambient concentrations 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, 1981) 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 1,000 ppm exposure. The linear model predicts no incidence below 99 ppm in humans. The probit model predicts a human risk of 1.5×10^{-6} at 1 ppm. Thus, a mechanism for adjusting for the difference in metabolism between animals and humans appears 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 curvilinearity at low doses. It

which this can be extended is not known. See Section XB for further discussion.

These authors also used the Crump-Guess model (Crump, Guess 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 g/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.

13. Carlborg, 1981, also applied the Weibull model to 31 bioassay reports on a variety of animal carcinogens. He concluded that the one-hit model was not appropriate and that carcinogens could be divided into categories according to the shape of curve, e.g., concave or convex. He found that the early Maltoni data on VC fell into the former category. Application of his parameter estimates to the early Maltoni data, assuming no spontaneous incidence of ASL, gives 2.5×10^{-6} ppm for a lifetime risk of 10^{-6} for rats.

He found the Weibull shape parameter, which often is assumed to be half the number of stages for tumor initiation, to be approximately 0.5. This is consistent with the finding by Gehring (1977) of a saturable metabolic path which produces the proximate carcinogen. It also suggests that the number of "stages" is the number of finite-rate steps before the rate-limiting step. There may be other stages following, but they are not rate controlling. Actually, there appears to be at least two saturable mechanisms involved in the pharmacokinetics of VC, the metabolism to the ultimate carcinogen (which itself may have more than one route) and the detoxification by sulfhydryl groups.

These estimates are compared in Table 10, using the sequential numbers of this section for reference. Estimates 5, (Dow 1979) and 12 (Scott, 1981) were not in a form to permit a 10^{-6} lifetime risk estimate. See OSHA, (1980), for references to a few other estimates that were not considered here.

OSHA (1980) has stated that this wide range of results from attempts to quantify the risks from VC is an indication of the unsuitability of the entire concept of quantitative risk assessment. This variability is, in part, a reflection of the early stage of development of the procedure. Subjectivity and necessarily (in some cases) arbitrary assumptions applied in the evaluation of the data are also responsible as are also differences in the mathematical treatment. It is apparent that some mathematical models fit the data better than do others. A reasonable fit with human experience was obtained when suitably biotransformed rat data were fitted by the product model, e.g., Gehring (1979) and Anderson (1980). The Food Safety Council (1980) has emphasized the need for appropriate consideration of biological factors in the application of mathematical models.

B. Further Calculations

1. Mathematical Considerations

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

observed incidence at finite exposures, but very small values, approximately 10^{-5} , were used rather than zero with the logarithmic and exponential programs to avoid machine error. These results 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. Omission of these points is based on the conclusion that competing toxicity resulted in incorrectly low death rates being ascribed to ASL.

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 ingestion 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-

2. Biological Considerations

The only difficulty with the Gehring risk estimation 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 (1981) 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%. This compares to a risk in the general population of about 10^{-6} or 10^{-8} from reported cases, although autopsy ratios show higher rates.

Personal experience would indicate that, for the period prior to 1962, when all of the first exposures of the fatal 26 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 (NCAB, 1979). Recent experience with extremely large bioassay experiments leads to the conclusion that no reliable estimate of human risk can be obtained from raw animal data alone, but must include suitable biological adjustments (Joint Conference, 1981).

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 (Landau, Charles, and Manos, 1975) that nearly 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

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 (1982) 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.
6. Continue efforts to understand more fully the human metabolic/detoxification processes for VC.

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}_D	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 2

Angiosarcoma Cases in the VC/PVC Industry
by Country
as of January, 1982

United States	28*
West Germany	21
France	14
Canada	10
United Kingdom	7
Sweden	5
Yugoslavia	4
Italy	3
Czechoslovakia	2
Japan	2
Norway	1
Belgium	<u>1</u>
Total	98

Data From Stafford (1982), except that the U.S. total includes one case reported only in the press.

*Includes one case still alive.

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TABLE 4
Chronology of U.S. Deaths From Angiosarcoma

	<u>Deaths</u>	<u>Year of First Exposure</u>
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	3	1945, 1948, 1958
1974	1	1942
1975	4	1945, 1947, 1954, 1962
1976	3	1943, 1947, 1955
1977	1	1946
1978	2	1941, 1944
1979	0	
1980	4	1942, 1951, 1955, 1964
1981 (as of July)	<u>0</u>	
Total	27	

Data From Stafford (1982). First exposure of living case was 1946.

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TABLE 6

ASL 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. Experiment No.	300	180	75	15	7.5	6.0	4.6	3.0	1.5	0.8	0.3	0.15	0.03
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 8

Equations for Curves Fitted to Various Single
and Combined Maltoni Experiments

Experiment	Linear $y = ax + b$			Log Probit $P = a \ln \text{dose} + b$			Concentration at 10 ⁻⁵ risk, (log-probit), ppm
	a	b	r	a	b	r	
BT-1 plus controls	0.4 0.4	3.36 2.47	0.97 0.97	0.35	2.76	0.99	0.03
BT-2 plus controls	3.4 1.1	-8.59 -1.13	1.0 0.88	1.60	0.88	1.0	23
BT-15 plus controls	6.4 5.4	-1.06 -0.30	1.0 0.95	0.69	3.46	1.0	0.34
All inhalation studies (4) plus controls	0.4 0.4	3.07 2.80	0.91 0.91	0.27	2.98	0.82	0.002
All ingestion studies (2) plus controls	1.4 1.4	0.15 0.20	0.95 0.95	0.30	3.22	0.88	0.002
All studies (6) plus controls	0.4 0.4	3.60 3.41	0.73 0.72	0.27	3.05	0.82	0.001
All studies; low doses only, plus controls	1.4	0.97	0.79	0.51 0.17	2.53 2.71	0.75 0.49	0.42 0.0002

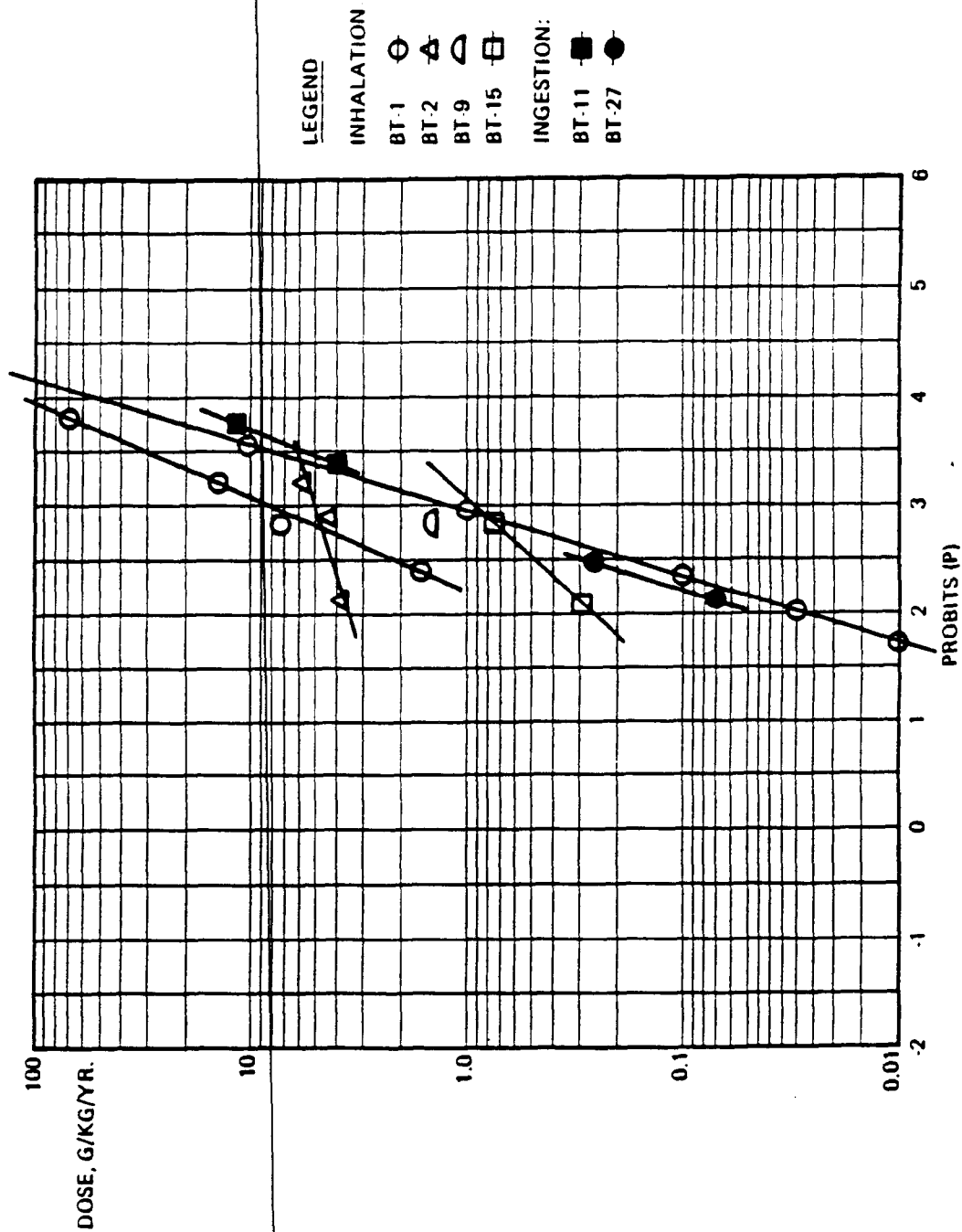
TABLE 10

Summary of Quantitative Risk Assessments for VC

Sec. X. A. No.	Author	Base Species	Exposure for 10 ⁻⁶ Lifetime Risk	Comments
1	Schneiderman, 1975	rat	73 ppb 119 ppb 2 ppb	log probit logit slope = 3.45 logit slope 2.3, 1-hit
2	Kusmack and McGaughy, 1975	rat, human	14 ppb 140-1400 ppb	linear log-probit
3	Gehring, 1975	rat, human	> 1 ppm	biotransformation data
4	Food Safety Council, 1980	rat	2 x 10 ⁻⁶ ppb	Weibull
6	Hehir, 1980	rat, mouse	thresholds seen in both species	
7	Anderson, 1980	rat, human	> 1 ppm	DNA binding
8	EPA, 1980	rat	4 μ g/day	food or water
9	NAS, 1980	rat	3 x 10 ⁻⁵ mg/kg/day	water
10	Gaylor and Kodell, 1980	rat	0.7 ppb 0.5 ppb	upper 97.5 % confidence limit of linear model Armitage-Doll model
11	Crump and Guess, 1980	human	0.7 μ g/day 0.5 μ g/day	applying worker data to water, upper 95% confidence limits
13	Carlborg, 1981	rat	2.5 x 10 ⁻⁵ ppb	Weibull
14	This paper (Section X. B.), 1981	human	> 1 ppm	negative epidemiology

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FIGURE 1
GRAPHICAL REPRESENTATION OF
TABLE 8
LOG-PROBIT PLOT



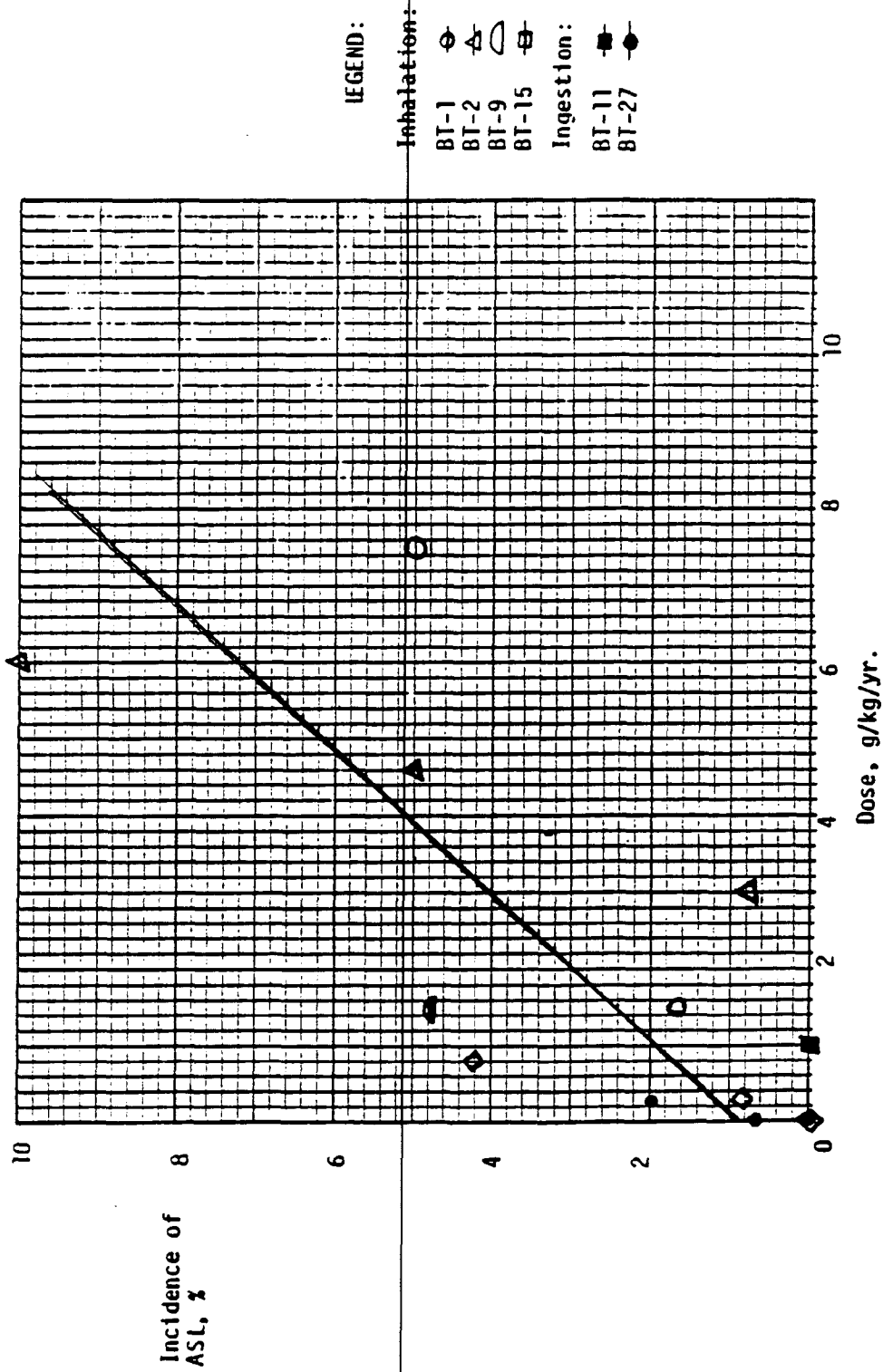


FIGURE 3
Graphical Representation of the
Low-Dose Data of Tables 6 and 7
Linear Plot

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