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VINYL CHLORIDE: HOW MANY UNKNOWN PROBLEMS?

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The chemistry, biotransformation, toxicology, and carcinogenicity of vinyl chloride have been reviewed. There is little doubt that this chemical produces angiosarcoma in both animals and man. However, the conditions for cancer induction in man cannot at this point in time be related to ambient exposure levels. An increase in reported cases of vinyl chloride-induced cases of liver malfunction, angiosarcoma, Raynaud's syndrome, scleroderma, and acroosteolysis should be expected in the near future due to past exposures. The exposure of the general population to vinyl chloride-propelled aerosols and household products may be a contributor to these disease states. Occupational exposures will probably decrease as VC/PVC plants meet the new exposure standard of 1 ppm. However, epidemiological surveys should be continued to ascertain the latent period and the degree of exposure involved in angiosarcoma development. Animal experiments should be initiated to determine the relationship of short exposures at high concentrations or long exposures at low concentrations to the development of liver malfunction and pathology. A pharmacokinetic evaluation of both animals and exposed workers should indicate the biotransformation products in the blood. Great emphasis should be placed on development of better, more rapid diagnostic and therapeutic measures. Health protection should involve government, industry, and labor in efforts to protect the worker from noxious chemicals.

INTRODUCTION

In January 1974, Creech reported on four cases of angiosarcoma of the liver in workers in a vinyl chloride plant in Louisville, Kentucky (Creech and Johnson, 1974). The report of this rare liver cancer (25 cases annually in the United States) caused a retrospective search, which ultimately uncovered 14 cases, all associated with the vinyl chloride industry (How surgeon's probe led . . . , 1974). At a fact-finding hearing one month later, differences of opinion were expressed by witnesses for labor and industry. It was agreed that vinyl chloride limits should be reduced from 500 ppm to 100 ppm; but most industries had already reduced the level to 50 ppm, a concentration which had not produced liver pathology in experimental animals. One difficulty in assessing the limit of exposure and the induction of angiosarcoma is the long latent

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period, 19 years, for development of the lesion (Battle lines drawn . . . , 1974). This latency coincides with the growth of the U.S. polyvinyl chloride industry. A similar situation has been reported in England (Evidence mounts . . . , 1974). At a meeting between industry, labor representatives, government officials, and scientists, emergency temporary standards for vinyl chloride (VC) and polyvinyl chloride (PVC) were discussed; this resulted in a major disagreement between industry and labor (Industry claims . . . , 1974). NIOSH (National Institute for Occupational Safety and Health) subsequently recommended a zero exposure limit for vinyl chloride and suggested that workers be given air-supplied respirators and protective clothing as well as strict medical surveillance (NIOSH recommends . . . , 1974; Key, 1974). In March 1974, the Occupational Safety and Health Administration (OSHA) issued a temporary vinyl chloride standard of 50 ppm and proposed a permanent standard of 1 ppm (OSHA to issue . . . , 1974). NIOSH proposed further safety measures to assist in achieving the recommended zero level of exposure (NIOSH proposes standard . . . , 1974). Both temporary and permanent standards for vinyl chloride were published in May 1974 (Stender, 1974b; Permanent vinyl chloride standard . . . , 1974). The influence of vinyl chloride and liberated monomer (VCM) from polyvinyl chloride films on the environment, particularly in the packaging industry, have been evaluated from a medical viewpoint. It was suggested that adequate ventilation and entrapment of VCM on charcoal would prevent atmospheric contamination (Vinyl chloride studies . . . , 1974). Hearings on a permanent vinyl chloride standard have further exaggerated the differences of opinion expressed by both industry and labor. Labor insisted on a zero tolerance level, while industry suggested a reduction from 25 ppm in 1974 to 10 ppm by 1975. It was also pointed out that immediate shutdown of VCM and PVC plants during a changeover to lower limits would result in the loss of 1.7-2.2 million jobs and 60-90 billion dollars (Vinyl chloride hearings . . . , 1974). The Department of Labor has disputed these latter figures (Hearings under way . . . , 1974). In October, the proposed standard for vinyl chloride was adopted (Stender, 1974a). Industry has taken legal action against the standard, 1 ppm, because the technology required to meet it does not exist today (Firms challenge . . . , 1974). This is supported by British industry, which reported that existing plants could reduce exposure to 10 ppm while new ones might reach the level of 5 ppm; levels below that were inconceivable (Vinyl chloride issue . . . , 1974). However, the U.S. Court of Appeals sustained the level of 1 ppm.

To further complicate the situation, a controversy has arisen concerning the Italian data reporting angiosarcoma of the liver in rats exposed to 50 ppm of vinyl chloride. European industry controlled the release of the data and, although the Manufacturing Chemists Association (MCA) had access to the finding, they could not release them

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(Withholding of . . . data hinted, 1974). The chronology was discussed by the MCA, and it was reported that liver cancer of rats from 30,000 ppm of vinyl chloride was seen in 1971 with further reports continuing through 1974. The first angiosarcoma was observed in August 1972. NIOSH has accused MCA of withholding this data (Vinyl chloride cancer . . . , 1974). MCA-sponsored research has shown that vinyl chloride also produces angiosarcoma in mice (New tests link . . . , 1974). Vinyl chloride workers have shown chromosome changes indicative of a mutagenic effect, but the group examined is too small to be considered a body of hard data (More trouble . . . , 1974). A class action suit has been filed charging that thermal decomposition of PVC wrappings causes skeletal deterioration and permanent cardiac and brain damage. The decomposition products include vinyl chloride. The only proven effect is a respiratory syndrome known as "meat-packers asthma" (PVC makers hit . . . , 1974).

The controversy between industry, labor, and government requires a full review of the vinyl chloride situation to ascertain the total problems in industrial hygiene, animal and human toxicology, and carcinogenesis in order that solutions may be suggested.

CHEMISTRY

Synthesis and Physical Properties

Table 1 lists the physical and chemical properties of vinyl chloride (Patty, 1962; McDonald et al., 1959; Gallant, 1966). Vinyl chloride has

TABLE 1. Physical and Chemical Properties of Vinyl Chloride

Physical state	Gas (usually handled as a liquid under pressure)
Molecular weight	62.5
Specific gravity	0.9121 (20°/4°C)
Melting point	-159.71°C
Boiling point	-13.8°C
Vapor density	2.15
Vapor pressure	2580 mm Hg (20°C)
Solubility	sl. sol. H ₂ O, sol. ETOH, (ET) ₂ O, CCl ₄ , C ₆ H ₆
Flash point	-78°C (open cup)
Explosive limits	lower 4% and upper 22% (vol. in air)
Autoignition temperature	472.22°C
Viscosity, liquid	0.281 centipoise at 20°C
Specific heat, liquid	0.27 cal/g C° at 20°C
Specific heat, gas	0.206 cal/g C° at 25°C, 1 atm
Critical temperature	158.4°C
Critical pressure	774.7 psia at 52.7 atm
Refractive index	n_D^{20} 1.4066

Technical vinyl chloride contains the following impurities (in mg/kg): unsaturated hydrocarbons—10; acetaldehyde—2; dichloro compounds—16; H₂O—15; HCl—2; nonvolatiles—200; Fe—0.4; and phenol as a stabilizer—25–50.

been synthesized by reacting dichloroethane with ethanolic potash or acetylene with hydrogen chloride in the absence or presence of HgCl_2 as a catalyst. Recently, it has been prepared by passing gaseous ethylene dichloride over alumina, activated charcoal, or pumice at high temperatures (Fairhall, 1969, p. 356). The bulk of vinyl chloride is now synthesized by oxychlorination of ethylene using a modified Deacon catalyst. This catalyst is a eutectic mixture containing 20% or more Cu with either KCl, NaCl, CaCl_2 , or PbCl_2 . The ratio of Cu:K ions must be greater than 0.5:1 to proceed at the reactor temperature of 250°C . Alumina, silica, or other porous materials are used as catalyst supports, and size and porosity are important for catalyst performance. Graphite, silicon carbide, and nickel are used as diluents for the granular catalyst; temperature control of the exothermic reaction is critical for good yields. Newer catalysts contain rare earths. During the oxychlorination process, temperatures must be 250°C or higher, pressures are 1–10 atm and the feed stream ratios of ethylene, HCl, and O_2 are 1:2:0.5. Different ratios result in increased HCl in the product. The reaction has been carried out in packed-bed reactors, fluidized-bed reactors, or liquid-phase reactors. Pyrolysis of 1,2-dichloroethane to vinyl chloride is accomplished with catalytic or noncatalytic processes at temperatures of 450 – 650°C and pressures of 20–35 atm (Albright, 1967a). An overall discussion of vinyl chloride processes has been reported (Albright, 1967e). Storage of the monomer is critical as increased storage time increases the unstable polyperoxide content, increasing the explosive capability (NFPA Committee on Chemicals and Explosives, 1971). Procedures for storage and safe handling of vinyl chloride have been reported (Shelley and Sills, 1969). Vinyl chloride is converted to polyvinyl chloride by emulsion, bulk, and solution polymerization processes; each procedure has its good and bad features (Albright, 1967c). The conditions for initiating the reaction and controlling the polymer size, length, and molecular weight have been reported. End uses for the year 1965 are given in Table 2 (Albright, 1967b). The factors involved in the suspension processes for production of PVC resins have been discussed (Albright, 1967d). Total production in the United States for 1973 was 2,428,000 kg.

Analysis

Vinyl chloride has been determined in air and breath samples with an infrared spectrophotometer. The procedure is able to detect 0.05 ppm (Baretta et al., 1969). Gas chromatography using an electron capture detector has been used to monitor marine pollution from vinyl chloride production. The method can detect 0.1–0.6 mg/g (Jensen et al., 1971a,b). Combustion products of PVC have been determined by gas chromatography, infrared absorption, ultraviolet absorption, and mass spectroscopy (Boettner and Weiss, 1967). Gas chromatographic determination of pyrolysis of vinyl chloride found HCl 27,000 ppm, CO_2

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TABLE 2. End Uses of PVC Polymers in the United States During 1965

Type	Percentage
Flexible	
Cable coatings	12
Films and sheets	18
Flooring	17
Coatings	15
Extruded products	14
Miscellaneous	14
Rigid	
Tubes and fittings	5
Bottles, records, etc.	3
Films and sheets	2

Source: Albright, 1967b.

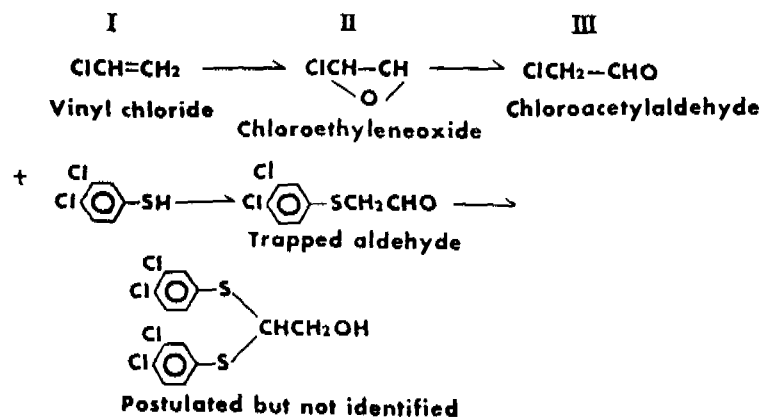
58,100 ppm, CO 9,500 ppm, phosgene 40 ppm, and VC a trace. HCl is considered the main hazard in VC fires (O'Mara et al., 1971). Thermal decomposition of PVC gives rise to more toxic products (see Table 3) (Tsuchiya and Sumi, 1967). PVC film releases similar products and, in addition, dibutyl phthalate and unreacted vinyl chloride (Popov and Yablochkin, 1967). Standardized procedures for gas chromatographic analysis have been reported for vinyl chloride and other aliphatic halogenate compounds. Comparison of electron capture and micro-coulometer detectors indicates that the latter is more sensitive (Williams and Umstead, 1968; Foris and Lehman, 1967). Comparison of gas chromatographic and infrared analysis of vinyl chloride shows that the former is 100 times more sensitive than the latter (Arena, 1970). Waste water analysis of PVC production using a polarographic method found unreacted vinyl chloride, polymerization initiators, and metal chlorides in the water (Meshkova et al., 1971).

Biotransformation of Vinyl Chloride

It has been suggested that vinyl chloride is converted to ethylene monochlorohydrin by the hepatocyte with subsequent conversion to chloral and chloroacetic acid. This latter compound has been found in vinyl chloride workers (Grigorescu and Tiba, 1966). Exposure of cell-free liver microsomal preparation to vinyl chloride results in the active species shown in Figure 1. 3,4-Dichlorobenzeneethiol was used as the trapping agent and the metabolites were identified by gas chromatography-mass spectrometry (Gothe et al., 1974). *In vivo*, the reactions may involve the glutathione S-transferases which catalyze the reaction of glutathione with α,β -unsaturated compounds (Clapp et al., 1969).

^aValues expressed as wt % sample.

Decomposition products	Temperature of decomposition (°C):	350	600	850	350	600	850	350	600	850
	Weight of sample (g):	0.5	0.5	0.5	0.5	0.5	0.5	0.25	0.25	0.25
	Atmosphere:	He	He	He						
HCl		53.2	55.5	57.9	47.2	46.0	40.6	48.5	42.3	24.3
CO		—	—	—	1.0	35.6	16.6	1.2	43.0	18.5
CO ₂		—	—	—	1.7	40.8	54.8	2.5	65.7	99.7
H ₂		—	0.06	0.47	—	0.16	0.5	—	0.11	0.37
CH ₄		—	1.0	3.2	—	1.7	3.4	—	1.7	2.4
C ₂ H ₆		—	0.69	0.32	—	0.14	0.06	—	0.14	0.03
C ₂ H ₄		—	0.52	2.5	—	0.63	1.3	—	0.38	0.41
Benzene		5.9	5.6	5.9	5.4	4.7	3.1	5.1	4.8	1.3
Toluene		0.05	0.67	0.87	—	0.22	0.89	—	0.18	0.31
Residue		37.4	6.3	5.1	40.2	2.4	—	39.5	0.3	—



Alternate pathway—spontaneous rearrangement of II to III

FIGURE 1. Biotransformation of vinyl chloride by mixed function of oxygenase (reprinted from Gothe et al., 1974).

INDUSTRIAL HYGIENE

When any chemical becomes important from a production and usage standpoint, the American Conference of Governmental Industrial Hygienists set limits on human exposure in the working area; the vinyl chloride threshold limit value (TLV) was set originally at 500 ppm (1971, p. 277). The AIHA Hygienic Guide Series also lists a TLV of 500 ppm but suggests that the TLV should be 100 ppm (1964). The Governmental Industrial Hygienists in 1971 proposed a new TLV for vinyl chloride of 200 ppm (Threshold limit values . . . , 1971). An English review of various countries' TLVs and MACs (maximum allowable concentration) points out the overall disagreement between governments on the degree of protection to be afforded the worker (Trevethick and Adam, 1969). The appearance of angiosarcoma has resulted in the revision of the vinyl chloride TLV, but a sharp disagreement arose between OSHA and the Society of the Plastics Industry over the no-detectable limit. Table 4 lists the two proposals (Conflicting views . . . , 1974). Prior to this, the State of Kentucky reduced the TLV to 75 ppm (Company, government tighten . . . , 1974). In August 1974, temporary vinyl chloride standards were put forth by OSHA, followed by hearings on a permanent standard (Field information memorandum . . . , 1974; Public hearings . . . , 1974). Discussion of the cost and use of respirators during plant modification to meet the no-threshold limit and their effect on productivity raised further controversy (Industry scores . . . , 1974; Economic impact study . . . , 1974; OSHA asked to reopen . . . , 1974). The final impact statement was filed on September 24, 1974, and released on October 1, 1974 (Final environmental impact statement . . . , 1974a,b). Specifications for

TABLE 4. Vinyl Chloride Rules Proposed by Government and Industry

Occupational Safety and Health Administration	Society of the Plastics Industry
1. A no-detectable level for employee exposure as determined by a sampling and analytical technique capable of detecting vinyl chloride concentrations of 1 ppm with an accuracy of $1 \text{ ppm} \pm 50\%$. This would apply to monomer, polymer, and fabricating operations.	1. For polyvinyl chloride resin plants, a ceiling of 40 ppm vinyl chloride in 1974, 25 ppm in 1975. For vinyl chloride plants, a ceiling of 25 ppm in 1974, 10 ppm in 1975. PVC fabricating plants would be excluded from the standard.
2. Labeling for regulated areas and vinyl chloride-polyvinyl chloride containers with the warning to include the words "cancer suspect agent."	2. Labeling should provide those who need the information with methods for dealing with the problem; it should not be a basis for panic because of a disease characterization.
3. Use of air-supplied respirators in cases of emergency and when vinyl chloride concentrations rise above detectable levels.	3. Use of air-supplied respirators is impractical except for short periods of time. Air-supplied breathing apparatus also should be allowed.

Source: Conflicting views . . . , 1974.

respiratory protective devices for vinyl chloride have been published and include gas masks, chemical cartridge and powered air-purifying respirators (Carlson, 1974). Similar problems have arisen in Soviet PVC production plants, where cases of toxic angioneurosis have been produced by concentrations of vinyl chloride of 10-40 $\mu\text{g/l}$ whereas the MAC was 1,000 $\mu\text{g/l}$ (Filatova and Gronsberg, 1957). Remote control automated equipment and mechanization of the operations in the work area to decrease environmental contamination has been suggested to control vinyl chloride emissions (Filatova, 1966). Thus, the world-wide overall solution to the vinyl chloride problem requires the use of respiratory protective devices to protect the workers while automated production lines with scrubbers and traps are being developed and installed. In plants, atmospheric monitors have been developed using automated gas chromatographs, infrared spectrophotometers, chlorine sensitive strip chart recorders, and organic vapor analyzers (Vinyl chloride monitors . . . , 1974). The Environmental Protection Agency requested information on environmental emissions of vinyl chloride by plants making it or PVC, but it was later shown that no environmental problem existed (EPA asks emission data . . . , 1974; Vinyl chloride no menace . . . , 1974).

Vinyl chloride produces a problem in waste water but pH adjustment and coagulation allows the solids to be incinerated (Morris, 1954). Coagulation with CaO is more efficient than NaCl , allowing the various PVC polymers to be disposed of in the sewage (Kotulski, 1965).

Waste recycling has also been utilized in Soviet plants (Arkhipov et al., 1973).

Drying units in PVC plants must be adequately ventilated and the resultant gases trapped to prevent environmental contamination; vacuum rabble, atomized and drum-type driers are recommended (Gavruseyka and Filatova, 1959). The latest drying unit removes VC, coarse particles, and fines with a combination of venting, air purging, a cyclone separator, and a cloth filter. This self-contained unit is adaptable to existing dry-blending equipment (System reduces VCM content . . . , 1975).

PVC floor coverings present yet another area for human exposure to VC. The continuous liberation of VC is definitely hazardous to health (Dyachuk, 1970b). PVC is recommended for places of short-time residence: bathtubs, corridors, or railway coaches, but not for homes or offices (Stankevich et al., 1968). If PVC is used as a floor covering, the area should be well ventilated for at least one month after laying to reduce VC exposure (Kalmanovich, 1968). Such precautions should also be followed where PVC is used in upholstery and interior automobile trimming (Slepek and Teplyakova, 1974). The use of PVC in homes (e.g., wall paper, upholstery, etc.) presents a toxic gas hazard (HCl, CO) in case of fire (Stark, 1969).

Migration of VC from PVC bottles and films into food or beverages produces a slight hazard. It is proposed that the VC content of the former be limited to 10 ppm and of the latter to 1 ppm (Interim food additive order . . . , 1974). The variable migration of VC depends on its initial concentration in the product. Heat sealing and cutting of PVC food packaging films result in local environment contamination of HCl, 0.3-2.3 mg/m³; and particulates, 7.5-19 mg/m³ (Van Houten et al., 1974). Although these contaminant levels are low they can produce "meat packers asthma" (PVC makers hit . . . , 1974). Adequate ventilation over the working area will prevent exposure.

AEROSOLS

One of the largest uses of vinyl chloride to which the public at large is exposed is its use as an aerosol propellant in household and cosmetic products. Vinyl chloride has been widely used as a propellant for hair sprays, pesticides, and room deodorants (Kuebler, 1958; Iosaki, 1958). Newer propellant mixtures of vinyl chloride and fluorocarbons contain 22% or more VC than earlier mixtures. Such blends in hair sprays, pesticides, and room deodorants are less corrosive to containers, have good flammability characteristics, low tendency to fractionate, and are safe for both pressure and cold filling (Scott and Terrill, 1962). Other propellants used include hydrocarbons and inert inorganic gases. A gas chromatographic method has been published for the analysis of paint propellants. It uses a thermal conductivity detector and a column packed

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with silicone grease on acid-washed 60-80 mesh fire brick. Propane, fluorocarbons, isobutane, butane, and vinyl chloride are easily separated but carbon dioxide and nitrous oxide are not (Esposito and Swann, 1967). Other columns and detectors probably give better results. The extent of products in aerosol containers is wide and includes deodorants, hair sprays, cosmetics, cleaners, laundry aids, polishes, room deodorants, coatings, finishings, insect sprays, food, and automotive and industrial products (Aerosol products . . . , 1974). When vinyl chloride was identified as a carcinogen, all of the above products became suspect; the result was the banning of vinyl chloride as a propellant even though the extent of its use in the above products was unknown (Carcinogens . . . , 1974).

The pharmacological properties of various aerosols have been reported but no lung pathology was found in short-term studies (Kuebler, 1964).

TABLE 5. Cancelled Pesticide Products Containing Vinyl Chloride

Reg. no.	Product	Company
4206-25	Barcolene Spray Disinfectant	Barcolene Co.
7572-4	Blue White Ant & Roach Killer	Blue White Chemical Co.
4-12	Bonide Household Flea Killer Spray	Bonide Chemical Co.
106-19	Brulin Bug Bomb	Brulin & Co.
2382-53	Clipper Mate Lubricates, Sanitizes, Cools	Carson Chemicals
2382-33	Fogging Dispenser	Carson Chemicals
2382-30	Lice and Mite Spray	Carson Chemicals
2382-47	Paracide with Sevin	Carson Chemicals
498-56	Flea Killer for Dogs & Cats	Chase Products Co.
2337-1	Demert Raw Roach, Ant & Wasp Killer	Dougherty
1990-361	Coop Dairy Insecticide for Milk Houses and Animals	Farmland Industries
1990-334	Insect Repellent for Personal Use	Farmland Industries
1304-24	NcNess Push-Button Spray Insect Killer	Furst-McNess Co.
2270-222	Excelcide 16 oz. Aerosol Bomb	Huge Co.
334-306	"K" Insect Spray	Hysan Corp.
334-134	Mothrid Moth Proofer	Hysan Corp.
334-356	Nokout 25 Aerosol Insecticide	Hysan Corp.
344-251	Pet Repel	Hysan Corp.
334-387	Spritz Metered Air Sanitizer	Hysan Corp.
7555-3	Rodgers' Insecticide & Repellent	Jay-Rodgers & Co.
622-4	Cat-ette Flea Killer	Lora Labs.
6222-2	Dogette Flea Killer & Coat Conditioner	Lora Labs.
1926-44	Kilzum Crawling Insect Killer w/Bagon	Navy Brand Mfg. Co.
1926-43	Kilzum Fly & Mosquito Insecticide w/Allethrin	Navy Brand Mfg. Co.
2196-176	Patterson's Aerosol Insect Killer	Patterson Chemical Co.
4691-102	Anchor Flea, Lice & Tick	Phillips-Roxane
4691-38	Research FLT Bomb	Phillips-Roxane
9688-12	Total Release Insect Fogger	Spray-Chemical Corp.
4684-3	African Violet Spray	Stim-U-Plant Labs.
731-12	Chaperone Flea & Tick Killer	Sudbury Lab.
449-543	Pyrethrin Insecticide, Pressurized Dairy Insect	Woodbury Chemical Co.

Sources: Agee, 1975; Quarles, 1974; Train, 1974.

TABLE 6. Estimated Weekly Exposure from Vinyl Chloride in Aerosol Products

Product	Direct exposure (ppm/hr/week)	Indirect exposure (ppm/hr/week)	Total exposure (ppm/hr/week)
Hair spray	175	70	245
Deodorant	42	21	63
Pesticide	25	10	35
Room deodorant or disinfectant	25	50	75
Furniture polish or window cleaner	50	100	150
Total	317	251	568

Source: Adapted from B. W. Gay, Jr., W. A. Lonneman, K. Bridbord and J. Moran, unpublished data, April 1974.

Regardless of the above findings, the Food and Drug Administration (FDA) has been requested to suspend pesticide formulations containing vinyl chloride (FDA requested . . . , 1974). Another request asked the banning of vinyl chloride as a propellant in products under the jurisdiction of FDA and CPSC (EPA is expected to act . . . , 1974). After notification, the pesticide products listed in Table 5 had their registration cancelled (Agee, 1975; Quarles, 1974; Train, 1974). The degree of exposure to vinyl chloride in the breathing zone from spraying hair spray, pesticide, deodorant, disinfectant, or furniture polish inside a room is shown in Table 6.¹ The extent of effect of such exposures on the overall health of the individual is unknown and if detrimental will require many years to develop. However, other ingredients in such sprays have been shown to produce thesauriosis, sudden death from cardiac failure, allergies, asthmatic attacks, oropharyngeal irritation, dermatitis, bronchioconstriction, hypersensitivity reactions, and granulomatous lung disease. This latter condition has been associated with aerosol deodorants containing zirconium salts (Bernstein, 1972). Thus, the problem is compounded by both the propellant and other ingredients in the various spray products and the possibility of a synergism which will produce more than one variety of detrimental effect in the user.

ANIMAL TOXICOLOGY

General Toxicology

Two small reviews have appeared on the toxicology of vinyl chloride (Flimm, 1946; Schotter, 1969). Vinyl chloride has a local irritating effect on skin and mucous membranes. It readily distributes in blood and is readily eliminated, 82% in 10 min. Heart rate and blood pressure are not affected at low concentrations but a hypertension occurs at high

¹ B. W. Gay, Jr., Lonneman, W. A., Bridbord, K. and Moran, J., unpublished data, April 1974.

concentrations. Respiratory paralysis, salivation, and later emesis occur in dogs at a concentration of 20 vol %. No liver or kidney changes were seen at this narcotic concentration. Similar results were obtained in mice, rats, guinea pigs, and rabbits (Lehmann and Flury, 1938). Vinyl chloride anesthesia of the dog produces muscle incoordination and serious cardiac arrhythmias (Carr et al., 1947) and sensitized the heart to catecholamines (Carr et al., 1949). Vinyl chloride perfusion of the frog leg vessels produces no effect (Krantz et al., 1936). Chronic feeding of diets containing 1.5-15% vinyl chloride-vinyl acetate copolymer for two years had no effect on rats (Smyth and Weil, 1966).

The implantation of plastics has produced severe fibroblastic reactions in guinea pig and rabbit muscle, but it has not been possible to determine whether the reaction was produced by monomer, polymer, plasticizer, or other additives (Little and Parkhouse, 1962; Guess and Haverman, 1967). *In vitro* techniques using tissue culture and antigen-antibody reactions indicated a toxic potential from materials migrating from polyvinyl chloride (Guess et al., 1967). Chick embryo heart cells in culture grown in media exposed to polyvinyl chloride tubing showed blistering and granularity and stopped beating. The toxic agent was not identified (DeHaan, 1971).

Inhalation Toxicology

Acute inhalation of vinyl chloride in concentrations of 0.5-40 vol % by guinea pigs resulted in deaths by respiratory paralysis at levels of 2.5-40 vol %. The chemical produced unsteadiness and ataxia, rapid jerky respiration followed by shallow respiration and surgical anesthesia. Gross pathologic findings included congestion and edema of the lungs and hyperemia of the liver and kidneys (Patty et al., 1930). At 10 vol %, dogs showed cardiac irregularities, including tachycardia, bradycardia, inversion of the R-wave, abnormalities in the QRS interval, sinus arrhythmia, transitory left axis deviation, A-V block, ventricular tachycardia, ventricular multiform extrasystoles, and inversion of the T-wave with an elevated ST segment (Von Oettingen, 1955). Acute exposure of mice, rats, and guinea pigs at 10, 20, or 30 vol % vinyl chloride at time intervals varying from 1-30 min produced pulmonary edema and hemorrhages, congestion of the liver and kidneys, and hypocoagulability of the blood (Mastromatteo et al., 1960). Repeated exposures to 200-500 ppm 7 hr daily for 4.5 months cause histological changes in the liver and kidneys of rats and rabbits but not in guinea pigs and dogs. All species tolerated exposure to 50 ppm for 6 months (Torkelson et al., 1961). Another study in rats exposed to 2% vinyl chloride 8 hr/day for 3 months revealed changes in liver and spleen weights and a decrease in leukocytes and an increase in erythrocytes but no effect on growth rate, hemoglobin, hematocrit, or prothrombin time (Lester et al., 1963). Liver and kidney changes have also been reported from Germany (Schotter, 1969). Soviet

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investigators reported cardiac arrhythmias and bradycardia as well as changes in the phonocardiogram in rats exposed to 0.03–0.05 mg/l vinyl chloride for 5 months (Vazin and Plokhova, 1969b).

Such exposures caused an increased secretion of catecholamines in rabbits and changes in the biopotential in the posterior hypothalamus (Vazin and Plokhova, 1969a). It has been suggested that cardiovascular changes in rabbits induced by vinyl chloride would be useful for studying the angioneurotic syndrome (Vazin and Plokhova, 1968a). Exposure of rats, rabbits, and monkeys to 250 or 500 ppm vinyl bromide for 6 months produced no compound-related symptoms or pathology. However, 20 7-hr exposures to 10,000 ppm vinyl bromide caused a decrease in body weight and activity in male rats (Leong and Torkelson, 1970). Six-month exposure of rats and rabbits to 0.03–0.04 mg/l vinyl chloride produced central nervous system and cardiovascular dysfunction and bone resorption and osteoporosis (Basalaev et al., 1972). Prolonged exposure, 4 months, to vinyl chloride induced a significantly slower formation of defensive conditional reflexes in rats (Vazin and Plokhova, 1970). Vinyl chloride also affects the bioelectric activity of the cortex and the anterior and posterior hypothalamic nuclei of rabbits (Vazin and Plokhova, 1968b). Exposure of rats to vinyl chloride, 30,000 ppm, 4 hr/day for 12 months produced degeneration of the brain, liver, and kidneys. Of even greater importance was the development of a histopathological picture in the skeleton and connective tissue similar to human acroosteolysis. Bones undergo processes of intense periosteal growth and diffuse, chondroid metaplasia. Connective tissue dissociates into collagen bundles with reduced numbers of cells, the elastic reticulum is markedly reduced and fragmentary, and the dermal vessels lumen is hypertrophied. Fibrous tissue even surrounds and infiltrates the nerve endings (Viola, 1970).

ANIMAL CARCINOGENESIS

In 1971, the first report of the carcinogenic action of vinyl chloride appeared. Rats exposed to 30,000 ppm vinyl chloride 4 hr/day, 5 days a week for 12 months developed epidermoid carcinomas, papillomas, and mucoepidermoid carcinomas of the skin, adenocarcinoma of the lungs, and osteochondroma of the metacarpal and metatarsal regions of all four limbs (Viola et al., 1971). Another Italian study using 10,000, 6,000, 2,500, 500, 250, and 50 ppm vinyl chloride with the same exposure times resulted in the induction of Zymbal gland carcinomas, nephroblastomas, and hepatic and extrahepatic angiosarcomas in rats and pulmonary tumors, mammary carcinomas, and liver angiosarcomas in mice. All levels of exposure except 50 ppm were carcinogenic (Maltoni and Lefemine, 1974b). Vinyl acetate at a concentration of 2,500 ppm for the same time interval was not carcinogenic. A direct dose-time relationship and neoplastic response was established for vinyl chloride exposure (Maltoni and Lefemine, 1974a). It

has now been shown that levels of 50 ppm also are carcinogenic (Withholding of... data hinted, 1974). The above results on liver angiosarcoma and mammary carcinoma in mice exposed to 50, 200, and 2,500 ppm vinyl chloride have been confirmed.²

Mutagenicity

Vinyl chloride is not mutagenic per se but does produce mutants in the *Salmonella typhimurium* TA1535, TA1536, TA1537, and TA1538 strains after activation by a rat liver microsomal enzyme system (Rannug et al., 1974).

Polyvinyl Chloride Carcinoma

Imbedding polyvinyl chloride film in the anterior abdominal wall of rats produced sarcoma in 31.8% of the animals (Oppenheimer et al., 1952, 1953). It has been suggested that the slow rate of plastic degradation and the release of breakdown products was related to the long latent period for cancer development (Oppenheimer et al., 1955). These observations have been confirmed (Russell et al., 1959). Cancers are also produced when PVC films are implanted on the rat kidney (Kogan and Tugarinova, 1959). The stages of carcinoma formation are granulation, hyperplasia, presarcoma, and sarcoma (Kogan and Raikhlin, 1961). Histochemical investigation showed that abnormal collagen was formed in the capsule surrounding the plastic insert prior to tumor development (Raikhlin and Kogan, 1961). A significant proliferation of fibroblastic cellular elements also surrounds the plastic implant (Stankevich, 1962; Shabad, 1967). It has been suggested that a single specific premalignant cell clone resides dormant on the plastic, and it detaches and produces a tumor four weeks later (Brand et al., 1967). Oral administration of an aqueous extract of PVC resin retarded weight gain in rats and decreased blood catalase activity but had no carcinogenic activity (Radeva and Dinoeva, 1970). Although it is known that all polymers contain unreacted monomer and various other chemicals as stabilizers, etc., none of the above studies gave any evidence that this was considered in the experimental designs. Studies should be initiated to determine the oncogenic potential of plasticizers, antioxidants, and monomers prior to concluding that the plastics themselves are oncogenic (Autian, 1964; Bischoff, 1972).

HUMAN TOXICOLOGY

General Toxicology

Vinyl chloride has anesthetic properties and causes respiratory tract irritation with dryness and mucous membrane atrophy followed by

²M. L. Keplinger, Goode, J. W., Gordon, J. C. and Calandra, J. C., Interim results of exposure of rats, hamsters and mice to vinyl chloride. Unpublished results, April 15, 1974.

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chronic bronchitis. Hepatitis has also been reported (Tribukh et al., 1949). Euphoria and intoxication have also been reported. Hypersomnia persists even after leaving the contaminated environment. Repeated exposures lead to neurological asthenia. Vinyl chloride produces the skin sensations of formication and heat. Other toxic effects include dyspeptic disturbances, epigastric pain with swelling of the hypochondrium, anorexia, hepatomegaly, splenomegaly, hepatitis without jaundice, ulcers, Raynaud's syndrome, allergic dermatitis, and scleroderma (Suciu et al., 1963). Such poisonings are progressive even in the absence of further exposure (Antonyuzhenko, 1968). Long-term side effects include functional disturbances of the CNS with adrenergic sensory polyneuritis (Smirnova and Granik, 1970). ECG recordings showed changes in rhythm, conductance and repolarization processes, and an increased systolic index (Kudryavtseva, 1970). German studies reported Raynaud's syndrome, skin disease, osteolytic syndrome, and thrombocytopenia (Jules et al., 1973). Thermoregulation is disturbed in chronic vinyl chloride intoxication with body temperature increasing 1-2°C as a result of peripheral vasoconstriction (Stalova, 1973). Soviet work indicated changes in the visual, auditory, taste, and olfactory analyzers referable to the effects of vinyl chloride on the brain stem reticular formation (Antonyuzhenko et al., 1972a). Chronic vinyl chloride exposure, 1.75-18 years, produced scleroderma with thickening and homogenization of collagen bundles and fragmentation and rarefaction of elastic fibers. Finger clubbing, osteolysis of distal phalanges, and a Raynaud's syndrome were also seen. Thrombocytopenia, splenomegaly, and liver malfunction with marked fibrosis in the portal areas, pulmonary insufficiency with restrictive changes in the lungs were also reported (Lange et al., 1974). Similar changes in workers' health have been reported in the USSR (Filatova et al., 1965). Visual and vestibular dysfunction also occur in chronic vinyl chloride intoxication (Antonyuzhenko et al., 1972b). Correlations of clinical and environment measurements for workers exposed to vinyl chloride have been made. This is one of the few studies in which clinical parameters—blood pressure, bromsulphalein retention, icterus index, hemoglobin and beta-protein—were collected along with ambient air samples of vinyl chloride (Kramer and Mutchler, 1972). Two accidental deaths from acute vinyl chloride poisoning showed the following: cyanosis, local burns of the conjunctiva and cornea, congestion of internal organs (lungs and kidneys), and failure of the blood to clot. Blood levels of vinyl chloride could not be obtained (Danziger, 1960).

Clinical symptoms of chronically intoxicated vinyl chloride workers included: headache, dizziness, heightened fatigue, sleep disorders, decreased memory capacity, diaphoresis, paresthesia, pain in the extremities, paling of fingers and toes, edema of these extremities, and pain and unfavorable sensations in the region of the heart. An ACTH test correlated these changes with modification in adrenal cortical function

(Rumyantseva and Goryacheva, 1968). Increased urinary excretion of monochloroacetic acid has been correlated with atmospheric vinyl chloride and the duration of such exposures. There is an increased excretion under such circumstances (Grigorescu and Tiba, 1966). There is a decrease in blood catalase activity and an increase in peroxidase, indophenoloxidase, and glutathione content after 1 year of vinyl chloride exposure (Gabor et al., 1962). Romanian investigators found no change in blood catalase of serum and pyruvic acid activity in vinyl chloride workers. However, decreases were seen in blood albumin, serum cholinesterase, and pseudocholinesterase. The beta and gamma globulins increase, but there is a decrease in the beta-to-alpha lipoprotein ratio (Gabor et al., 1964). Thyroid impairment and skin and muscle collagenosis have also been reported (Suciu et al., 1967).

Allergic Manifestations

Vinyl chloride, PVC, and vinyl acetate cause a sensitization dermatitis in workers (Morris, 1953). This effect has been attributed to the plasticizers used (Key, 1968). Hypersensitivity has also been reported in consumers using polyvinyl chloride products which contain epoxy resins used as plasticizers-stabilizers (Fregert and Rorsman, 1963). The use of tricresylphosphate as a plasticizer-stabilizer for PVC has caused contact dermatitis (Pegum, 1966). Vinyl chloride and dibutylphthalate released from floor coverings have caused an eczematous dermatitis in children (Kalmanovich, 1968). Liberation of volatile materials from PVC floor tile also produced mucosal irritation of the eyes and respiratory tract of infants and adults (Dyachuk, 1970a). It has also been shown that the plasticizer, di-2-ethylhexyl phthalate, migrates from PVC blood bags into stored blood, thence into body tissues. The toxicological implications of such migrations are unknown but the plasticizer is lethal to the embryonic chick heart in culture. It has been suggested that other plastic formulations should be used for storing blood (Jaeger and Rubin, 1972). In contrast to vinyl chloride, vinyl acetate does not appear to cause contact dermatitis (Deese and Joyner, 1969).

Acroosteolysis

Dissolution of the bones, acroosteolysis, of the terminal phalanges of the fingers and sacroiliac joints occurs in PVC workers. The patella and phalanges of the feet may also be involved. The condition is accompanied by Raynaud's phenomena and skin lesions (Harris and Adams, 1967). Thirty-one cases of the disease have been reported from one American company. The disorder may be related to physical insult, chemical insult, and personal idiosyncrasy because there is no known specific cause (Wilson et al., 1967). Similar cases have been reported in PVC workers in France (Chatelain and Motillon, 1967). The progression of the bone lesion can lead to fragmentation of the distal phalanx (Angheliescu et al., 1969).

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After examination of 20 PVC workers, Italian investigators attributed the lesion to sympathetic neurocirculatory dystonia connected with an unidentified pathogenic cofactor (Nitti et al., 1970). A Soviet investigator suggested the involvement of higher centers in the hypothalamus in acroosteolysis (Basalaev, 1970). The latent period for the development of acroosteolysis can be only 5 days or up to 30 days. Furthermore, the portal of entry, lungs or skin, is not precisely known (McCord, 1970). An epidemiological study of 5,011 workers in 32 VC and PVC plants in the United States and Canada uncovered 25 cases of acroosteolysis. The condition is associated with hand cleaning of polymerizers and appears to be a systemic rather than a local disease (Dinman et al., 1971). There was a strong association between the development of the disease and manual cleaning of the reactors (Cook et al., 1971). Clinical evaluation of 4 cases of the disease revealed that Raynaud's phenomena antedated the osteolytic lesions. Negative Ca and PO_4 balance could be present, and ^{18}F scintiscans revealed variable fluoride uptakes correlated with the radiographic lesions. A wide variety of clinical parameters were normal (Dodson et al., 1971). Industrial hygiene precautions to reduce exposure and prevent the disease include water wash and reduction of the vinyl chloride air content to 50 ppm, gloves, a yearly physical examination, and X-ray examination of the hands (Gitsios, 1971).

German experience with long-term vinyl chloride exposure, 1-3.5 years, not only showed circulatory, skin, and bone disorders but also deafness, vision failure, giddiness, and liver dysfunction (Juhe and Lange, 1972). It has been suggested that 3% or less of the workers engaged in PVC production are affected by the disease (Markowitz et al., 1972). The occurrence of idiopathic acroosteolysis with papular skin lesions makes it essential that VC or PVC exposure be documented in all cases diagnosed as acroosteolysis (Meyerson and Meier, 1972). It must be remembered that the bone lesions can progress even after VC exposure has been terminated, then recovery can occur (Misgeld et al., 1973). Rapid diagnosis to prevent progression of VC-induced scleroderma, Raynaud's syndrome, and acroosteolysis is essential if mortality, now at least 10%, is to be reduced. Periodic thrombocyte counts have been suggested as the diagnostic tool because thrombopenia occurs much earlier than any other sign of vinyl chloride intoxication (Jules et al., 1973).

HUMAN CARCINOGENESIS

A Soviet survey of 350 workers covering the years 1957-1960 found chronic epithelial hepatitis in 15% of the workers in PVC production. No cancer was recorded (Pushkin, 1965). Inhalation studies of vinyl chloride effects in rats demonstrated liver angiosarcoma; it was suggested epidemiological studies should be instituted to ascertain if this rare tumor occurred in PVC workers (Maltoni, 1973). German studies of 120 PVC

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workers in 1973 revealed liver dysfunction but no cancer (Marsteller et al., 1973). The first liver angiosarcoma cases in PVC workers were reported in the United States in 1974. However, retrospective studies show one case in 1968, one in 1971, and one in 1973. Death occurred within 14 months of diagnosis of the condition regardless of the treatment instituted (Creech and Johnson, 1974). It has been suggested that extensive epidemiological studies should be undertaken on the problem of vinyl chloride exposure, the levels of exposure, and their consequences. Both clinical and experimental pathological studies should be instituted to develop better diagnostic methods for liver cirrhosis and angiosarcoma (Manucuso, 1974). Such studies are important because the usual battery of liver function tests does not detect the periportal fibrosis which precedes sarcoma development. Moreover, there are at least 6,500 workers at risk and unknown thousands in the same category in subsidiary industries utilizing both vinyl chloride and polyvinyl chloride (How hazardous . . . , 1974). Diagnostic difficulties in vinyl chloride-induced angiosarcoma are illustrated by three cases in which the primary diagnosis was gastric ulcers. For more precise diagnosis, serum alkaline phosphatase and SGOT determinations coupled with liver photoscans using ^{131}I rose bengal and ^{198}Au are recommended. Needle biopsy, while useful, can result in an exsanguinating hemorrhage because of the vascular nature of the tumor (Block, 1974). A recent epidemiological study indicated that vinyl chloride and polyvinyl chloride workers may develop cancers at multiple sites, thus further complicating the problem (Tabershaw and Gaffey, 1974). A systematic detection program for surveillance of PVC workers has been developed, employing laboratory tests, roentgenographic examinations, and clinical evaluations to detect liver damage in an early and possibly reversible or curable state. Although other laboratory tests were useful, α -glutamic transpeptidase determinations were the most useful in detecting abnormalities and reflecting the extent of liver damage (Makk et al., 1974). A further survey of workers in a PVC plant revealed 11 cases of hepatic disease, including 7 cases of angiosarcoma. Ages at diagnosis ranged from 28 to 56 years in the hepatic disease cases and 36 to 58 years in those with angiosarcoma. Exposure periods ranged from 5 to 29 years. The nonmalignant hepatic disease was characterized by portal fibrosis and portal hypertension (Falk et al., 1974). Hepatic angiosarcoma has been found in one British PVC worker (Lee and Harry, 1974). The total extent of the vinyl chloride problem is illustrated in Table 7, which covers the number of hepatic angiosarcoma cases reported worldwide. More cases will probably be reported from other countries in the future (Angiosarcoma of the liver . . . , 1974).

COMMENTS AND CONCLUSIONS

The seriousness of the vinyl chloride/polyvinyl chloride problem should not be underestimated because the number of exposed workers

TABLE 7. Reported Cases of Liver Angiosarcoma in Workers Exposed to Vinyl Chloride or Polyvinyl Chloride

Country	Case no.	Birth date	First VC or PVC exposure	DX angio-sarcoma	Age at DX	Years from first exposure to DX	Total years exposure	Date of death
VC monomer production workers								
Sweden	02*	11-27-11	00-00-45	05-15-72	61	27	23	08-16-72
Polymerization workers								
Great Britain	01*	00-00-01**	00-00-46	12-00-72	71	26	20	12-00-72
Norway	01*	12-23-15	03-00-50	12-20-71	56	22	21	01-04-72
Sweden	01*	06-23-27	08-14-51	02-00-70	43	19	18	10-20-70
United States	01*	10-17-23	12-09-48	03-03-73	49	22	16	03-03-73
United States	02*	08-19-33	11-15-55	05-00-70	36	14	13	09-28-71
United States	03*	05-25-15	11-28-45	12-19-73	58	28	28	12-19-73
United States	04*	01-15-24	07-06-52	08-19-67	43	15	15	01-07-68
United States	05*	01-25-12	06-19-44	04-09-64	52	20	18	04-09-64
United States	06*	00-00-29	01-17-62	02-00-74	45	12	12	alive
United States	07*	05-03-22	03-00-44	00-00-68	45	24	18	03-23-68
United States	08*	05-06-20	10-07-46	08-00-61	41	15	15	08-29-61
United States	09*	00-00-31	05-28-45	03-01-74	43	29	17	alive
United States	10*	08-16-13	06-12-51	05-00-68	55	17	17	05-10-68
United States	11*	05-27-09	10-14-46	03-00-70	61	23	23	03-16-70
United States	12*	11-17-18	09-13-49	05-02-69	50	20	15	05-02-69
United States	13*	12-01-21	08-19-44	05-00-74	53	30	30	07-04-74
United States	16*	11-04-27	05-08-50	00-00-69	41	17	4	03-27-69
West Germany	01	07-26-31	10-14-57	00-00-71	40	14	14	12-14-71
West Germany	02	06-04-30	10-01-57	00-00-69	39	11	11	01-25-69
Compounders, fabricators, etc.								
Great Britain	02*	09-08-14	00-00-46	02-00-70	55	24	11	12-00-70 ^d
United States	14	00-00-13	18-18-38	06-00-73	60	36	00	07-03-73 ^{b-e}
United States	15*	00-00-25	00-00-00	07-00-72	47	00	00	02-15-73 ^c
Other VC exposure								
West Germany	03	00-00-00	00-00-00	00-00-00	43	14	00	00-00-00 ^d

Source: Angiosarcoma of the liver . . . , 1974.

*Indicates microscopically confirmed angiosarcoma of the liver.

**"00" indicates unknown data.

^aPouring PVC oil mixture onto fabric bases.^bMachine operator covering electrical wire with PVC plastic insulation.^cAccountant at several fabrication plants (work history under review).^dLoading pesticide cans with VC propellant.^eDiagnosis sarcoma (possibly "angiosarcoma") of the liver; possibility of generalized neoplasm of the reticuloendothelial cell system cannot be ruled out.

who may in the future develop hepatic dysfunction and/or angiosarcoma cannot, at this time, be estimated. However, if other occupationally induced cancers, for example, mesotheliomas from asbestos or bladder cancers from benzidine, are any guideposts, an upsurge in angiosarcoma cases must be expected. This is substantiated by the report of eight new cases of hepatic angiosarcoma in Canada (Eight angiosarcoma cases . . . , 1975). An increase in scleroderma, Raynaud's syndrome, and acroosteolysis cases should also be expected. An unknown quantity in the VC/PVC situation is the extent of exposure of the general population to VC-propelled aerosols and household products, for example, floor coverings and upholstery, made from PVC. Whereas programs have been initiated to reduce worker exposure to a minimum, the household exposure can only be decreased by banning the use of vinyl chloride as a propellant, which has been initiated, and informing the public of the possible dangers of aerosol cans presently in their possession. This problem could be reduced by a recall such as is instituted for contaminated food and drugs.

The situation in PVC manufacturing is complicated by the length of time required to bring the various plants into compliance with the 1 ppm or less exposure standard and the present unavailability of proper respirators (Machinists union poll shows . . . , 1974). Further epidemiological studies to determine, insofar as it is possible, the actual latent period for the development of hepatic angiosarcoma should be instituted. Studies should be undertaken to establish whether short exposures at high concentrations or long exposures at low concentrations are most likely to induce angiosarcoma. Experimental studies with large groups of animals and a serial sacrifice design might assist in the solution of this problem.

A pharmacokinetic study employing both experimental animals and exposed workers would assist in establishing the biotransformation products in the blood and show which species respond similarly to humans. The rate of excretion could be ascertained by measuring urinary monochloroacetic acid and possibly other biotransformation products and/or their conjugates.

Epidemiological studies on the other aspects of vinyl chloride toxicity—skin lesions, Raynaud's syndrome, and acroosteolysis—should be pursued to more fully understand the overall implications of VC/PVC exposures. Research to develop better, more rapid means for diagnosis and treatment must be actively pursued. Information on the health status of VC/PVC workers must be readily available to labor, industry, and government in order to become part of the decision-making process involved in overall occupational health protection.

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