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Vinyl Chloride: a Review

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Summary

The polymerization process for the industrial production of polyvinyl chloride from vinyl chloride was discovered in Germany in the mid 1930s. Since then, both have been produced in increasing quantities. The first cases of occupational acro-osteolysis in workers engaged in the industry were reported some thirty years later in 1963, and the first cases of angiosarcoma of the liver in workers similarly engaged were reported some forty years later in 1974. Intense public and medical interest were aroused and resulted in extensive investigations into the medical problems now seen to be associated with the industry.

The chronology of these events is outlined, and the epidemiological, chemical, histopathological and biochemical investigations which resulted are briefly reviewed. Finally, possible metabolic processes, which could result in the known clinical manifestations, are discussed.

Physical Characteristics

Vinyl chloride (VC), $CH_2 = CHCL$, is gaseous at normal ambient temperature and pressure having a boiling point of −13·5 °C. It is approximately twice as heavy as air, having a vapour density of 2·15. It is only slightly soluble in water, but soluble in ethanol, ethyl ether and polyvinyl chloride (PVC). The gas is highly flammable and explosive, having a lower explosive limit of 4 per cent and an upper explosive limit of 22 per cent in air.

It is easily liquified by pressure, and in this form has the property of being readily polymerized at temperatures in the range of 40–70 °C by exothermic reaction to form PVC, each molecule of which contains between 500–1500 molecules of vinyl chloride, and which in the raw state has the appearance of a fine white powder.

History

Vinyl chloride was first synthesized in 1833. The polymerization process was discovered some 100 years later in Germany in the mid 1930s. Thereafter, the industry developed rapidly, both in Europe, which accounts for about 50 per cent of world production, and in the United States, which currently accounts for some 25 per cent of world production.

The fire and explosion risks of vinyl chloride were fully appreciated from the beginning of the industry, as was the acute narcotic effect induced by exposure to high concentrations of the gas. Indeed, as early as 1933 Peoples and Leake had investigated the use of vinyl chloride as a possible general anaesthetic. It was abandoned principally because of the adverse cardiac effects it produced in dogs at anaesthetic concentrations.

Apart from the acute narcotic effect, vinyl chloride was regarded as being relatively non-toxic, and the first maximum acceptable concentration published by the Manufacturing Chemists Association (1954) in the United States recommended 500 ppm for worker exposure on the premise that 'in concentrations well above 500 ppm vinyl chloride acts as a mild general anaesthetic'. No attention appears to have been paid to a report by Tribukh et al. (1949) of hepatitis-like liver changes in exposed Russian workers.

Until 1960 when two fatalities were recorded in a Canadian polymerization plant (Danziger, 1960), there had been no reported industrial fatalities, and these only served to underline the need for further precautions to prevent narcosis and effect rescue and resuscitation if it should occur.

In 1961, the Dow Chemical Company reported slight liver damage in animals exposed to levels of 100 ppm and recommended that worker exposure levels be reduced to a 50 ppm time-weighted average (TWA) level. Despite this report, in 1962 the American Conference of Governmental Industrial Hygienists, on the basis of further work at Yale, adopted a recommendation that a TWA of 500 ppm provided an adequate margin of safety for human exposure. This standard was subsequently

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adopted by the US Occupational Safety and Health Administration in 1971 as a National Standard which remained unchanged until April 1974, although, by 1970, the American Conference of Governmental Industrial Hygienists had signified an intended change to 200 ppm.

Suciu et al. (1963) reported a symptom complex occurring in Rumanian workers involved in the polymerization of PVC which consisted of Raynaud's phenomenon allied with skin changes resembling, but not identical to, scleroderma. In 1966 two cases which were similar but which also had osteolytic changes in the terminal phalanges, and to which was given the name acro-osteolysis (AOL), were reported by Cordier et al. (1966) from Belgium. Further reports soon followed (Harris and Adams, 1967; Wilson et al., 1967).

Dinman et al. (1971), of the University of Michigan, published the results of a survey which had been commissioned in 1967 by the Manufacturing Chemists Association into the clinical, epidemiological and industrial hygiene aspects of acro-osteolysis. The authors, however, were unable to determine the precise aetiology and recommended that animal studies be carried out. These were quickly forthcoming. Viola et al. (1971) of the Regina Elena Cancer Institute in Rome had been working with rats exposed to atmospheric levels of 30 000 ppm VC for 4 h per day, 5 days per week for a year, in an attempt to develop an experimental model for acro-osteolysis. They failed to do so, but noted the occurrence of tumours of the skin, lungs and bones which Viola first reported at the 10th International Cancer Congress in Houston in May 1970 and subsequently published in 1971 (Viola et al., 1971). Their findings were subject to criticism, however, for technical reasons and for the excessive concentrations employed. Nevertheless, the report was of serious concern, and in order to produce unambiguous results, a group of European chemical producers shortly thereafter commissioned Maltoni of the Oncological Institute, Bologna, to carry out further animal studies (Maltoni, 1974). In addition, epidemiological studies were commenced, both in the United States and Britain (Manufacturing Chemists Association, 1974).

By mid 1973, although the epidemiological studies had as yet shown no increase in the incidence of cancer of any type, preliminary results of Maltoni's (1974) work became available which revealed the development of angiosarcoma, a tumour rare in both rats and humans, and one which might well therefore have been thought to have shown up during nearly 40 years of PVC production. Notwithstanding, updating of the epidemiological surveys continued, and on 22 January 1974 three deaths due to angiosarcoma of the liver in former employees were reported to the National Institute of Occupational Safety and Health from the B. F. Goodrich Plant in Louisville, Kentucky (Creech and Johnson, 1974), and on the following day the news was transmitted to the Department of Employment in the UK (Gauvain, 1976). On 29 January, ICI issued a press statement that a single suspect death in a 70-year-old retired autoclave worker who had died in 1972, was under investigation. This was subsequently confirmed to be due to angiosarcoma of the liver.

Polymerization of Vinyl Chloride

Polymerization is carried out in cylindrical pressure vessels, surrounded by water jackets to control the temperature of the exothermic reaction. These vessels are termed variously, 'autoclaves', 'polypots' or 'polykettles'. In the UK, reactor sizes range from 10 m^3 to 40 m^3 with monomer charges ranging up to 15 tons. Paddles situated within the vessels enable the contents to be stirred as the reaction proceeds.

Two types of process are in use, namely the 'suspension' process in which polymerization takes place in a disperse phase of de-ionized water, and the 'mass' process in which polymerization occurs in the dry state. Apart from the water, in both cases the vessels receive an initial charge of liquid vinyl chloride (termed vinyl chloride monomer in industry to distinguish it from the polymer), organic peroxide initiators, surfactants, buffers, chain transfer agents such as trichlorethylene and emulsifying agents.

The reaction proceeds under pressure, in the absence of oxygen. As polymerization reaches 90–92 per cent conversion, the rate of reaction slows down, and, by 95 per cent conversion, has become so slow as to render 100 per cent conversion uneconomic. The residual unchanged vinyl chloride monomer is vented back to a gasholder to be re-used, and the newly formed polymer is transferred from the autoclave, dried (in the case of suspension polymer), graded and bagged or sent to bulk storage. The autoclave is then further evacuated by lowering the pressure to remove as

much gaseous vinyl chloride as possible, before opening to atmosphere in readiness for the polycleaners to enter and remove the residue of PVC 'cake' from the walls and stirring paddles in the vessel. This was formerly done mainly by hand chipping and scraping, and vessel entry for this purpose was required after every batch of polymer, normally twice daily, with an average reaction time of 8 hours.

In retrospect, based on experience with the very accurate methods now available for measuring ambient vinyl chloride levels, it is certain that this was the operation which involved exposure to the highest concentrations of monomer for the longest periods and with the greatest frequency.

In the earliest days of the industry, it has been suggested that polycleaners may have been exposed to levels as high as 3000 ppm, whilst in the decade 1945–55, 1000 ppm would have been the likely norm. In the period 1955–60 the exposure level would have been approximately 500 ppm, from 1960 to 1970 perhaps 300–400 ppm and by mid 1973, 150 ppm. At the present time, the average levels in this country are 5 ppm or less, and, due to modifications in the process, vessel entry is much less frequent, in some instances only being required after every 50 or 60 batches. In addition, cleaning is now mainly accomplished by high pressure water jetting which is quicker and does not always require vessel entry. For additional safety, every vessel opening and entry is now continuously monitored using infra red spectrophotometry sensitive to 1 ppm vinyl chloride and any increase in vinyl chloride level above the present UK TLV of 10 ppm (TWA) necessitates immediate withdrawal or the donning of breathing apparatus of an approved type.

Apart from the problem posed by vessel entry, the problem of 'fugitive' vinyl chloride escaping from the numerous pumps, valves, stirrer glands and blinds, required the development of a new order of engineering design and technology to reduce polymerization building levels of vinyl chloride in air to between 2–5 ppm. This is probably the limit which can be achieved with the present generation of plant.

Clinical Manifestations of Vinyl Chloride Exposure

Acro-osteolysis

This is a rare clinical syndrome of which only some 75 cases of the familial type have been reported (Dinman, 1969). All the occupationally-induced cases have, with one exception (who was subsequently found to have been regularly and repeatedly exposed to vinyl chloride) (Steward et al., 1975), occurred in workers engaged in the hand cleaning of polyvessels as described above.

The fully-developed syndrome has three main components:

1. Raynaud's phenomenon affecting the fingers and sometimes also the toes. Full development of the condition may be preceded by the feeling of tingling and numbness in the digits.
2. Skin changes resembling scleroderma, situated usually on the back of the hands or distal third of the flexor aspect of the forearm, and very rarely in other sites.
3. Bony changes, which, as the name implies, affect the terminal phalanges, usually of the fingers, but which may also affect the toes, radial and ulnar styloid processes, sacroiliac joints and lower poles of the patellae. The radiological appearances in the phalanges are those of band-like translucencies due to bony absorption, and, if the condition is advanced, there may be complete destruction of the tuft of the phalanx with a foreshortened spatulate appearance of the affected digits. Arteriography in these cases frequently demonstrates partial or complete occlusion of the digital arteries.

The extensive epidemiological survey carried out by Dinman et al. (1971) involved 5011 employees with 21 510 man years' experience in various phases of vinyl chloride and PVC manufacture in 32 plants throughout the United States and Canada. It revealed 25 definite and 16 suspect cases (one of whom subsequently developed the syndrome). The 'attack rate' varied between one case in 40 and one case in 60 polycleaners, or in terms of exposure time, one case per 25 man years in this specific job.

In the survey by Wilson et al. (1967) the attack rate was less than 3 per cent with no age specificity and the condition was found to be virtually non-existent in workers with less than 12 months' polycleaning experience. The low attack rate is suggestive of individual biological susceptibility being a factor in the aetiology.

From the published cases, it would appear that any of the above changes may be present either alone, or in combination. Raynaud's phenomenon would appear to be the most frequently occurring condition in Britain, although there is doubt about its genuine occupationally induced incidence, since

in all but one PVC plant in this country workers were not previously screened for Raynaud's phenomenon before assignment as polycleaners (UK Vinyl Chloride Industrial Medical Advisory Sub-Committee, 1977).

In their original papers, Suciu et al. (1963) and Cordier et al. (1966) state that upon removal from exposure, Raynaud's symptoms diminish or disappear. This does not accord with recent British experience (UK Vinyl Chloride Industrial Medical Advisory Sub-Committee, 1977). It is of interest that Suciu et al. (1963) make no mention of radiological appearances in their cases, whilst in Dinman's survey (1969) most of the cases were found by radiological examination of the hands, only a few having sought medical attention because of symptomatic complaints. In contrast to the persistence of symptoms, on removal from exposure, improvement in the radiological appearances of phalangeal lesions, with recalcification, has been demonstrated to occur (Williams and McLachlan, 1976).

Angiosarcoma of the Liver

This is a rare malignant tumour. A recent survey by Baxter et al. (1977) revealed that between 1963 and 1973, on average, there were only four recorded cases per year in Great Britain and, when available histological material was subsequently re-examined by a specially constituted panel of histopathologists, in only one-third of the cases did the panel agree with the original diagnosis, and in only one of these cases could there be a confident association with exposure to vinyl chloride. In a further one-third of the cases, the panel rejected the original diagnosis of angiosarcoma of the liver. Baxter et al. (1977) could trace only nine published cases of angiosarcoma of the liver occurring in Britain before 1963. The survey revealed no evidence of the occurrence of environmental cases.

By August 1977, following a search throughout Western Europe, North America, Japan and Yugoslavia, some 63 cases of vinyl-chloride-associated angiosarcoma of the liver had been reported to the US National Institute for Occupational Safety and Health for confirmation. Thirteen of these cases were still outstanding.

The average duration of exposure in the 50 confirmed cases for which data is currently available is 17·8 years, with a range of 4–32 years.

Other Effects Associated with Vinyl Chloride Exposure

Hepatic Fibrosis

There have now been numerous reports (Juhe et al., 1973; Marsteller et al., 1973; Lilis et al., 1975; Smith and Williams, 1975; Thomas et al., 1975) of hepatic fibrosis of a non-cirrhotic type, frequently associated with splenomegaly and portal hypertension, in workers exposed to vinyl chloride, these changes being significantly more frequent in workers with longer exposure (Lilis et al., 1975). In some of these cases the changes observed were identical the changes described by Banti (Thomas et al., 1975) and the changes described in association with prolonged exposure to inorganic arsenicals, which, like vinyl chloride, may also induce the development of angiosarcoma of the liver.

The fibrosis which can be demonstrated in livers affected both with, and without, angiosarcomas, is of a peri-portal type, and frequently accompanied by marked capsular thickening of a 'rice grain' appearance. In some cases it appears to be progressive, and although the relationship of the fibrotic lesions to the development of angiosarcoma requires further study, Thomas et al. (1975) have found evidence which they consider to be suggestive of a transitional stage.

A feature of the condition is that hepatocytes do not appear severely damaged, nor is reactive intralobular inflammation seen, a finding which could account for the erratic, or even normal, results at this stage of those liver function tests which depend upon the integrity of the hepatocytes. This might also account for the apparent conflict in the findings of blood and liver function surveys in this country where no significant differences between the exposed population and normal controls were observed (Lee et al., 1977) and other surveys by Lange et al. (1974) and Lilis et al. (1975), who reported the finding of significant abnormalities.

Tumours of Other Sites

Maltoni and Lefemini (1975) and Keplinger et al. (1975), in addition to observing angiosarcomas of the liver in rats, mice and hamsters exposed to vinyl chloride, also reported the induction of other tumours including cerebral neuroblastomas and pulmonary adenomas. The epidemiological studies carried out in the United States (Tabershaw and Gaffrey, 1974) indicated an excess of cancer of the

respiratory system and brain in humans, but not such as to be statistically significant.

In a more recent survey in the United Kingdom (Fox and Collier, 1977) of the mortality data of over 7000 men who were at some time exposed to vinyl chloride between 1940 and 1974, no evidence was found to support the hypothesis that cancers of sites other than the liver are associated with exposure to vinyl chloride. The authors point out, however, that since over 50 per cent of the workers in this country have entered the industry only within the last decade, any conclusions on mortality experience must be viewed with reserve, since the full impact of exposure may not yet have had time to become manifest.

Mutagenicity and Chromosomal Effects

In common with many other chemical carcinogens, vinyl chloride has been demonstrated to produce mutagenic effects in bacterial test systems (Rannug et al., 1974; Malaveille et al., 1975; Bartsch et al., 1975).

Reports on chromosomal studies of exposed workers are conflicting. Funes-Cravioto et al. (1975), Ducatman et al. (1975) and Purchase et al. (1975) reported increases in chromosome aberrations, mainly breakages, in the groups they studied, as compared with controls. Fleig and Thiess (1974), however, could find no evidence of increased aberrations in a group of ten workers, nor could Picciano et al. (1977), who, in much the largest study so far carried out, examined a group of 209 workers who had been employed in vinyl chloride manufacture for up to 28 years. They postulate that the reported differences may be accounted for by the small numbers involved in some of the earlier studies, or by differences in exposure levels to which the groups were subjected, or both. They conclude that the level of chromosome aberrations in exposed workers is probably related to the length and level of exposure, and that adverse cytogenetic effects are unlikely to occur in controlled minimal exposure environments.

The possibility of genetic risks to man has been raised by the work of Infante et al. (1976), who carried out a study on fetal wastage among wives of workers exposed to vinyl chloride in polymerization processes by means of interviews with the workers on the outcome of pregnancies in their wives. The group exposed to vinyl chloride was matched for age with a similar number of current rubber workers selected from areas known to be relatively free from toxic substances. The results were claimed to indicate a significant excess of fetal loss in the wives of husbands who had been exposed to vinyl chloride, whereas there were no significant differences between the groups before such exposure.

Very little experimental work has so far been published on the possible effects on germ cells. However, Purchase et al. (1975) demonstrated that in male mice, exposure to vinyl chloride at levels up to 30 000 ppm did not produce any dominant lethal effects in the offspring of virgin female mice with whom they were subsequently mated. Thus in mice, vinyl chloride did not produce a mutagenic effect in germ cells even at the very high levels to which they were exposed.

Embryotoxic and Teratogenic Effects

Although Maltoni (1975) exposed animals *in utero* to determine the oncogenic potential of inhaled vinyl chloride, the investigations were not specifically intended to be a teratological study. John et al. (1977) have, however, recently reported the results of such an investigation designed to assess the effects of maternally inhaled vinyl chloride on embryonal and fetal development in groups of pregnant mice, rats and rabbits during the period of major organogenesis. Concentrations of vinyl chloride to which the animals were exposed ranged from 50 to 250 ppm.

Although exposure levels were sufficiently high to produce maternal toxicity in some instances, vinyl chloride alone did not cause significant embryonal or fetal toxicity, and was not teratogenic in any of the species at the concentrations tested.

Pulmonary Effects

Darke (1976) investigated 14 cases of breathlessness in exposed workers. There were no abnormal physical signs, chest radiographs were normal as were routine respiratory function tests with the exception of carbon monoxide diffusion which was slightly below predicted values in 6 subjects. The most striking abnormalities were marked perfusion defects of the upper lobes. Histology of lung specimens taken from one patient who underwent open biopsy revealed focal alveolar wall thickening with increased reticulin and collagen formation seen on electron microscopy. Some of the most severely affected of the men had however been

working with a 'paste' polymer which in powder form has a particle size in the range 0·5–1 μm and is therefore well within the respirable range, in contrast to the more usual type of polymer, which consists of powder with a particle size mainly in the 80–100 μm range. It is not, therefore, clear whether these findings were due to vinyl chloride *per se* or to inhaled particulate polymer, or possibly vinyl chloride absorbed onto the polymer. There is so far no very convincing evidence of the production of a pneumoconiosis in workers exposed to PVC powder.

Szende et al. (1970) reported the case of a 31-year-old male worker who had been exposed to PVC powder for one year and in whom lung biopsy revealed some granuloma formation and fibrotic changes. Granular material, which was non-crystalline and non-birefractive in polarized light, was stated to have been found in association with the histological changes. No previous medical or occupational history was given and there do not appear to have been any follow-up reports.

Frongia et al. (1974) reported the occurrence of histological changes in the lungs of guinea-pigs and rats subjected to continuous exposure, both day and night, to extremely heavy concentrations of PVC powder in a bagging plant for periods ranging from 2 to 7 months.

A recent study of British workers, all with at least 10 years' exposure in the bagging of dry powder, independently carried out by the National Coal Board Radiography Service revealed no abnormalities of any kind (UK Vinyl Chloride Industrial Medical Advisory Sub-Committee, 1977). In view of Darke's (1976) findings, however, and the prolonged exposure time which may be required to produce pneumoconiosis, continued observation would seem prudent.

Metabolism and Possible Mechanism of Action

Major metabolites which have been identified in the urine are thiodiglycolic acid, S-(2 chlorethyl) cysteine and N-acetyl-S-(2 chloroethyl) cysteine. The cysteine-containing metabolites may be presumed to have arisen from the reaction of vinyl chloride with hepatic non-protein sulphydryl groups (Williamson, 1976), which therefore exert a protective action by detoxifying the vinyl chloride. If the available sulphydryl groups are limited in quantity or in speed of replacement, this action could well cause their depletion thus reducing the protective mechanism. Watanabe et al. (1975) have in fact reported such progressive depletion in rats exposed to levels of 250 ppm, but no such depletion was found at 10 ppm exposure levels. At higher exposure levels up to 100 ppm, the primary metabolic pathway appears to be via the alcohol dehydrogenase route involving sequential oxidation to 2-chloroethanol, chloroacetaldehyde (a known mutagen) and monochloracetic acid. At even higher exposure levels, this route also becomes saturated, and it is speculated that one alternative pathway may be by direct epoxidation to chlorethylene epoxide or peroxide, both short-lived, but powerful alkylating agents, which break down sequentially to mono-chloracetic acid and thiodiglycolic acid (Hefner et al., 1975).

Ward et al. (1976) have postulated that chlorethylene oxides could bind with free sulphydryl or amino radicals and that the incorporation of these into protein synthesis would give a confirmationally altered molecule that would be antigenic. The antigen could then stimulate the formation of antibody and their interaction could produce a soluble cryoprecipitable complex capable of initiating complement fixation. These reactions could then in turn produce platelet aggregation, apparent thrombocytopenia, fibrinogen/fibrin conversion and vascular occlusion, either temporary or permanent. Such occlusion would be enough to explain the observed clinical, radiological and histological findings in skin, skeletal and soft tissues and lung. By producing ischaemia, vascular occlusion would also stimulate new collagen synthesis as observed by Jayson et al. (1976).

Conclusion

In summary, it now appears that all the varying manifestations of vinyl chloride exposure, namely acro-osteolysis, angiosarcoma of the liver, hepatic fibrosis, splenomegaly, portal hypertension, thrombocytopenia and lung changes, may be different manifestations of a single disease entity for which the term 'vinyl chloride disease' would seem appropriate, and for which it is possible to postulate a common underlying pathogenic mechanism.

Despite the widespread search for cases, angiosarcoma of the liver was, and still remains, one of the rarer tumours, although many thousands of workers must, during the past 40 years, have been exposed to high levels of vinyl chloride. More vinyl-chloride-induced cases may be expected, but

with the passage of time it seems increasingly reasonable to speculate that there exists a level of exposure below which there may be no discernible carcinogenic effect.

Finally, if manifestations such as acro-osteolysis are associated with individual susceptibility to vinyl chloride as the evidence would seem to suggest, it will be interesting to observe whether any further cases develop in association with the more recent low levels of exposure.

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