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SUMMARY

In 1974 the first evidence that occupational exposure to vinyl chloride (VC) could lead to a rare type of liver cancer in man, angiosarcoma, was published. Since then an enormous amount of epidemiological, clinical and toxicological research has been carried out and a large volume of data on occupational exposure and exposure of the general public has been collected. This information is scattered in many types of publications by numerous authors. The purpose of this report is to present under one cover a coherent picture of the most important aspects of the toxicology of VC (with the emphasis on carcinogenicity and mutagenicity), and the risk it poses for human health at current levels of exposure.

A brief Introduction and Historical Review is given in which the processes for producing VC and its polymer (polyvinyl chloride, PVC) are described; the sources and types of exposure to VC are given; the various diseases arising from excessive exposure are noted, and the evolution of exposure limits is summarised.

Human occupational exposure is predominantly via inhalation at plants where VC and PVC are manufactured and at factories where PVC is processed to give various fabricated articles. In practice skin exposure from the liquid phase is negligable. The development of methods for determining VC concentrations in air is briefly noted, and the historical levels of VC at the various types of plants are reviewed. By far the highest levels (hundreds of ppm) were experienced periodically at PVC-production plants, but by mid-1974 they had been reduced to, typically, around 50 ppm. Progress in lowering the levels continued, and since 1978 they have been at a few ppm or lower.

The general public is exposed to very small amounts of VC : i) from inhalation of ambient air in urban areas typically in the order of 5µg/person/day with higher amounts in the vicinity of VC and PVC plants, ii) by ingestion of food and drinks packed in VC-containing polymers as films, cartons or can-linings from which residual VC can migrate into the packed material and iii) by inhalation of tobacco smoke (a few ng/person/day). Since 1978 emissions from VC and PVC producing plants have been reduced considerably. Between mid-1973 and mid-1975 the amount of

residual VC in polymers was also drastically reduced, typically from more than 10 ppm to about 1 ppm, and the concentrations in food and drink fell from around 100 to about 2 ppb over the same time period, and data obtained in 1986 show typical values of 0.1 ppb or less.

The carcinogenic, mutagenic, clastogenic and related effects of VC on humans are reviewed. Twenty-six papers describing epidemiological studies are critically assessed and it is concluded that, apart from the well-established fact that exposure to the high levels of VC experienced in the past can cause angiosarcoma of the liver, there is no convincing evidence that it causes cancer at other sites, nor is there any evidence of teratogenic or heritable mutagenic effects in man. Clastogenicity was only seen at higher occupational exposure levels experienced before the marked reduction in exposure in the mid-1970's.

Various non-carcinogenic effects of chronic occupational exposure to VC have been described under the collective heading "Vinyl Chloride Disease", and these are briefly reviewed. There have been no reports of such effects in workers exposed to VC after the early 1970s when VC levels were lowered to a few ppm.

The experimental studies on the carcinogenicity, mutagenicity and genotoxicity of VC are also reviewed. From the extensive work on carcinogenicity, much of it by Maltoni, it is concluded that VC is a versatile carcinogen in animals when administered by inhalation or orally. In the three species tested (rat, mouse and hamster) it induced hepatic haemagiosarcomas, Zymbal gland tumours, nephroblastoma, pulmonary and mammary gland tumours, and forestomach papillomas. The minimum dose at which compound-related tumours were induced by inhalation was 10 ppm for rats, 50 ppm for mice and 500 ppm for hamsters. When VC in PVC powder was administered orally to rats, the minimum effective dose was 1.7 mg VC/kgbw per day. When it was administered as a solution in water to the same species, the minimum effective dose was 25 ppm.

VC is mutagenic and clastogenic in vivo. It is also mutagenic and clastogenic in vitro but only in the presence of appropriate metabolic activating systems. Chloroethylene oxide appears to be the most potent mutagenic metabolite.

The liver is the primary site of structural damage by VC, and it appears that the effect is due to toxic metabolites whose formation is induced by the mixed function oxidase system. The fact that, in experimental animals, tumours were induced in

organs which were not adversely affected in acute and sub-acute studies, and that tumours developed in the liver at dose levels well below those found to cause hepatotoxicity, is consistent with a genotoxic mechanism of action.

The major pathways in the metabolism of VC have been established. In experimental animals the key metabolic step is its conversion by mixed function oxidase into chloroethylene oxide. Although this process is readily saturable, the ability of chloroethylene oxide to bind covalently to DNA at levels which do not induce saturation probably accounts for the induction of tumours at such low levels. From studies on the clearance rates of inhaled VC in rats, mice and humans it is concluded that rats and mice exposed to VC produce more of the carcinogenic metabolite per kgbw than do humans.

As to the current risks, our conclusions are that although it is not possible to set definitely safe levels of exposure for genotoxic carcinogens, the evidence presented in this report suggests that occupational exposure at current levels, as would be achieved when in compliance with, for example the EEC limit of 3 ppm, does not present any significant risk to health. At the atmospheric levels to which the general public is exposed, in the order of 5 µg/person/day with higher values in the vicinity of VC and PVC plants, and less elsewhere, the risk of adverse health effects is even less. The content of residual VC in PVC and copolymers in food and liquid packaging materials has fallen, typically from more than 10 ppm in the early 1970's to below 1 ppm in subsequent years. There has been a corresponding reduction in the VC content of packed food and drink from about 100 ppb, to below 2 ppb from about 1977 onwards. Conservative estimates have indicated that the current intake of VC from food and drink presents a negligible risk of cancer.

A. INTRODUCTION AND HISTORICAL REVIEW

Since about 1974 vinyl chloride (VC) has become one of the most intensively studied of all industrial chemicals from the point of view of its toxic effects. An enormous amount of clinical and toxicological research has been carried out and a large amount of data relating to occupational exposure and exposure of the general public has been collected. By about 1985 many epidemiological or animal studies had been completed and reported. Most of the information necessary to understand the toxic effects of VC have been obtained. As this information is widely scattered it is difficult to have a coherent view of the results and developments which form the background of control measures currently in force. This is necessary for all who are concerned with the voluntary and regulatory control of VC.

As a consequence ECETOC set up a Task Force composed of experts to assess the carcinogenicity and mutagenicity of VC and their significance for the health of exposed workers and the general public. Emphasis was placed on carcinogenicity and mutagenicity because measures taken to reduce the risk from these effects would automatically minimise, and probably eliminate entirely, the risk of those VC-related diseases and conditions, which develop only after exposure to "high" concentrations. These other VC-related diseases are described briefly for the sake of completeness.

The report is set out as follows. The short historical review which completes this Chapter is followed by an account of human exposure (Chapter B) and the effects of exposure to VC on human health (Chapter C). Experimental studies are then assessed under the headings: experimental toxicology (Chapter D), and metabolism and related studies (Chapter E). Conclusions from the whole review are drawn in Chapter F. It is emphasised that only those publications relevant to the task in hand are considered.

1. VC AND PVC PRODUCTION PROCESSES

Vinyl chloride (VC) is a colourless, inflammable, explosive gas, slightly soluble in water, and soluble in fats and organic solvents (Appendix 1).

It was first synthesised by Regnault in 1835. Research on the polymerization of VC was carried out in Germany to provide a substitute for rubber during the First World War, but it was not until a century after its discovery, i.e. in the 1930s,

that the production of VC and its polymerisation to polyvinyl chloride (PVC) was developed industrially. After the Second World War production expanded considerably and PVC became one of the most important synthetic resins produced by the plastics industry. Worldwide annual production of the polymer in 1985 was about 12 million tons.

Apart from its use in the production of PVC and the manufacture of copolymers with monomers such as vinyl acetate or vinylidene chloride, VC still retains some minor use as a raw material for the manufacture of 1,1,1-trichloroethane and monochloroacetaldehyde. Certain of its less important uses have been abandoned since the early days and are not considered further. eg aerosol propellant and general anaesthesia.

There are two methods for the industrial production of VC. Formerly it was made from acetylene and hydrogen chloride but nowadays ethylene and chlorine are mainly used. They are reacted to give 1,2-dichloroethane, which is thermally cracked to produce VC and hydrogen chloride. There is very little exposure to VC, since production is carried out as a continuous process in plant closed to the outside atmosphere.

Descriptions of VC polymerization processes have been given by Cook et al (1971), Cohan (1975), Barnes (1976), Bonnefoy (1977) and Stafford (1977). There are two main processes : the dispersion process and the bulk process. Because most of the adverse effects of VC on human health occured at plants in which PVC was manufactured by the dispersion process, this is described in some detail below. The bulk process was introduced only in the later 1960s and a much shorter description of this is given.

1.1 Dispersion Process

As VC is a gas at ambient temperatures polymerisation is carried out in autoclaves at 40-70°C. The reaction is exothermic, and the most common method of dissipating the heat is to disperse the monomer in fine droplets in an approximately equal quantity of water. The reaction takes place in a three-phase system; the solid polymer is precipitated in the monomer droplets, which in turn are dispersed in the aqueous phase. Despite more than 30 years of research, no way has yet been found to prevent a film of PVC forming on the inside wall of the reactor. This film interferes with the transfer of heat between the reactor and its contents, and the

process has to be interrupted periodically to allow the reactor to be cleaned. The fact that it is technically impossible to polymerize VC by a continuous process in a permanently-closed system lies at the origin of the occupational pathology of autoclave cleaning personnel.

Over the years, the size of the autoclaves has gradually been increased. Whereas the first had a capacity of only a few cubic metres, those in current use have a volume of several tens of cubic metres, and even larger autoclaves are being designed.

In a typical process, deionized water is first introduced into the autoclave, followed by emulsifiers, catalysts, surfactants, buffers, etc. Air is purged from the reactor, and the liquid VC is then pumped into the sealed autoclave under pressure. The autoclave is heated to between 50 and 60°C in order to initiate polymerisation which then continues exothermically. Once polymerisation has ended, the autoclave charge is emptied into degassing tanks, and the non-polymerized VC is degassed and pumped into a gasometer where it is compressed and then stored under refrigeration in pressurised spheres. The wet PVC is transferred to mixers in which the charges from several reactors are combined in order to make the product uniform. It is then transferred to driers, and the resulting dried powder is sent either to bulk storage silos, or to hoppers for bagging. The autoclave, after being emptied, is opened, rinsed and washed either with solvents or by means of automatic high-pressure water jets.

Nowadays, many precautions are taken to guarantee the best achievable sealing involving the complex system of piping, tanks, pumps and valves in which the VC flows. This even applies to the autoclave which only needs to be opened occasionally. A combination of technologies are used for autoclave cleaning all of which involve washing between individual, or a limited number of batches, thereby reducing the formation of crusts or deposits resulting from polymerisation. In the past, the autoclaves were cleaned manually ; gloves were worn, whilst the inside of the autoclave was scrapped with a spatula, or sometimes a hammer and chisel, to remove the encrusted polymer adhering to the walls of the vessel and the mixing devices. Lumps of polymer often released monomer when broken, resulting in dangerously high concentrations in the autoclave. The usual practice up until about 1970 was not to go into the vessel, in which the atmosphere was still lader with monomer, until an explosimeter had been used to check that the autoclave contained less than about 400 ppm, ie. a safety margin of around two orders of magnitude

below the lower limit of explosivity of VC. Nowadays much more sensitive instruments are used to ensure that entry into autoclaves occurs only when the VC level is at or below 10 ppm.

1.2 Bulk Process

Liquid VC under pressure, plus a free-radical catalyst and other additives, are charged to an autoclave where pre-polymerisation occurs. When 8 to 12% of the monomer has been converted into polymer this "seed" material is passed to the main polymerisation autoclave where further VC, catalyst, etc. are added and the polymerisation is allowed to go substantially to completion. The remaining VC is removed and recovered, and the dry polymer is then screened, and passed to storage.

In the period between its production and use, PVC is stored in warehouses for periods of several days or weeks and can lose significant amounts of its residual monomer by diffusion into the atmosphere.

2. PVC CONVERSION PROCESSES

PVC is converted into a wide range of products by various processes, including dry blending. Most of which involve heating until it softens or melts. It can then be formed into solid articles (by extrusion, thermo-forming, or rotational moulding), or rigid or flexible film (by extrusion or callendering). During the processes, part of the residual VC is expelled from the PVC. The industrial operations described above can lead to occupational exposure to VC.

3. PVC PACKAGINGS FOR FOOD AND DRINK

Exposure of the general public can arise from the packaging of a wide variety of foods and drinks in containers or film made of PVC or VC co-polymers. Residual VC in the polymer may migrate into food or drink and minute amounts can thus be ingested by the consumer.

4. EXPOSURE TO VINYL CHLORIDE

An inventory of the population groups liable to be exposed to VC shows a steeply-decreasing degree of exposure, in the following order (Bonnefoy, 1977):

1. Polymerisation unit workers - the most heavily exposed because of the many manual operations, the frequent opening of equipment and the fact that the installations are often situated inside buildings.
2. Workers in monomer production units - only slightly exposed since the continuous process under pressure necessitates sealed systems, and the installations are situated in the open air.
3. Workers in plants where PVC is converted into manufactured articles. The levels have always been very low, as the only source of VC is traces released from the resin.
4. People living near plants.
5. Consumers of food and drink packed in PVC or VC copolymers containing residual monomer.

More details about the levels of exposure of these groups are given in Chapter B.

The concurrent publication in 1974 of papers on angiosarcoma of the liver in VC exposed experimental animals and man stimulated a major technological effort to reduce the exposure at workplaces. The result was that exposure was markedly reduced and atmospheric concentration limits in the workplace were lowered, e.g. from 500 ppm (ACGIH, 1970) to a "harmonized" long-term Limit Value of 3 ppm as an annual average in the European Communities (EEC, 1978), cf table 1. At the same time there was a sustained effort to lower the amount of residual monomer in PVC, and hence in food and drink packaged in PVC-containing materials. In 1978 the EEC set a limit of 1 ppm of residual VC in PVC polymers, and a migration limit of 10 ppb in food or drink resulting from the packaging (EEC, 1978).

5. EFFECTS OF VINYL CHLORIDE ON HEALTH

There are many reviews of the toxicology of VC, eg. Schottek (1969), Viola (1974), Foa et al (1974), CIRC (1974), Haley (1975), Hublet (1975), Truhaut et al (1975), Szadkowski (1976), Heuse (1978), Binns (1979) and Veltman (1980). In addition Cavigneaux (1975), Heiman et al (1975), Warren et al (1975) and Szadkowski et al (1982), have produced bibliographic inventories.

Our understanding of the toxicology of VC developed in three historical stages as set out below.

5.1 Effects on the Central Nervous System (CNS) (roughly from 1930)

During the early period of the industrial development and use of VC and PVC, the effects of VC on the CNS, at what would now be considered to be very high concentrations, were recognised in experimental animals and man (Patty, 1930). The symptoms include euphoria, headaches, dizziness and loss of consciousness which are manifested in man at concentrations of several thousand ppm. See, for example, Mastromatteo et al (1960), Cordier et al (1966), Berod et al (1972), Lange et al (1974), Moulin et al (1974), Lilis et al (1975), Truhaut et al (1975), Walker (1976) and Delorme et al (1978).

5.2 "Vinyl Chloride Disease" (roughly from 1957)

In the 1950s a variety of other effects became recognised as resulting from chronic exposure to VC at concentrations of (probably) several hundred ppm. Some of them were first described by Filatova (1957) and were later collectively called "vinyl chloride disease". The effects included a sclerotic condition of the connective tissue of the fingers accompanied by a thickening of the dermis, and from fibrosis of the liver tissue and spleen. Another effect is acro-osteolysis, a rare bone-disease resulting in de-calcification of the terminal phalanges of the hand and affecting largely the "autoclave scrapers" (Cordier et al, 1966). Less commonly, osteolytic lesions are observed at other sites in the skeleton.

Acro-osteolysis is frequently preceded by a Raynaud-type phenomenon in which there is a reversible constriction of the arterioles of the fingers leading to numbness, pallor, and cyanosis of the fingers.

5.3 Carcinogenicity (1970 and onwards)

While attempting to reproduce acro-osteolysis in rats exposed to VC by inhalation, Viola (1970) and Viola et al (1971) found an increased incidence of tumours of the skin, lungs and bones. A few years later Maltoni et al (1974) confirmed this, and identified in addition an increased incidence of angiosarcoma of the liver. A most significant finding was also made in the same year when Creech and Johnson (1974) reported that a search of the medical files at a Goodrich plant in the USA had revealed three cases of death from angiosarcoma of the liver (a very rare form of cancer) among the deceased workers. It was recognised that the cause was likely to be inhalation at high levels (probably a few hundred ppm) of VC over long periods.

This finding, in combination with results from experimental studies, initiated an urgent and radical worldwide revision of measures for protecting the health of groups of people exposed to VC, and simultaneously led to extensive epidemiological and animal studies which are described in the following chapters.

6. EVOLUTION OF OCCUPATIONAL EXPOSURE LIMITS

In parallel with the discovery of the toxic properties of VC, the development of technology to lower the concentration in occupational atmospheres, and improved analytical capability, the various recommended exposure limits were lowered, as summarised in Table 1.