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Review

Vinyl chloride and the liver☆

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Vinyl chloride monomer is a known cause of angiosarcoma of the liver. It also has other toxic effects on the liver, and it has recently been suggested that exposure to vinyl chloride also causes hepatocellular carcinoma. However, the data on which this conclusion is based is incomplete. There is inadequate ascertainment of unequivocal diagnoses. In the largest studies lack of data meant that confounding diseases such as viral hepatitis or alcoholic liver disease could not be assessed. At best, the increase in risk is minimal, based on more than 22,000 exposed workers and more than 640,000 person years of observation.

However, based on the available data the hypothesis that vinyl chloride causes or contributes to the development of hepatocellular carcinoma remains unproven.

***Keywords*: Vinyl chloride; Hepatocellular carcinoma; Angiosarcoma**

1. Introduction

Vinyl chloride monomer (VCM) is a colourless gas at room temperature. Polyvinyl chloride (PVC) is a polymerized form of vinyl chloride that is extensively used in the plastics industry. VCM does not occur naturally, and thus is found almost exclusively in factories making PVC. Small amounts of VCM are found in finished plastic products, curiously, it is to be found in highest concentration in vinyl records. VCM is also present in cigarette smoke; the amount depends on the chloride concentration of the tobacco. VCM has not been identified in food, pharmaceuticals or cosmetic products in recent years [1].

Vinyl chloride has been in commercial production in the USA for more than 70 years [2]. In 2001 about 6.2 million tones were produced [3]. Around the world about 35 million tons were produced in 2005 [4]. About 40,000 workers in Europe and 80,000 workers in the USA have been potentially exposed to VCM up to 1997 [5].

Detailed descriptions of toxicity first appeared in the 1970s. VCM is causally associated with the development of a form of non-cirrhotic portal hypertension related to sinusoidal endothelial damage, and to angiosarcoma of the liver (ASL). More recently it has been suggested that VCM also causes hepatocellular carcinoma (HCC). This review was triggered (but not sponsored) by a workshop convened by the European Council of Vinyl Manufacturer's to examine the causal relationship between exposure to VCM and the development of HCC. It is important that the strength of the association between VCM exposure and HCC be evaluated. Unlike angiosarcoma, HCC is not a rare cancer. In fact, it is increasing in incidence in many countries. Therefore even if VCM has no role in the development of HCC some VCM workers are likely to develop HCC. In many cases the main etiologic agent of the HCC, namely chronic hepatitis B or C, will be easily identifiable, but in

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Abbreviations: VCM, vinyl chloride monomer; PVC, polyvinyl chloride; ASL, angiosarcoma of the liver; HCC, hepatocellular carcinoma; IARC, International Agency for Research in Cancer; SMR, standardized mortality ratio; AFP, alpha-fetoprotein.

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patients who develop HCC on the background of diabetes or non-alcoholic fatty liver disease it will not be easy to document the pre-existing liver disease that was responsible for the development of HCC. This clearly demonstrates the need to confirm whether VCM causes or contributes to HCC. This issue has been addressed by the International Agency for Research in Cancer (IARC) which has concluded that there is sufficient evidence that VCM is a cause of HCC [6].

As the toxicity of VCM was recognized the industry took steps to protect workers, resulting in a progressively decreasing measured concentration of VCM in workshop areas. In 1978 the European producers of VCM established a registry of cases of angiosarcoma [7]. This registry has shown a decreasing annual number of cases, with no new case in whom exposure began after 1972. The register currently contains 231 cases. Most of the cases come from Europe and North America, with few coming from Eastern Europe or China, both producers of VCM. This is likely due to inadequate reporting, rather than more stringent safety precautions in those parts of the world. The annual incidence of ASL in workers from the USA included in the registry was 0.014/100,000. There is a decreasing trend in reported cases over time, suggesting that the industry has been successful in reducing worker exposure. Nonetheless, because the mean latency between exposure and the development of ASL in the registry was 27 years additional cases of VCM-related ASL might still be observed. Recorded levels of human exposure in VCM factories vary widely. Prior to environmental controls being instituted exposure levels were high, measured up to 7800 mg/m^3 [8] (10 ppm equals about 26 mg/m^3). In recent years, in countries with strict and strictly enforced environmental standards current exposure levels are usually less than 1 mg/m^3 [9]. However, in countries where environmental controls are less strict relatively high levels of exposure (e.g., up to 800 mg/m^3) still occur [10,11].

2. Metabolism of VCM and genotoxicity

VCM is rapidly absorbed through the lungs and is rapidly metabolized by the liver [1,12]. The metabolic pathway of elimination of VCM is shown in Fig. 1 [1]. Chloroethylene oxide is a reactive intermediate metabolite that is detoxified by conjugation with glutathione or via aldehyde dehydrogenase [1]. However, chloroethylene oxide can also form DNA adducts that are mutagenic [1]. VCM has been shown to be genotoxic in *in vivo* studies in rats (summarized in Ref. [1]). VCM vapour induces DNA strand breaks, sister chromatid exchanges, micronucleus formation and other chromosomal aberrations. VCM is mutagenic in a number of different *in vitro* assays (summarized in Ref. [1]). Mutations of Ki-*ras*-2 and p53 genes have been described in ASL; although it has been suggested that some of these mutations may be characteristic of VCM exposure, the same mutations have also been reported in other tumors and in other ASL, in absence of any exposure to VCM [13–17]. There is a characteristic mutation in the Ki-*ras*-2 gene at codon 13 (GGC to GAC), or less commonly at codon 12 (also G to A) [13,14]. The mutations in the p53 gene that are found in VCM-induced ASL occur in several different positions on the p53 gene and do not appear to be characteristic for vinyl chloride exposure [15,16]. The presence of these mutations in non-tumour liver tissue has not been evaluated. This would obviously be important to document as an important piece of evidence as to whether VCM exposure could lead to HCC. Although mutations in liver tissue have not been investigated mutated Ki-ras and p53 proteins have been discovered in the blood of workers exposed to VCM [14,17–20]. In particular a dose–response relationship was present between level of exposure to VCM and likelihood of finding the mutated protein in blood. However, it is not yet clear whether these changes are sufficiently specific or sensitive that they can be used to detect significant exposure to VCM, or to quantify degree of risk for ASL.

3. Experimental evidence of liver injury from VCM

There have been numerous studies of exposure to VCM in different species of experimental animal. VCM has been administered orally, by inhalation or intra-tracheal administration or by intramuscular or intraperitoneal administration, and by inhalation exposure in the pregnant animals and the offspring monitored for tumour development. These studies have consistently demonstrated the development of the histological changes described below, and the development of angiosarcoma of the liver and other tissues. The development of HCC has not been uniform. HCC was not seen in mice exposed to VCM by inhalation at exposures ranging from 50 to 10,000 ppm for periods exceeding 24 weeks [21–25]. HCC has been reported in rats exposed to VCM by inhalation or by oral feeding [23–28], but not when exposed by subcutaneous or intraperitoneal injection [23,29–31]. Doses up to 30,000 ppm for 52 weeks found only occasional HCC. Maltoni and Cotti [30], did not find a dose–response between VCM and the development of HCC, but HCC only occurred at a dose that was many multiples of what a human might be exposed to. Drew et al. [25], described an increased incidence of hepatic adenomas and HCC in VCM-exposed rats, but there was no dose–response relationship. Feron et al. [26,32] and Til et al. [31], also described dose–response relationships between the degree of exposure to VCM and the development of