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Journal of Hepatology 51 (2009) 1074–1081

Journal of Hepatology

www.elsevier.com/locate/jhep

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

Associate Editor: M. Colombo

☆ The author declared that he is a paid consultant to the European Council of Vinyl Manufacturer's for the workshop on the relationship between VCM and HCC, a consultant to Bayer and a speaker for Bayer Inc.

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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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doi:10.1016/j.jhep.2009.09.012

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

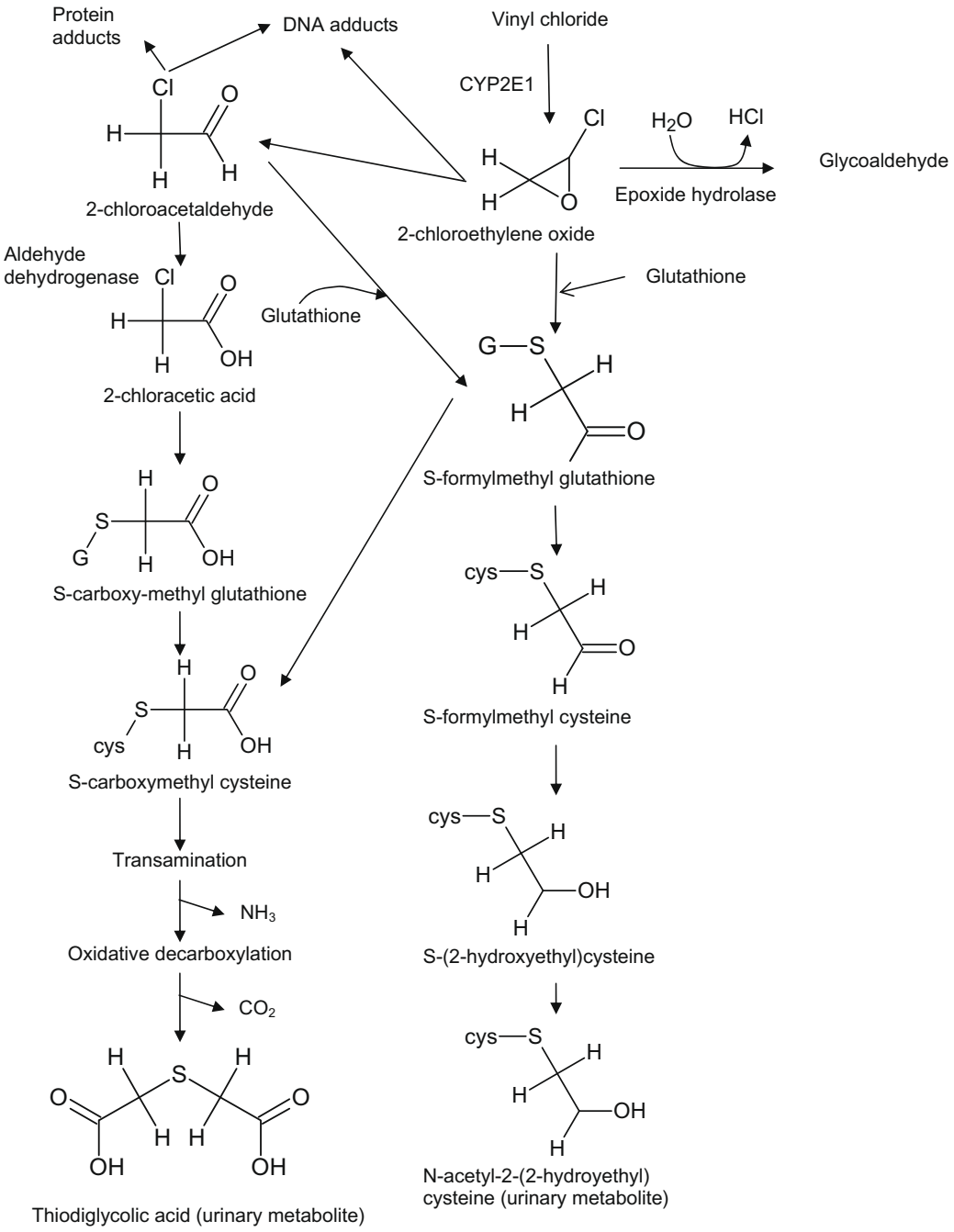

Fig. 1. The metabolic pathway of elimination of VCM.

HCC. However, once again, the doses at which HCC developed were very much higher than would be expected in VCM plants. Only in the offspring of female rats exposed during pregnancy was HCC found at appreciable rates [30].

4. Pathology

The pathology of VCM-induced liver injury has been described in experimental animals and in humans [33–36]. The changes are similar. The brunt of the injury is at the sinusoidal level but hepatocytes may also be involved. There may be simple sinusoidal dilatation, with or without endothelial cell hyperplasia. In milder cases there is perisinusoidal and perivascular fibrosis. In more advanced cases there is periportal, portal and subcapsular fibrosis. Subcapsular fibrosis in particular is a characteristic of this kind of injury, and is similar to that caused by thorotrast or arsenic. Ultimately, if fibrosis is extensive enough the fibrosis coalesces so that the appearances are typical of cirrhosis. Endothelial cell

nuclei enlarge, become irregular and hyperchromatic. These may be pre-neoplastic changes, although it has not been possible to study the sequential changes from dysplasia to neoplasia. Hepatocyte nuclear changes similar to dysplasia seen in other causes of cirrhosis may also occur. This has been taken as evidence that VCM can cause HCC. All these changes were described in an era before hepatitis C, and in some cases, before even hepatitis B was identified, so that at least some of the changes might have been due to chronic viral hepatitis. This is particularly true in cases coming from southern Europe, where chronic viral hepatitis was prevalent.

The extensive sinusoidal fibrosis has a clinical correlate in the development of non-cirrhotic portal hypertension. Patients can develop varices that can bleed, splenomegaly and ascites despite the absence of cirrhosis.

5. Angiosarcoma of the liver

Angiosarcoma of the liver is a rare tumour, even in VCM workers. It is this very rarity that allowed identification of the causal relationship with VCM, when three cases were reported from a single plastics plant [36]. Since then a number of studies have been conducted, including large-scale epidemiologic surveys [37–40] comparing all cause mortality and disease-specific mortality in VCM workers with regional mortality results, to case-control studies using non-exposed workers as controls [40,41].

There have been two large-scale multicentre epidemiological studies of cancer and mortality risk in VCM workers, one in North America and one in Europe. Periodic updates of these series have also been published. The North American study [39] included 37 plants with 10,173 workers. In the latest update the standardized mortality ratio (SMR) from cancer of the liver and biliary tract was 3.59 (95%, CI 2.84–4.46) [39]. The reference for SMR was the rate in the state in which the plant occurred. Of the 80 deaths from primary liver cancer 48 were apparently due to angiosarcoma. The SMR's from primary liver cancers increased with increasing duration of exposure. Death from angiosarcoma was also associated with duration of exposure, but the rarity of this disease in the general population made development of SMR's impossible.

In the European study originally published in 1986 and updated up to 1993–1997 [40] there were 19 factories and 12,700 male exposed workers. Reference rates of SMR were national mortality rates for workers in the different countries. The SMR for primary liver cancer was 2.4 (95%, CI 1.8–3.14). Of the 71 cases of primary liver cancer there were 37 confirmed cases of ASL and 10 confirmed cases of HCC. The cumulative exposure estimates (Table 1) from this study did not suggest that there was a dose–response relationship between exposure and the development of HCC.

Table 1
Cumulative exposures to VCM and the likelihood of HCC being present [40]. Only at the highest exposure is the likelihood of HCC increased, and this is based on only two subjects. There is no dose–response relationship.

VCM exposure (ppm years)	Number of cases	Relative risk of HCC (95%, CI)
0–734	3	1.0 (reference)
735–2379	2	3.02 (0.50–18.1)
2380–5188	1	2.47 (0.26–23.9)
5189–7531	1	5.33 (0.54–52.5)
>7532	2	RR not given (2.98–138)

6. Vinyl chloride and HCC

The most up-to-date and most comprehensive analyses is a pooled analyses of cohorts of VCM workers from plants in the USA and Europe [41]. The results from the two large multicenter studies and the pooled meta-analysis are presented in Table 2. This analysis includes more than 22,000 workers with about 640,000 person years of observations. In these two cohorts 1,778 cancer deaths were observed, *vs.* 1829 expected, giving a standardized mortality ratio of 0.97 (95%, CI 0.93–1.02), i.e., not statistically different. There were 71 confirmed angiosarcomas and 60 additional deaths from liver cancer *vs.* 44 expected liver cancer deaths (SMR 1.35, 95%, CI 1.03–1.74), i.e., barely statistically significant. Misclassification, ascertainment bias, and inadequate assessment of confounding factors makes it likely that the minor increased risk of liver cancer other than ASL that was found is spurious. This meta-analysis confirmed that there was an increase in mortality from primary liver cancer and that ASL was the most common form of primary liver cancer [41]. The calculated SMR of 1.35 (95%, CI 1.04–1.77) for liver cancer other than ASL is lower than the SMR calculated in the two studies from which the meta-analysis was derived. The original studies calculated the SMR for all primary liver cancers, including angiosarcoma and liver cancer other than ASL. However, in the meta-analysis using raw data from the two previous studies the authors were able to subtract confirmed angiosarcomas from the total number of liver cancers and calculate the SMR for HCC alone. These studies, coupled with the rarity of ASL in the general population have been taken as evidence that VCM does indeed cause ASL. Few would argue with this conclusion, even though standardized mortality rates could not be calculated.

The large-scale multicentre North American study [39] did not provide data on the SMR for death from HCC. In the European study [40] there were 10 confirmed cases of HCC. A further analysis suggested that the risk of dying from HCC was significantly associated

Table 2
Risk of primary liver cancer in VCM workers [6].

Site	Number of subjects	Study population	Type of cancer	SMR/RR/Hazard ratio/Relative risk (95%, CI)	Reference population	Comment	Reference
USA [39]	10,109	All exposed VCM factory workers	All primary liver cancer	SMR 3.59 (2.84–4.46)	State and US population		Mundt et al. [39]
			All primary liver cancer except angiosarcoma	SMR 1.8 (1.3–2.5)		Derived from raw data by Boffetta et al. [41]	
Italy, Norway, Sweden, UK [40]	12,700	All exposed VCM factory workers	All primary liver cancer	SMR 2.4 (1.8–3.14)	Country population		Ward et al. [40]
		1–9 years of exposure	HCC	Reference			
		10–16 years of exposure		HR 6.94 (0.71–67.5)			
		17–20 years of exposure		HR 12.6 (1.11–143)			
		21–25		HR 7.34 (0.44–122)			
		⩾26		HR 35.3 (3.34–377)			
			Cirrhosis	SMR 0.77 (0.57–1.02)			
Meta-analysis [41]	22,809	All exposed VCM factory workers	HCC	SMR 1.35 (1.04–1.77)[a]			Boffetta et al. [41]

[a] SMR of HCC only, exclusive of angiosarcoma.

with duration of exposure and for ever *vs.* never exposed. This study found decreased mortality for cirrhosis, overall, although a trend with cumulative exposure was observed. However, there did not appear to be a correlation between cumulative exposure and death rates from cirrhosis. A separate cohort study of workers at one of the plants that contributed to this study also found that there was an association between exposure to VCM and mortality from HCC or cirrhosis [42].

Wong et al. [43,44] analyzed mortality in a cohort of 3293 male PVC workers, and found that there was an increased SMR for malignant neoplasms of the liver (SMR 1.78, 95%, CI 1.15–2.62). There were 25 deaths from liver neoplasms, of which 5 were confirmed as HCC. An additional 5 had appropriate radiology with an AFP >1000 μg/L. Therefore, only 40% of cases were confirmed as HCC, although death certificates suggested that all were due to HCC. Thus, no deaths from ASL were recorded. However, in Taiwan, where this study was performed HCC is common, and in the absence of histological proof patients dying a cancer death with a mass in the liver would be assumed to have died of HCC. Hence, absence of confirmation in 60% of cases makes these results uncertain.

7. Vinyl chloride and cirrhosis

The IARC monograph on the carcinogenicity of VCM takes for granted that exposure to VCM causes cirrhosis, without examining the data. This association is then used to support the argument that VCM also causes HCC. Three publications examined the relationship between VCM exposure and the presence of cirrhosis, all coming from European cohorts. Ward et al. [40], in the large European multicenter study actually found an overall decrease in deaths from cirrhosis in the VCM-exposed workers. Cumulative VCM exposure and the risk of having cirrhosis is shown in Table 3. Mastrangelo et al. [42] retrospectively analyzed VCM workers involved in a lawsuit. These cases were also included in the European multicenter study. There were 643 workers, among whom 40 cases of cirrhosis were identified either histologically or on biopsy. The authors attempted to evaluate the effect of multiple risk factors on the development of HCC and cirrhosis. They examined three variables, VCM exposure (three strata),

Table 3
Cumulative exposure to VCM and the risk of developing cirrhosis (taken from Ward et al. [40]). There does not appear to be a dose–response relationship between exposure and cirrhosis.

Cumulative exposure (ppm years)	Number of cases	Relative risk of cirrhosis (95%, CI)
<524	8	1.0 (reference)
524–998	8	9.38 (3.52–25.0)
999–3429	9	4.01 (1.55–10.4)
3430–5148	8	9.77 (3.66–26.1)
>5149	9	8.28 (3.15–21.8)

alcohol consumption (three strata) and the presence of absence of chronic viral hepatitis. They describe that overall those with cirrhosis had a higher exposure to VCM than those who did not, with an odds ratio of 1.37 (95%, CI 1.13–1.69). However, in looking at the interaction of variables each cell contained 10 or fewer cases, making the findings of an interaction unreliable, even if statistically significant. Since the cumulative exposure is to a large extent a function of duration of exposure, cumulative exposure is also a function of age.

Pirastu et al. [45] examined workers from the same plant. It is not clear to what extent, if any, this cohort overlapped with the previous cohort. They found an increasing prevalence of cirrhosis with increasing exposure to VCM. However, the same objection applies as with the previous study.

Others have used fibrosis as an endpoint, but did not use biopsy to make the diagnosis of fibrosis. Hsieh et al. [46] attempted to evaluate the effect of CYP2E1 polymorphisms on the development of liver fibrosis in those exposed to VCM. Fibrosis was diagnosed by ultrasound. They described that there was a relationship between VCM exposure and the diagnosis of fibrosis. Hsiao et al. [47] and Maroni et al. [48] again using ultrasound to diagnosis fibrosis came to a similar conclusion. However, as all hepatologists know, ultrasound is an inappropriate tool to diagnose fibrosis. Ultrasound can only diagnose the presence of fibrosis with any degree of certainty when cirrhotic nodules can be detected, indicating relatively late-stage disease. Lesser degrees of fibrosis cannot be diagnosed by ultrasonography. Therefore all studies using ultrasound to diagnose fibrosis are unreliable.

8. Evaluation of the evidence

Thus, the evidence in favour of VCM as a cause of HCC and cirrhosis rests upon retrospective studies that showed in some cases an increased mortality from liver cancer other than ASL above what would have been expected for a similar population, and upon some studies that showed a dose–response relationship between the degree of exposure to VCM and the likelihood of dying of HCC.

All these studies are open to criticism on a number of different grounds. The first is ascertainment bias. This is the bias that is introduced when the disease of interest has not been diagnosed conclusively. Thus the question arises: how certain can we be sure that those labeled as HCC were indeed HCC and not some other liver cancer or ASL, and how certain can we be that those labeled as cirrhosis did indeed have this condition?

Most of the patients included in these studies died before 1995, and many were diagnosed in the 1960s and 1970s. Ultrasound and CT scanning were only introduced in the 1970s. Prior to that the diagnosis of HCC rested upon autopsy data, biopsy data, angiography or a diagnostically elevated AFP. In the absence of such confirmation a death certificate diagnosis of HCC is unreliable. In the absence of histologic or radiographic proof, patients presenting with liver failure and what seemed to be a mass in the liver would be much more likely to be labeled as HCC than angiosarcoma, since angiosarcoma was a rare tumour, whereas HCC, although not common, was much more frequent than ASL. This criticism applies doubly to the Taiwan study that found all the primary liver cancers to be HCC. HCC is one of the most common cancers in Taiwan. Thus, in the absence of histology primary cancers of the liver are much more likely to be called HCC than ASL, and it is conceivable that at least some of the cancers in this study were not HCC. Thus ascertainment bias may have influenced the apparent incidence of HCC. The meta-analysis, looking only at cases not confirmed as ASL found that VCM was only marginally significantly associated with liver cancer other than ASL. Given the small overall numbers of cases (10 cases) misclassification of only a few liver tumours would change a non-significant association to a significant association.

Ascertainment bias may also have influenced the apparent mortality from cirrhosis. First, not all studies found an increase in cirrhosis deaths. In fact the meta-analysis found a lower than expected mortality from cirrhosis. But it is important to also consider that VCM causes non-cirrhotic portal hypertension. In the 1960s and 1970s the diagnosis of cirrhosis was usually made clinically and referred to a syndrome of ascites, variceal bleeding, hepatic encephalopathy and possibly jaundice. In the absence of liver biopsy data, and in the era in which these patients were affected it is quite possible that at least some of the patients diagnosed with cirrhosis actually had non-cirrhotic portal hypertension. Since the number of patients diagnosed with cirrhosis was not large, misclassification of only a few cases of non-cirrhotic portal hypertension as cirrhosis would alter the statistical significance of the association between VCM and cirrhosis from non-significant to significant.

This may seem like a semantic argument, whether VCM causes cirrhosis or not, but it has more significance than simple semantics. If these patients truly had cirrhosis then it could be argued that cirrhosis is a precursor to HCC, and therefore the development of cirrhosis is an argument in favour of the association between VCM and HCC. If, on the other hand, the clinical presentation was due to non-cirrhotic portal hypertension the strength of this argument is reduced. Ascertainment bias may be very important in assessing the relationship between cirrhosis and VCM.

Thus, the statistical association between VCM and the development of HCC would seem to be less certain than presented by IARC.

It is also worth considering the dose–response relationship between VCM and HCC. If the dose–response relationship is real, this is indeed support for a causal relationship association. However, the European study [40] that evaluated the dose–response relationship included only 10 cases of HCC stratified into 4 dose categories. Thus each dose category cannot have contained more than 2–3 subjects. Therefore, although there seems to be a trend towards a higher HCC death rate with increasing dose, the possibility of a type I error is very high.

Finally, patients included in the multicenter studies were largely diagnosed before testing for viral hepatitis was available. Testing for hepatitis B was introduced in the late 1960s and for hepatitis C only in 1990. Thus, the contribution of these infections to the development of HCC cannot be assessed. Standardized mortality rates assume that the population being studied i.e., VCM workers, would have the same prevalence of confounding diseases as the regional population. Case-control studies make a similar assumption when e.g., office staff is used as controls. However, these assumptions have not been tested. For example, office workers may have a different level of education than factory floor workers, and since hepatitis C is associated with socioeconomic status the office workers may not be a suitable control for e.g., HCC mortality. The prevalence of viral hepatitis in VCM workers may not be the same as in the local general population for similar reasons. The level of alcohol consumption may also be different between factory floor workers and office workers or regional controls.

9. Summary

To conclude, although a reputable and influential organization (IARC) has indicated that VCM does cause HCC, the basis for these statements seems to be less than solid. Others have raised this issue, suggesting that apart from angiosarcoma there is no evidence that chronic exposure to VCM causes any other cancer [49,50]. More recent analyses don't really contradict this. It is not possible to say the there is no association, but to this reader the evidence is less than convincing. Perhaps the most appropriate statement would be that the proposition that exposure to VCM causes HCC remains to be proven.

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