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Recently two review articles were published on the epidemiologic evidence for the carcinogenicity of vinyl chloride monomer (VCM) (1, 2). We re-evaluated the original research articles to gain an insight into the existing discrepancies between the two reviews.

The meta-analysis by Boffetta et al (1) included two recently updated multicenter cohort studies, one done in Europe (3) and one in the United States (4), and six smaller cohort studies, in the Soviet Union, France, Canada, Germany, China, and Taiwan. The meta-analysis, as most individual studies do, clearly indicated that VCM workers are at an increased risk for angiosarcoma of the liver. This is such a rare tumor in the general population that no standardized mortality ratio (SMR) has been calculated for it. Had such a calculation been done, the SMR would have been excessively high. The SMR for liver cancer, other than angiosarcomas of the liver, was also elevated, giving an SMR of 1.35 [95% confidence interval (95% CI) 1.04–1.77]. Two arguments are given for the proposition that these other liver cancers are related to VCM exposure. First, the excess correlates very well with the year of first employment, a measure corresponding with exposure intensity. Second, Boffetta and his colleagues argue that there seems to be a deficit of cirrhosis of the liver, which could indicate that benign proliferative processes turn malignant under exposure to VCM. These considerations can also be interpreted differently. First, if the liver cancers not coded as angiosarcoma are, in reality, angiosarcomas, they would follow the same time pattern as the deaths rightfully coded as angiosarcomas. Therefore, it is not surprising that the SMR values of liver cancers excluding the known angiosarcomas are strongly correlated with the year of first exposure. Thus the fact that the SMR values of other liver cancer deaths are strongly correlated with the year of first employment can also be interpreted as supporting the possibility that the increased SMR for other liver cancer mortality is caused by misdiagnoses of angiosarcoma cases. Second, the hypothesis that the cases with cirrhosis of the liver may have evolved into malignant liver cancer under the presence of VCM is purely speculative. There is no evidence in the literature to support such a change from benign neoplasia to malignant cancer. Liver cancer generally arises from the hepatocytes, whereas liver cirrhosis involves the connective tissue and fibrous cells, which are from a different histological origin. It is very unlikely that fibrous cells could be the origin of liver cancer.

The main results of the meta-analysis and the comments given by Boffetta et al (1), as well as the comments given by us in this letter, are displayed in table 1. In their meta-analysis, Boffetta and his colleagues statistically assessed the heterogeneity of the study-specific results, using a P-value of ≥0.01. Because of the low power of the statistical tests for heterogeneity and the possibility of type II errors, experts recommend a

Table 1. Main results of the meta-analysis conducted by Boffetta et al, 2003 (1) on the mortality experience of 43 810 workers exposed to vinyl chloride monomer (VCM). (SMR = standardized mortality ratio)

Results of the meta-analysis	Interpretation by Boffetta et al, 2003 (1)	Interpretation by Swaen & Duijts
SMR for all liver cancer = 2.96 SMR liver cancer excluding angiosarcomas of the liver = 1.35	Angiosarcoma is a result of VCM exposure. Other liver cancers are also likely to be related to VCM because of their statistical significance and clear association with the year of first employment. This assumption is supported by the lack of mortality from liver cirrhosis, which indicates that benign processes in the liver may have become malignant in the presence of VCM.	The angiosarcomas are VCM-related. The other liver cancers, after exclusion of the angiosarcomas, may be VCM-related. The excess mortality from liver cancer decreased over time, which may reflect improved diagnostics. The hypothesis that liver cirrhosis, in the presence of VCM, turns malignant remains to be proved and is not substantiated by any other example in which this occurs.
SMR for lung cancer = 0.90 SMR for soft-tissue sarcomas = 2.52 (all studies) and 2.41 (two multicenter studies).	There is no association with VCM exposure. Seven of the 18 soft-tissue sarcomas were miscoded and were metastases of angiosarcomas of the liver. It is difficult to clarify whether or not the remaining soft-tissue sarcomas are related to the exposure.	Agree, there is no association with VCM. Seven of 18 soft-tissue sarcomas were incorrectly coded as soft-tissue sarcomas. If these seven are treated as angiosarcomas, the SMR will drop significantly, and probably no substantial excess remains.
SMR for skin cancer = 1.11 SMR for brain cancer = 1.23, mainly due to an excess in the United States study	There is no association with exposures. It is difficult to assess whether the workers for whom the excess mortality was noted had been exposed to other industrial exposures.	There is no association with exposures. There was only a small excess of brain cancer mortality, which was confined to the United States cohort. It is not likely that an occupational exposure was responsible for this small excess. Targeted studies of these workers have not come up with a suspect exposure.

significance level of 0.10 instead of the more traditional level of 0.05, or even 0.01 (5, 6). Furthermore, if there is no component of variability between studies, the results of methods based on fixed and random effects modeling are essentially identical (5, 7). When there is a component of variability between studies, the confidence interval for a summary estimate of effect size is wider when random effects modeling is used. Thus the null hypothesis of no effect will be more often accepted if based on the random effects model. In case of true homogeneity of study-specific results, fixed effects modeling is recommended, yielding smaller confidence intervals for the regression coefficients than random effects modeling (8). If residual heterogeneity exists, random effects modeling is appropriate. When the P-value of the test of heterogeneity was ≥0.01, Boffetta and his co-workers concluded that the study-specific results were adequately similar, and they conducted a meta-analysis based on random-effects modeling. As mentioned earlier, a significance level of 0.10 is recommended because of the low power of statistical tests for heterogeneity. Consequently, the meta-analysis, based on fixed and random effects modeling, had to be conducted differently. We have repeated the meta-analysis using the proposed modeling procedures (table 2).

Bosetti and his colleagues (2) published a review of the epidemiologic literature on occupational exposure to vinyl chloride and cancer risk. In this review only the two large multicompany studies in Europe and the United States were included, encompassing the mortality of over 22 000 VCM workers. From data on the two large cohort studies, Bosetti et al concluded that they "are reassuring in excluding any mortality from lung, laryngeal, soft tissue sarcoma, brain and lymphoid neoplasms, as well as cirrhosis. There appears to be a slight excess risk for liver cancer other than angiosarcomas, which is difficult to interpret since it is likely to be due in part to residual misclassification of angiosarcomas as liver cancers".

The disagreement between the two reviews lies with the interpretation of the data concerning the risk of soft-tissue sarcoma. Where Boffetta et al concluded that there may be an excess of soft-tissue sarcoma (two multicenter studies: SMR 2.41, 95% CI 1.45–3.99), Bosetti calculated an SMR for soft-tissue sarcoma (excluding cases with liver angiosarcoma) of 1.31 (95% CI 0.63–2.41) and interpreted these data as not supporting an excess related to industrial exposures. Because of misclassification of three out of six deaths in the European multicenter study and four out of twelve deaths in the North American study, the combined analysis of Bosetti et al on the presence of an excess of soft-tissue sarcoma should be correct. Nonetheless, the quantification of an overall meta-SMR (two multicenter studies and two individual studies) for the data of Boffetta et al, including the correct numbers for the two multicenter studies, results in an SMR of 1.69 (95% CI 1.01–2.83). Hence there still may be a small excess of soft-tissue sarcoma for VCM workers. The key issue is how the cases of soft-tissue sarcoma, which later turned out to be misdiagnosed cases of angiosarcoma, should be treated. According to classic epidemiologic principles, the comparability of health effect data between an exposed group and an unexposed group should never be compromised, and the quality and completeness of health data from the exposed group should be similar to that of the unexposed group. Only the deaths from soft-tissue sarcoma

Table 2. Results of the re-analyses, using fixed and random effect models. (SMR = standardized mortality ratio, 95% CI = 95% confidence interval)

Cause of death [a]	Number of studies	All studies			Two multicenter studies		
		SMR	95% CI	P-value	SMR	95% CI	P-value
All malignancies (140–208)	8	1.02	0.95–1.08	0.20 [b]	0.97	0.93–1.02	0.51 [b]
Liver (155)	6	4.95	2.32–10.56	0.00 [c]	2.96	2.00–4.39	0.02 [c]
Liver, except angiosarcoma of the liver	4	2.37	1.27–4.44	0.00 [c]	1.54	1.21–1.97	0.16 [b]
Lung (162)	5	0.90	0.75–1.08	0.05 [c]	0.88	0.76–1.02	0.08 [c]
Bone (170)	2	0	.		1.15	0.59–2.23	0.90 [b]
Soft tissue (171)	4	2.52	1.66–3.82	0.52 [b]	2.39	1.52–3.77	0.47 [b]
Skin (172–173)	3	1.20	0.86–1.68	0.02 [c]	1.18	0.84–1.66	0.01 [c]
Brain (191–192)	5	1.28	1.01–1.61	0.30 [b]	1.20	0.93–1.55	0.11 [b]
Thyroid (193)	2				1.34	0.59–3.04	0.97 [b]
Neoplasms of the lymphatic and hematopoietic systems (200–208)	6	1.61	0.96–2.70	0.00 [c]	0.90	0.76–1.06	0.61 [b]
Non-Hodgkin's lymphoma, myeloma (200, 202, 203)	3	1.31	0.71–2.41	0.00 [c]	0.92	0.73–1.15	0.58 [b]
Hodgkin's lymphoma (201)	2	0	.		0.74	0.33–1.67	0.20 [b]
Leukemia (204–208)	3	1.43	0.67–3.02	0.00 [c]	0.91	0.70–1.19	0.78 [b]

[a] Code of the ninth revision of the International Classification of diseases in parentheses.
[b] The meta-analysis was performed, using fixed effects modeling, when the P-value of the test for heterogeneity was ≥0.10.
[c] The meta-analysis was performed, using random effects modeling, when the P-value of the test for heterogeneity was ≤0.10.

among the VCM workers were re-evaluated, and misdiagnoses were looked for only in this group but not in the unexposed group, the general population. According to this line of reasoning, the soft-tissue sarcoma deaths that later turned out to be angiosarcomas should still be treated as soft-tissue sarcomas. However, in the general population, angiosarcoma is almost nonexistent, and this cancer can almost be regarded as specific for VCM exposure. Since the prevalence of angiosarcoma among VCM workers is much higher than in other populations, the chances of mistakenly diagnosing angiosarcoma for a soft-tissue sarcoma is much higher for VCM workers than for the general population and, for practical purposes, only exists for VCM workers. Given that this chance is much higher for VCM workers, there is the likelihood that a true relationship between VCM and angiosarcoma may result in a spurious association between VCM exposure and soft-tissue sarcoma. If the prevalence of angiosarcoma would have been similar for the VCM workers and the general population, we would have agreed with Boffetta et al, and we would have argued not to change the diagnoses from the soft-tissue sarcoma deaths to angiosarcoma, following a better inspection of the cases. However, in this case, with a very large difference in the prevalence of angiosarcoma between the VCM workers and the general population, it is imperative to use the most correct causes of death, in accordance with Bosetti et al (2). Nevertheless, it is very difficult to make any definitive statement in this respect. The collection of additional data on the histological cell type of these soft-tissue sarcomas could help clarify this matter. Furthermore, this matter could be investigated in more detail in, for example, a small nested case–control study on soft-tissue sarcomas in these two cohorts. To conclude, in many meta-analyses, heterogeneity can and should be investigated to increase the clinical relevance of the conclusions drawn and the scientific understanding of the studies reviewed (9). Therefore, exploring sources of heterogeneity, by means of meta-regression analyses, is recommended.

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