

~~TGG:~~ ~~JCL:~~ MMG: ~~AJO:~~ RF
XF: QSL

TO: Dick Conrad-LCVCM

FROM: T. G. Grumbles

DATE: July 27, 1989

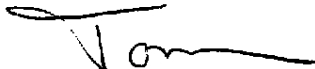
Interoffice
Communication

SUBJ: LITERATURE RESULTS OF BRAIN TUMORS AND VCM EXPOSURE STUDIES

VISTA

Attached is an example of what papers summarizing the literature say. In general, excesses have been seen but the excess is probably not significant, or in other words no more than the normal population.

These pages are from a "summary" paper that will go in the book. I think we want to put this type of paper first and direct their attention to them.


T. G. Grumbles

dlj

Attachment

VVV 000009422

CONCLUSION

Occupational exposure to concentrations of VC of the order of 1,000 ppm has caused the classical 'vinyl chloride illness'. Exposure to such levels, or perhaps lower levels of the order of several hundred ppm, has caused angiosarcoma of the liver after a latent period that is seldom less than 15 years.

→ The evidence now available from following up many thousands of men occupationally exposed to vinyl chloride suggests that a small risk of lung cancer may also have been produced, which must, however, have been substantially less (in absolute terms) than the risk of angiosarcoma of the liver. The balance of evidence does not support the idea that VC has caused cancer in any other organ, but it is impossible to state categorically that it has not. Clearer evidence, one way or the other, could be obtained if the various investigators would present their results in comparable forms that would allow them to be combined and subjected to the standard tests for an occupational hazard.

→ There is no evidence that exposure to VC has caused any other disease.

Suggestive evidence has been obtained that past levels of environmental pollution with vinyl chloride may have caused a few cases of cancer in the general public.

VVV 000009423

German and the Swedish studies derived the expected numbers of deaths from national mortality rates for a single year towards the end of the study period. The expected numbers of deaths are likely, therefore, to have been overestimated and the SMRs correspondingly underestimated as the mortality from lung cancer had been rising throughout the period of observation.

Brain Cancer

The idea that VC might cause brain cancer was suggested by Monson et al. (1974), when they reported 5 cases against 1.2 expected, in the same paper in which they suggested that VC might cause lung cancer. The combined data that are shown in Table 4 provide some support for this hypothesis. Monson et al.'s cases were, however, observed in US workers and must be presumed to be included in the total reported by Environmental Health Associates (1986), in which case they will have contributed a substantial proportion of the total in Table 4. To test the hypothesis we ought, therefore, to subtract Monson et al.'s data. Their study was not a cohort study and their expected deaths do not correspond exactly to those in Table 4; we can, however, only subtract both the observed and the expected cases from the present totals. This leaves 24 observed against approximately 18.3 expected, a difference which might easily occur by chance (P , one-tailed, = 0.1).*

Additional information from two other sources is given in Table 5.

The small excess reported provides little further evidence of an occupational hazard, as one of the two deaths observed in the Swedish study occurred in a young man who had been employed for less than a year when the diagnosis was made, while the excess death rate for brain cancer observed

*If we regard Waxweiler et al.'s (1976) study as the origin of the hypothesis we should be left with 26 deaths against 18.94 expected (P , one-tailed, = 0.07).

in the German study was less than that observed in chemical workers not exposed to vinyl chloride (2.9 deaths after allowance for deaths from unknown causes against 1.6 expected) and in workers in the PVC fabrication industry (5.9 deaths after allowance for deaths from unknown causes against 1.1 expected).

Cancers of Lymphatic and Haematopoietic Tissues

The idea that VC might cause cancer of the lymphatic and haematopoietic tissues - and more specifically the lymphatic tissue - was suggested by Tabershaw and Gaffey (1974) and by Waxweiler et al. (1976) when they found, respectively, in two cohort studies (i) 5 deaths from lymphomas in the most heavily exposed workers against 2.54 expected, and (ii) 4 deaths from cancers of the lymphatic and haematopoietic tissues against 2.5 expected. These small excesses might have been ignored if the laboratory findings had not been interpreted as suggesting that lymphomas were produced experimentally in animals exposed to vinyl chloride by inhalation (Maltoni and Lefemine, 1975). On this basis, the idea that similar exposure might also cause lymphomas in Man needed serious consideration. The data from the four principal studies that are summarized in Table 4 provide little support for the hypothesis when all cancers of the lymphatic and haematopoietic tissues are considered together (57 deaths against 50.87 expected, SMR 112) and very little more is obtained from the separate data for cancers of the lymphatic system (using Tabershaw and Gaffey's definition of ICD list numbers, 8th revision, 200-203 and 205) that are shown in Table 1 (35 deaths against 29.40 expected). The position is, moreover, hardly altered by subtracting the data in Tabershaw and Gaffey's initial report (29 deaths against 23.36 expected, SMR 124).

Some little additional information is provided by the results of the German study, some of which are shown in Table 5. This obtained an SMR of 214 for exposed workers (based on 15 observed deaths, increased to 16.5

absolutely almost as large as the risk of developing the normally very rare angiosarcoma.

One of the many hazards that have been suggested can be dismissed, as there is no evidence to support it: namely, the idea that VC causes any cancer of the digestive tract other than angiosarcoma of the liver. Two hazards (of melanoma and cancer of the thyroid) have been suggested only very recently and few of the available studies have provided information about them. There is no good theoretical reason or laboratory evidence to suggest that either should be produced by VC and, on present evidence, the simplest explanation is that the reported excesses are the chance effects that must be expected when many different types of cancer are studied in several different populations. So far as melanoma is concerned it has to be remembered that the disease has become much more common in recent years in Scandinavia (where the excess has been reported) due, it is believed, to the popularity of sunbathing and the increased opportunities for Scandinavians to travel to the warmer parts of Southern Europe and North Africa. The extent to which this may have affected the observation in Norway needs to be examined.

Two other hazards (of lymphoma and of brain cancer) were suggested by the early results of some of the American studies. That VC might produce a hazard of lymphoma was initially supported by the preliminary results of animal studies, but the complete results of the many studies that have now been undertaken (see Maltoni and Lefemine, 1984) do not suggest that lymphoma or any other cancer of the haematopoietic system is liable to be produced. There is, however, some evidence that brain tumours can be produced in rats (see Maltoni and Lefemine, 1984). The hypotheses that lymphomas and brain cancers might be produced by VC have been supported by the observation that both these types of cancer have caused death more often than might be expected from national mortality rates, but the

excesses observed in the combined data from the four principal studies are small and not statistically significant and the hypotheses remain unproven. The small excess of brain cancer is particularly difficult to evaluate as mortality rates from this disease have changed rapidly over time in company with improved methods of diagnosis and the suspicion of an occupational hazard (which was raised in 1975) could have influenced the findings. What excess has occurred has been limited to the USA and Germany and the German findings carry little weight, as the excess was found in each of the three occupational groups studied, irrespective of the chemicals to which they were exposed. The supplementary data from the German study showing an increased mortality from lymphatic and haematopoietic cancers are more impressive, particularly as the excess was most marked for men who had been employed for at least 5 years. In these circumstances, we must still suspend judgment until the data for each study are analysed for each specific type of cancer, by intensity and duration of exposure, and time since exposure began.

There remains the suggestion that VC might cause lung cancer. At first sight, this is ruled out by the SMR of 97 for the combined data for respiratory cancer for the four principal studies. Lung cancer is, however, normally so common (accounting for about 8% of the expected deaths) that an increase in mortality that was half as important (numerically) as the mortality from angiosarcoma of the liver might easily be overlooked (95% confidence limit of the SMR, 85-112). The incidence of the disease is moreover very variable within a country and there must be doubts whether the national experience provides a suitable control for men employed in plants that are not evenly distributed about the country. In these circumstances we cannot exclude an occupational hazard unless it can be shown that the mortality within the exposed men is independent of the factors that might be expected to influence it, if some of it were