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Dear Has:

At the January 27 meeting of the Vinyl Chloride Panel (or at least of those hardy members who braved the weather to get there) there was general agreement that if any further analysis of the results of the recent EHA study were to be done, it should consist of a pathology review of the deaths coded to liver and biliary cancer rather than of a case-control study of those deaths or of the emphysema deaths.

In the case of the emphysema deaths, the observed excess was not related to the circumstances of exposure in such a way as to be consistent with vinyl chloride exposure as an explanation. We know that the surrogate measures of vinyl chloride exposure are pretty good because they are associated with deaths from angiosarcoma. Therefore the lack of association with emphysema mortality means either that the excess was a statistical anomaly or was associated with some other exposure. In addition, no other studies have shown such an excess. This means that there is no reason to analyze the emphysema deaths further.

On the other hand, there was a statistically significant excess mortality from liver and biliary cancer, not stated to be angiosarcoma on the death certificates, which increased with duration of exposure and showed some signs of increase with latency of exposure. The most plausible explanations appear to be either that vinyl chloride causes liver and biliary cancers other than angiosarcoma, or that the excess is due to angiosarcomas that were misdiagnosed as other liver and biliary cancers.

There is no way in which a case-control study based on the death certificate cause could resolve this issue. From the results of the EHA study it is obvious that a case-control study would show that the cases had more vinyl chloride exposure that the controls. No matter what else the case-control study found, it would therefore not eliminate either of the two possibilities mentioned above. Suppose, for example, that a careful review showed the angiosarcomas to have had a greater exposure than the other liver

and biliary cancers. An impartial observer would be justified in conjecturing that low exposure caused the other liver and biliary cancers and that high exposures caused them to develop into angiosarcomas. If the reverse were found, the reverse conjecture would be tenable (although weak).

In either case, the only resolution would be to determine whether or not the other liver and biliary cancers contained enough misdiagnosed angiosarcoma to account for the outcome, in other words, to do a pathology review. However, if that were done there would be no reason that I can see to do a case-control study. All that would be necessary would be to subtract all of the known angiosarcomas (after the pathology review) from the observed liver and biliary cancers and to recalculate the SMRs. Since angiosarcoma is so rare in the general population, the changes in the expected values could be ignored. In any event, doing a pathology review does not preclude doing a case-control study at some later date, if there appears to be some reason for doing so.

There are 37 deaths from liver and biliary cancer in the EHA study 15 of which are stated on the death certificate to be due to angiosarcoma. It would be prudent to have the histology of all 37 deaths reviewed, because if that were not done, we would be accepting some deaths as angiosarcomas on the basis of histology and others on the basis of the death certificate statement.

It is not likely that adequate histology will be available for all of the cases. Even so, the results could be informative. If a substantial percentage of the apparent liver and biliary deaths for which data are available turn out to be angiosarcomas, the conjecture that vinyl chloride causes other liver and biliary cancers is weakened. On the other hand, if none of them is an angiosarcoma the conjecture is strengthened. Finally, if this kind of review is not attempted, we will have left unexplored a line of investigation that might resolve the question.

Although I have used my own words and interpolated some of my own reasoning, I believe the above correctly states the conclusions of the group and summarizes the spirit of their reasoning.

Yours sincerely,

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