UNIVERSITY OF WASHINGTON

*School of Public Health and Community Medicine*
*Department of Environmental Health, Box 357234*
SEATTLE, WASHINGTON 98195-7234

Tel.(206)543-2052
Fax(206)685-3990

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Kenneth Mundt, Ph.D.
Applied Epidemiology, Inc.
P.O. Box 2424
Amherst, MA 01004

RE: "Protocol for CMA Vinyl Chloride Mortality Study"

Dear Dr. Mundt:

I have reviewed the protocol and have some comments and suggestions for finalizing the protocol.

General Comments

The study objectives and procedures are very clearly presented, following accepted epidemiologic methods. The proposed update of the Wong study should, by virtue of a longer follow-up and additional deaths, provide much needed information about potential hazards related to VCM and other chemicals in this industry. It seems evident that your group has given an appropriate level of attention to issues of data quality and completeness, which will certainly be necessary for producing a valid study.

The approach to the data analysis, basically SMR comparisons against external rates as an initial screening for effect estimates, followed by in-depth analyses relying on internal risk comparisons, is sensible. This is standard practice in such studies, and usually provides an adequate characterization of mortality risks.

The main areas that could use further clarification in the protocol concern the amount and detail of exposure information, and how these data will be incorporated into the analysis. In particular, the description of the original Wong study indicates that a fairly crude exposure classification system (exposed vs. not exposed) was adopted. As correctly mentioned, this scheme is only minimally applicable for estimating dose-response relations (more specific comments on this issue will follow). I think it would be of considerable value to append to the proposal a copy of the most recent Wong report to permit a comparisons of existing knowledge with what should be obtained from the update. The proposal would also benefit from some description (brief) of the plants and the study populations to orient uninitiated readers. There is a listing of boxes of study materials provided by ENSR, but the meaning of this obscure to me.

There is some passing reference to the desirability of performing nested case-control studies for diseases of prior concern (e.g., liver cancer) and other diseases for which consistent excesses are seen. More should be said about how this would proceed, i.e., how diseases for case-control studies would be selected, control sampling strategies, collection of additional data (e.g., industrial hygiene data, smoking), if this is envisioned.

On balance, this is a well formulated proposal that outlines the plans for what should be a scientifically valid investigation.

Specific Comments and Suggestions

1. A considerable effort will be given to the construction of external reference rates, apart from those currently available by standard lifetable programs (e.g., Marsh). Is this effort really necessary? The University of Pittsburgh can provide state- and county-specific mortality rates that are useful; that has been my experience.

2. Unknown race my pose a problem for some diseases. Is this the case for brain cancer or liver cancer?

3. As mentioned earlier, the quality of the exposure data will be a critical determinant of the study's ultimate value. The dichotomous classification and subjective rating schemes used previously do not appear to be rigorous enough for meaningful dose-response estimation. It might be worth including a feasibility study to determine the availability and quality of historical exposure data that could be exploited, perhaps in subsequent nested case-control studies. It is likely that exposure information is generally sparse, but there may be some plants among the 37 included in the study that have reasonably good data. If this were true, then subcohort analyses of these plants might be explored.

4. The diagnoses of liver and brain cancer from death certificates may be uncertain (e.g., confusion with metastatic cancers of other primary sites). The possibility of diagnostic errors will need to be addressed.

5. Some planning for nested case-control or case-cohort studies would improve the study, even if the planning were limited to a determination of feasibility.

6. The discussion of statistical power (p20) is not especially enlightening. The study needs to be done; thus, whatever power might be attained is really a moot point.

7. If intense VCM exposures are neurotoxic, then there may be a healthy worker survivor effect that could attenuate observed associations. This might be mentioned, although analytic methods to rectify the problem are very complex and may not yield interpretable results in the absence of quantitative exposure data.

8. Other analytic features that could be considered are induction/latency analyses (exposure lagging and time windows), and stratification of person-time by actively employed status.

I hope that these comments are clear and useful. Please do not hesitate to contact me if you need clarification of these remarks or additional comments.

Sincerely yours,

Harvey Checkoway

Harvey Checkoway, Ph.D.
Professor of Environmental Health
and Epidemiology