APPLIED EPIDEMIOLOGY INC.

July 30, 1997

Dr. Hasmukh Shah
Manager, Vinyl Chloride Panel
Chemical Manufacturers Association
1300 Wilson Boulevard
Arlington, VA 22209

Reference: Tamburro Protocol

Dear Dr. Shah:

As requested, I have reviewed Dr. Tamburro's protocol for the study, "Brain Cancer Occurrence in Vinyl Chloride Exposed Chemical Workers." My comments follow.

1. GEP's: First, it is evident in this latest version of the protocol that the ERIC Guidelines for Good Epidemiology Practices (GEP's) were taken into consideration. All key protocol elements are addressed to some extent.

2. Abstract: The background material does not state that the cohort studied by Tabershaw and Gaffey (1974) later updated by Tabershaw (1975) and Wong (1991) *included* a substantial part of the cohort proposed for this investigation. Thus, the proposed study is not an independent investigation on a "new" population, but a more detailed pursuit of an ongoing hypothesis. Logically, then, the methodology should be described in a different order: confirmation of the excess brain cancer mortality using standardized mortality analysis; case-control investigation of the brain cancer cases using the Greenberg-Tamburro method; and then confirmatory logistic regression, if necessary.

3. Study Tasks and Milestones: Tasks generally appear reasonable (except for the Protocol Development, which was not completed in a comprehensive and timely fashion, leading to significant delays in defining the study methodology), except that many imply a cohort design. In other words, updating the entire database for a case-control study is inefficient in that data on large numbers of individuals will be sought and incorporated into the cohort database, but not necessarily used in the analysis. The beauty of the case-control design is that only the cases and a finite sample of controls is required for the detailed analysis, and for this reduced study group more effort may be exerted in capturing important exposure and confounding factor information.

Several tasks state that interim reports will be prepared. A timetable for submission of these reports is needed.

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Comments about specific tasks:

Under Task 4, and elsewhere, 22 chemicals are mentioned. Here, and in other places, reference to any chemicals other than VCM should be deleted, and the focus of the study on VCM exposure should be made clear, as the purpose of the present investigation is to elucidate the possible role of VCM exposure on brain cancer risk. Although the Appendices need not be modified, the 14 pages of formal protocol text should contain no reference to any chemical other than VCM. Furthermore, the report to be produced for CMA should also be limited to the VCM focus.

Task 6 does not mention how deaths will be ascertained. At our last meeting in Louisville, we discussed strategies for identifying deaths more comprehensively.

Is it necessary (as in Task 7) to pathologically confirm cancers other than brain cancers and possibly those mis-diagnosed as cancer of some other site? For example, would a colon or prostate cancer require histological confirmation for a case-control study of brain cancer?

4. Research Objectives, Aims and Rationale: This section is clear overall. Specific Aim 3 suggests that a "case controlled" study will be conducted for each case, rather than the conventional terminology "a case-control study will be conducted using all histologically-confirmed brain cancer cases and a sample of matched controls." Specific Aim 4 should be deleted.

5. Review of the Relevant Literature: This section is adequate.

6. Research Methods: Under "Cohort Description" it is not stated whether the 3330 individuals constitute a *comprehensive* enumeration of the cohort of all employees working at least one year between 1942 and 1995, or if they are simply all those for which some information has been obtained. For those in the database, the data available appears substantial.

Although industrial hygiene monitoring data appear to be available, it is not clear from the protocol if and how these data will be used in the analyses. Retrospective exposure assessment constitutes one of the most difficult aspects of an epidemiological investigation, and should be clearly defined. Will exposure measures for cases be compared with those of controls? Later it is stated that CERM's will be translated into ppm exposures. What if some cases or controls have no measures? Are area exposure values to be summarized into a job exposure matrix?

Under "Data Sources" (note that many data sources are described in the two paragraphs preceding this section), it is stated that employee vital status was identified through the National Death Index. Was the NDI truly used? I do not recall any previous mention, although there has been some discussion of whether Applied Epidemiology, Inc. might be able to share NDI results with the University of Louisville (NDI will not allow such transfers).

7. Methods of Data Analysis: The description of the Greenberg-Tamburro method is largely redundant with the cited paper. How the methodology is to be applied to the current study is not well

described. More disappointingly, the several improvements to the method (addressing such problems as lagging of exposure to account for latency, appropriateness of cumulative exposure as a sole metric, the non-independence of the 22 chemicals, and the specificity of the potential brain cancer / VCM relationship vs. the specificity of the angiosarcoma of the liver / VCM relationship) discussed by Dr. Buncher (biostatistical consultant to the project) and myself do not appear in the protocol. I suggest that Dr. Buncher be asked to review and revise the relevant analysis sections so that they more accurately reflect these improvements.

Choice of the Cuzik logistic regression approach implies that the ranking of exposure will be maintained. While this appears appropriate, I would also like to see a range of analyses breaking from the CERM approach, as indicated under the SMR analysis. However, logistic regression is not an appropriate method to confirm an excess discovered through analysis of a cohort; rather, the logistic regression is intended to elucidate the relationship between brain cancer and several potential risk factors. Foremost among the risk factors of interest are various characterizations of the VCM exposure.

How the SMR analysis will be performed is not described. Although straightforward, the methodology can be cumbersome, especially since there are few standard programs available for such analyses.

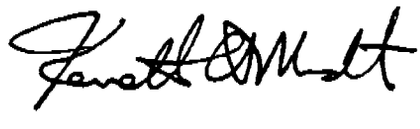
No consideration of statistical power, given the current estimate of 10-12 cases, is provided.

8. Additional general comments: A revised time table would be helpful, indicating dates of milestones and interim reports.

A more detailed section discussing the rationale for a case-control approach (vs. analysis of the database as a cohort study) might help the investigators understand the specific strengths, weaknesses, advantages and disadvantages of this approach. Currently, given the tremendous efforts being put into the cohort database, I do not see the particular advantage of the case-control approach except to apply the Greenberg-Tamburro analytic method. Full use of exposure and confounder data is encouraged through the use of conventional case-control methodology, which may serve to validate the Greenberg-Tamburro method as well as contribute to an enhanced understanding of the possible VCM / brain cancer relationship.

I hope that these comments are helpful. Please call if you have any questions or comments, or require further information. Thank you.

Sincerely yours,



Kenneth A. Mundt, Ph.D.