APPLIED EPIDEMIOLOGY INC.

TO: Drs. Hasmukh Shah and Jonathan Ramlow

FROM: Kenneth A. Mundt, Ph.D.

DATE: April 14, 1997

RE: University of Louisville Case-Control Study on Vinyl Chloride Exposure and Brain Cancer

Following are several thoughts on what we might seek to accomplish with Dr. Tamburro and his team in Louisville on April 18, 1997.

1. To date, we have not seen a detailed protocol which clearly addresses all the items specified in CMA's Guidelines for Good Epidemiological Practices (GEP). At our last meeting, Dr. Tamburro suggested that he will prepare a more complete study protocol after the upcoming meeting, so that he may incorporate appropriate ideas from our discussions.

Suggested Action: Establish a time line for preparation, review and approval of the final protocol. Peer review and sign-off should take place as soon as possible.

2. Additional elements of the GEP's should be addressed, including quality control (which is apparently quite high with regard to the database), standard operating procedures, various review mechanisms, etc.

Suggested Action: Review the GEP's in detail to identify specific areas to be addressed.

3. Several of the external reviewers' comments are still germane, and have not been appropriately addressed. Some of these points should be addressed directly in the revised protocol. For those determined to be inappropriate or for which a decision is made not to incorporate suggested changes, an explanation should be made in a separate memorandum. This memorandum should accompany the protocol when re-submitted to the reviewers.

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Suggested Action: Request that Dr. Tamburro prepare individual responses to the points raised by the external reviewers, Drs. Checkoway and Marsh, and incorporate any that are determined to be appropriate directly in the protocol. A time line for this action should be established.

4. One of the main concerns of the reviewers (as well as Dr. Ramlow and myself) is that the proposed statistical methodology (Greenberg/Tamburro method) may not be adequate to reveal an association between brain cancer and VCM/PVC, should one exist. Part of this concern stems from the small anticipated sample size, leading to low statistical power, and part from the lack of documentation of the performance of these techniques outside of extremely strong and highly specific associations (such as VCM and angiosarcoma of the liver).

Suggested Action: Discuss extending the proposed analytical methodology to include classical case-control analyses (logistic regression) in parallel with the proposed approach. Statistical power will remain a problem. Perhaps estimates of power should be determined for each analytical approach to enhance the interpretation of the study results.

5. A less tangible concern about the study is whether it will be seen as credible by the scientific community. On the other hand, the study has been developed as a case-control study *nested* in a larger cohort; however, primary assessment of the cohort giving rise to the cases apparently has not occurred. For example, does the set of cases proposed for the case-control study represent an excess of such cancer cases (deaths)? Are there other patterns of specific causes of death which might help us understand the context in which the brain cases were identified (e.g., a marked deficit of cardiovascular disease deaths)? In many ways, the surveillance database constructed by Dr. Tamburro and his team is impressive, and much of its value will not be realized in the current case-control effort.

Suggested Action: Evaluate the role this case-control study plays in the context of the broader research objectives being pursued by this team, with the aim of enhancing the total package. If the case-control study is perceived by the scientific community as a preliminary strategy for assessing the potential risk of interest, what next steps might be considered? Linking it with other planned analyses/studies might help capitalize on this unseen value. Perhaps conducting a proper cohort analysis first or in parallel would be informative.