APPLIED EPIDEMIOLOGY INC.

April 30, 1997

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

Reference: Tamburro Study

Dear Dr. Shah:

As requested, I have assembled below some notes from our April 18, 1997 meeting with Carlo Tamburro and his staff in Louisville, Kentucky.

1. The meeting opened with introductions. Present were Carlo Tamburro, Ralph Buncher, Philip Fortwengler, Stephen Looney, Greg Rempala, Karl Hall, Jonathan Ramlow, Has Shah and Ken Mundt.

2. Carlo proposed a series of discussion topics: review the original study objectives; discuss the Greemberg-Tamburro (G-T) method; confirmation of brain cancer cases; and comparison of case and control work histories.

3. Jonathan requested that we review the agenda prepared by Has, and suggested that the group begin with item 4.0, discussion of the G-T method.

4. Carlo proposed that a brief update of the progress to date (item 2.0) would benefit the group. Handouts were distributed, including tables on work history accounting, BFG death accounting and case verification. As two pages of the handout contained personal identifiers, these were returned to Phil before the end of the meeting. According to the first page of the handout, there are 3330 employees on roster, including 505 active employees and 69 inactive with missing dates of separation. Work history is available for 3291 cohort members.

CMA 121195

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To date, 768 deaths have been identified among the cohort, 144 with cause unknown. Ken agreed that if Phil submitted a list of those with unknown cause of death and who are also in the Applied

Epidemiology, Inc. study, AEI would review this list for any indication of additional brain cancer deaths. Should any be found, Has would request permission from Robert Bilgrad of NDI to transfer the death certificates to University of Louisville for these brain cancer deaths.

To date, 10 brain cancer deaths have been identified and confirmed, including six glioblastomas, two astrocytomas, one posterior fossa and one tumor (not specified).

5. The G-T method was discussed. Carlo read a statement (transcription of a phone conversation) from Richard Greenberg indicating that the power of the G-T method should be no less than that of more conventional analytical approaches. This, however, was not a relevant concern; rather, identifying the power of any analytical approach used would be important for a negative study, including one using the G-T method. Steve noted that a power algorithm could be developed, and cited a paper published by Jack Cuzick in *Biometrics* (1985;41:609-621).

6. Next, a plan for the analysis of the study database was discussed. Clearly, the G-T method would be used, as well as conventional methods such as logistic regression to the extent possible. In addition, Jonathan and Ken recommended, and Ralph concurred, that a basic cohort analysis (SMR) would improve the overall value of the case-control analyses. Optionally, a Cox Proportional Hazards analysis might be considered if appropriate. Ken suggested that AIE might perform the basic SMR analyses if Carlo and Phil do not already have this capacity, but this would need to be discussed further.

7. Ken raised several points which need to be considered in the G-T analysis, including the role of latency and the appropriate risk periods; the total dependency on a cumulative exposure model in the presence of possible threshold phenomena; the clear non-independence of the various exposures proposed as possible risk factors for brain cancer; and the possibly lower specificity (than VCM and angiosarcoma of the liver) in the relationship between VCM and brain cancers. Ralph, Jonathan and Ken discussed several strategies for overcoming these problems in the application of the G-T method.

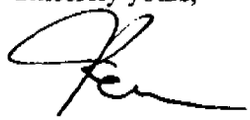
8. Ralph raised two additional concerns regarding the G-T method: the possibility of over-matching (as originally posed by the peer-reviewers) and the reduced range of cumulative rank months assigned over time, especially in time periods since the reduction of exposure in 1974. Tentative solutions were discussed; however, no final resolution was reached.

9. Discussion turned to the protocol. Some changes/updates have been made by Carlo, but revision of the analytical plan was delayed so that it might benefit from this meeting. Level of detail and scope required were discussed, and Carlo agreed to submit a revised version for CMA and external peer-review within 60 days.

10. Review of the expert reviewers comments suggested that all points could now be addressed, and the revised protocol will reflect this. Courtesy copies of the protocol will be sent to the reviewers; however, no formal comments will be solicited.

I hope that this is helpful. Please call if you have any questions or comments.

Sincerely yours,



Kenneth A. Mundt, Ph.D.

Carl Hall - Univ. of Louisville
Carlo Tamburo Has Shah Greg Rempala
Ralph Buncher Ken Mundt 4/15/97
Phil Fortwengler Jonathan Ramlow Univ of Louisville, KE
Steve Looney

Lay out sequence of analysis when all data are collected.

Objective of the Carlo Tamburo study.
Determine whether an association exist between VC exposure and brain cancers.

Based on current data there may be all brain cancers cases the study cohort.

Carlo will send information on 144 cases of unknown causes to Ken to see if there are any brain cancers in those 144 unknown causes. Ken will respond as appropriate being cognizent of state confidentiality provisions.

Methodology for Data Analysis

Greenberg Methodology
SMR analysis comparing to U.S. and State SMRs.
Logistic Regression/odds ratio analysis

Ken discussed his concerns about use of Greenberg methodology in analyzing data on BFG cohort.

1) Latency
2) Cumulative Exposure
3) Independent of Exp.
4) Specificity

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Ralph expressed concern about over matching

Publication of final study results would describe different analytical methodology.

Carlo will revise the protocol based on comments received for ~~appl~~ in one month. comments by Ken & Jonathan h The final protocol will be sent to Harvey Checkoway and Gary Marsh, Thanking them for Their earlier comments and request additional comments that They may have.