

UNIVERSITY of LOUISVILLE

January 13, 1998

Hasmukh C. Shah, Ph.D.
Managing Director
ChemStar Panels
Chemical Manufacturing Association
1300 Wilson Boulevard
Arlington, VA 22209

Dear Has:

I'd like to reiterate the original reason for the submission of our investigative protocol. To the present time, there has been no epidemiological study showing a causal relationship between brain cancer and vinyl chloride. All previous epidemiological studies and their repeated updates have, at best, shown a small increased SMR suggesting that an association between vinyl chloride and brain cancer may exist. None of these cited associations were strong enough to support a causal relationship. Many other studies reported negative findings.

The standard epidemiological approach has been and continues to be inadequate due to the small numbers of brain cancer cases, the lack of disease verification, and the absence of accurate exposure data. The use of the standard SMR analysis requires large population sizes and high disease occurrence in order to show any association. This approach is again being used by Dr. Mundt to update the original vinyl chloride worker cohort. To follow Dr. Mundt's analytic suggestion would be to duplicate his present work on a smaller cohort. This would not fulfill what was originally requested of us.

Our submitted proposal was requested so as to allow the application of Dr. Greenberg's unique nonparametric approach to determine if any causal relationships exist between vinyl chloride exposure and the small number of brain cancer cases in our well-characterized cohort. An inherent part of this proposal agreement was to further validate the ability of the Greenberg method to accomplish the same type of assessment for brain cancer as it had done for liver angiosarcoma and to also provide a comparison to the standard epidemiology methods of analysis.

We realize that the proposal was originally submitted without knowledge of the new CMA guidelines recently instituted regarding grant proposal structure and approach. We've made a very strong effort to meet those standards even though the changes are being done retrospectively and require some proposal structure remodeling. This has been done adequately to make clear our approach, in an *a priori* fashion, so that anyone reading this later would clearly understand that we had followed our original plan.

The reviewers comment regarding our literary style at this point is not substantive to the scientific capability or the biological plausibility of the approach we propose.

External reviewers like Dr. Ralph Buncher at the University of Cincinnati, Dr. Arthur Frank at the University of Texas, Dr. Leonard Goldstein at Robert Wood Johnson Medical School and the Institute of Environmental Health Sciences, have all visited our institution, spent two or more days reviewing this methodology and have been fully supportive of our efforts.

I have expressed my views in this separate letter, and entitling it *Confidential*, to prevent a conflict over style rather than substance. I believe the revisions made address the substantive concerns regarding chemical identification, etc., and have sufficiently met the guidelines set forth by the CMA. Thank you for all your help and patience in this difficult process.

Kind regards,



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Professor of Pharmacology & Toxicology
Director, Liver Research Center & Lab

CHT:mam

P.S. As an update, I have enclosed a draft of our manuscript on the power statistic for Dr. Greenberg's rank test. Its submission for publication is awaiting Drs. Greenberg and Buncher's comments.