THE UNIVERSITY OF NORTH CAROLINA
AT
CHAPEL HILL

The School of Public Health
Department of
Environmental Sciences and Engineering

The University of North Carolina at Chapel Hill
CB# 7400, Rosenau Hall
Chapel Hill, N.C. 27599-7400

October 19, 1994

Dr. Hasmukh C. Shah
Manager, Vinyl Chloride Panel
Chemical Manufacturers Association
2501 M Street, NW
Washington, D.C. 20037

Dear Dr. Shah:

I enjoyed seeing you at the CIIT Open House last week. This letter is a follow up to our conversation regarding the discussions that the Vinyl Chloride Panel held following our visit to the EPA. I would be interested in working with you on some of the issues that are still of concern such as determining the $T_{1/2}$ of the ethenoguanine DNA adduct (EG), and quantitating the amount of the methyl purine DNA glycosylase (MPG) and P450 2E1 in tissues of humans of different ages.

only 1 adduct ?

We discussed the approach that I would use to determine the $T_{1/2}$ of EG. This would require the synthesis of [$^{13}C_2$]-vinyl chloride. I would then expose groups of 3-4 rats using the closed chamber technique to the stable isotope and sacrifice them at different times (0, 4, 12, and 24 hours) after a 6 hour exposure to ~1000 ppm VC. This would be repeated several times to determine the average $T_{1/2}$ of EG using our GC/ high resolution MS methodology. Dr. Johannes Filser will visit me next week and I plan on discussing the details of the animal exposure with him, as he is an expert in the closed chamber technique.

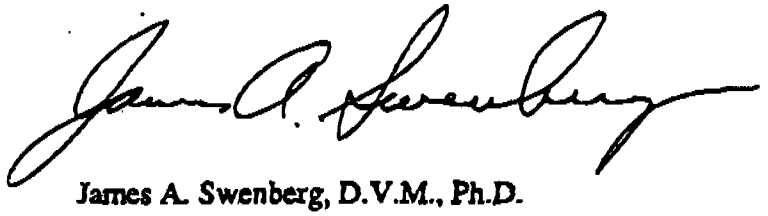
We are just setting up a quantitative polymerase chain reaction (PCR) method for measuring the expression of the MPG DNA repair protein. We plan to evaluate age differences in rats and mice under our Superfund Basic Research Program proposal, providing it gets funded. What I hadn't considered until I met with the VC Panel was doing this in human tissues of different ages. This may require slight adjustments in methodology and the synthesis of different primers. I believ that I can obtain human tissues from various tissue banks such as Vanderbilt University and the University of

Maryland. It may also be possible to get them from UNC and Duke. You indicated a desire to also examine P450 2E1 expression in similar tissue. I would probably ask Dr. Fred Guengerich to collaborate on this aspect. He has all of the methods in place and could use the same tissue specimens that we use for MPG.

These studies would be modest in size and scope, but should provide very important information relevant to human risks associated with vinyl chloride exposure. The direct cost of this research would be ~ $50,000 per year for two years, with half of this for the DNA adduct studies, 35% for the MPG determinations and 15% for the P450 2E1 studies. If this is handled as a grant to the university, there would be 44.5% overhead charged on the direct costs. If it is provided as a gift, there is no overhead. If a grant is desired, I will need to submit a research proposal and budget for university approval.

I hope this provides enough information for your next year's budget meeting. We can obviously increase or decrease the effort if this is deemed to little or to great. Please let me know what the Panel decides. Thank you again for your interest in our research.

Sincerely,



James A. Swenberg, D.V.M., Ph.D.
Director, Curriculum in Toxicology
Professor, Environmental Sciences and
Engineering, and Pathology