ITEM 1

UNIVERSITY OF LOUISVILLE
LOUISVILLE, KENTUCKY 40202

SCHOOL OF MEDICINE
DEPARTMENT OF MEDICINE
DIGESTIVE DISEASES AND NUTRITION SECTION

HEALTH SCIENCE CENTER
WALNUT & PRESTON STREETS

April 20, 1976

Dr. T. R. Torkelson
Dow Chemical Company
Corporate Medical Department
2030 Dow Center
Midland, Michigan 48640

Dear Doctor Torkelson:

May I express our delight in having had members of the Manufacturing Chemists Association Research Committee visit us earlier this month; we hope that their visit was both enjoyable and informative. Our post-luncheon meeting helped to clarify a number of points concerning our Manufacturing Chemists Association Grant proposal and I would like to take this opportunity to submit for the members consideration a modification of our original proposal in light of the expressed interests of the members of the research committee.

Since the members expressed interest in supporting proposals A and G, having to do with the study of immunological systems, it seems that these would require no further elaboration or adjustment. My understanding is that the same would be true for proposal G, concerning electron microscopic evaluation of liver tissue. What I would like to do here is (a) amplify on the immediate clinical applicability of some of the other proposals presented, (b) provide a modified budget for these proposals and (c) suggest that if cuts must be made in the program, the cuts that would be least damaging in terms of ongoing efforts and in terms of a cohesiveness of the overall research program, would be the proposals by Dr. Hoffman (H) and Dr. Sigdestad (1) and parts of Drs. Du (B2 B5 B6 B7) and Wong (E2) (see revised budget attached). Firstly, proposal C concerning the glycosaminoglycans in the early detection and etiology of angiosarcoma of the liver presented by Dr. Charles E. Kupchella: this has already produced significant results. Most chemical injury and cancer appear to be associated with "scar" or collagen formation. This collagen formation is associated with the increased production of glycosaminoglycans. Dr. Kupchella's preliminary study indicates that there is a characteristic pattern of glycosaminoglycan urinary excretion among long-term vinyl-chloride-exposed individuals not seen in individuals with alcoholic liver injury, hepatitis, and cancers not directly involving the liver. These urinary excretion patterns appear to change as one develops primary liver cancer such as angiosarcoma. At this point, the findings reported by Dr. Kupchella at the Third

International Symposium on the Detection and Prevention of Cancer, require additional verification and modifications of this method for use as spot urine testing in large worker population. If future studies continue to verify our present finding, i.e. that this test is indicative of early vinyl chloride injury, it could be applicable throughout the industry where chemically induced fibrosis may occur. This proposal could yield a sensitive, simple and inexpensive means of surveillance for early liver injury. A copy of the paper to be presented in New York is enclosed.

Concerning the proposal by Dr. Wong, and the related proposal by Dr. Streips; I would like to elucidate on the value of this work in determining and directing priorities as to which metabolite should be studied for their potential carcinogenicity. Dr. Wong's ability to synthesize metabolic products of various chemicals allows immediate mutagenic bacterial studies for the identification of those chemicals with greatest carcinogenic capability. In order to control costs and increase benefits for the amount of time and money invested, these mutagenic studies must be performed in order to realistically develop strategies for blocking the etiologic chemical changes leading to the initiation of angiosarcoma. Considering the overall complexity of studies of this sort, we feel that the combined work of Drs. Wong and Streips provides a reasonably straight forward approach to unravelling sequences leading to angiosarcoma.

In addition, Dr. Wong's work will develop a method of detecting trace amounts of chemicals and their metabolic products by use of multivarient analysis in biological tissue. Our present system of storing bloods, urines, and tissue on all workers in the medical surveillance program gives us the equivalent of an immediate clinical trial in a carefully observed worker population with known exposure. This procedure could give us an applicable test system within three years.

Finally, Dr. Du's work will make use of animal studies in determining the most specific and earliest enzymatic and biochemical alterations produced by chemical exposure. Although some have expressed the view that biochemical alterations have all been identified and worked out, our clinical experience indicates the need for studies which will objectively determine which screening methods should be applied and to which of the exposed industrial population. The animal studies proposed by Dr. Du will allow us to apply these methods under controlled conditions of exposure, dose and duration, providing useful information in just a few years. This will be far more efficient means of determining the best screening methods to employ based on hard scientific data rather than clinical opinion.

Simultaneously, Dr. Wong will utilize these same animal tissues for verifying the sensitivity and specificity of the multivarient analysis system for trace organic element detection in biological tissue. The detection of a trace product does not by itself prove a causal relationship nor indicate recent or past exposure. Therefore, it is vital that these studies be done (simultaneously with the studies for sensitivity and specificity) for verification of the relationship of detection to cause of injury. This information will greatly help in the interpretation of our findings from our stored human blood, urine and tissue samples.

We would like to again point out the importance of our being able to continue to pursue this multidisciplinary research approach in the study of the vinyl chloride problem. By addressing the vinyl chloride problem as a model and in this systematic manner we feel that this unique combination of investigations will go far toward providing understanding chemical carcinogenesis in general and the etiology of angiosarcoma. Our program can be left essentially intact with the attached budget. The work proposed, we feel, is clearly defined and should produce positive results well in excess of investment. In addition, we would also like to point out that funding of such a program will sharpen our overall skills and further develop this approach applicability to other chemicals and in other situations. I believe that the budget proposed is well within the desirability and capability of the Manufacturing Chemists Association's constituency. In essence, we are asking the vinyl chloride industry to support the program at somewhat less than a level that has been supported by the B.F. Goodrich Company alone for the past two years.

Thank you for your serious consideration.

Sincerely yours,

Carlo H. Tamburro

Carlo H. Tamburro, M.D.
Associate Professor of Medicine
Chief, Digestive Diseases & Nutrition Section

CHT:mma
Enclosures

cc: Dr. Zeb G. Bell, Jr.
Dr. Walter D. Harris
Dr. Maury Johnson
Mr. Howard L. Kusnetz
Dr. W.E. Rinehart
Dr. W. Mayo Smith
Mr. R.N. Wheeler

REVISED BUDGET
UNIVERSITY OF LOUISVILLE
RESEARCH PROPOSAL

RESEARCH TECHNIQUES AND METHODS FOR DETECTION AND PREVENTION OF CARCINOGENESIS IN INDUSTRIAL WORKERS

This revised budget is for proposals A1-4, G, D, C, E1, B3-4, and F, all of which have the most clinical applicability. We have excluded proposals B1, B2, B5, B6, B7, E2, H, and I.

INDIVIDUAL BUDGETS

Proposal	Title	Investigator	Personnel Budget	Supplies	Total
A 1-4	Immunological Systems for the Detection of Vinyl Chloride and Other Chemical Injury	P. Fortwengler	34,100	16,795	50,895
G	Tissue Antigenic Systems of Detection	E. Espinosa	9,000	5,000	14,000
D	Electron Microscopic Evaluation of Liver Tissue from Chemical Workers	R. Schrodt		7,000	7,000
C	Tissue and Urinary Acid Mucopolysaccharide Changes Related to Vinyl Chloride Injury: Use In Early Detection and Diagnosis	C. Kupchella	8,000	7,500	15,500
E 1	Multivarient Analysis of Biological End Products and Biochemicals to Document Chemical Exposure for Early Diagnosis	J. Wong	10,000	15,000	25,000
B 3 & 4	Biochemical Enzymatic Systems for Detection of Vinyl Chloride and Other Chemicals	J. Du	27,000	7,332	34,332
F	Assays for Identification of the Carcinogenic Potential of Industrial Chemicals	U. Streips	12,000	11,000	23,000
		Subtotals	100,100	69,627	169,727
	Indirect Costs	Total	65,065		234,792

A. SUMMARY OF BUDGETS

Salaries:	100,100		
Supplies:	69,627		
Indirect Cost: 65%	65,065	TOTAL:	234,792

B. POSSIBLE ALTERNATE FUNDING SUGGESTION:

Salaries:	100,100		
Supplies:	69,627		
Indirect Cost: 30%	30,035	TOTAL:	199,757