December 3, 1971

Mr. R. M. Wheeler
Union Carbide Corporation
437 McCorkle Avenue, S.W.
South Charleston, West Virginia

Dear Mick,

Pursuant to the MCA meeting of November 16 on vinyl chloride, the following are writer's questions and suggestions concerning the proposed manufacturer-sponsored toxicological research.

(1) After I left the meeting, it suddenly occurred to me to question the diagnosis of the lesions as cancers vs. tumors. I presume the evaluation is conclusive but, if it is not, some part of the proposed protocol should include a recovery period to note whether the lesions regress.

(2) It is presumed that no human tumor has yet been attributed to VCM, but it would appear to be worthwhile to review the working population that was used by the University of Michigan for study of acroosteolysis. This certainly includes the most highly exposed population and, if no tumors exist here, it can be argued that human experience, if of reasonable magnitude, should take precedence over animal studies. It is conceded that this lesion was not sought in Dr. Dinman's study but, from the available records, it might be easier to review this population than another complet ly new one. I am thinking of a limited edipemialogical study, possibly at a substantially lower cost.

(3) In the matter of analysis of EDC or acetylene derived samples of VCM, we do not expect to discover known carcinogens. However, it does seem desirable to know whether there are any gross differences in the sampl s used by Dr. Viola and those to be used here. Certainly the 25 (or 29) impurities mentioned are not all present in equal quantities even if made by the same process, and I suspect that process difference may be substantial. At least we should know the variation which can be expected and be certain that the material used is within limits set by analysis of at least six samples from ach process. To be certain that sample impurities do not reveal proprietary process secrets of any manufactur r, MCA could act as a clearing house for analyses. A look at the analyses does not necessarily mean that the

toxicology project need be delayed. Each manufacturer should be able to report analyses of a few batches within one month and, if no major deviations appear which are of major concern, study could start immediately. Will one sample (single unit tank car) of VCM be used, or will it be used from "one-ton" or smaller cylinders?

(4) We have no serious objection to the exposure protocol but would prefer one non-rodent species even if numbers of animals (possibly dogs or monkeys) were substantially lower in number. We realize that statistical result will not be as significant, but the opportunity to observe a completely different species where metabolic pathways may be substantially different would appear to justify the statistical sacrifice.

(5) Mutagenicity and teratogenicity were mentioned briefly at the meeting, but we can recall no decision as to whether such studies would be included. We think tests in this area might be desirable but have no strong feeling that they should be included in this protocol. Dr. Legator of FDA believes that mutagenicity may be predictive of carcinogenicity.

In view of the lack of any similar visible lesion in a substantial exposed human population, we doubt that regulatory agencies in this country will take any precipitous action before confirming th results here. We do believe that samples of food-wrapping films should be tested for migration into solvents simulating food to discover levels which may be expected from reasonably standard PVC formulations.

We will be happy to cooperate with the industry group in this matter of safety and health of employees and public.

Sincerely yours,

W. A. Knapp
Toxicology-Consultant

WAK:pb

cc: Dr. Norman G. White
Shell Chemical Company

Dr. Benjamin M. G. Zwicker
B. F. Goodrich Chemical Company

bcc: Mr. J. C. Fedoruk, DAB-2
Mr. K. K. Sheth, Plastics Division, Painesville, Ohio