DOW CHEMICAL U.S.A.

MIDLAND, MICHIGAN 48640

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MEMO FOR T. R. TORKELSON

cc: R. R. Cook, M.D.

ENVIRONMENTAL HEALTH ASSOCIATES (EHA) PROPOSAL FOR UPDATE OF VINYL CHLORIDE (VC) COHORT

1. Background. You asked me to comment on this 26 page proposal. A cover letter by Carol R. Stack, Ph.D. of CMA provides excellent background as follows:

"As you may know, the original epidemiological study was done by Tabershaw Cooper Associates/Equitable Environmental Health, Inc., from 1973 through 1976, and presented as a final report in January 1978. The study followed a cohort of 10,173 male employees whose jobs had exposed them to vinyl chloride for at least one cumulative year prior to December 31, 1972. The cohort was drawn from 37 individual plants operated by 17 companies.

There are several reasons why a follow-up of this cohort is considered desirable at this time. In the original study it was recognized that the cohort was relatively young and would generate a modest number of deaths. For this reason, a large cohort was selected in order to supply sufficient person-years of observation to detect statistically significant increases in short-latency diseases. In the final analysis, 707 deaths were observed however, the disease associations seen were considered to be tenuous at best.

An additional 7 years of observation provides an opportunity to further evaluate observed associations, as person-years of observation will increase 40% and an additional 350-400 deaths are anticipated. Of particular interest is a clarification of the excess in brain tumors found in the original study and questions raised about cancer in sites other than the liver".

2. General. As written, this proposal is to update and modify the original cohort. I have no philosophical problem with updating vital status; just surprise at the effort which will apparently be needed to do so. I do object to permitting any changes in the cohort or in estimations of its exposures. If companies are going to be permitted to add or delete from the original cohort, one might as well do the study all over again; otherwise the potential for gerrymandering is overwhelming. Also, updating exposures since 1972 is probably not appropriate in view of the long latencies associated with cancer, presumably the disease which motivated the update proposal.



A major problem of the original study was that certain kinds of disease mortalities (brain, cancer; cardiovascular and renal disease) were in clear excess but did not correlate with duration or intensity of exposure. Unless the exposures are somehow to be changed, it doesn't appear that the update will correlate any better, and trying to use duration as a surrogate for intensity is a clumsy stopgap.

3. Specific. By and large, the proposal was well written and to the point; CVs of the investigators were not included but, to my knowledge, they are quite well-trained and capable. The costs seem high and Mr. Davis' caveats that they will probably become even higher (and time delays longer) should be taken seriously. Critical comments are:

(a) Weaknesses of the original study are addressed but not solved. These include "arbitrary" exposure data, which the present proposal hopes to overcome by analysing according to duration only. There was incomplete followup in the first study which will almost certainly be even worse in the update. In fact, one might end up with less than 90% ascertainment, which is unacceptable. An additional weakness of the original study was lumping high exposure companies with low; that weakness remains.

4. Suggestion. Per our converstion today I'd recommned that:

(a) EHA be asked to revise their protocol to a simple update of vital status of the original cohort of 10,173, and delete any attempts at modifications. Exposure categories should remain those used originally (total integrated dose, duration of exposure, years since exposure began, and maximum level of exposure).

(b) Ask a reputable investigator each from EPA or NIOSH or NCI to comment on acceptability of the revised proposed study to his or her agency. I'd suggest this be done before entering into any further agreements with CMA or EHA. Basically, the

questions to be answered are: will this proposal answer questions about brain and lung carcinogenicity of VC at historical levels? In its present form, I'm not sure it will; or that government colleagues would believe the results in any event. Frankly, I'd be much happier with several small studies such as an update of Jerry Ott's admittedly small cohort of 594, which was current as of January 1, 1974, had beautiful exposure data, and was limited to one company.

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