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Mr. Joseph E. Hadley, Jr.  
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Dear Joe:

After the vinyl chloride conference last week we agreed that it might be useful if I prepared a brief commentary. This I have done - it is by no means a critical review of the entire meeting.

My general impression was that the broad range of subjects and the limited time for discussion made it an unproductive meeting with little depth. The last session on research needs and public health in prevention was particularly non-illuminating. Most of those who spoke seemed to have learned nothing from the preceding two days and adhered to their predetermined texts.

I will now address a few of the highlights:

It is impossible to review Dr. Maltoni's long paper without access to tables and details. I saw nothing in it, however, to warrant being panicked into fear that the 1 ppm standard is inadequate, but it will be so interpreted by some.

Papers 3, 4 and 5 were interesting refinements on the toxicology of VCM, showing the influence of factors such as age, concurrent ethyl alcohol, and dosage patterns, but these have no immediate practical impact.

Papers 6 and 7, describing animal studies of polyvinyl chloride, showed that the polymer is practically inert but remains in the lungs for extremely long periods of time without producing very much reaction. The evidence that there is little or no collagen production or fibrosis makes it misleading to speak of its causing a pneumoconiosis, although by some definitions any dust accumulation falls into this category. The negative result by Groth using extremely high concentrations (12.8 mg/m3 for 464 days) was most encouraging.

Paper 8 on sputum cytology in plastic workers provided a baseline for comparison but cannot be used for predicting long-term effects on the lungs.

The epidemiologic papers, 9, 10, 11 and 12, were essentially consistent, in demonstrating that the excess in digestive tract cancers

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is largely due to angiosarcomas, that there is is probably a modest excess in brain tumors, but that otherwise VCM is not a strong carcinogen. There was clearly not enough evidence to say more about brain tumors than that apparently an excess hazard occurs in the industry. The specific chemical involved was not defined, but VCM is still likely.

The report by Jay Beaumont on power considerations (#12) reflects the concern by OSHA and NIOSH that negative studies can be misleading. They are right in insisting that the power of a study to detect a specified relative risk, e.g. a doubling, should be stated in the report. It should be remembered, however, that this is still a mathematical game, and independent of study design and factors such as sufficient time having elapsed between exposure and the end of the observation period. The power can be less than calculated if the study is not done right. On the other hand, it cannot be stressed too strongly that several properly designed studies corroborating each other, i.e. giving similar results, have a cumulative power that is more than additive. It is extremely unlikely that several well-executed negative studies would occur by chance, even though no single one had sufficient power to rule out a doubling of rate with an 80% degree of assurance.

Paper 13 (Dr. Falk's epidemiologic review of angiosarcoma) confirms a continuing relatively low incidence for the U.S. and the likelihood of multiple causes. This is borne out by a later report (No. 31, by Dr. Vianna -- read by Landrigan) which showed that only about one-third of the liver angiosarcomas in N.Y. could be related directly to vinyl chloride. Those living within a mile of a plant should not be included in this category. Eliminating those having had direct contact with VC reduced the rate in N.Y. to approximately that for the U.S. as a whole. This is probably close to the background from unknown causes. This contrasts with mesothelioma as a "signal" for asbestos, where 75%-85% seem asbestos-related.

Paper 16 on liver screening tests showed interesting statistics on the incidence of abnormal tests. There was insufficient emphasis on the fact that there is a considerable proportion of positive tests (possibly 20 to 25%) for some of the tests in non-exposed individuals, i.e. new hires. How these were handled should have been discussed. Whether the tests are of value in predicting those who will get angiosarcomas was not demonstrated, or, if it occurred, whether it affected the outcome.

Papers 17 and 18 on industrial hygiene measurements, particularly the former, provided valuable information for all who are doing epidemiologic studies.

The very important session on human experience with polyvinyl chloride was uncritical and inconclusive. I am unable to draw any conclusions from the reports by Dr. Chiazze and Dr. Molina, and would like to read

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them and see the slides again. Dr. Seaton's report (#21) was consistent with an extremely mild effect of prolonged dust inhalation on chest film and lung function. In the absence of any instances of more than a slight number of opacities (1/1 or less), marginal reduction of function, and no pathologic backup, I think one is unwarranted in referring to PVC pneumoconiosis as an entity. The reactions are probably those that would result from any insoluble nuisance dust inhaled in large amounts. It was of interest that Dr. Seaton's radiologists reported round opacities while Dr. Mastrangelo of Italy described predominantly irregular opacities. Dr. Lilis' report, describing work already published, added nothing to indicate that PVC is capable of producing a pneumoconiosis of major concern. It is almost certain that strict adherence to the nuisance dust standard of 5mg/m<sup>3</sup> of respirable dust would protect workers from any impairment of lung function. It is also likely that occasional individuals will respond to the inhalation of PVC dust by developing a granulomatous lesion as reported by Pimentel & Vilar in Portugal.

Dr. Waxweiler's report, #24, on cell types in lung cancer in PVC plants, was an illuminating one, and strongly suggested that there is an excess of large-cell undifferentiated lung cancers in loaders and packers of PVC, i.e. those exposed to PVC dust. If this is borne out by additional studies, the most likely explanation is residual VCM, which would reach individual sites in the lungs in comparatively high concentrations if released from retained respirable particles.

The session on reproductive effects of vinyl chloride, papers 26-29, supplied no new substantive or surprising evidence. The concentrations of VC used in the Ames test (2% and 20%) reported by Dr. Fabricant were phenomenally high. Dr. Hatch, in her description of power considerations in studies of reproductive effects, made it plain how very difficult it is to get acceptable evidence in this field from studies in human populations. As a result, this highly emotional area is readily exploited by those who promote anxiety, and the results can be very sad.

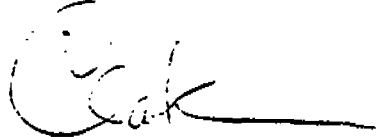
The most important point that came up for discussion in the session on structural analogues, papers 32-34, was the purity of chemicals used in animal experiments. The argument that use of technical grades, containing known contaminants, was desirable because they represented the real world, ignored the use that is made of results. The separation of science from public health which was made by one commentator is fallacious. Public health is not well served by setting up controls for a substance if they should have been applied to the contaminant.

As I pointed out earlier, the summation provided some mild heat but little light. No succinct recommendations for research were made, although there were many gaps in our knowledge disclosed during the talks that pointed to needs. Fortunately there is still recognition of the fact that prolonged epidemiologic followup of exposed populations is needed.

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It was a pleasure meeting you, and I look forward to our paths crossing again soon.

Sincerely,

A handwritten signature in dark ink, appearing to read "Clark", with a long horizontal stroke extending to the right.

W. Clark Cooper, M.D.

WCC:bs

cc: Seawell  
Torkelson

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