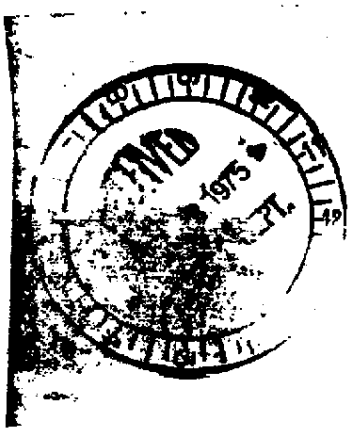

Air Products and Chemicals INC.
ALLENTOWN, PA.

11 March 1975

Office of:

W. Mayo Smith

cc: A. Ross Adams
W. L. Ball
J. T. Barr
T. L. Carey
E. Donley
Richard Fleming
G. J. Mantell

Dr. M. Kuschner (direct mail)

Manufacturing Chemists Association

Minutes of Meeting

VINYL CHLORIDE RESEARCH COORDINATORS

MCA Conference Room — Washington, D. C.

February 13, 1975

Dr. Torkelson presided and convened the meeting at 9:30 a.m.

MEMBERS PRESENT:

Dr. T. R. Torkelson, Chairman	The Dow Chemical Company
Dr. W. D. Harris	UNIROYAL, Inc.
Mr. H. L. Kusnetz	Shell Oil Company
Dr. W. M. Smith	Air Products and Chemicals, Inc.
Mr. R. N. Wheeler	Union Carbide Corporation
Mr. M. Freifeld	MCA Staff

GUEST PRESENT:

Dr. D. P. Duffield	Imperial Chemical Industries, Ltd.

MEMBERS ABSENT:

Dr. Z. G. Bell, Jr.	PPG Industries, Inc.
Dr. M. N. Johnson	The B. F. Goodrich Company
Dr. W. E. Rinehart	Ethyl Corporation

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1. Minutes of the Meeting of December 11, 1974

The subject minutes were approved as distributed.

2. Funding of Continuing Projects

The secretary reported that sufficient commitments had been received to carry forward all three items regarding ongoing research programs in Mr. A. C. Clark's letter of December 20, 1974.

These are (a) follow-on work at Dow on metabolism, teratology, and mutagenisis, (b) extraordinary expenses and contingency funds for the Industrial BIO-TEST program, and (c) work-up of the Union Carbide personnel data and reanalysis of the expanded data base by Tabershaw/Cooper Associates (TCA).

3. Modification of Proposed Epidemiology Study Extension

The Research Coordinators agreed with the modifications in TCA's December 9, 1974 protocol suggested in Dr. Torkelson's letter of January 13, 1975 to Dr. Gaffey. These include: (a) adding data on Union Carbide Corporation workers terminated before January 1, 1946, (b) examining data in terms of type of plant, e.g. monomer, polymerization, and (c) analysis in terms of maximum reported exposure intensity, duration of exposure, and years since exposure began. In the discussion of (c), some felt the interval of four years for presenting total exposure data may be too short and that ten-year intervals would probably be more suitable. Dr. Torkelson thought he could resolve this with TCA when re-examination of the data begins.

Alternate methods of expressing maximum exposure intensity were discussed at some length. Dr. Torkelson pointed out the high, medium, and low categories suggested in his proposal to Dr. Gaffey might be assumed by some to have linear ratios (e.g. 1:2:3). Although there is no firm evidence, he thought the ratios of exposure intensities would more likely be geometric (1:10:100) or other values, perhaps 1:5:20. It was pointed out however, that most of the reliable measurements of concentration in the work place have been made only recently and would not apply to the cases under study. The group agreed to ask TCA to try various ratios with the available data.

A motion was passed unanimously to recommend to the Technical Task Group approval, by letter ballot, of the modifications suggested in Dr. Torkelson's letter cited above plus recalculation of the data with varying exposure ratios. (Dr. Torkelson reported to the secretary on February 20 that since this meeting he consulted by telephone with Dr. Gaffey and determined there would probably be considerable additional expense in calculating exposure indices based on various assigned ratios for exposure categories. Furthermore, Dr. Gaffey indicated such an analysis is not likely to produce tables useful for interpretation. Dr. Torkelson then telephoned the Research Coordinators who had attended the meeting February 13 that he could reach, and a majority, but not all of those who had been at the meeting agreed to drop the previously recommended calculations with various

exposure ratios. The Task Group still has the option to reconsider this at a later date.)

4. NIOSH Review of Angiosarcoma Cases

Dr. Lloyd summarized NIOSH information on angiosarcoma of the liver related to vinyl chloride in a letter to Dr. Torkelson January 22, 1975 (which was distributed to the Task Group February 11, 1975). A motion was passed to have the secretary write to Dr. Lloyd, after clearing a draft with Dr. Torkelson, requesting details backing up the data in the tables attached to his letter.

5. Future Research Programs at Industrial BIO-TEST Laboratories, Inc. (IBT)

Dr. Torkelson reported he has not heard from Dr. Rall's committee. The group concurred that until a written reply is received from them, no further action need be taken on proposed low-level chronic inhalation or spill-simulating studies.

6. Epidemiology Study at Georgetown University

It was reported that the above study on polyvinyl chloride (PVC) fabricators, under the administration of Organization Research Counselors, by Dr. Cachiazzi is proceeding, but no report has been issued yet.

7. Reports due on MCA-Sponsored Work

The secretary reported that Dr. Goode promised over the telephone to submit a status report on the IBT work by the end of February.

Completed parts of the Dow studies on metabolism and teratology will be reported on in April, per Dr. Torkelson. Also, the slides for cytogenic study (from IBT work) look clean so far, but no formal report has been received yet on the duplicates Dow sent out to confirm their findings.

8. Items for Secretary to Follow Up

Subjects discussed at previous meetings requiring further action are:

a) Obtain and distribute information on vinyl chloride-related work underway and planned at various government agencies such as National Cancer Institute, National Institute of Environmental Health Sciences, Environmental Protection Agency, and the Consumer Product Safety Commission.

b) Contact EPA to learn extent of their work on photochemistry of vinyl chloride monomer (VCM).

c) Provide update on developments following verbal report to Task Group by MCA's Mr. Sam Watts on regulations affecting transportation of PVC.

d) Request of IBT's Dr. Gordon to publish a paper on his work. It was moved that a formal letter be sent to IBT reminding them that such papers should be cleared in advance by MCA before being submitted for publication.

e) Remind Dr. Brookman of Firestone of his offer to supply a list of regulatory actions on VCM taken in foreign countries.

9. Litigation Involving MCA

The secretary brought to the group's attention a case in a Philadelphia court naming MCA, among others, as a defendant. MCA's published data on VCM is specifically mentioned.

10. Request for Support of Research

The secretary cited a letter of October 23, 1974 from Dr. E. S. Reynolds of Peter Bent Brigham Hospital in Boston to Dr. M. N. Johnson of B. F. Goodrich Company requesting support for toxicological and metabolic work with VCM, some of which has been started. Since this is similar to research already in progress under MCA administration, the group noted the request with interest but felt a response was not necessary.

Respectfully submitted,

Milton Freifeld

Milton Freifeld, Project Manager

MF/etv

Minutes subject to approval

3/5/75

FEBRUARY 7, 1975

The National Cancer Institute (NCI) recently convened an ad hoc workshop, at which it introduced a detailed set of guidelines for carcinogenicity testing in small rodents. These guidelines are detailed in their philosophy, in prescribing details of the design, conduct and monitoring of such a study, and for monitoring the environment and other variables, as well as insuring the complete documentation of the procedures and the events that occurred during and after the conduct of the study.

The guidelines increase the need for documentation and proof of such documentation, and as such, will provide for an increased work load by the laboratory to do so. In addition, they specify specific protective operations and procedures to prevent contamination of the environment and exposure of personnel involved. These will undoubtedly be reflected in increasing costs.

There were several points introduced during the discussions, and these may be summarized as follows:

1. Adequate screening should involve a sufficient number of animals (50 per sex per exposure level) and an adequate number of species (generally two).

2. Of the species available, the rat and the mouse are preferred, but the hamster may be substituted for the mouse. Mention was made that with the passage of time, the utility of the mouse (including the mouse liver tumor) for carcinogenicity testing has been reinforced. Mention was also made of the fact that although the pesticide compounds (specifically chlorinated hydrocarbon compounds) seemed to evidence their carcinogenicity in mice, most of the drugs with this characteristic appeared to express it in rats. NCI suggests this reflects varying susceptibility for compounds by different species (unpredictable).

3. Chlorinated hydrocarbon levels in animal feed are approaching those which might be anticipated to produce a carcinogenic response, therefore continuing monitoring of levels of these materials in the feed used for experimental studies should be carried out.

4. The chlorinated hydrocarbon pesticides, as a group, as suggested above are identified in an absolute sense as carcinogens.

5. Ethylene dibromide and dibromo-chloropropane were referred to as "strong metastasizing carcinogens".

6. Following an initial screen at the maximum tolerated dose, and a fractional dose thereof (in two species), the NCI program proposes to undertake a detailed evaluation of those compounds found to produce a positive carcinogenic response. Such a program is proposed to include a study of the pharmacokinetics of the material, its metabolism in several species (including man), a determination of the mechanism of activity of the compound (i.e., as the definitive carcinogen or pro-carcinogen), and a re-examination of its carcinogenicity in one or two species, with at least four appropriate dose levels to which a "Mantel-Bryan" may be applied. (For the uninitiated, "Mantel-Bryan" refers to a specific statistical exercise which enables one to predict very low risk levels, i.e., one per hundred million, with given levels of probability.)

An initial proposal for expansion of the guidelines to include in utero exposure of fetuses met with considerable objection. At the moment, this kind of study will not be required. Monitoring of further considerations of such a proposal should be maintained so that we can modify our protocols, if necessary, to include such exposure.

Representatives from other regulatory agencies (i.e., Food & Drug Administration, Environmental Protection Agency) were there affirming their organizations' intent to adopt these guidelines as part of their agencies' toxicology and safety evaluation requirements. It is reasonable to assume that these and other federal agencies that may become involved with other product types will apply them in those areas as well (i.e., Toxic Substances Act).

The importance of using appropriate routes of administration was stressed, and it was noted that most worker exposures are through inhalational routes. The lack of adequate testing facilities for conducting chronic studies via this route of administration was noted.

There was additional discussion regarding the greater relevance of associating tissue residue levels of compounds with effects rather than nominal exposure levels irrespective of the route of administration. Although no direction was established at this meeting, it is reasonable to anticipate the need to redesign experimental protocols to reflect this consideration.