



CHEMICAL MANUFACTURERS ASSOCIATION

February 29, 1980

To: Vinyl Chloride Project Panel
Subject: Vinyl Chloride Epidemiological Studies

The enclosed proposal prepared by CMA is based, in part, on the letter-proposal dated January 15, 1980 submitted by Environmental Health Associates, Inc. (EHA) (see copy of EHA letter-proposal enclosed).

As shown in the schematic diagram (see page 2 of CMA proposal) the overall proposal is comprised of five investigations. Some of these are prerequisites for studies that would follow and all of them are interrelated.

Cost estimates and analyses of all study components are presented on pages 3, 4, 5, 7 and 8 of the CMA proposal and on pages 3, 4, 5, 8, 9 and 10 of the EHA letter-proposal. Should there remain excess funds upon completion of the separate brain study, these funds will be applied to the five-year epidemiological update and its allied investigations.

You are requested to complete the enclosed questionnaire and return it to the undersigned no later than March 17, 1980.

Sincerely,

A handwritten signature in dark ink, appearing to read 'J. T. Seawell', is written over the typed name.

J. T. Seawell
Project Administrator
Vinyl Chloride

JTS:das

Enclosures

CUSAROSS 02462

Formerly Manufacturing Chemists Association—Serving the Chemical Industry Since 1872

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CHEMICAL MANUFACTURERS ASSOCIATION

To: Vinyl Chloride Project Panel

Subject: Proposal for Vinyl Chloride Epidemiological
Studies and Five-Year Update

Introduction and Background Information

Five year ago Tabershaw-Cooper Associates (TCA) conducted their epidemiological study of workers engaged in the synthesis and/or the polymerization of vinyl chloride (VC). Equitable Environmental Health, Inc. (EEH), the successors to TCA, completed the study and the final report that issued during January, 1978.

The employment period covered by the TCA/EEH mortality study ended December 31, 1972. Therefore, it is now possible to add at least five years' experience if deaths through 1977 are included. Practically, it might not be feasible to go beyond December 31, 1977 since all death records might not be available.

Due consideration should be given to the fact that in the final EEH report (see pages 19, 20, 21 and 24 as well as Table 23) the investigators include the recommendations to 1) conduct a thorough investigation of the brain cases, and 2) complete a five-year epidemiological update of the vinyl chloride cohort. In the original study, the investigators were prompted to suggest an excess of deaths under the classification entitled, "Malignant Neoplasm, Brain and Other Parts of Nervous System (193)." In this cause of death category, 12 cases were observed against an expected 5.90. Prima facie, this is a doubling of risk in the study population and requires further investigation.

In addition to the five-year update, the VC Research Coordinators are of the opinion that it is advisable to 1) study in depth the 12 brain tumors identified in the 1978 EEH report, 2) determine the feasibility of studying subpopulations exposed to PVC dusts, and 3) the feasibility of studying subpopulations exposed to ethylene dichloride.

We have discussed with representatives of Environmental Health Associates (EHA) a number of possible approaches to the study parameters cited in the preceding paragraph. EHA responded with a formal letter-proposal, a copy of which is enclosed.

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The following diagram shows the sequence in which the inter-related investigations will progress and affords a schematic picture of the overall study:

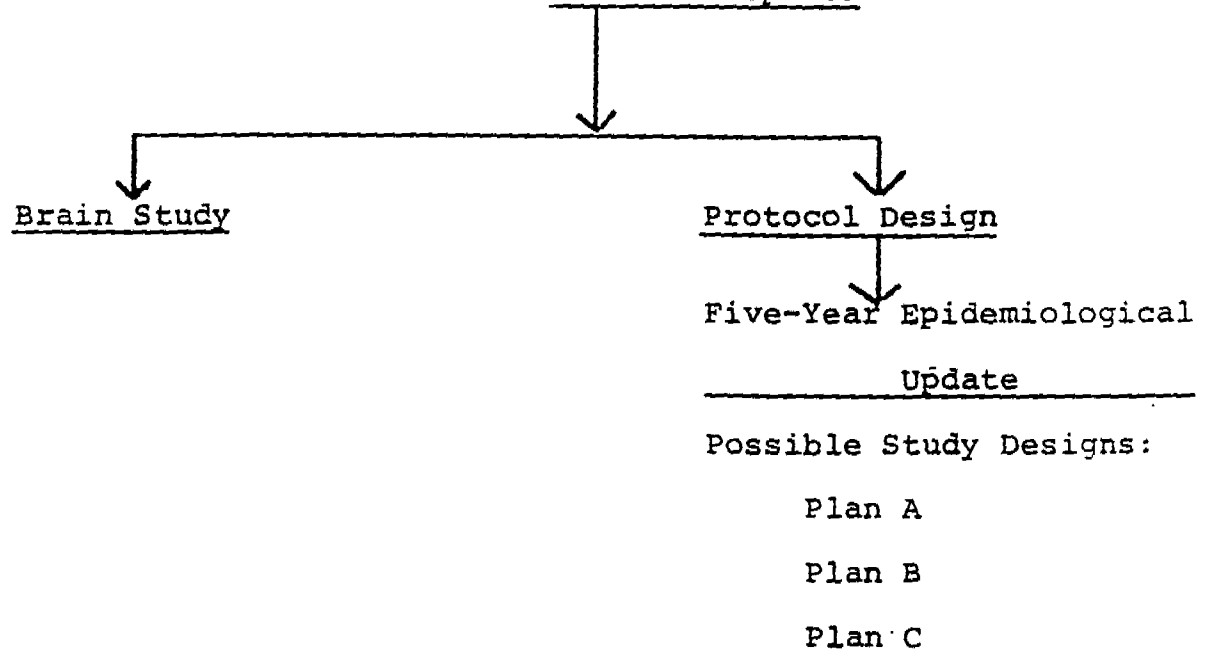
Schematic of Interrelated Epidemiological Studies

and

Five-Year Update

Evaluation of Current Data Base

- Applicable to:
- Brain Study
 - Protocol Design
 - Five-Year Update



Evaluation of Current Data Base and Development of a
Protocol for the Five-Year Update

As shown in the schematic presented above, the evaluation and assessment of the current data base is a necessary prerequisite to all three study components, which are, 1) the brain study, 2) the protocol design, and, ultimately and primarily, 3) the five-year epidemiological update. Therefore, Panel members deem it important that this phase of the overall study begin as soon as possible.

Perhaps it is advisable to cite at this point some of the imponderables that would mitigate against preparation of a definitive protocol without benefit of an evaluation of the data base. For example, in the original study, raw data were collected in two ways: for approximately 6,700 of the total cohort of 10,173, complete job histories were collected by the contractor for each individual identified as having held a job involving VC exposure for at least one year. Job titles involving VC exposure were identified by plant management. For the remaining 3,300, job histories were supplied by plant managements on forms provided by the contractor. Only those job periods which involved exposure to VC were included on the form. The identity of plants participating in these two types of raw data collecting systems is not known at this time, but must be ascertained by examining the unit files. The foregoing may or may not affect the ability of an investigator to assess the effect of exposure to PVC dusts or to ethylene dichloride. If the VC study cohort includes all individuals at risk from exposure to these two substances, then such an assessment would be feasible without the necessity of collecting additional data from the plants. If it contains only a portion of them, it would be necessary to re-search plant records for individuals so exposed. This would significantly affect cost and performance time.

Cost of Evaluation of Current Data Base. Costs of an evaluation of the current data base are summarized as follows:

Personnel	\$5,232
Consultants	865
Other Direct Costs	100
Meeting Costs	<u>3,210</u>
Total Costs	\$9,407

The Brain Study

The VC Research Coordinators recommend that a follow-up study of the 12 cases identified as "brain cancer" be initiated as soon as possible. EHA will require early assistance from CMA and personnel of sponsoring companies to identify a contact person at each plant who will be responsible for expediting EHA requests for information.

EHA proposes to obtain copies of the following files for each brain case:

- a) Company medical file
- b) Company personnel file
- c) Company or insurance carrier Worker's Compensation file
- d) Additional information from supervisors or fellow workers concerning work history, previous employment, hobbies, etc. The extent to which this search can be performed depends on information obtained from the company's files.

If adequate data are available from the sources listed above, EHA will attempt to obtain:

- Pertinent medical history from personnel physician
- Surgical and/or autopsy histopathology results

Where this information is obtained on a confidential basis, no source citation will be provided.

At the decision of the sponsoring/participating companies, EHA will contact the deceased's family for additional information. This can be decided on a case-by-case basis in consultation with both sponsoring and participating companies. If a particular case has been adjudicated, there is little reason to avoid family contacts as these can be valuable information sources.

On the basis of data collected for each case, EHA will establish to the extent possible, the following:

- 1) Verification of diagnosis
- 2) Histologic diagnosis
- 3) Complete job history to include:
 - Likelihood of exposure to other chemicals
 - Employment before and after vinyl chloride exposure, and
 - Other sources of confounding exposures such as hobbies, etc.

Information concerning the validity of the association between the 12 deaths from brain cancer and exposure to VC will be evaluated by Drs. Whorton and Milby of EHA. The investigators will examine these data for commonality of exposure variables, time between onset of exposure and disease development, cell type, association with exposure to other agents, and other related factors.

Cost of Brain Study. Based on the assumptions presented above the cost of this study is as follows:

<u>Basic Study</u>	
Personnel Costs	\$ 9,780
Other Direct Costs	800
Total Estimated Cost	<u>\$10,580</u>

Cost of meeting with Drs. Milby and Whorton to discuss matters pertaining solely to the brain study.

Total Meeting Costs \$4,270

The Five-Year Epidemiological Update

At the onset of the original study during 1972, it was recognized that this cohort was relatively young and thus would generate only a modest number of deaths for analysis. Two thirds of the cohort contributed less than 20 years of observation since the onset of exposures. To offset this deficiency a large cohort was collected in an effort to generate sufficient person-years of observation to detect increases in short-latency diseases at an acceptable level of statistical significance. Nonetheless, the disease associations detected by this study were tenuous at best. While the original investigators were careful to report this fact, subsequent reporters have at times failed to recognize the tentativeness of these conclusions, and some associations have been accepted at times as proved facts.

EHA is of the opinion that the additional five years of observation now available for this population would begin to clarify the validity of reported associations. Person-years of observation will be increased by 40 per cent. An additional 350 to 400 deaths will be generated for analysis. While the population will still be at the front-end of its maturity curve, the additional data should prove meaningful.

A second justification for further study of this population concerns the specific question of the association between death rates from brain tumors and exposure to VC. The present data indicate the presence of a doubling of risk from this cause. If this association is real, the five-year follow-up should generate seven or eight additional brain tumor deaths. Should only three or four be found, the validity of this association will be diminished.

Re-examination of the VC population offers still another opportunity to the chemical industry. The original data represent a working population exposed to relatively high levels of vinyl chloride monomer. At a single point in time, this exposure level dropped dramatically. Employees entering this population beginning in 1972 experienced a substantially lower exposure than those employed in the industry prior to that time. With the passage of time, this difference should begin to manifest itself by a leveling off of certain cause-specific death rates if the suspected disease associations are valid. This trend should continue into the future. Because of this unique situation, EHA recommends that

the present data base be converted to a registry and individuals employed since December 31, 1972 be added to the population for future investigation. The experience of the current 9,677 individuals could then be compared to the experience of those entering after 1972 with potential noteworthy results.

Development of Cost Estimates Relevant to the Five-Year Follow-Up. The development by EHA of an accurate estimate of the probable costs to complete the five-year follow-up requires more precise data than is currently available. Until existing data are reviewed, it is not possible to ascertain the study design that will be the most productive and cost effective. As a result, EHA has developed several study plans or proposals that are summarized as follows under their respective headings:

Study Plan A

This plan is a straight-forward five-year follow-up of the existing data base. This basic approach will be the most economical. It represents the least rigorous of the three plans and has some intrinsic deficiencies that would influence the cost/effectiveness ratio.

The tasks required for Study Plan A would include:

- 1) Develop computer programming to translate current study cards to tape format and provide master tape.
- 2) Select all "Alives" and "Unknown Vital Status" by plant and return names to plants for update.
- 3) Submit master roster of all "Unknowns" (both from original data base and from update) to SSA.
- 4) Request Death Certificates for those identified as "Dead" by SSA.
- 5) Reduce new vital status data to computer comparability format.
- 6) Develop computer programming for update of data bank and update present data .
- 7) Analyze for cause-specific SMR's and PMR's.
- 8) Interpret results and prepare report.

Cost of Study Plan A. Based on the study requirements listed above the cost of Study Plan A is as follows:

Total EHA staff charges \$30,256

Consultants

Biostatistician \$10,175
Physician/Epidemiologist 2,720

12,895

Other Direct Costs 11,700

Total Cost \$54,851

Study Plan B

part of 9,000 cohort
In addition to the work required under Study Plan A, the existing data base would be augmented with complete job histories for the approximately 3,300 cohort members for which job histories are now deficient. This more rigorous plan may make it possible to control for exposure to PVC dust and ethylene dichloride. While this work will substantially increase the cost, it may prove to be worth the effort. In addition, Study Plan B would require the following:

- 1) Secure complete job histories for the approximate 3,300 cohort members with incomplete job histories. This would involve nine study plants. Costs, according to EHA, will vary greatly depending on the data collection technique employed. If plants will provide the data on EHA prepared forms, the cost of this study will be minimized. If EHA must send a researcher to each plant to collect the data, the cost will be greater.
- 2) Determine jobs with exposure to PVC dust and ethylene dichloride.
- 3) Code complete cohort for these variables.
- 4) Update master tape.
- 5) Analyze data for the effect of these variables.

Study Plan C

In addition to the work performed under Study Plan A and B, Study Plan C would include the following:

- 1) Collect full study data from 37 plants for all individuals employed since 1972, estimated to be between 1,500 and 2,500.
- 2) Code new cohort member data.
- 3) Update master tape.
- 4) Analyze the enhanced population data.

Recapitulation of Cost of All Study Components

Preparatory study components, the basic study (Study Plan A), and the elective studies, Study Plans B and C have costs that are summarized as follows:

Assessment of the current vinyl chloride mortality study data base (with meeting)	\$ 9,407 .
Case study of 12 brain tumor cases (with meeting)	14,350
Five-Year follow-up, Study Plan A	54,851
Five-Year follow-up, Study Plan B	36,564
Five-Year follow-up, Study Plan C	55,910
Total	\$171,082

Complete Cost of Study Program

The costs of the entire study program are as follows:

Preparatory studies, Brain Study, and Study Plans A through C	\$171,082
Supplemental or Elective Research	25,662
Administrative Costs	40,000
Total Cost	\$236,744

Panel Survey of Interest in and Possible Financial
Support for Preparatory Studies and Five-Year Epidemiological
Update on Vinyl Chloride

** No cost here, but can use our records.*

Item No.

Inquiry

1. *** ☐ We agree to permit CMA's contractor to use the records provided by our company for the Tabershaw-Cooper Associates (TCA)/Equitable Environmental Health (EEH) study completed and reported January, 1978.

☐ We do not agree.

2. *** ☐ We agree that it is important to preserve the continuity of the cohort and we agree to assist in the update of the mortality records for those employees alive on December 31, 1972 who have died prior to December 31, 1977.

☐ We do not agree.

3. *** ☐ We agree that Environmental Health Associates (EHA) be authorized to examine the current records, prepare a protocol for a five-year update, and conduct a re-analysis of death certificates according to the EHA letter-proposal dated January 15, 1980, a copy of which is attached.

Not financial sponsor, but preserve the cohort in letting records be used

☐ We do not agree. *(This is an agreement in principle)*

4. Introductory Comment. As is described in the attached CMA proposal, the preparatory evaluative and protocol design studies, the brain study, and the component studies can be important integral parts of a five-year update. All constitute a program comprised of five interrelated studies. To permit CMA to arrive at fair and equitable pro rata estimates of individual company funding, the following expressions of interest are necessary:

- 4.1 ☐ We are interested in financially sponsoring an assessment and evaluation of the current vinyl chloride study data base.

☐ We are not interested.

Do not have exact cost \$10,000

Assessment & Preparation of Protocol for A, B, & C, which is a five-year update and not the case control.

Item No.

Inquiry

Approximately
\$50,000

control including clinical evaluation

- ☐ We are interested in financially sponsoring a thoroughgoing case study of the brain tumor cases with a cost estimate.
- ☐ We are not interested.

\$55,000 plus
\$1,000-\$15,000

4.3

- ☐ We are interested in financially sponsoring Study Plan A (see pages 6, 7, and 8 of CMA Proposal and pages 6, 7, and 9 of EHA letter-proposal) under the five year epidemiological follow-up.
- ☐ We are not interested.

4.4

- ☐ We are interested in financially sponsoring Study Plan B (see pages 7, 8 of CMA Proposal and pages 6, 7, 8 and 9 of EHA letter-proposal) under the five-year epidemiological follow-up.
- ☐ We are not interested.

TABLE D

4.5

- ☐ We are interested in financially sponsoring Study Plan C (see page 8 of CMA proposal and pages 6, 8 and 9 of EHA letter-proposal) under the five-year epidemiological follow-up.
- ☐ We are not interested.

5.

Introductory Comment. The importance of a follow-up on brain tumor cases (and the preparatory assessment of data that is a necessary prerequisite to this follow-up) is, in the opinion of a number of companies, a separate study that should be initiated as soon as possible.

DELETE

- ☐ We intend to financially sponsor the preparatory study and the follow-up of brain tumor cases and are willing at this time to commit up to a maximum of \$3,000.
- ☐ We do not intend at this time to financially sponsor this study.