



CHEMICAL MANUFACTURERS ASSOCIATION

March 21, 1980

To: Vinyl Chloride Project Panel

Subject: Second Quarterly Report covering research performed under the Agreement for Fiscal Year 1979-1980 on "Research Techniques and Methods for Detection and Prevention of Carcinogenesis in Industrial Workers", University of Louisville.

Gentlemen:

Enclosed is your copy of the subject report. Dr. Tamburro extends his regrets to the Panel members for the delay in the preparation of this report. Family illness and hospitalization of staff members are the causes for the late mailing.

Dr. Tamburro informs us that he expects to mail the third quarterly report within the next several weeks.

Sincerely,

A handwritten signature in dark ink, appearing to read "J. T. Seawell", is written over a horizontal line.

J. T. Seawell
Project Administrator
Vinyl Chloride

JTS:das

Enclosure

CONFIDENTIAL
Subject to Protective Order in
Ross v. Conoco, Inc., No. 90-4837
14th Judicial District Court
Calcasieu Parish, Louisiana

CMA 004346

Formerly Manufacturing Chemists Association—Serving the Chemical Industry Since 1872.



University of Louisville
Health Sciences Center

School of Medicine
Department of Medicine
Division of Digestive Diseases and Nutrition

Louisville, Ky. 40232
P.O. Box 35260
Walnut & Preston Streets

Subscribed by _____ in
Ross v. _____ No. 00-4037
14th Judicial District Court
E. Calcasieu Parish, Louisiana

Mr. Joseph T. Seawell
Program Manager
Manufacturing Chemists Association
1825 Connecticut Avenue, N.W.
Washington, D.C. 20009

RE: 2nd Quarterly Report for the Manufacturing Chemists Association's
Agreement with the University of Louisville for the 1979-80 Fiscal
Year.

Dear Mr. Seawell:

The following describes what has been completed during the 2nd quarter of the Manufacturing Chemists Association's agreement with the University of Louisville entitled, "Research Techniques and Methods for Detection and Prevention of Carcinogenesis in Industrial Workers". Progress for each technical proposal will be reported separately.

Technical Proposal A -- Immunological Systems for the Detection of Vinyl Chloride and Other Chemical Injury. H.P. Fortwengler

Fortwengler's laboratory has continued evaluating the immune system of industrial workers to determine whether cancer can be detected earlier or to identify those at high risk.

HLA Frequencies in V.C. Workers.

A compilation of HLA frequencies in V.C. workers is continuing to determine if a possible increased association of certain "tissue types" can be determined in individuals with angiosarcoma or other chemically related disease. To date, approximately 494 individuals from the Louisville vinyl chloride polymerization plant have had their lymphocytes isolated and typed for more than 27 different HLA-A and HLA-B antigens.

A Search for Evidence of a VC-Induced Tumor Antigen.

A search for evidence of a VC-Induced tumor antigen has lead to a finding that these tumors have an increased concentration of antigenic coagulation Factor VIII. Factor VIII is a known

Calcasieu Parish, Louisiana
14th Judicial District Court
1980-06-06, No. 90-4837
Subject to Protective Order in
CONFIDENTIAL

marker for vascular lining cells of the endothelial type. Further experiments in animals gave us results indicating that normal endothelial cells found lining the liver sinusoids had little, if any, Factor VIII fluorescence (content). Endothelial cells found lining larger vessels, on the other hand, demonstrated a striking fluorescence as did experimentally transplanted mouse angiosarcomas. Conversely, mouse hepatic Kupffer cells, a second type of hepatic lining cells, distinguished in histological cross section following engorgement with carbon particles, failed to demonstrate positive fluorescence. An increase in antigen Factor VIII in hepatic angiosarcomatous endothelial cells as compared to normal, leads us to believe that the aberrant cells have increased production or storage capacity for antigenic Factor VIII.

Technical Proposal B -- Biochemical Enzymatic Systems for the Detection of Vinyl Chloride and Other Chemical Injury and Cancer Development in Industrial Workers. J.T. Du

Staining techniques have been applied to various liver cell types to help identify the isolated liver cells. In the non-hepatocytes, the Kupffer cell is the peroxidase positive and the endothelial cell is the peroxidase negative cell. In a non-hepatocyte preparation, we found 18% peroxidase positive. After further separation of the non-hepatocytes by elutriation, only about 1% of the endothelial cell fraction was peroxidase positive.

We also did some experiments feeding chloroethanol, a vinyl chloride metabolite, to rats (30 mg/kg/day for 10, 20 and 40 days). The non-protein sulphhydryl content, (mostly glutathione), was increased after 20 days, but the glutathione-related enzyme activities, glutathione transferase and glutathione reductase, were not altered, suggesting either the dose is not high enough or that chloroethanol and vinyl chloride metabolize via different routes. Further experiments with higher doses will be performed to elucidate the mechanism.

Technical Proposal C -- Glycosaminoglycan Changes in Earlier Detection of Fibrotic Injury and Hepatic Cancer. C.E. Kupchella

The original aim of this study was to determine the usefulness of urinary and tissue glycosaminoglycan (GAG) measurements in the detection of chemically-induced liver injury. We have made substantial progress toward this end and this has been described in previous reports. Within the period July 1979 - September 1979, specifically, we accomplished the following:

CONFIDENTIAL
Subject to the provisions of the
Ross v. Commission No. 50-4887
14th Judicial District Court
Calcasieu Parish, Louisiana

- 1) We have completed data reduction and have a manuscript now under review by all co-authors for January or February, 1980 submission to the Journal of Clinical Pathology relative to the following study. We developed complete urinary GAG excretion profiles from 24 hour urines from 24 vinyl chloride workers, half with and half free of liver disease. Our conclusion is that GAG profiles may reflect active liver disease. A copy of the final manuscript will be submitted with the final report.
- 2) We completed the laboratory work involved in a repeat of the study we reported in Gastroenterology 73:1229 in 1977. At the end of the quarter, we had not yet started data reduction on this project.
- 3) We completed an extension and a repeat of the Morris Hepatoma study. We reported in Gastroenterology 75:972, 1978.

In the earlier study, we evaluated three tumor lines; in 1979 we looked at these three plus three more. A paper will be submitted in January for presentation at next May's meeting of the American Federation for Clinical Research in Washington.

These studies address the role of GAGs in the behavior of hepatic malignancy as well as the usefulness.

Some recent presentations made as a result of our work are listed below.

Secskas, E., Kupchella, C.E., Kennedy, J. and Espinosa, E. Glycosaminoglycan Changes Associated with Hepatic Tumors: The Contributions of Regeneration and Necrosis. Presented at the Association for American Physicians/American Society for Clinical Investigation/American Federation for Clinical Research National Meeting, Washington, D.C., May 7, 1979.

Kupchella, C.E., Drake, E. and Secskas, E. Glycosaminoglycan Patterns in Necrotic Liver, Regenerating Liver, and in Three Morris Hepatomas having Different Growth Rates. Presented at the Seventh Bi-Annual Hepatoma Conference, Washington, D.C., May 10, 1979.

Technical Proposal D -- Histological Systems of Detection. C.H. Tamburro,
G. Barrows, R. Schrodt.

The means of analyzing light electron microscopic sections of liver tissue quantitatively for the amount of collagen (scar tissue) in individuals exposed to vinyl chloride has demonstrated a great variation in the amount of stainable collagen present. This can vary from non-detectable collagen without the use of special collagen stains, such as the trichrome, to 35-40% of the total biopsy being occupied by fibrous tissue in the terminal stages of the disease. At this point all 110 biopsies from the vinyl chloride workers have been reviewed as to the degree of collagen deposition present. Morphometric analysis previously had been delayed in order to develop standards for the normal human collagen content at various ages. The study of the normal distribution of collagen content at the various ages in individuals without history of chemical, viral or medical disease, or injury to the liver, has had 14 individuals accessed. Approximately 4 are in the under 25 age group, 6-7 in the 25-40 age group, and 3 in the 40-50 age group. Preliminary data demonstrates an increase in the collagen deposition in the normal human liver associated with age. In the younger age group less than 1% of the studied area is occupied by stainable collagen. In the older age group stainable collagen in the sinusoidal areas may range as high as 5-6%. There is considerable overlap between individuals but close agreement between biopsies in the same individual. At present, the lower age ranges has sufficient cases to develop standards. A few additional cases are needed in the upper ranges. The acquisition of these additional cases depends on the availability of accidental deaths occurring in normal individuals of the older age group without evidences of hepatic disease. However, sufficient data is available for us to resume the morphometric analysis of the vinyl chloride exposed worker's liver biopsies utilizing the Hewlett-Packard 9864-A digitizer and a 9815-A micro computer.

Technical Proposal E -- Chemical Systems of Detection of Toxicity of Vinyl Chloride. J.L. Wong

In the previous report we have delineated the reaction pathways of chlorooxirane with 3,4-dichlorobenzenethiol and N-acetylcysteine. In both cases, the major product is the sulfur conjugate S-acetaldehyde. Since chlorooxirane can spontaneously rearrange to chloroacetaldehyde, we have proceeded to investigate the reaction intermediates of the latter in the detoxification by cellular sulfhydryl compounds. The reaction of chloroacetaldehyde with N-acetylcysteine under controlled pH conditions in aqueous medium at 0°C produced an intermediate compound. Upon warming up the reaction mixture to room temperature, our previously identified thiazene was isolated as the final product. In order to

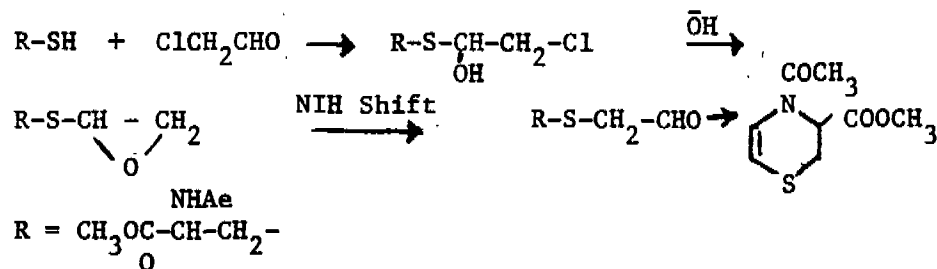
CONFIDENTIAL
Subject to Protective Order
Ross v. Cuccoo, No. 237
14th Judicial District Court
Calcasieu Parish, Louisiana

elucidate the stepwise formation of the thiazene-N-acetylcysteine methyl ester was allowed to react with chloroacetaldehyde in chloroform at 0°C. The initial product, plausibly the hemithioacetal $\text{H}_3\text{CO}-\overset{\text{O}}{\underset{\text{OH}}{\text{C}}}-\text{CH}-(\text{NHCOCH}_3)\text{CH}_2\text{S}-\underset{\text{OH}}{\text{CH}}-\text{CH}_2\text{Cl}$,

eliminated HCl upon neutralization with aqueous sodium hydroxide to produce the corresponding epoxide $\text{H}_3\text{COCOCH}(\text{NHCOCH}_3)\text{CH}_2\text{S}-\underset{\text{O}}{\text{CH}}-\text{CH}_2$. This structural assignment is supported

by its pmr spectrum. Furthermore, when this epoxide was extracted into chloroform, it rearranged to the S-acetaldehyde $\text{H}_3\text{COCOCH}(\text{NHCOCH}_3)\text{CH}_2-\text{S}-\text{CH}_2\text{CHO}$, identified by its pmr spectrum and comparison with that formed from the reaction of N-acetylcysteine with chlorooxirane.

Even though chlorooxirane and chloroacetaldehyde eventually give the same final product with N-acetylcysteine, the rate of reaction and the intermediates in the two reactions are different. The chlorooxirane conjugates instantaneously with the sulfhydryl compound, while chloroacetaldehyde takes about 2 1/2 hours for a comparable reaction. The reaction pathway for chloroacetaldehyde is proposed as follows.



These two metabolites are therefore both similar and different in their detoxification reaction with the RSH. Further study will continue to unravel the significance of either or both of chlorooxirane and chloroacetaldehyde in the mutagenesis/carcinogenesis problem of vinyl chloride.

Technical Proposal F -- Assays for the Carcinogenic Potential of Industrial Chemicals Utilizing Prokaryotic and Eukaryotic Systems. U.N. Streips in collaboration with G. Sonnenfeld

During the 2nd quarter we have concentrated on developing the interferon induction assay as a valid test for the carcinogenic potential of industrial chemicals. To this end the following results have been obtained:

14th Judicial District Court
Calcasieu Parish, Louisiana
No. 90-4837

14th Judicial District Court
Calcasieu Parish, Louisiana
No. 90-4837
Ross V. Seawell

- 1) Benzo-(a)-pyrene, #4 fraction of tobacco smoke condensate, 1,2-dimethylbenz (a) anthracene, 2-aminofluorine, aflatoxin-B₁, and styrene oxide all inhibited the induction of interferon by Newcastle disease virus.
- 2) MMS, a highly carcinogenic mutagen, inhibited the induction of interferon, while its analog, EMS, a rarely carcinogenic mutagen, had no effect on interferon induction.
- 3) Chloroacetaldehyde, the metabolite of vinyl chloride that is believed to be responsible for the actual carcinogenic event perpetrated by vinyl chloride, inhibited the induction of interferon by virus, but chloroethanol and chloroacetic acid, benign metabolites of vinyl chloride, had no effect on interferon induction.

These results suggest that the inhibition of interferon induction by chemicals may be a useful marker of the carcinogenic potential of a chemical, after extensive further study and collaboration of the results. The results were presented at the 1979 Annual Meeting of the American Society for Microbiology and at the International Symposium on Interferon of the Wadley Institutes of Molecular Medicine, and will appear in the form of two manuscripts. The Manufacturing Chemists Association has been recognized for its support to the completion of the data in the manuscripts.

Technical Proposal G -- Tissue Antigens and Antibodies in the Detection of Vinyl Chloride Injury. Enrique Espinosa

In order to further investigate antigen production by hepatoma application of the indirect immunofluorescent procedure to this question was investigated during this quarter. To accomplish this, several conditions for optimal growth of tumor cells sheets (PLC/PRF/5) in culture were studied. Satisfactory results were obtained by growing stationary cultures on coverslips in Leighton tubes at 37°C in a modified Eagle's medium containing 10% fetal calf serum. Cell morphology appeared excellent after 1/2 to 1/3 of confluency had developed in the coverslips. This was accomplished following seeding of 300,000 cells and culturing for 5-6 days. For the immunofluorescent staining the coverslips were then rinsed in Eagle's medium at room temperature and in cold ethanol in order to get rid of medium proteins. After fixation in ethanol (-75°C) for 10 minutes, The cells were tested for presence of several serum proteins (albumin, fibrinogen, transferrin, alpha 1-antitrypsin and alpha 2-macroglobulin). Specificity of the staining was

Mr. Joseph T. Seawell
2nd Quarterly Report
Page 7

CONFIDENTIAL
Subject to Protective Order in
Case V. S. No. 90-4837
14th Judicial District Court
Calcasieu Parish, Louisiana

shown by absence of fluorescence with absorbed antiserum, non-immune serum or buffered saline. With each protein, the fluorescence was restricted to the cell cytoplasm and an intense degree of fluorescence indicated relatively high levels of these proteins in a large proportion of the cells. Other individual cells showed varied degrees of fluorescence suggesting heterogeneity of the cell population with respect to the synthesis of these plasma proteins. Demonstration of presence of these proteins in the tumor cells by immunofluorescence is in agreement with results obtained by immunodiffusion as previously reported and thus provide another approach for the study of serum proteins and possibly other protein antigens by hepatoma.

Technical Proposal I -- Vinyl Chloride Metabolism in Isolated Liver Cells.
Richard C. Feldhoff

As reported for the preceding quarter we have experienced some difficulty in purchasing all of the special supplies needed for the in situ liver perfusion technique using our recently acquired liver perfusion apparatus.

In the meantime, we have continued to produce and purify rabbit anti-rat albumin antiserum. The antibodies which we are purifying will be used to quantitate the effects of ethanol and chemical monomers on the synthesis of serum albumin relative to total protein synthesis. Albumin is a constitutive product of the liver and perturbations in its rate of synthesis reflect alterations in normal cellular metabolic processes. Albumin synthesis has been reported to be particularly influenced by the levels of essential amino acids and ethanol. One of the primary intracellular effects is polysome disaggregation. Techniques are being developed to quantitatively recover undegraded polysomes from detergent-treated post-mitochondrial supernatants.

This completes the quarterly report from the University of Louisville Chemical Monomer Research Group. If there is need for further information or clarification, please do not hesitate to contact me.

Sincerely yours,



Carlo H. Tamburro, M.D.
Professor of Medicine
Chief, Division of Digestive
Diseases and Nutrition

CHT:vb

CMA 004353



CHEMICAL MANUFACTURERS ASSOCIATION

March 20, 1980

To: Vinyl Chloride Project Panel

CONFIDENTIAL
Subject to Protective Order in
Ross v. Conoco, Inc., No. 90-4837
14th Judicial District Court
Calcasieu Parish, Louisiana

Gentlemen:

Enclosed is a copy of a communication to Mr. Frank D. Kover that serves as a letter of transmittal for the report from Experimental Pathology Laboratories, Inc. (EPL) entitled "Vinyl Chloride Pathology Report". Please note the last paragraph of the letter and the fact that CMA has not attempted to evaluate the report as a Section 8(e) TSCA report because CMA does not have a reporting obligation under Section 8(e).

Also enclosed is a record of the Panel meeting held on March 18, 1980.

A copy of the EPL report is being sent to all Panel members who were unable to attend the March 18 meeting.

Sincerely,

J. T. Seawell
Project Administrator
Vinyl Chloride

JTS:db

Enclosures

CMA 004354

Formerly Manufacturing Chemists Association—Serving the Chemical Industry Since 1872.



BY MESSENGER

CHEMICAL MANUFACTURERS ASSOCIATION

March 19, 1980

Mr. Frank D. Kover - TS 792
Chief
Chemical Hazards Identification
Branch
Assessment Division
Environmental Protection Agency
401 M Street, S.W.
611 East Tower
Washington, D.C. 20460

CONFIDENTIAL
Subject to Protective Order in
Ross v. Conoco, Inc., No. 90-4837
14th Judicial District Court
Calcasieu Parish, Louisiana

Dear Mr. Kover:

On January 14, 1977, Mr. Albert Clark forwarded to Mr. Robert McGaughy of EPA, on behalf of the Manufacturing Chemists Association (now the Chemical Manufacturers Association), a copy of the protocol and the 23-month status summary for the Association-sponsored research on vinyl chloride at Industrial Bio-Test Laboratories (IBT). Mr. Clark stated in that letter that the final report was expected to be submitted soon, and when available, would be forwarded to the Agency.

As you know, all testing undertaken at IBT has come under a cloud. In particular, serious flaws were discovered in the vinyl chloride study, and no final report of the IBT study was ever issued. The Association undertook to determine whether the vinyl chloride study could be validated through an audit of the pathology by Experimental Pathology Laboratories (conducted by Dr. William Busey). Dr. Busey subsequently submitted a report of his audit to the Association on January 9, 1979. It was reviewed by an Association task force and, because it was part of a larger audit (including a review of compliance of IBT with good laboratory practices), was not further distributed at that time. Unfortunately, because of the interim change in the management of the Association and the extraordinary increase in the scientific work of the Association caused by the Toxic Substances Control Act and related environmental legislation, we failed to send it to the Agency as a follow-up to Mr. Clark's letter of January 14, 1977.

CMA 004355

Formerly Manufacturing Chemists Association—Serving the Chemical Industry Since 1872

1825 Connecticut Avenue, NW • Washington, DC 20009 • Telephone 202/328-4200 • Telex 89617 (CMA WSH)

Mr. Kover
March 19, 1980
Page Two

Recently, the Association has established a task force to oversee and coordinate all scientific testing projects. In the course of reviewing existing projects, this group discovered that we had not made Dr. Busey's audit report on the vinyl chloride study available to the Agency. Accordingly, I am enclosing a copy of the audit report as a follow-up to Mr. Clark's letter of January 14, 1977.

As shown in the interim report sent to the Agency in January, 1977, three suspect brain tumors were noted in male rats at the high dose level. These brain tumors, plus one at the lower dose level, were confirmed by pathology subsequently conducted by IBT and then by Dr. Busey. Unfortunately, not all of the brain specimens were retained by IBT and not all retained specimens were examined. The Association has therefore concluded to determine whether additional information can be obtained from whatever brain specimens remain at IBT from this highly-flawed study by conducting histopathological examination of all remaining brain tissues. We have not identified any other findings that would appear to warrant further attempts to salvage other information from this study.

We apologize for failing to follow-up on Mr. Clark's earlier letter, and wish to assure you that we will, in the future, keep you apprised of any additional relevant information as it becomes available to us.

While CMA does not itself have a Section 8(e) reporting obligation, and while it appears that this information would not be reportable under Section 8(e) in any event, pursuant to our earlier commitment we are submitting it to the Agency.

Sincerely yours,

Hasmukh Shah

Hasmukh C. Shah, Ph.D.
Director, Special Projects

cc: (with enclosure)
Mr. Robert McGaughy
Office of Research &
Development
Environmental Protection Agency

2287-03
MAR 20 1980
EPA

CMA 004356

Subject to Protection in
Ross v. Conoco, Inc., No. 90-4837
14th Judicial District Court
Calcasieu Parish, Louisiana

Chemical Manufacturers Association

Record of Meeting

VINYL CHLORIDE PROJECT PANEL

March 18, 1980

Washington Hilton Hotel

Washington, D. C.

CONFIDENTIAL

Subject to Protective Order in
Ross v. Conoco, Inc., No. 90-4837

MEMBERS PRESENT:

W. M. Smith
H. W. Blakeslee
T. R. Torkelson
T. J. Benya
R. Park
M. N. Johnson
Z. G. Bell
R. N. Wheeler

J. T. Seawell

14th Judicial District Court
Calcasieu Parish, Louisiana
Air Products & Chemicals, Inc.
CertainTeed Products
Dow Chemical Company
Ethyl Corporation
Firestone Plastics Co.
BFGoodrich Company
PPG Industries, Inc.
Union Carbide Corporation

CMA Staff

PRESENT BY INVITATION:

C. R. Hopper
J. P. Murphy
R. M. Walter
H. Shaw
R. W. Hill
G. K. Hatfield
J. Hanson
D. F. Zoll
E. Frost
W. Busey
W. F. Carroll
R. T. Gottesman

Gulf Oil Chemicals Co.
Stauffer Chemical Co.
Firestone Plastics Co.
CMA Staff
Diamond Shamrock
Diamond Shamrock
Dow Chemical Co.
CMA Staff
CMA Staff
Experimental Pathology Labs., Inc.
Firestone Plastics Co.
Tenneco Chemicals, Inc.

MEMBERS ABSENT:

J. T. Carter
W. Bittenbender
F. Kennedy
R. W. McBurney

BP Chemicals, Ltd.
Borden Chemical
Continental Oil Co.
Diamond Shamrock

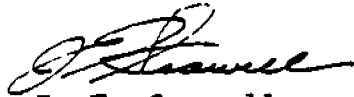
J. Lynch
R. W. Laundrie
J. Gabbett
C. A. Johnson
R. B. Judge
P. Cohen
R. L. Gibson
R. J. Abramowitz
G. Roush
A. G. Wheeler
S. K. Law
R. L. O'Connell
R. Brookman
V. L. Kirkland
J. Stauffer
P. M. Reed
W. D. Harris

CONFIDENTIAL
Subject to Protective Order in
Ross v. Conoco, Inc., No. 90-483/
14th Judicial District Court
Calcasieu Parish, Louisiana

Exxon Chemical Co.
General Tire & Rubber Co.
Georgia-Pacific Corp.
Goodyear Tire & Rubber
W. R. Grace & Company
Great American Chemical Co.
Gulf Oil Chemicals Co.
Hooker Chemicals & Plastics Corp.
Monsanto Company
ICI Americas, Inc.
Keysor-Century Corp.
Olin Corporation
Pantasote Company
Shell Chemical Co.
Stauffer Chemical Co.
Tenneco Chemicals, Inc.
Uniroyal, Inc.

-
- 1.0 Edmund Frost, Esq., summarized the purpose of the meeting and briefly described the history of the Panel's research project with Industrial BIO-Test and an audit of the study by the Experimental Pathology Laboratory (EPL).
 - 2.0 Following a discussion of EPL's January 9, 1979 "Vinyl Chloride Pathology Report" a motion was made, duly seconded and passed to submit the Report forthwith to the U. S. Environmental Protection Agency.
 - 3.0 Following a discussion of the research project conducted by Industrial BIO-Test, a motion was made, duly seconded and passed to immediately conduct further pathologic analysis of all remaining brain tissue salvageable from the study.

PRIVILEGED MATERIAL REDACTED



J. T. Seawell
Project Administrator
Vinyl Chloride

JTS:md

Record Subject to Approval

March 20, 1980

CONFIDENTIAL
Subject to Protective Order in
Ross v. Conoco, Inc., No. 90-4837
14th Judicial District Court
Calcasieu Parish, Louisiana

- 4.0 Following discussion of CMA's efforts to terminate the Industrial BIO-Test contract and to seek reimbursement of funds, it was the consensus of the Panel that no additional efforts were required at this time and that the CMA Legal Department would handle the remaining aspects of the matter.



J. T. Seawell
Project Administrator
Vinyl Chloride

JTS:md

Record Subject to Approval

March 20, 1980

CONFIDENTIAL
Subject to Protective Order in
Ross v. Conoco, Inc., No. 90-4837
14th Judicial District Court
Calcasieu Parish, Louisiana

Chemical Manufacturers Association

VINYL CHLORIDE PROJECT PANEL

Washington Hilton
Georgetown West

March 18, 1980

11:00 a.m.

CONFIDENTIAL
Subject to Protective Order in
Ross v. Cenoco, Inc., No. 90-4837
14th Judicial District Court
Calcasieu Parish, Louisiana

PROPOSED AGENDA

1. Introduction and Purpose of the Meeting
2. Background Information on Industrial BIO-TEST research project and an audit of this study by Experimental Pathology Laboratory
3. Disposition of Busey Report
4. Additional treatment and disposition of Industrial BIO-TEST data and tissues
5. Termination of Industrial BIO-TEST Contract and legal claim
6. Other follow-up work

CMA 004360



CHEMICAL MANUFACTURERS ASSOCIATION

February 29, 1980

CONFIDENTIAL
Subject to Protective Order in
Ross v. Conoco, Inc., No. 90-4837
14th Judicial District Court
Calcasieu Parish, Louisiana

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,

J. T. Seawell
Project Administrator
Vinyl Chloride

JTS:das

Enclosures

CMA 004361

Formerly Manufacturing Chemists Association—Serving the Chemical Industry Since 1872.



CHEMICAL MANUFACTURERS ASSOCIATION

~~CONFIDENTIAL~~

Subject to Protective Order in
Ross v. Conoco, Inc., No. 90-4837
14th Judicial District Court
Calcasieu Parish, Louisiana

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.

CMA 004362

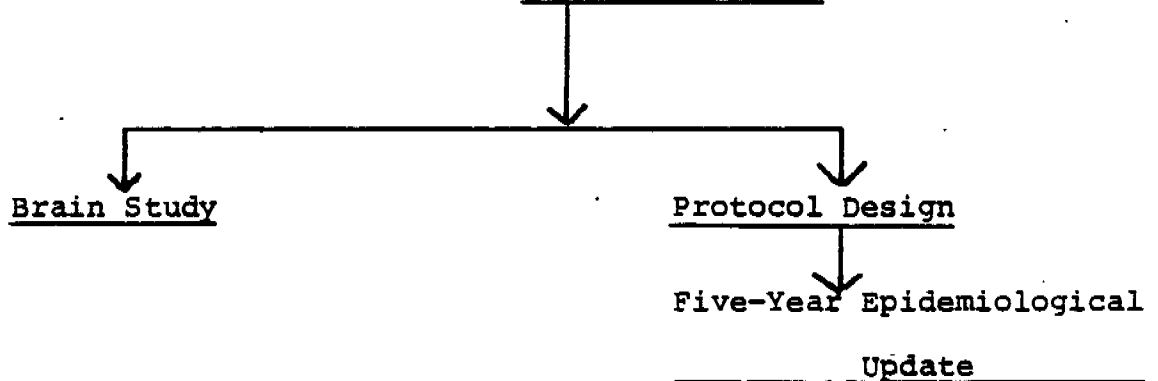
Formerly Manufacturing Chemists Association—Serving the Chemical Industry Since 1872.

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



CONFIDENTIAL
Subject to Protective Order in
Ross v. Conoco, Inc., No. 90-4837
14th Judicial District Court
Calcasieu Parish, Louisiana

Possible Study Designs:

- Plan A
- Plan B
- Plan C

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.

CONFIDENTIAL
Subject to Protective Order in
Ross v. Conoco, Inc., No. 90-4837.
14th Judicial District Court
Calcasieu Parish, Louisiana

CMA 004364

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	\$10,580

CONFIDENTIAL
Subject to Protective Order in
Ross v. Conoco, Inc., No. 90-4837
14th Judicial District Court
Calcasieu Parish, Louisiana

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

CONFIDENTIAL

Subject to Protective Order in
Ross v. Conoco, Inc., No. 90-4837
14th Judicial District Court
Calcasieu Parish, Louisiana

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.

CONFIDENTIAL

Subject to Protective Order in
Ross v. Conoco, Inc., No. 90-4834
14th Judicial District Court
Calcasieu Parish, Louisiana

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
<u>Consultants</u>	
Biostatistician	\$10,175
Physician/Epidemiologist	<u>2,720</u>
	12,895
Other Direct Costs	<u>11,700</u>
Total Cost	\$54,851

Study Plan B

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.

CONFIDENTIAL
Subject to Protective Order in
Ross v. Conoco, Inc., No. 90-4837
14th Judicial District Court
Calcasieu Parish, Louisiana

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.

CONFIDENTIAL
Subject to Protective Order in
Ross v. General Corp., No. 90-4837
14th Judicial District Court
Calcasieu Parish, Louisiana

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

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.
- ☐ We do not agree.
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.

CONFIDENTIAL
Subject to Protective Order in
Ross v. Conoco, Inc., No. 90-4937
14th Judicial District Court
Calcasieu Parish, Louisiana

CMA 004370

Item No.

Inquiry

- 4.2 ☐ We are interested in financially sponsoring a thoroughgoing case study of the brain tumor cases.
- ☐ We are not interested.
- 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 th 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.
- 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.
- ☐ We intend to financially sponsor the preparatory study and the follow-up of brain tumor cases and ar 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.

CONFIDENTIAL

Subject to Protective Order in
Ross v. Conoco, Inc., No. 90-4837
14th Judicial District Court
Calcasieu Parish, Louisiana