DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Agency for Toxic Substances
and Disease Registry
Atlanta GA 30333

November 8, 1995

Hasmukh C. Shah, Ph.D.
Manager, Vinyl Chloride Panel
Chemical Manufacturers Association
2501 M Street, N.W.
Washington, DC 20037

Dear Dr. Shah:

This is in response to your October 23 letter in which you enclosed (1) a revised study protocol, "Vinyl chloride: Combined inhalation two-generation reproduction and developmental toxicity study in CD rats," and (2) the Chemical Manufacturers Association's (CMA) response to the Agency for Toxic Substances and Disease Registry's (ATSDR) peer reviewers' comments on the protocol. The study protocol was submitted by CMA to ATSDR for the purpose of conducting voluntary research to address ATSDR's priority data needs for vinyl chloride.

We have reviewed the CMA responses and the revised study protocol and found them to be satisfactory. Also, we agree with CMA's rationale for reducing the number of animals in the developmental study to 25 per group from 30 per group as described in the original protocol. With regard to a neurotoxicity component for this study, we confirm that the Environmental Protection Agency does not require additional neurotoxicity data at this time.

Therefore, we ask that you complete a memorandum of understanding (MOU) for the combined inhalation two-generation reproduction and developmental toxicity study and forward it to ATSDR. A hard copy and an electronic version of the ATSDR MOU are enclosed for your use.

In addition to reproductive and developmental toxicity studies via inhalation, I would like to bring to your attention two other ATSDR priority toxicity data needs for vinyl chloride, specifically, dose-response data in animals exposed via inhalation for acute- and chronic-duration. This was described in the Agency's March 10, 1994, Federal Register notice, "Status of the Superfund Substance-Specific Applied Research Program; Notice" (59 FR 11434), and Priority Data Needs Document for Vinyl Chloride.

Recently, we reevaluated the toxicity database for inhalation exposure for acute-duration. We determined that, at the present time, there is no need to obtain additional data as originally stated in the ATSDR Federal Register notice and priority data

needs document. This is reflected in the updated Toxicological Profile for Vinyl Chloride that is available for public comment.

With regard to chronic-duration studies via inhalation, we believe that the available data do not provide a suitable lowest-observed-adverse-effect level (LOAEL) or a no-observed-adverse-effect level for deriving ATSDR's Minimal Risk level (MRL). The MRL is defined as an estimate of daily human exposure to a dose of a chemical that is likely to be without an appreciable risk of adverse noncancerous effects over a specified duration of exposure.

The lowest LOAEL identified in a chronic-duration study was for a serious end point (testicular necrosis) in a rat study. However, MRLs are not derived using a serious end point. In addition, carcinogenicity was observed at concentrations equal to and less than that for testicular necrosis. Therefore, we have identified a priority data need to conduct additional animal studies via the inhalation route, the most relevant exposure route for populations living in the vicinity of hazardous waste sites. These studies are needed for determining exposure concentrations of vinyl chloride that establish dose-response relationships and defining threshold levels for chronic adverse health effects.

In light of the leadership role of CMA in conducting research on vinyl chloride, and the Agency's need to obtain additional data on vinyl chloride, we would also be interested in discussing opportunities for collaborative research to address this need. Please let me know of your interest in discussing this potential research.

We look forward to signing the MOU with CMA and to a continuing dialogue with CMA leading to additional successful voluntary research efforts to address ATSDR's data needs for vinyl chloride. If you have any questions, please call me at 404-639-6306.

Sincerely yours,

William Cibulas

William Cibulas, Ph.D.
Chief, Research Implementation Branch

Enclosures

cc:
Dr. Christopher T. DeRosa
Mr. Caffey Norman

MEMORANDUM OF UNDERSTANDING FOR VOLUNTARY RESEARCH PROGRAM

Under Section 104(i)(5) of CERCLA

An agreement between

THE AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY
Division of Toxicology
Research Implementation Branch

and

(Name of Participating Company)

(Date of signing this Memorandum of Understanding)

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I. PURPOSE

This Memorandum of Understanding (MOU) is entered into by the Agency for Toxic Substances and Disease Registry (ATSDR) and the private sector organization(s) identified in Paragraph I below (hereinafter referred to as the "company") in order to implement Section 104(i)(5) of the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA), as amended by the Superfund Amendments and Reauthorization Act of 1986 (SARA). These Congressional acts direct ATSDR to assure the initiation of a program of research designed to determine the health effects of hazardous substances for which adequate health effects information is not available. In order to facilitate the discharge of ATSDR's responsibilities under Section 104(i)(5) of CERCLA, and in recognition of the fact that the company includes manufacturers and/or processors, or registrants of the hazardous substance(s) that is the subject of this MOU, ATSDR and the company hereby agree as follows:

II. IDENTIFICATION OF THE COMPANIES THAT ARE PARTIES TO THIS MEMORANDUM OF UNDERSTANDING

The following companies are parties to this MOU and shall be responsible for ensuring that the obligations and undertakings of the companies under this MOU are discharged and carried out as provided herein:

Names and Addresses of Participating Companies

III. IDENTIFICATION OF THE SUBSTANCE(S) SUBJECT TO RESEARCH REQUIREMENTS UNDER THIS MEMORANDUM OF UNDERSTANDING

The chemical substance(s) that is the subject of this MOU is _____ (CAS No._____). The chemical substance to be tested shall be as pure as reasonably can be attained. However, under certain circumstances, ATSDR recognizes that it may be more desirable to test mixtures or technical grade products. [Note: Substitute alternative language when the subject of the research is a human population as in epidemiologic studies].

IV. IDENTIFICATION OF THE EFFECTS OR CHARACTERISTICS FOR WHICH RESEARCH IS TO BE CONDUCTED

The health effects, environmental fate or other characteristics for which research is to be conducted by the company under this MOU are listed below:

[To be listed by the company]

V. IDENTIFICATION OF STUDY PLANS AND TESTING PROTOCOLS AGREED TO BY ATSDR AND THE COMPANY PRIOR TO SIGNING OF MOU

The research to be conducted on (name of chemical substance) pursuant to this MOU is identified in Table 1 below. The study plan, guidelines and protocols that were agreed to by ATSDR and the company are listed in Table 1 and described in detail in an Attachment to this MOU. The company agrees to perform (or sponsor and fund the performance of) the research identified in Table 1 in accordance with the guidelines and schedules established pursuant to the study plan and testing protocols agreed to prior to signing of this MOU.

TABLE 1
IDENTIFICATION OF STUDY PLANS AND TESTING PROTOCOLS AGREED TO BY ATSDR AND THE COMPANY PRIOR TO SIGNING OF MOU

COMPANY _____

TEST SUBSTANCE _____

IDENTIFICATION OF STUDY PLAN

Title _____

ID # _____

TEST TO BE CONDUCTED	GUIDELINES		
	TSCA*	Other EPA Guidelines	Alternate Guidelines

* Citation to 40 C.F.R. where appropriate

VI. SUBMISSION OF STUDY PLANS AND ESTABLISHMENT OF SCHEDULE FOR INITIATION OF RESEARCH AND SUBMISSION OF INTERIM AND FINAL REPORT

A. Prior to signing of this MOU the company shall submit to ATSDR the study plan for each test that is to be conducted pursuant to this MOU (see Appendix 1).

B. Prior to entering into this MOU, the study plan including all testing protocols and guidelines shall be reviewed by an ATSDR appointed peer review panel. Consistent with CERCLA section 104(i)(13), the peer review panel will consist of no fewer than three nor more than seven peer reviewers who a) are selected by the Administrator of ATSDR; b) are disinterested scientific experts; c) have a reputation for scientific objectivity; and d) lack institutional ties with any person involved in the conduct of the study under review.

C. The study shall be initiated within 8 weeks of the date on which ATSDR and the company have signed this MOU. Written notification of the starting date of the test will be submitted to ATSDR by the company. The completion date of the study will be established from the approved study plan.

D. Unless modified pursuant to Paragraph VII, a final draft report on the results of testing conducted pursuant to the approved study plan and signed into agreement under this MOU

shall be submitted to ATSDR within 20 weeks of the end of the study for ATSDR's peer review, consistent with CERCLA section 104(i)(13). Following acceptance by ATSDR, upon recommendation by the peer review panel, the company will submit a final report of the study to ATSDR within 4 weeks. Final reports will not be accepted if the data is designated Confidential Business Information (CBI) or otherwise restricted from public disclosure with the exception of personally identifiable information on study subjects. [Note: When the MOU covers multiple tests, different final report periods could be established for the different tests].

E. Unless modified pursuant to Paragraph VII, interim progress reports on each testing program conducted pursuant to a study plan approved by ATSDR under this MOU shall be submitted to ATSDR within 6 months after the initiation of testing, and thereafter, within 6 months after the submission of each previous interim report. If the study is scheduled to be completed in one year, an interim brief letter addressing the status of the research must be submitted to ATSDR within 6 months of the initiation of the study.

VII. MODIFICATION OF STUDY PLANS, GUIDELINES, AND SCHEDULES

A. If the company seeks to modify a study plan, guidelines, or schedules that have been approved by ATSDR pursuant to this MOU, the company shall notify ATSDR in writing of the proposed modifications and the reasons therefor. ATSDR shall respond in writing to the proposed modifications within 2 to 6 weeks either: (i) approving the modifications as proposed, (ii) approving the modifications as revised by ATSDR, or (iii) disapproving the modifications entirely. If ATSDR does not approve the modifications as proposed, the company will have 2 weeks within which to: (i) accept ATSDR's decision and proceed in accordance therewith, (ii) request that ATSDR reconsider its decision, or (iii) withdraw from the MOU. ATSDR will respond to request for reconsideration within 2 weeks (see Figure 1).

B. If the company submits a request for modification to ATSDR pursuant to Paragraph VII. A., the time schedule established for completion of these tests shall be extended by the length of time required by ATSDR and the company to respond to and approve the modifications.

VIII. OBSERVANCE OF GOOD LABORATORY PRACTICES

All research agreed to in this MOU shall be conducted in accordance with the Good Laboratory Practice (GLP) standards

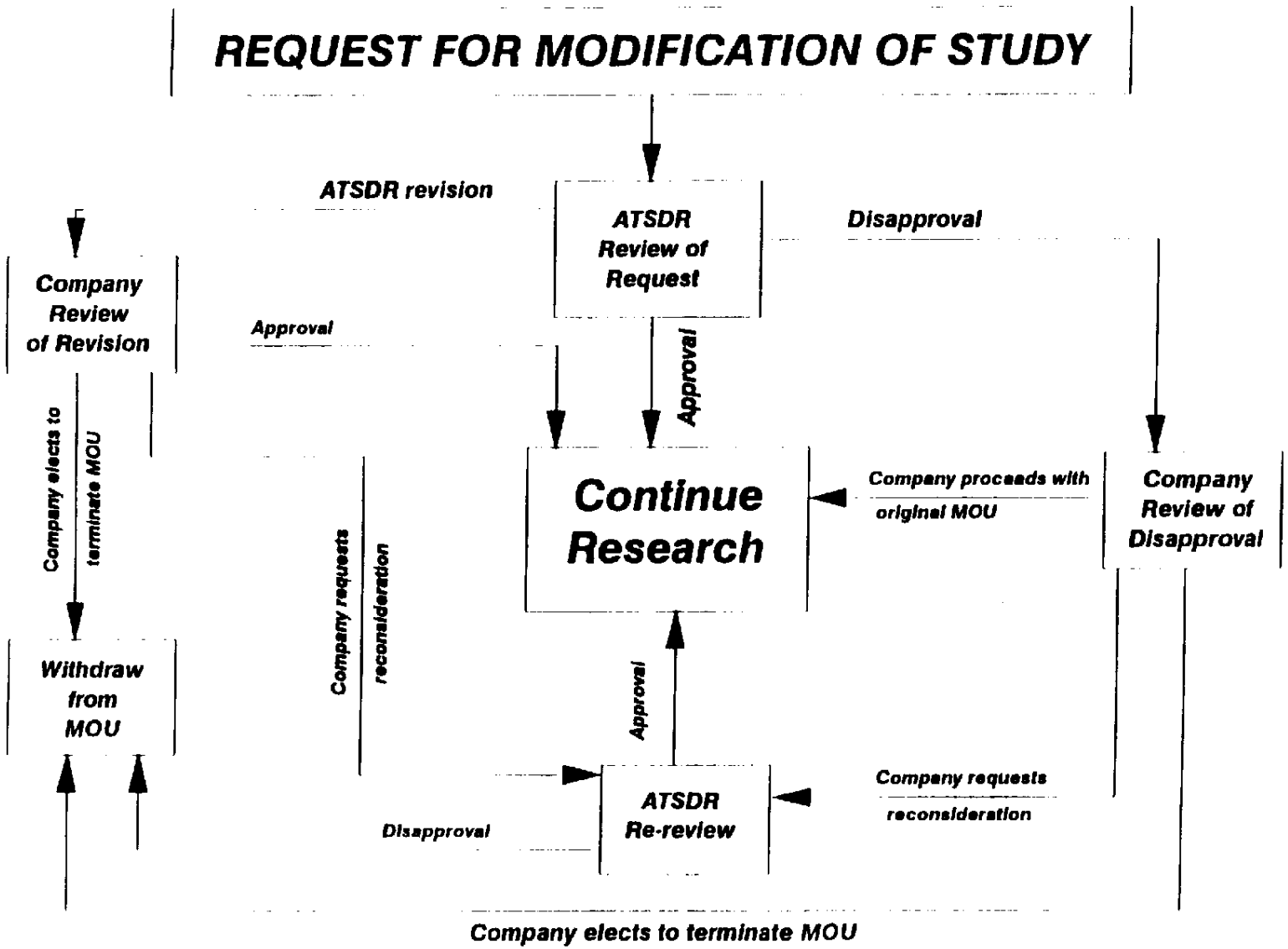
REQUEST FOR MODIFICATION OF STUDY
ATSDR revision
ATSDR Review of Request
Disapproval
Company Review of Revision
Approval
Approval
Company elects to terminate MOU
Continue Research
Company proceeds with original MOU
Company Review of Disapproval
Company requests reconsideration
Withdraw from MOU
Approval
ATSDR Re-review
Company requests reconsideration
Disapproval
Company elects to terminate MOU

Figure 1.

codified in 40 C.F.R. Part 792, Subparts B, C, D, E, F, G, J, and L, to the extent that such GLP standards apply. Should Good Epidemiology Practices ("e.g., Guidelines for Good Epidemiology Practices for Occupational and Environmental EPidemiologic Research"--The Chemical Manufacturers Association's Epidemiology Task Group, Journal of Occupational Medicine, Volume 33, 1221-1229, 1991) be relevant to a research project, those Practices should be affixed to the study plan.

IX. INSPECTIONS

The company shall ensure that an authorized employee or duly designated representative of ATSDR is permitted, at reasonable times and in a reasonable manner, to (i) inspect any research or testing facility that is conducting research pursuant to this MOU, and (ii) inspect (and, in the case of records, copy) any records and specimens required to be maintained in connection with research performed pursuant to this MOU.

X. PAYMENT OF COST AND EXPENSES

The company agrees to pay all costs, direct and indirect, associated with the research programs. ATSDR will assume responsibility for administrative costs including the cost of peer review as part of its overall program.

XI. EVENTS CONSTITUTING A BREACH OF THIS MEMORANDUM OF UNDERSTANDING

Failure by the company to:

i) initiate any test agreed to in the approved study plan, appended to this MOU, by the date established pursuant to the study plan;

ii) adhere to GLP's or established test procedures to the extent that these standards apply;

iii) submit any interim report required under this MOU by the date established pursuant to this MOU; or

iv) submit any final report which receives ATSDR's approval following the peer reviewers' recommendations

shall constitute a breach of this MOU. In the event of a breach, ATSDR will not impose any claim to damages, but at the Agency's discretion may terminate the MOU.

Since this MOU is entered into voluntarily by both parties, termination by ATSDR is not considered reviewable agency action pursuant to the Administrative Procedures Act or any other applicable federal law, and there will be no appeal process beyond that set out in the agreement or otherwise mutually agreed to by the parties.

XII. FINAL REPORT - SUBMISSION AND PUBLICATION OF DATA

All data and reports submitted to ATSDR pursuant to this MOU shall be sent to ATSDR, in duplicate, at the address indicated in Paragraph XIV below. Acceptance of the final report is contingent upon approval by ATSDR following the peer review panel's recommendations, consistent with CERCLA peer review requirements. The company maintains all rights to publication of data and results, however all results of research conducted pursuant to this MOU and all supporting data associated with the final research report will be made available by ATSDR to the public as part of its implementation of Section 104(i)(5) of CERCLA. The final report will not be accepted if the data is designated Confidential Business Information (CBI) or otherwise restricted from public disclosure with the exception of personally identifiable information on study subjects.

XIII. STATUTORY COMPLIANCE

Nothing in this MOU shall be construed to delay or otherwise affect or impair the authority of the President, the Administrator of ATSDR, or the Administrator of EPA to exercise any authority of the President, the Administrator of ATSDR, or the Administrator of EPA under any other provision of law, including TSCA and FIFRA, or the response and abatement authorities of CERCLA.

XIV. ADDRESSES

Any notifications, reports, or other written statements required to be submitted or sent to a party to this MOU shall be sent by certified mail to the parties at the following addresses:

Agency for Toxic Substances and Disease Registry
Division of Toxicology, Research Implementation Branch
Mail Stop E-29
1600 Clifton Road, N.E.
Atlanta, GA 30333

Attention: Dr. William Cibulas

Company I
Address

Attention: _____

Company II
Address

Attention: _____

XV. SIGNATURES

Agency for Toxic Substances and Disease Registry

Date: _____ By: _____

Company I.

Date: _____ By: _____

Company II.

Date: _____ By: _____

Appendix 1

Study Plan and Testing Protocols

Prior to study plan negotiations, ATSDR and the company shall sign a Letter of Intent indicating the good faith intention of both parties to achieve a mutually acceptable study plan. The study plan shall be negotiated and agreed upon prior to the signing of the MOU by ATSDR and the company. The following describes minimal requirements of the study plan. The attached time schedule (Table 2) reflects only the time line contained within the MOU. Other scheduling will be negotiated prior to signing of the MOU

The study plan will consist of (1) the identity of the MOU under which testing will be performed; (2) the specific tests to be performed; (3) the name(s) and address(es) of the company which will conduct the study; (4) the test protocol, including, where appropriate; (i) the rationale for any combination of test protocols, (ii) the rationale for species/strain selection, (iii) dose selection (and supporting data), (iv) route(s) or method(s) of exposure, (v) description of diet to be used and its source, including nutrients and contaminants and their concentrations, (vi) for in vitro test systems, a description of culture medium and its source, (vii) and a summary of expected spontaneous chronic disease (including tumors), genealogy, and life span; (5)

a schedule, with reasonable timetables and deadlines, for initiation and completion of each short-term test and of each major phase of long-term tests, and submission of interim progress report and final report to ATSDR; and (6) supporting data on the chemical substance(s) being tested, including physical constants, spectral data, chemical analysis, and stability under test and storage conditions, as appropriate. In some cases, the obligation to conduct research is contingent upon the results of certain tests that are to be performed first.

Prior to a company entering into an MOU with ATSDR, the study plan including all testing protocols and guidelines shall be reviewed by an ATSDR appointed peer review panel. Consistent with CERCLA section 104(i)(13), the peer review panel will consist of no fewer than three nor more than seven peer reviewers who a) are selected by the Administrator of ATSDR; b) are disinterested scientific experts; c) have a reputation for scientific objectivity; and d) lack institutional ties with any person involved in the conduct of the study under review.

TABLE 2

TIME SCHEDULE FOR STUDY PLANS					
Action		Secondary Action	Weeks to Implement Action	Weeks (Total)	Additional Review (Weeks)
Submit Statement of Interest for TASARC review		----------	----	----	----
Submit Letter of Intent		----------	0	0	----
Negotiation of study plan		----------			----
ATSDR study plan peer review		----------			----
Signing of approved study plan		----------			----
Signing of MOU		----------			----
Begin study		----------	8		----
	Request to modify study plan	ATSDR's response to modified study plan			2-6
		Disapproval	Company requests reconsideration		2
			ATSDR response to request		2
Interim Report		----------	Due every 6 months	----	----
End of study		----------			----
	Final Draft Report	----------	20		----
	ATSDR's Peer Review	----------			----
Final Report		----------	4		----