DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Agency for Toxic Substances
and Disease Registry
Atlanta GA 30333

JAN 23 1995

received
1/25/95

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 November 28 letter regarding the intent of the Chemical Manufacturers Association (CMA) Vinyl Chloride Panel to address vinyl chloride data needs identified by the Agency for Toxic Substances and Disease Registry (ATSDR). We have discussed your letter with Dr. Auer and his staff at the Environmental Protection Agency (EPA). ATSDR and EPA will continue to coordinate all voluntary research interests concerning chemicals identified in the September 30 notice (59 FR 49934).

We are pleased that CMA is interested in conducting voluntary research to address ATSDR's data needs for vinyl chloride. In your letter, you indicated that a Memorandum of Understanding (MOU) to address these data needs will be executed by May 31, 1995. Also, you suggested that CMA and ATSDR scientists meet to discuss the design of a two-generation reproductive study by the inhalation route, however, we request that CMA take the lead role in developing the study protocol. Consistent with ATSDR's published procedures for conducting voluntary research (57 FR 54160), we ask that CMA submit a study protocol to be reviewed by Agency scientists and a panel of peer reviewers selected by the Associate Administrator for Science, ATSDR. At that time, it would be appropriate for the Agency to discuss the study plan with CMA including study protocol and time schedule. The Agency and CMA may then choose to enter into an MOU after agreeing upon an approved study plan. A copy of the Federal Register notice describing these procedures is enclosed for your information.

With regard to ATSDR's data need for a 2-species developmental toxicity study via inhalation, please clarify the statement in your letter concerning the existing 2-species developmental study and other available developmental toxicity data. Specifically, we would like to know how such studies "might be

enhanced to include measures of developmental toxicity as an alternative to the two-species developmental toxicity referred to EPA."

We look forward to our continuing dialogue with CMA leading to the signing of an MOU to conduct research to address ATSDR's data needs for vinyl chloride. If you have any questions, please contact me at 404-639-6300.

Sincerely yours,

Christopher T. DeRosa

Christopher T. DeRosa, Ph.D.
Director, Division of Toxicology

Enclosure

cc:
Dr. Charles Auer

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Agency for Toxic Substances and Disease Registry

[ATSDR-61]

Revised Procedures For Conducting Voluntary Research

AGENCY: Agency for Toxic Substances and Disease Registry (ATSDR), Public Health Service (PHS), Department of Health and Human Services (HHS).

ACTION: Notice.

SUMMARY: This notice announces the revised procedures for volunteering to conduct research as part of the ATSDR Substance-Specific Applied Research Program authorized by the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA or Superfund), as amended. The procedures for conducting voluntary research were initially announced in the Federal Register on February 7, 1992 (57 FR 4758). The public was invited to comment on the procedures and the attendant Memorandum of Understanding (MOU). The voluntary research will be conducted by the private sector to fill priority data needs for hazardous substances that are the subjects of the ATSDR toxicological profiles. This notice describes the revised procedures.

DATES: The ATSDR considers this voluntary research effort to be of significant importance to the continuing development of the Substance-Specific Applied Research Program. Therefore, public comments concerning this Federal Register notice will be accepted throughout the Agency's involvement with voluntary research.

ADDRESSES: Comments on this notice should bear the docket control number ATSDR-61 and should be submitted to the Division of Toxicology, Research Implementation Branch, Agency for Toxic Substances and Disease Registry, Mailstop E-29, 1600 Clifton Road NE., Atlanta, Georgia 30333. Requests for a copy of the model Memorandum of Understanding should be addressed similarly.

Comments on this notice will be available for public inspection at the Agency for Toxic Substances and Disease Registry, Building 4, Suite 2400, Executive Park Drive, Atlanta, Georgia (not a mailing address), from 8 a.m. until 4:30 p.m., Monday through Friday, except for legal holidays.

FOR FURTHER INFORMATION CONTACT: Dr. William Cibulas, Division of Toxicology, Research Implementation Branch, Agency for Toxic Substances and Disease Registry, Mailstop E-29, 1600 Clifton Road NE., Atlanta, Georgia 30333, telephone 404-639-6306.

SUPPLEMENTARY INFORMATION:

Background

The Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA), as amended by the Superfund Amendments and Reauthorization Act of 1986 (SARA) (42 U.S.C. 9604(i)), requires that ATSDR: (1) Develop jointly with the Environmental Protection Agency (EPA) a list of hazardous substances found at National Priorities List (NPL) sites (in order of priority), (2) prepare toxicological profiles of these substances, and (3) assure the initiation of a research program to fill identified data needs associated with the substances.

The identification of the priority data needs for 38 priority hazardous substances was described in the Federal Register (56 FR 52178, October 17, 1991), public comments were invited, and companies were requested to volunteer to conduct research to fill specific priority data needs during the public comment period for that notice. The Federal Register notice, "Announcement of Final Priority Data Needs for 38 Priority Hazardous Substances", which includes a second call for private sector voluntarism, is being published in this issue of the Federal Register. Future Federal Register notices will announce the names of companies that have volunteered to fill specific priority data needs.

The major purpose of this ATSDR Substance-Specific Applied Research Program is to supplement the substance-specific information needs of the public and scientific community, and to supply necessary information for conducting comprehensive public health assessments for populations living in the vicinity of hazardous waste sites. This program will also provide data that can be generalized to other substances or areas of science, including risk assessments of chemicals, thus creating a scientific base for filling a broader range of data needs.

Procedure for Conducting Voluntary Research

CERCLA, as amended in section 104(i)(5)(D), states that it is the sense of Congress that the costs for conducting this research program be borne by the manufacturers and processors of the hazardous substances under the Toxic Substances Control Act (TSCA) and registrants under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), or by cost recovery from responsible parties under CERCLA. Furthermore, section 104(i)(5)(C) states that in developing and implementing the research program, the Administrator of ATSDR and the Administrator of EPA shall coordinate such program with the National Toxicology Program (NTP) and with programs of toxicological testing established under TSCA and FIFRA. To achieve this coordination, ATSDR established the Triagency Superfund Applied Research Committee (TASARC) as a forum for ATSDR, EPA, and NTP to discuss and coordinate use of potential mechanisms for developing and implementing this CERCLA Substance-Specific Applied Research Program. Meetings of the TASARC are not open to the public. The first meeting of TASARC was held on April 20, 1992, to inform the Committee on the Agency's progress in implementing the Substance-Specific Applied Research Program, and to seek the Committee's input in planning for the Agency's public meeting on voluntary research held on April 29, 1992.

The ATSDR encourages private sector organizations to conduct voluntary research to fill specific priority data needs identified in the Agency's Substance-Specific Applied Research Program. Toward that end, the procedures for conducting voluntary research, and the attendant Memorandum of Understanding, were developed by ATSDR and announced in the Federal Register on February 7, 1992 (57 FR 4758). The Agency is aware of concerns within some segments of the public regarding voluntary research conducted by companies with vested interests in the research. Therefore, the Agency encouraged the public to comment on ATSDR's procedure for conducting voluntary research. Additionally, for each research project conducted voluntarily, the MOU (signed by ATSDR and the interested company), the ATSDR approved study plan, peer reviewer's comments, and the final research report and supporting data will be available for public inspection at the location and times indicated in the **ADDRESSES** section of this notice.

ATSDR intends to enter into voluntary research projects in ways that lead only to high quality scientific work. This necessitates peer review of study protocols and results consistent with CERCLA section 104(i)(13). CERCLA requires the peer review panel to consist

of three to 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 or research under review.

The ATSDR held a public meeting on April 29, 1992, to discuss the proposed procedures for voluntary research. Comments were received from industry groups, environmental groups and Federal agencies. As a result of discussions at these two meetings and other public comments received by the Agency, ATSDR has revised the voluntary research procedures. The major revisions and clarification of the procedures are described below.

ATSDR now believes that prior to negotiation of the study plan, it would be more appropriate to have a Letter of Intent submitted by the interested company, rather than to have the MOU signed by the interested company and the Agency as originally indicated. In the revised procedures, the interested company and ATSDR will enter into an MOU after the study plan has been approved by the Agency. Furthermore, the procedures will now indicate that ATSDR encourages innovative protocols, where appropriate. With respect to the role of peer review, ATSDR will continue to pursue its policy of peer review of both study protocols and results as mandated under CERCLA. However, to the extent that research protocols entail accepted test guidelines developed under TSCA, FIFRA or by organizations such as the Organization for Economic Cooperation and Development (OECD), less rigorous peer review of the study protocol may be required. Furthermore, the peer review process will not supersede the function of Institutional Review Board activities related to protection of human subjects or animals.

With respect to potential termination of the MOU at the convenience of either party, ATSDR intends that this action will be taken as a last resort, and that prior to such an action, all possible avenues of dialogue with the private sector organization would be pursued, within reasonable limits. However, decisions as to what constitutes a breach of the MOU will be at the discretion of ATSDR. Moreover, ATSDR recognizes that in the course of conducting research, unexpected and unanticipated delays may occur and wherever possible this will be negotiated with the private sector organization in the spirit of mutual cooperation.

The Agency is cognizant of the private sector's concern that EPA may require industry testing during or following a voluntary research effort with ATSDR which may be regarded as duplicative of that effort. There are several safeguards to prevent this from happening. First, ATSDR, EPA, and NTP are coordinating to conserve the testing resources of both the government and the private sector and avoid unnecessary or duplicative testing. This coordination occurs at many points: the review of ATSDR's toxicological profiles, review of ATSDR data needs documents, meetings of TASARC and the Interagency Testing Committee, and review of research proposals developed under ATSDR's voluntary research program. EPA intends to review research proposals developed under this program for conformity with basic testing concepts under TSCA, FIFRA, and the OECD.

Second, the Toxic Substances Control Act expressly requires EPA to find that data are inadequate to reasonably determine or predict the effects of a chemical substance. EPA has already interpreted this to mean that it cannot require duplicative testing. As a matter of policy EPA will not require testing in a rule which duplicates ongoing testing by government or the private sector pursuant to an MOU until the test data are submitted, reviewed and determined to be inadequate. There may be instances where research conducted under an industry/ATSDR MOU will yield results which indicate additional testing is necessary or where the testing under the MOU is not intended to address the endpoint of concern to EPA. In these cases, EPA may exercise its authority to require testing under TSCA or FIFRA.

It is generally the policy of ATSDR to rely on data and studies which are publicly available, with the exception of personally identifiable information on study projects. Therefore, research conducted under this program should be designed so as not to disclose Trade Secrets or other Confidential Business Information. If the company finds that such research is impossible to conduct under this restriction, ATSDR will enter into discussions of alternative solutions, or may choose to terminate negotiations.

Finally, in reference to research costs, the direct and indirect costs associated with the research program are those incurred by the research sponsor and not by ATSDR. The Agency will assume responsibility for administrative costs including the cost of peer review as part of its overall program.

The procedures for conducting voluntary research are described below. Private sector organizations (companies) interested in volunteering to conduct research on priority data needs are asked to submit to ATSDR, in writing, a brief statement that addresses the priority data need(s) to be filled and the methods to be used. It should be noted that ATSDR encourages innovative protocols, where appropriate. Therefore, the interested company should indicate when innovative protocols are being proposed. Interested companies may address substance-specific data needs or, where appropriate, propose to conduct research that will provide information relevant to classes of chemical substances or which may be generalized to other areas of science. It should be noted that all voluntary research conducted to fill ATSDR's priority data needs should comply with the Department of Health and Human Services' Laboratory Animal Welfare Act of 1966 (Pub. L. 89-544, as amended, 7 U.S.C. 2131 et seq.) or Protection of Human Subjects (45 CFR part 46).

The interested company's statement will be reviewed by TASARC. Based on TASARC's recommendations, ATSDR will determine which, and how, specific voluntary research projects will be pursued with volunteering companies. In instances where volunteered research initiatives are considered by TASARC to be more appropriate for EPA response, EPA may negotiate directly with the interested company.

If ATSDR decides to pursue a specific voluntary research project submitted by a company, the Agency will request the company to forward a Letter of Intent within four weeks of the approval of the company's statement. The Letter of Intent should indicate that the company is prepared to enter into discussion with ATSDR regarding the research plan to fill a specific data need identified by the ATSDR Substance-Specific Applied Research Program. Furthermore, the Letter of Intent will state that if the research plan is approved by ATSDR, the company will negotiate an MOU with ATSDR prior to initiation of the research.

The Agency recognizes that two or more companies or a consortium of interested firms may elect to enter into collaborative efforts in pursuing one or more research projects, therefore, where appropriate, a single MOU will be signed between ATSDR and multiple companies. Following the submission of the Letter of Intent and prior to the initiation of the research, the interested company will negotiate with ATSDR to agree upon an approved study plan including testing protocols and time schedules.

The company shall submit to ATSDR a study plan for each test six weeks after submitting the Letter of Intent. The study plan shall include test protocols and a schedule with reasonable timetable and deadlines for initiation and completion of each test and submission of interim and final reports. The test protocols will be reviewed by an ATSDR-appointed peer review panel. If ATSDR disapproves the study plan, it will inform the company of the deficiencies of the plan. The company may request reconsideration of the study plan, resubmit a modified study plan, or elect to terminate further discussion on the proposed research with no obligation of either party. In the event that the company resubmits a modified study plan and ATSDR disapproves it, the Agency may elect to terminate further discussion.

If the study plan is approved by ATSDR upon the recommendations of the peer reviewers, the company will enter into an MOU with the Agency. The content of the MOU is described below:

(1) Identification of the party or parties comprising the company which enters into the MOU—This section consists of the name and address of each party responsible for the conduct of the research.

(2) Identification of the substance(s) subject to research requirements under the MOU—This section consists of the name and Chemical Abstract Service (CAS) Number of the chemical substance(s) that is the subject of the MOU. The chemical substance(s) 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. Furthermore, alternate language will be substituted when the subject of the research is a human population, as in epidemiologic studies.

(3) Identification of the effects or characteristics for which research is to be conducted—In this section, the health effects, environmental fate or other characteristics for which research is to be conducted under the MOU shall be listed.

(4) Initiation of Research and Submission of Interim and Final Reports—The starting date of the research project may be negotiated depending on the type of research being conducted. However, as a general guideline, the research effort shall be initiated within eight weeks of the approval of the study plan and attendant test protocols, and the signing of the MOU. Written notification of the starting date of the test will be submitted to ATSDR by the company. The testing schedule and completion date of the study will be established from the approved study plan. Interim progress reports shall be submitted to ATSDR within six months after the initiation of testing and thereafter within six months after submission of each previous interim report. The final report on the results of testing shall be submitted to ATSDR no more than 20 weeks following the end of the study. Final reports will not be accepted if the data are designated Confidential Business Information (CBI) or otherwise restricted from public disclosure, with the exception of personally identifiable information on study subjects. Moreover, ATSDR's acceptance of the final report will be contingent upon approval by ATSDR following the peer reviewers' recommendations, consistent with CERCLA section 104(i)(13) peer review requirements. All results of research conducted pursuant to the MOU and all supporting data associated with the research report will be provided to ATSDR and made available by the Agency to the public as part of its implementation of sections 104(i)(3) and (5) of CERCLA.

(5) Modifications of study plans, guidelines, and schedules—If a company intends to modify a study plan, protocol, or schedule that was approved by ATSDR, it must notify ATSDR in writing of the proposed modifications and reasons therefor. If ATSDR approves of the modifications, the time schedule established for completion of the tests shall be re-negotiated and appended to the existing MOU. If ATSDR disapproves the company's request and the company does not accept ATSDR's decision to disapprove the modified study plan, the company may terminate the MOU.

(6) Observance of Good Laboratory Practices—All research agreed to in the MOU shall be conducted in accordance with the Good Laboratory Practice (GLP) standards codified in 40 CFR part 792, to the extent that such GLP standards apply. Should Good Epidemiology Practices ("Guidelines for Good Epidemiology Practices for Occupational and Environmental Epidemiologic Research"—The Chemical Manufacturer 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 protocol.

(7) Inspections—The company shall ensure that authorized employees of ATSDR are permitted, at reasonable times and in a reasonable manner, to (i) inspect any research or testing facilities that is conducting research pursuant to the 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 the MOU.

(8) Submission and publication of data—All data and reports submitted to ATSDR pursuant to the MOU shall be sent to ATSDR, in duplicate, at the address indicated in the **ADDRESSES** section. Final reports will not be accepted if the data is designated Confidential Business Information (CBI) or otherwise restricted from public disclosure. Furthermore, acceptance of the final report is contingent upon approval by ATSDR following the peer reviewers' 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 the MOU and all supporting data associated with the final research report will be provided to ATSDR and made available by the Agency to the public as part of its implementation of section 104(i)(5) of CERCLA.

(9) Payments of costs and expenses—Each company shall agree to pay all costs, direct and indirect, associated with the research programs. The Agency will assume responsibility for administrative costs including the cost of peer review as part of its overall program.

(10) Events constituting a breach of the MOU—Failure by the company to:

(a) Initiate any test agreed to in the MOU by the date established pursuant to the MOU;

(b) Adhere to GLP standards, established test procedures or accepted practices of good science to the extent that these standards and practices apply;

(c) Submit any interim report required under the MOU by the date established pursuant to the MOU; or

(d) Submit any final report that receives ATSDR's approval following peer review conducted by the Agency, shall constitute a breach of the 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.

For research completed subsequent to termination of an MOU, or termination of negotiations in anticipation of an MOU, companies may not represent endorsement of such research by ATSDR based on ATSDR's approval of a study protocol, plan or other aspect of the research.

(11) Termination—Since the MOU is entered into voluntarily by ATSDR and the company, 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 MOU. The company may elect to terminate the MOU at any time.

(12) Statutory compliance—Consistent with section 104(i)(12) of CERCLA, as amended (42 U.S.C. 9604(i)(12)), nothing in the 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 of their authority under any other provision of law, or the response and abatement authorities of CERCLA.

As previously stated, EPA is not currently planning to participate as a potential signatory in MOU negotiations arising from this Notice. However, if EPA were to participate, the contents described above would need to be appropriately revised to reflect commitments made by or to EPA, and other matters deemed appropriate by the parties.

The results of the research via this ATSDR Substance-Specific Applied Research Program will be used for public health assessment purposes and to reassess ATSDR's substance-specific priority data needs. It is the intention of the Agency, at this time, to re-evaluate the priority data needs for the listed hazardous substances every three years.

Dated: November 6, 1992.

William L. Roper,

Administrator, Agency for Toxic Substances and Disease Registry.

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