



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

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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, Ph.D.
Chief, Research Implementation Branch

Enclosures

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

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