



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Agency for Toxic Substances
and Disease Registry
Atlanta GA 30333

MAY 4 1995

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

Received
5/8/95

Dear Dr. Shah:

This is in response to your March 22 letter to Dr. William Cibulas 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). In the letter, you enclosed a preliminary study protocol for a two-generation reproductive toxicity study of vinyl chloride by the inhalation route. You asked if ATSDR would consider including measures of developmental toxicity endpoints in the reproductive toxicity study protocol. You also submitted a review of the available data on the developmental toxicity of vinyl chloride.

After evaluating the available data on developmental toxicity studies for vinyl chloride, we determined that the CMA reproductive toxicity study protocol including examination of developmental toxicity endpoints provides an acceptable alternative to separately conducting a two-species developmental toxicity study. Generally, the Agency will consider proposals to simultaneously acquire reproductive and teratologic information in the absence of any reproductive or teratologic data. In view of the suggestive human data and limited animal data for developmental toxicity, as stated in the ATSDR Priority Data Needs Document for vinyl chloride, we believe it would be appropriate and efficient to simultaneously examine both toxicity endpoints in the same study.

In merging the study protocols for developmental toxicity and reproductive toxicity, we ask that you adopt the Environmental Protection Agency testing guidelines for inhalation developmental toxicity studies (Code of Federal Regulations, Part 798.4350, "Inhalation developmental toxicity study," July 1, 1992). For example, exposure duration shall be at least six hours daily and the exposure period shall cover the period of major organogenesis (days 6-15 for rats for this study protocol). At the time of sacrifice or death during the study, the dam shall be examined macroscopically for any pathological changes which may have influenced the pregnancy.

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Furthermore, the degree of resorption shall be described, and the number of corpora lutea shall be examined. Each litter shall be prepared and examined for skeletal and soft tissue anomalies using appropriate methods. Please justify if you do not incorporate any procedure in the EPA developmental toxicity testing guidelines into the combined study protocol under discussion. We believe that combining both study protocols will allow the opportunity to evaluate possible developmental toxicity in both the F_1 and F_2 generations.

Similar to reproductive toxicity assessment, ATSDR places importance on acquiring developmental toxicity data to meet the needs of susceptible populations. Therefore, it may be necessary to conduct a two-species developmental toxicity study in the future if the results of the combined study discussed above clearly indicate that developmental toxicity is an endpoint of concern.

We look forward to receiving your final study protocol, including dose levels, to address ATSDR's priority data needs to conduct reproductive and developmental toxicity studies for vinyl chloride. The study protocol will be reviewed by a panel of peer reviewers selected by the Associate Administrator for Science, ATSDR. Upon satisfactory response by CMA to the peer reviewers' comments and upon agreement between the two organizations on the study plan (including the time schedule), the Agency and CMA may then choose to enter into a memorandum of understanding.

If you have any questions, please call me at 404-639-6300. Thank you for your interest in ATSDR's voluntary research program. We are genuinely enthused about this opportunity to forge new partnerships with the private sector in the interest of public health.

Sincerely yours,

Christopher T. DeRosa

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

CC:
Dr. William Cibulas
Ms. Yee-Wan Stevens
Ms. Deborah Weimer
Dr. John Wheeler