

Response: ATSDR agrees with the commenter and will more explicitly state its support of innovative methodologies, including non-animal testing, in future notices about the agency's Substance-Specific Applied Research Program. In a recently published **Federal Register** Notice updating the status of this research program (67 FR 4836, January 31, 2002), the agency stated that "ATSDR encourages the use of *in vitro* assessment methods and other innovative tools for filling priority data needs. For example, the agency believes that physiologically based pharmacokinetic (PBPK) modeling could serve as a valuable tool in predicting across route similarities (or differences) in toxicological responses to hazardous substances. Therefore, on a case-by-case basis, a priority data need can be filled using existing data and modeling." In fact, in the ATSDR voluntary research program (a component of ATSDR's Substance-Specific Applied Research Program), the Halogenated Solvents Industry Alliance, Inc. (HSIA) has conducted studies to fill ATSDR's priority data needs for volatile organic compounds using PBPK modeling.

Also, ATSDR is a member of the National Toxicology Program's (NTP) Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) and supports development, validation, and acceptance of alternative toxicological test methods that reduce, refine, and replace the use of animals, as appropriate. Through its participation on ICCVAM, ATSDR keeps informed of reliable and valid alternative test methods.

Comment: Request for ATSDR to withdraw the endocrine disruption and developmental neurotoxicity priority data needs because there are no validated animal tests for these end points.

Response: ATSDR has identified a priority data need to assess the potential for pentachlorophenol to affect endocrine functions and for reproductive studies with ethylbenzene. As a result of the agency's evaluation of the comments received from the Pentachlorophenol Task Force, the priority data need for *in vivo* endocrine disruptor studies via oral exposure to pentachlorophenol has been changed. This change resulted because the Pentachlorophenol Task Force submitted a recently completed two-generation reproduction study that was subsequently published in a peer-reviewed journal. ATSDR accepted the data and no longer assigned priority to this research need. With regard to

ethylbenzene, no new information has been available to ATSDR, and the priority data need for ethylbenzene remains unchanged. For the same reason, ATSDR will not withdraw the priority data need for developmental neurotoxicity testing for xylenes.

ATSDR is a nonregulatory, science-based agency. The agency is mandated (in consultation with EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of hazardous substances is available. Where adequate information is not available, ATSDR, in cooperation with NTP, is required to assure the initiation of a research program to determine these health effects. Toward this end, ATSDR established the Tri-Agency Superfund Applied Research Committee (TASARC) consisting of scientists from ATSDR, EPA, and NTP to collaborate on mutual research needs and to discuss issues relevant to the proposed studies, such as the validation status and regulatory acceptance of proposed test methods. It should be noted that ATSDR does not develop testing guidelines or methodologies for toxicological research.

Consistent with the CERCLA mandate, on August 14, 2001, ATSDR published a **Federal Register** Notice announcing the identification of key research needs for 10 additional hazardous substances, and provided a rationale for these determinations in support documents (*i.e.*, priority data needs documents are available for all 10 substances). However, the agency did not identify, propose, or discuss specific test methods to be used to fill the data needs (66 FR 42660). There are no universally agreed upon and validated animal tests to fill the priority data needs for endocrine disruption and developmental neurotoxicity, similar to a lack of such tests to fill the priority data needs for biomarker and mechanistic studies. Consequently, these studies require basic research or other mechanisms to satisfy the information need. Therefore, in filling these research needs, ATSDR does not specify or require that certain (animal) tests be performed. Instead, ATSDR remains open to receiving scientific information to fill these research needs from a variety of sources, including organizations that may propose innovative methodologies involving non-animal tests. In such cases, the agency generally consults with programmatic experts at the National Institute of Environmental Health Sciences (NIEHS) and EPA, and outside scientists to advise the agency on the appropriateness and validation status of

the proposed methods for filling its research needs. Also, ATSDR is working closely with organizations such as NTP's Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM) to stay abreast of testing validation issues. In fact, ATSDR is participating fully in this committee's effort to validate a battery of *in vivo* and *in vitro* tests to assess endocrine disruption.

Comment: Concern about ATSDR calling for more lethal poisoning tests on animals and request that ATSDR withdraw its proposal to conduct more acute toxicity tests on animals for these 10 substances.

Response: The ATSDR Substance-Specific Applied Research Program is designed to address the most important public health research needs for citizens exposed to hazardous environmental substances. ATSDR has not required, and will not require, LD₅₀ or other lethality data as an adjunct to the process. However, ATSDR often requests short-term (acute) toxicity data on non-lethal end points in order to determine the agency's health guidance values (minimal risk levels [MRLs]) for citizens who are possibly exposed to chemicals for durations of 14 days or less.

If the agency considers the existing acute duration (14 days or less) database to be inadequate for fully characterizing the short-term toxicity of a particular hazardous substance, it will identify the need to conduct additional [inhalation and/or oral] studies for determining critical targets and establishing dose-response relationships.

Comment: Concern that ATSDR's requests for more information ignore sophisticated analyses that can be conducted using, for example, structure-activity relationships (SAR).

Response: In evaluating the need for additional data on a particular end point and assigning priority to data needs for the 10 substances, ATSDR first reviewed the available chemical-specific data for a given end point. In addition, ATSDR conducted SAR analyses on these substances and used the information in a strength-of-evidence approach to determine the need to assign priority for the missing information.

Comment: Request that ATSDR defer final assessment of its priority data needs until the industry groups have completed their work under EPA's voluntary children's chemical evaluation program (VCCEP), the hazardous air pollutants (HAPs) test rule, and an enforceable consent agreement (for 1,2-dichloroethane) among others.