The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) mandates that the Agency for Toxic Substances and Disease Registry (ATSDR) shall assess whether adequate information on health effects is available for the priority hazardous substances. Where such information is not available or under development, ATSDR shall, in cooperation with the National Toxicology Program, initiate a program of research to determine these health effects. The Act further directs that where feasible, ATSDR shall develop methods to determine the health effects of substances in combination with other substances with which they are commonly found. The Food Quality Protection Act (FQPA) of 1996 requires that factors to be considered in establishing, modifying, or revoking tolerances for pesticide chemical residues shall include the available information concerning the cumulative effects of substances that have a common mechanism of toxicity, and combined exposure levels to the substance and other related substances. The FQPA requires that the Administrator of the Environmental Protection Agency (EPA) consult with the Secretary of the Department of Health and Human Services (which includes ATSDR) in implementing some of the provisions of the act.

To carry out these legislative mandates, ATSDR’s Division of Toxicology (DT) has developed and coordinated a research program for chemical mixtures that includes trend analysis to identify the mixtures most often found in environmental media, in vivo and in vitro toxicological testing of mixtures, quantitative modeling of joint action, and methodological development. These efforts are interrelated. For example, the trend testing suggests mixtures of concern for further research, the mixtures toxicological testing contributes to the design and calibration of the models and validation of the methodology, and the modeling and methodology efforts suggest further testing to resolve issues and enhance understanding.

In this manner, ATSDR scientists, in collaboration with mixtures risk assessors and laboratory scientists, have been evolving an approach to the assessment of the joint toxic action of chemical mixtures over a number of years. This body of work, including published articles and book chapters, government documents, meeting reports, and unpublished reports, is the foundation of this document.
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THE GUIDANCE HAS UNDERGONE THE FOLLOWING ATSDR INTERNAL REVIEW:

Agency-wide review.
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These experts collectively have knowledge of experimental, statistical, and modeling methods for mixtures, and quantification of risk to humans. All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in this document. A listing of the reviewers' comments, with a brief explanation regarding their inclusion or the rationale for their exclusion, exists as part of the administrative record for this document.

The citation of the expert panel review should not be understood to imply its approval of the document's final content. The responsibility for the content of this document lies with the ATSDR.
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EXECUTIVE SUMMARY

The *Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures* (Mixtures Guidance Manual) is intended to assist environmental health scientists and toxicologists of ATSDR’s Division of Toxicology (DT) in determining whether exposure to chemical mixtures at hazardous waste sites may impact public health. It serves a basis for interaction profiles, as the basis for health assessments and health consultations.

The ATSDR approach outlined in the Mixtures Guidance Manual is consistent with the approach articulated by EPA in 1986 and used to some extent, formally or informally, by a number of agencies. The approach is grounded in the law (CERCLA and the Food Quality Protection Act), and affords greater assurance of protection against adverse health effects than does the assessment of each chemical separately. The Expert Peer Review Panel, assembled on May 30-31, 2000 (see page iii), strongly approved of ATSDR’s efforts to provide guidance for assessing joint toxic action of chemical mixtures and endorsed the ATSDR approach presented herein, which incorporates their comments and recommendations. The Mixture Guidance Manual also underwent ATSDR agency-wide review and incorporates comments received from these reviewers.

This guidance is designed to be used in conjunction with the ATSDR Public Health Assessment Guidance Manual, which provides the primary guidance for public health assessment, including aspects not covered in the Mixtures Guidance Manual. These additional aspects include exposure assessment guidance, recommended sources of health guideline values and toxicological information, and evaluation of health implications of other medical and toxicological factors, sensitive subpopulations, uncertainties, and community-specific health outcome data and community health concerns. The outcome of the public health assessment process is a determination of the category of public health hazard (ranging from urgent to no apparent public health hazard), and of follow-up actions including actions to protect public health, collection of additional health or site-characterization information, and community health education.

The systematic method outlined in the Mixtures Guidance Manual integrates ATSDR’s interaction profiles, toxicological profiles, and research on chemical mixtures into a practical screening approach for potential health hazards. The conclusions from this exposure-based screening assessment of mixture hazard can then be taken into account along with biomedical judgment, the community-specific health outcome data, and community health concerns, to determine the public health implications and follow-up activities for a hazardous waste site.
The Mixtures Guidance Manual is organized so that the first three chapters provide background information considered important in understanding the ATSDR approach to mixtures assessment. The fourth chapter presents the ATSDR approach to exposure-based assessment of the joint toxic action of chemical mixtures. This approach is a semi-quantitative screening process. A step-by-step procedure is outlined in a flow chart for the assessment of noncarcinogenic effects and discussed in the accompanying text, followed by a series of examples illustrating the strategy. The strategy for the assessment of carcinogenic effects is then presented in a similar manner, with a flow chart, discussion, and series of examples.

The strategies for noncancer and cancer effects are similar. Exposure data and toxicological information on the mixture of concern (or a similar mixture) are the preferred basis for an assessment. If available, toxicological information on mixtures of concern for hazardous waste sites are likely to be reviewed and evaluated in ATSDR documents, including interaction profiles and toxicological profiles. If specific ATSDR documents or comparable documents from other agencies are not available, or do not provide Minimal Risk Levels (MRLs) or comparable health guideline values for the mixture or guidance regarding a health assessment approach, and if suitable whole mixture studies are not available, a components-based approach is undertaken.

The components-based approach focuses on mixture components that are present at toxicologically significant exposure levels, based on estimated exposures and relevant health guideline values. Linked physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) models for two or more components, if available, may be used to predict the potential for interactions, or possibly for noncancer or cancer health effects from the mixture. The hazard index method is used to screen for noncancer health hazards from potential additivity of the components. Cancer risks for the components are summed to screen for health hazards from potential additivity of carcinogenic effects. A weight-of-evidence method is used to evaluate the potential impact of interactions on noncancer and cancer health effects.

Additional technical detail regarding the concepts of dose and response addition, and the methodology for evaluating potential interactions, is provided in the appendices.