INTERACTION PROFILE FOR: 1,1,1-TRICHLOROETHANE, 1,1-DICHLOROETHANE, TRICHLOROETHYLENE, AND TETRACHLOROETHYLENE

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PREFACE

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 mixtures program 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 for assessment of joint toxicity. These efforts are interrelated. For example, the trend analysis suggests mixtures of concern for which assessments need to be conducted. If data are not available, further research is recommended. The data thus generated often contribute to the design, calibration or validation of the methodology. This pragmatic approach allows identification of pertinent issues and their resolution as well as enhancement of our understanding of the mechanisms of joint toxic action. All the information obtained is thus used to enhance existing or developing methods to assess the joint toxic action of environmental chemicals. Over a number of years, ATSDR scientists in collaboration with mixtures risk assessors and laboratory scientists have developed approaches for the assessment of the joint toxic action of chemical mixtures. As part of the mixtures program a series of documents, Interaction Profiles, are being developed for certain priority mixtures that are of special concern to ATSDR.

The purpose of an Interaction Profile is to evaluate data on the toxicology of the "whole" priority mixture (if available) and on the joint toxic action of the chemicals in the mixture in order to recommend approaches for the exposure-based assessment of the potential hazard to public health. Joint toxic action includes additivity and interactions. A weight-of-evidence approach is commonly used in these documents to evaluate the influence of interactions in the overall toxicity of the mixture. The weight-of-evidence evaluations are qualitative in nature, although ATSDR recognizes that observations of toxicological interactions depend greatly on exposure doses and that some interactions appear to have thresholds. Thus, the interactions are evaluated in a qualitative manner to provide a sense of what influence the interactions may have when they do occur.

CONTRIBUTORS

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PEER REVIEW

A peer review panel was assembled for this profile. The panel consisted of the following members:

1. Dr. James V. Bruckner
   College of Pharmacy
   University of Georgia
   Athens, GA

2. Dr. Kannan Krishnan
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   Montreal, Quebec

3. Dr. Harihari Mehendale
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All reviewers were selected in conformity with the conditions for peer review specified in Sect 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 the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

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

SUMMARY

1,1,1-Trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene frequently occur together in water samples collected from and in the vicinity of National Priorities List (NPL) hazardous waste sites and other sites assessed by the Agency for Toxic Substances and Disease Registry (ATSDR). These chemicals occur together more frequently than other volatile organic chemicals at the sites. In an unpublished survey of ATSDR Public Health Assessments for 210 NPL hazardous waste sites, this mixture of chemicals was found in groundwater samples from 95% of the sites, in soil samples from 23% of the sites, and in air samples from 12% of the sites. The purposes of this profile are (1) to evaluate data on the toxicology of mixtures of 1,1,1-trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene, (2) to evaluate data on the joint toxic actions (e.g., additive, less-than-additive, or greater-than-additive joint actions) of these chemicals in producing health hazards, and (3) to make recommendations for exposure-based assessments of the potential impact of joint toxic action of the mixture on public health.

There are no studies available that directly characterize health hazards and dose-response relationships for exposures to "whole" mixtures containing 1,1,1-trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene. Furthermore, physiologically based pharmacokinetic (PBPK) models have not been developed to predict dispositional and toxicological outcomes of joint action of mixtures of these four chemicals.

Exposure to the each of the individual chemicals can produce neurological impairment via parent chemical-induced physical and chemical changes in neuronal membranes and cause non-carcinogenic and carcinogenic responses (via reactive metabolites) in the liver and kidney of animals. No studies are available that directly examine joint toxic actions of binary or trinary mixtures of these chemicals on the nervous system, but additive joint action is plausible. Limited studies of joint toxic action of binary or trinary mixtures of these chemicals on the liver and kidney provide no evidence of greater-than-additive joint toxic actions. Additive joint action on the liver and kidney is plausible for binary combinations of each of the components, with the exception of limited evidence that tetrachloroethylene may inhibit the toxic action of trichloroethylene on the liver and kidney (Goldsworthy and Popp 1987; Seiji et al. 1989).

A component-based hazard index approach that assumes additive joint toxic action and uses ATSDR Minimal Risk Levels (MRLs) based on neurological impairment is recommended for exposure-based assessments of possible health hazards from exposure to mixtures of 1,1,1-trichloroethane, 1,1-dichloroethane, trichloroethylene, and tetrachloroethylene. There is no evidence to indicate that greater-than-additive interactions would cause liver and kidney effects to occur at exposure levels lower than those influencing the nervous system.

CONTENTS

LIST OF FIGURES AND TABLES

LIST OF ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATSDR	Agency for Toxic Substances and Disease Registry
BINWOE	binary weight of evidence
bw	body weight
CYP	cytochrome P-450
DCVC	S-(1,2-dichlorovinyl)-L-cysteine
DCVG	S-(1,2-dichlorovinyl)glutathione
EPA	Environmental Protection Agency
IRIS	Integrated Risk Information System
kg	kilogram
L	liter
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
mg	milligram
mL	milliliter
mmol	millimole
MRL	Minimal Risk Level
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
PBPK	physiologically based pharmacokinetic
ppm	parts per million
RfC	Reference Concentration
RfD	Reference Dose
SDH	sorbitol dehydrogenase
U.S.	United States
WOE	weight of evidence
〉	greater than
≥	greater than or equal to
=	equal to
〈	less than
≤	less than or equal to