

**INTERACTION PROFILE FOR:
Benzene, Toluene, Ethylbenzene, and Xylenes (BTEX)**

**U.S. Department of Health and Human Services
Public Health Service
Agency for Toxic Substances and Disease Registry**

May 2004

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 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

CHEMICAL MANAGER(S)/AUTHORS:

Sharon Wilbur, M.A.
ATSDR, Division of Toxicology, Atlanta, GA

Stephen Bosch, B.S.
Syracuse Research Corporation, Syracuse, NY

PEER REVIEW

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

1. Dr. Harvey Clewell
KS Crump Group
602 East Georgia Avenue
Ruston, LA 71270
2. Dr. Kannan Krishnan
Department of Occupational and Environmental Health
University of Montreal School of Medicine
2375 Chemin de la Cote Ste-Catherine
Montreal, Quebec H3T 1A8, Canada
3. Dr. Christopher Borgert
Applied Pharmacology and Toxicology, Inc.
238 Turkey Creek
10514 Palmetto Boulevard
Alachua, FL 32615

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 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

Benzene, toluene, ethylbenzene, and xylenes frequently co-occur at hazardous waste sites. Various combinations of these chemicals are among the most frequently found binary mixtures in completed exposure pathways at hazardous waste sites. Media contaminated with these chemicals include air, water, and soil. Contamination of groundwater can result in volatilization into indoor air when the groundwater is used as household water. In addition, contamination of groundwater and subsurface soil can result in migration of these chemicals into basements as soil gas. The purposes of this profile are: (1) to evaluate data on the toxicology of mixtures of benzene, toluene, ethylbenzene, and xylenes (BTEX); (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.

No studies are available that directly characterize health hazards and dose-response relationships for exposures to “whole” mixtures of BTEX. Exposure to each of the individual chemicals can produce neurological impairment via parent chemical-induced changes in neuronal membranes. Benzene can additionally cause hematological effects, which may ultimately lead to aplastic anemia and acute myelogenous leukemia, and there is evidence that ethylbenzene is carcinogenic in other tissues. No studies were located that directly examined joint toxic actions of benzene, toluene, ethylbenzene, and xylenes on the nervous system, but additive joint neurotoxic action is plausible for environmental exposures based on predictions from physiologically based pharmacokinetic (PBPK) modeling studies with BTEX and a ternary mixture of its components, and supporting data from neurotoxicity interaction studies of binary component mixtures.

In the absence of data on toxic or carcinogenic responses to the whole mixture, possible health hazards from exposures to BTEX are best assessed using a component-based approach that considers both the shared (neurologic) and unique (hematologic/carcinogenic) critical effects of the constituent chemicals. A hazard index approach that assumes additive joint action and uses ATSDR Minimal Risk Levels (MRLs) and guidance values based on neurological impairment is recommended for exposure-based assessments of possible neurotoxic health hazards from the four components. The possible hematotoxic and carcinogenic hazards of BTEX exposures should be evaluated on the basis of benzene alone due to the causal relationship between the noncancer hematological effects of benzene and the development of leukemia, and the lack of a cancer risk value for ethylbenzene. It therefore is recommended that the cancer unit risk value for benzene be used to jointly assess possible hematotoxic and carcinogenic hazards from exposures to BTEX.

CONTENTS

PREFACE	iii
CONTRIBUTORS	v
PEER REVIEW	vii
SUMMARY	ix
CONTENTS	xi
LIST OF TABLES	xiii
LIST OF ACRONYMS, ABBREVIATIONS, AND SYMBOLS	xv
1. Introduction	1
2. Joint Toxic Action Data for the Mixture of Concern and Component Mixtures	3
2.1 Mixture of Concern	3
2.2 Component Mixtures	6
2.2.1 Benzene, Toluene, and Xylenes	6
2.2.2 Toluene, Ethylbenzene, and Xylene	8
2.2.3 Benzene and Toluene	13
2.2.4 Benzene and Ethylbenzene	24
2.2.5 Benzene and Xylenes	24
2.2.6 Toluene and Ethylbenzene	25
2.2.7 Toluene and Xylenes	25
2.2.8 Ethylbenzene and Xylenes	41
2.3 Relevance of the Joint Toxic Action Data and Approaches to Public Health	47
3. Recommendation for Exposure-Based Assessment of Joint Toxic Action of the Mixture	61
4. Conclusions	69
5. List of References	71
Appendix A: Background Information for Benzene	83
A.1 Toxicokinetics	83
A.2 Health Effects	86
A.3 Mechanisms of Action	88
A.4 Health Guidelines	89
A.5 References	90
Appendix B: Background Information for Toluene	97
B.1 Toxicokinetics	97
B.2 Health Effects	99
B.3 Mechanisms of Action	102
B.4 Health Guidelines	103
B.5 References	105
Appendix C: Background Information for Ethylbenzene	113

C.1	Toxicokinetics	113
C.2	Health Effects	115
C.3	Mechanisms of Action	118
C.4	Health Guidelines	119
C.5	References	120
Appendix D:	Background Information for Xylenes	125
D.1	Toxicokinetics	125
D.2	Health Effects	127
D.3	Mechanisms of Action	130
D.4	Health Guidelines	131
D.5	References	133
Appendix E:	Chemical Structures of Mixture Components	139

LIST OF TABLES

2-1.	Quaternary PBPK Model Predictions of Hepatic Venous Blood Concentrations of Benzene (B), Toluene (T), Ethylbenzene (E), and Xylene (X) in Rats After a 4-hour Inhalation Exposure to 100 ppm B Alone or Combined With 100 ppm of T, E, and/or X	5
2-2.	Comparison of Exposure-based Biological Hazard Indexes Calculated for Various Mixtures of Toluene (T), Ethylbenzene (E), and <i>m</i> -Xylene (X)	11
2-3.	Comparison of Increases in Total Concentration (Total AUC) of Parent Chemicals in the Blood Following 4-hour Inhalation Exposures to Ternary and Binary Mixtures of Toluene (T), Ethylbenzene (E), and <i>m</i> -Xylene (X) in Rats	12
2-4.	Summary of Available Data on the Influence of Toluene on Metabolism of Benzene and the Influence of Benzene on Metabolism of Toluene after Simultaneous Exposure	20
2-5.	Summary of Available Data on the Influence of Toluene on Toxicity of Benzene and the Influence of Benzene on Toxicity of Toluene after Simultaneous Exposure	22
2-6.	Relative Potency of Toluene, Xylene, and Their 1:1 Mixture on Rotarod Performance in Rats	30
2-7.	Summary of Available Data on the Influence of Toluene on Metabolism of Xylene and the Influence of Xylene on Metabolism of Toluene after Simultaneous Exposure	35
2-8.	Summary of Available Data on the Influence of Toluene on Toxicity of Xylene and the Influence of Xylene on Toxicity of Toluene after Simultaneous Exposure	37
2-9.	Summary of Available Data on the Influence of Ethylbenzene on Metabolism of Xylene and the Influence of Xylene on Metabolism of Ethylbenzene after Simultaneous Exposure	44
2-10.	Summary of Available Data on the Influence of Ethylbenzene on Toxicity of Xylene and the Influence of Xylene on Toxicity of Ethylbenzene after Simultaneous Exposure	46
2-11.	Health Effects Forming the Basis of ATSDR MRLs for Chemicals of Concern	53
2-12.	Binary Interaction Matrix for Metabolic Effects from Simultaneous Exposure to Chemicals of Concern	57
2-13.	Binary Interaction Matrix for Nervous System Effects from Simultaneous Exposure to Chemicals of Concern	57
2-14.	Binary Interaction Matrix for Hematological and Clastogenic Effects from Simultaneous Exposure to Chemicals of Concern	60
3-1.	Inhalation MRLs and Risk Guidance Values for Neurological Effects of BTEX	63

LIST OF ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienist	mg	milligram
AML	acute myelogenous leukemia	mL	milliliter
ATSDR	Agency for Toxic Substances and Disease Registry	mm	millimeter
AUC	areas under the blood concentration curves	MRI	magnetic resonance imagery
		MRL	Minimal Risk Level
B	benzene	NADH	nicotinamide adenine dinucleotide phosphate (reduced form)
BEI	biological exposure index	NADPH	nicotinamide adenine dinucleotide phosphate (oxidized form)
BHIs	biological hazard indexes	NE	norepinephrine
BINWOE	binary weight-of-evidence	NOAEL	no-observed-adverse-effect level
BTEX	benzene, toluene, ethylbenzene, and xylenes	NTP	National Toxicology Program
		OPT	olfactory perception thresholds
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act	PBPK	physiologically based pharmacokinetic
CI	confidence interval	ppm	parts per million
cm	centimeters		
CYP	cytochrome P-450	RD ₅₀	respiratory depression, 50%
DA	dopamine	RfC	reference concentration
DBTEX	dichloromethane, benzene, toluene, ethylbenzene, and xylenes	RfD	reference dose
		RNA	ribonucleic acid
DNA	deoxyribonucleic acid	SC	simulated concentration
DOPAC	3,4-dihydroxyphenylacetic acid	SD	standard deviation
DT	Division of Toxicology	STEL	short-term exposure limit
		T	toluene
E	ethylbenzene	TLV	threshold limit value
EC ₅₀	effective concentration, 50%	TTD	target-organ toxicity dose
EPA	Environmental Protection Agency	TWA	time-weighted average
		UDP	uridine-5'-diphosphate
FQPA	Food Quality Protection Act	µg	micrograms
HI	hazard index	µL	microliters
5-HIAA	5-hydroxyindoleacetic acid	µmol	micromole
5-HT	indoleamine serotonin	U.S.	United States
HVA	homovanillic acid	VMA	vanillylmanelic acid
IARC	International Agency for Research on Cancer	X	xylenes
IRIS	Integrated Risk Information System	>	greater than
		≥	greater than or equal to
kg	kilogram	=	equal to
L	liter	<	less than
LOAEL	lowest-observed-adverse-effect level	≤	less than or equal to
LSE	Levels of Significant Exposure		
m ³	cubic meters		