

Framework for Assessing Health Impacts of Multiple Chemicals
and Other Stressors
(Update)

U.S. Department of Health and Human Services
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PREFACE

The mission of the Agency for Toxic Substances and Disease Registry (ATSDR) is *to serve the public by using the best science, taking responsive public health actions, and providing trusted health information to prevent harmful exposures and disease related to toxic substances*. The U.S. Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA, also known as the Superfund act) mandates that ATSDR determine whether people living near or at a hazardous waste site are being exposed, have been exposed, or will be exposed to toxic substances, whether that exposure is harmful, and what can be done to stop or reduce harmful exposures. CERCLA requires that ATSDR consider the following factors when evaluating the possible public health impacts of communities near Superfund sites: (1) the nature and extent of contamination at a site; (2) the demographics of the site population; (3) exposure pathways that may exist at a site (the extent to which people contact site contaminants); and (4) health effects and disease-related data. In addition, ATSDR is also authorized to conduct public health assessments at storage, treatment, and disposal facilities for hazardous wastes when requested by EPA, under the 1984 amendments to the Resource Conservation and Recovery Act of 1976 (RCRA). In addition, ATSDR conducts public health assessments for toxic substances, when petitioned by concerned community members, physicians, state or federal agencies, or tribal governments.

The ATSDR *Public Health Assessment Guidance Manual* (ATSDR 2005a) describes a process to prepare public health assessments that evaluate environmental data, exposure data, health effects data and community concerns. The products of this process (public health assessments, consultations, and advisories) guide the development of public health actions or recommendations such as: (1) reducing exposures (carried out by other appropriate federal, state, or tribal agencies or principal responsible parties); (2) recommending further scientific investigations when key exposure or health effects data are missing; (3) developing health education programs within an affected community; or (4) identifying community health care needs (ATSDR 2005a).

This manual, *Framework for Assessing Health Impacts of Multiple Chemicals and Other Stressors*, is a revision of ATSDR's 2004 *Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures* (ATSDR 2004a). The revised manual serves as a supplement to the ATSDR (2005a) *Public Health Assessment Guidance Manual* by describing a recommended process to evaluate the potential public health impacts of exposures to multiple chemicals and other stressors, a frequent occurrence and concern for people living in the vicinity of sites with toxic substances. This revised "mixture" manual builds on the process described in the 2004 manual and reviews scientific research advancements since 2000 related to assessing health impacts from exposures to multiple chemicals and other stressors.

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ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
AEGL	Acute Exposure Guideline Level
AR	androgen receptor
ATSDR	Agency for Toxic Substances and Disease Registry
BBDR	biologically based dose-response
BINWOE	binary weight of evidence
BMD	benchmark dose
BMDL	95% confidence lower limit on the benchmark dose
BTEX	benzene, toluene, ethylbenzene, and xylene
CCRE	combined cancer risk estimate
CDD	chlorinated dibenzo- <i>p</i> -dioxin
CDF	chlorinated dibenzofuran
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CHAP	Chronic Hazard Advisory Panel
AChE	acetylcholine esterase
CHO	Chinese hamster ovary
CPSC	Consumer Product Safety Commission
CRE	cancer risk estimate
CREG	Cancer Risk Evaluation Guide
dB	decibel
DHT	alpha-dihydrotestosterone
DMSO	dimethyl sulfoxide
DNA	deoxyribonucleic acid
DOE	Department of Energy
EMEG	Environmental Media Evaluation Guide
EPA	Environmental Protection Agency
ER	estrogen receptor
ERPG	Emergency Response Planning Guideline
FQPA	Food Quality Protection Act
GC	gas chromatography
HBPS	high-boiling petroleum substances
HI	hazard index
HQ	hazard quotient
IARC	International Agency for Research on Cancer
IC	inhibitory concentration
IPCS	International Programme on Chemical Safety
IRIS	Integrated Risk Information System
IUR	Inhalation Unit Risk
kg	kilogram
LOAEL	lowest-observed-adverse-effect level
MCL	Maximum Contaminant Level
mg	milligram
MOA	mode of action
MOE	margin of exposure
MOS	margin of safety
MRL	Minimal Risk Level
MS	mass spectrometry
MTBE	methyl tert butyl ether
NAAQS	National Ambient Air Quality Standards

NAS	National Academy of Science
NATA	National Air Toxic Assessment
NHANES	National Health and Nutrition Examination Survey
NIOSH	National Institute for Occupational Safety and Health
NOAEL	no-observed-adverse-effect level
NRC	National Research Council
OAR	Office of Air and Radiation
OPP	Office of Pesticide Programs
ORD	Office of Research and Development
OSF	Oral Slope Factor
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBDE	polybrominated diphenyl ether
PBPK	physiologically based pharmacokinetic
PBPD	physiologically based pharmacodynamic
PCB	polychlorinated biphenyl
PEL	permissible exposure limit
POD	point of departure
PODI	point of departure index
ppm	parts per million
RA	risk assessment
RfC	reference concentration
RfD	reference dose
RMEG	Reference Dose Media Evaluation Guide
RPF	relative potency factor
TCDD	2,3,7,8-tetrachlorodibenzo- <i>p</i> -dioxin
TEEL	Temporary Emergency Exposure Limit
TEF	Toxic Equivalency Factor
TEQ	Toxic Equivalent
TLV	threshold limit value
TPH	total petroleum hydrocarbon
TTC	threshold of toxicological concern
TTD	target-organ toxicity dose
UF	uncertainty factor
U.S.	United States
VOC	volatile organic compound
WHO	World Health Organization
WOE	weight of evidence

EXECUTIVE SUMMARY

The *Framework for Assessing the Health Impacts of Multiple Chemicals and Other Stressors* is an update to ATSDR's 2004 *Guidance Manual for Assessment of Joint Toxic Action of Chemical Mixtures* (ATSDR 2004a). The revised manual is intended to assist ATSDR environmental scientists and toxicologists in determining whether combined exposure to multiple chemicals and other stressors (e.g., noise, radiation) at sites of environmental contamination may impact public health. It serves as a basis for ATSDR Interaction Profiles, as well as for ATSDR public health assessments and consultations for mixtures of toxic substances and other stressors that may be encountered by people living in the vicinity of sites of environmental contamination.

Chapter 1 of this manual provides background information that is considered important in understanding the ATSDR approach to assessing health impacts of exposure to multiple stressors. The recommended ATSDR approach described in Chapter 2 calls for a 3-tiered approach to the evaluation of exposure and toxic effects data to determine how exposure to multiple chemicals and other stressors may impact public health in ways not anticipated by single-agent analysis. Chapter 3 discusses background issues and options for assessing health impacts from multiple chemicals and other stressors, including:

1. Discussing quantitative and qualitative approaches to determining sufficient similarity among mixtures;
2. Reviewing the science underlying default assumptions of dose addition or response addition for component-based approaches;
3. Explaining (a) the hazard index approach, (b) the toxicity-organ target modification of the hazard index approach, and (c) the weight-of-evidence schemes to evaluate evidence for additivity and interactions among binary components of chemical mixtures; and
4. Briefly discussing the state of the science to incorporate other nonchemical stressors into health assessments.

The recommended ATSDR approach in Chapter 2 is meant to supplement the ATSDR (2005a) *Public Health Assessment Guidance Manual* and is generally consistent with approaches articulated by the U.S. Environmental Protection Agency (EPA) (1986, 2000, 2003) and other national and international public health or regulatory agencies (as described in Appendix C of this manual). The approach is grounded in the law (Comprehensive Environmental Response, Compensation, and Liability Act [CERCLA] and the Food Quality Protection Act [FQPA]) with the intent of affording greater assurance of protection against adverse health effects than does the assessment of each chemical separately.

The ATSDR approach outlined in Chapter 2 emphasizes the importance of an initial problem formulation to focus a practical 3-tiered approach to integrating exposure data and epidemiologic and toxicologic data and assessing potential health impacts from combined exposure to multiple agents. Parallel assessments are conducted for noncancer effects and cancer. The conclusions from this assessment can then be taken into account, *along with* biomedical judgment, community-specific health outcome data, and community health concerns, to determine the health impacts and public health actions for a site contaminated with multiple chemicals or other stressors of concern.

During problem formulation, the ATSDR approach starts with initial scoping, planning, and data collection activities. Problem formulation leads to the focus of the health assessment and includes evaluation of site history information, environmental fate and transport data, environmental media sampling data, exposure and demographics data, and community health concerns. Other outcomes of the problem formulation step include identification of chemicals and exposure pathways of concern and collection of available health-based guidance values (e.g., ATSDR Minimal Risk Levels [MRLs]) for the site-specific mixture, a sufficiently similar mixture, defined groups of chemicals within the mixture, or individual components.

In the Tier 1 preliminary evaluation, exposure estimates based on environmental media data are compared with health guidance values for single agents and chemical mixtures of concern to identify exposure pathways and agents requiring further Tier 2 or Tier 3 evaluation. Exposure pathways of concern are those with evidence that community members have, or are likely to, come in contact with a contaminant (e.g., drinking contaminated water, breathing in contaminated air, dermally contacting contaminated soil). The initial screening comparison of site-specific exposure estimates with health guidance values for single agents and defined mixtures are: (1) the ratio of an exposure estimate to the health guidance value for noncancer health effects (the hazard quotient) and (2) the product of the exposure estimate multiplied by an EPA-derived cancer slope factor for carcinogenic agents (the cancer risk estimate). Agents with hazard quotients ≥ 0.1 or cancer risk estimates $\geq 10^{-6}$ are retained for further Tier 2 analysis. Single agents with hazard quotients < 0.1 or cancer risk estimates $< 10^{-6}$ (e.g., 10^{-7} or 10^{-8}) are not expected to pose health impacts individually or in combination with other agents and are typically not included in Tier 2 analysis, except in those cases when scoping, planning, and data collection activities (including community health concerns) indicate that combined exposure to multiple agents could produce adverse health outcomes.

The Tier 2 analysis starts with preliminary screening evaluation of noncancer and cancer health impacts from combined exposure to multiple agents. For combined exposure to multiple agents, ATSDR recommends the use of: (1) a hazard index approach to preliminarily evaluate the potential for noncancer effects from multiple agents of concern and (2) combined cancer risk estimates from carcinogenic agents of concern. The preliminary hazard index is a sum of hazard quotients of all known agents for site-specific exposure pathways of concern (i.e., agents with individual hazard quotients ≥ 0.1), and is based on the assumption of dose addition. The combined cancer risk estimate is a sum of cancer risk estimates of all carcinogenic agents of concern associated with a site-specific exposure pathway (i.e., agents with individual cancer risk estimates $\geq 10^{-6}$), and is based on the assumption of response addition.

Further Tier 3 analysis is recommended when: (1) results of Tier 2 analyses indicate that site-specific exposure pathways have preliminary screening level hazard indices ≥ 1 or combined cancer risk estimates are $\geq 10^{-6}$; (2) concerns are high for additive or interactive joint actions (greater than or less than additive) from multiple site-specific agents of concern; and/or (3) additional site-specific health outcome data provide evidence of health effects from combined exposure to multiple agents. Depending on the availability of data and resources, additional Tier 3 analysis can include:

- evaluating and summarizing what is known and unknown about possible greater-than-additive or less-than-additive joint actions among site-specific agents of concern;
- applying a qualitative weight-of-evidence approach to assessing joint actions of binary combinations of agents of concern;
- using developed mixture/interaction physiologically based pharmacokinetic models to determine dose-dependency of possible interactions among agents of concern;
- applying more refined and stringent applications of the hazard index and combined cancer risk estimate approaches that group agents of concern based on common toxicity targets or common adverse outcomes mediated by a common mode of action;
- applying exposure estimates from probabilistic refinement of exposure models in calculating hazard indices and combined cancer risk estimates; and
- developing hazard indices and combined cancer risk estimates for specific subpopulations that may be more susceptible to the site-specific agents of concern, especially children.