Cumulative Risk Assessment Part 1: Chemical Mixtures Component-Based Methods

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Workshop Description

Public interest in the health effects of environmental exposures continues to grow as information increases about multiple stressors, especially contaminants in air, water and soil from a variety of sources. These sources extend beyond the traditional suite that includes industrial releases and pesticide applications (e.g., pharmaceuticals used in modern agriculture, nanomaterials). In addition, population vulnerability factors such as diet, behaviors, genetic traits, economic status, sensitivities, nutritional status and social characteristics are being recognized as important issues to be considered. Cumulative risk assessment (CRA) has been defined as "an analysis, characterization, and possible quantification of the combined risks to human health or the environment from multiple agents or stressors" (U.S. EPA, 2003). Ongoing research efforts are characterizing multiple stressors, environmental fate across exposure settings, and effects of concern to vulnerable communities. CRA provides the integrating foundation for linking these factors across space and time, to produce an overall population-based risk picture and better inform health protection programs.

This set of two independent, but related workshops highlights concepts, methods, and resources for assessing cumulative health risk, including lectures and hands-on exercises. Part 1 presents information on chemical mixture component-based risk assessment methods, mixture exposures, toxic mode of action and risk characterization for evaluating chemical mixtures, including multiple route exposures, with a look forward to CRA. Part 2 presents basic concepts, methods and resources for scoping and conducting a population based CRA, based on existing chemical mixtures risk assessment approaches. A central theme is the integration of information during the planning and scoping phase of a CRA by grouping chemicals or stressors by exposure and toxicity factors. These chemical/stressor groups can then be linked with vulnerability factors characteristic of the exposed population for use in developing risk characterization information. These workshops target people interested in developing knowledge of CRA concepts, methods, and resources. Either or both workshops may be taken depending on the goals of the participant, but Part 1 is recommended prior to taking Part 2 for those who are unfamiliar with chemical mixtures risk assessment methods.

Agenda

8:30-8:50	Welcome & Introductions
8:50-9:10	Overview of Chemical Mixture Methods and Mixture Exposures
9:10-9:35	Dose Addition Concept – Hazard Index, Target Organ Toxicity Doses (TTDs)
9:35-10:00	Methods to Assess Multi-Route Exposures to Mixtures – Cumulative Hazard Index (CHI)
10:00-10:30	Hands on Exercise Calculating the CHI
10:30-11:00	Break
11:00-11:25	Integrated Additivity Methods: Relative Potency Factors & Response Addition
11:25-11:50	Using Mode of Action Information to Develop Subgroups of Chemical Mixtures
11:50-12:15	Hands on Exercise on Integrated Additivity Methods for Mode of Action Subgroups
12:15-12:30	Moving Forward from Chemical Mixtures to Cumulative Risk Assessment

Background of Presenters

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Linda K. Teuschler has been a Mathematical Statistician with United States Environmental Protection Agency's (EPA) Office of Research and Development, National Center for Environmental Assessment (NCEA) since November 1989. She received a M.S. in Mathematics from the University of Cincinnati in 1987. She is currently serving as NCEA's Team Leader for the Chemical Mixtures Risk Assessment Team. Her specific area of expertise is the development of chemical mixtures health risk assessment methodologies, the technical transfer of these risk assessment methods through the development of guidance documents and publications, and the application of such methods to the risk assessment of complex mixtures such as drinking water disinfection by-products, polycylic aromatic hydrocarbons, dioxins, total petroleum hydrocarbons and other contaminant mixtures. More recently, her mixtures research has expanded to incorporate cumulative risk assessment issues. She served on EPA's Risk Assessment Forum (RAF) Technical Panel that authored and published the 2000 *Supplementary Guidance for the Health Risk Assessment of Chemical Mixtures*. She is a member of the Society for Risk Analysis.

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Rick Hertzberg is a faculty member at Emory, University in Atlanta, GA. He retired from the U.S. Environmental Protection Agency in January 2006 after working for 25 years as a Mathematical Statistician with EPA's Office of Research and Development, National Center for Environmental Assessment. Recently, he completed a two-year detail with EPA's newly created Homeland Security Research Center. He received his Ph.D. in Biomathematics in 1977 from the University of Washington, Seattle. Rick is the primary author of both the EPA's 1986 Mixtures Guidelines and 2000 Supplementary Guidance for the Health Risk Assessment of Chemical Mixtures, and chaired both workgroups that developed those reports. He has worked on EPA's Office of Pesticide Programs' Cumulative Risk Work Group, EPA's Risk Assessment Forum cumulative risk technical panel, and external advisory groups on mixture risk for ATSDR, NIOSH and the Dutch Health Council. He also initiated the Interagency Mixed Exposures Research Group to encourage collaboration and consistency across governmental agencies regarding mixtures risk assessment. His publication record includes journal articles, book chapters and EPA guidance documents. His knowledge of both the toxicologic and statistical issues concerning the risk assessment of complex chemical exposures and his development of methods and models to assess mixture dose response and interaction effects have made him an international expert in this field. Rick is a member of the Society for Risk Analysis, and the American Statistical Association.

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Dr. Moiz Mumtaz is Science Advisor, Division of Toxicology and Environmental Medicine, Agency for Toxic Substances and Disease Registry (ATSDR), Centers for Disease Control and Prevention (CDC) and an adjunct faculty at the Environmental Occupational Health Department, Emory University. Prior to joining ATSDR, Dr. Mumtaz served as Team Leader and Coordinator of the Superfund Chemical Mixtures Research program, Office of Research and Development, U.S. Environmental Protection Agency. His involvement in several agency wide activities has led to a) the establishment of a mixtures research program for determining significant human exposures to environmental chemicals, b) the establishment of a computational toxicology laboratory for characterizing the behavior of chemicals after they enter the human body or estimating the toxicity of chemicals based on structure-activity relationships (SAR), and c) the

revision of ATSDR guidelines and policy for publication clearance. Dr. Mumtaz obtained his Ph.D. in toxicology from the University of Maryland and received his M.S. in chemistry/entomology from Oregon State University. Dr. Mumtaz started his professional career as a chemist after completing his M.Sc. in analytical chemistry from Osmania University, India. Dr. Mumtaz has actively published his research findings in several peer-reviewed journals during the past two decades. These publications have covered a wide range of research areas pertinent to medicine and human health that included but were not limited to dopamine metabolism and mental health; chemical analysis of xenobiotics and environmental chemicals; health risk assessment of chemicals and susceptible human populations. Dr. Mumtaz is a full member of the Society of Toxicology (SOT), and the chair of the SOT Mixtures Task Force. He represents ATSDR on several inter-agency workgroups such as the Department of Health and Human Services (DHHS) Interagency Coordinating committee on the validation of alternative methods (ICCVAM), and Mixed Exposures Work Group, National Occupational Research Agenda, NIOSH.

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Glenn Rice has been an Environmental Health Scientist in the U.S. Environmental Protection Agency's National Center for Environmental Assessment (NCEA) since 1990. He is a member of the chemical mixtures risk assessment team in NCEA. His research interest is human health risk assessment methods. For NCEA, he served as a member of the Cancer Risk Assessment Verification Endeavor (CRAVE Work Group). He has lead both a multimedia exposure assessment team in NCEA and a comparative risk assessment project team. He also served as acting science advisor for the NCEA-Cincinnati Division. He is one of the primary authors of the EPA's *Mercury Study Report to Congress* and EPA's *Supplementary Guidance for the Health Risk Assessment of Chemical Mixtures*. Glenn has served as the Chapter President of the Ohio Chapter for the Society of Risk Analysis. He holds a Master's Degree in Microbiology from Miami University, as well as degrees in Biology and Chemistry from Thomas More College. Glenn is currently a doctoral candidate at the Harvard School of Public Health and is a member of SRA.

Method-Specific User Fact-Sheets

U.S. EPA's *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (2000) presents a number of method-specific user fact-sheets, which are intended to provide a concise overview of each currently available mixtures risk assessment method presented in that guidance document. Copies of these fact-sheets are provided here for quick reference. These fact-sheets provide the following information relative to the risk assessment approach:

- Type of Assessment: distinguishes whether the approach is a dose-response assessment or whether it combines dose-response and exposure information to perform a risk characterization.

- Data Requirements: details the types and amount of data that are needed to carry out the procedure.

- Section(s): refers the user to sections of this document that provide greater detail on the approach.

- References: cites reports or publications where the approach has been applied in practice or indicates that this is a new procedure.

- Strategy of Method: provides concise directions on how the calculations are performed.

- Ease of Use: gives a sense of how much effort, expertise, and data are required in order to apply the approach.

- Assumptions: lists the toxicologic or statistical assumptions that are inherently made when the data are treated by applying the approach; the user can then decide if the approach is appropriate for the available data.

- Limitations: suggests problems the user may encounter relative to data gaps or quality deficiencies, and statistical modeling requirements or goodness-of-fit issues.

- Uncertainties: indicates unknown elements of the analysis that must be considered and characterized in the presentation of the risk assessment (e.g., data are not available, mode-of-action is unknown, scientific judgments are made, exposures are not well characterized, extrapolations are made, etc.).

All references to figures, tables, sections, etc. are from:

U.S. EPA. 2000. Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures. Risk Assessment Forum. EPA/630/R-00/002.

User-Fact Sheet:
Mixture of Concern RfD/C or Slope Factor

The user of this Guidance document can use Figure 2-1 to determine that the data available are directly on the mixture of concern. Then, a procedure is suggested for estimating either a cancer slope factor or a Reference Dose/Concentration (RfD/C) as encapsulated in the following user-information fact sheet.

Approach:	Mixture of Concern RfD/C or Slope Factor
Type of Assessment:	Dose-Response Toxicity Value
Section(s):	3.1, 3.2
References:	Examples can be found on IRIS (U.S. EPA, 2008).
Data Requirements:	Toxicity data are available on the mixture of concern. Examples of such data are human epidemiologic data from an occupational setting, human data from a clinical study, or animal toxicology data on the complex mixture.
Strategy of Method:	Estimate dose-response toxicity value directly from data on complex mixture of concern, using the same procedures as those used for single chemicals.
Ease of Use:	Calculations are simple.
Assumptions:	Composition of the test mixture is functionally the same as what is found in the environment. Test data are adequate to account for all sensitive endpoints.
Limitations:	Data are rarely available.
Uncertainties:	Scientific judgments of the chemical composition of the mixture; toxicologic relevance of the laboratory data to the environmental mixture.

U.S. EPA. 2008. Integrated Risk Information System (IRIS). Online. National Center for Environmental Assessment, Washington, DC. http://www.epa.gov/iris.

User-Fact Sheet:
Sufficiently Similar Mixture RfD/C or Slope Factor

The user of this Guidance document can use Figure 2-1 to determine that the data available are on a mixture that is sufficiently similar to the mixture of concern. Then, a procedure is suggested for estimating either a cancer slope factor or a Reference Dose/Concentration (RfD/C) as encapsulated in the following user-information fact sheet.

Approach:	Sufficiently Similar Mixture RfD/C or Slope Factor
Type of Assessment:	Dose-Response Toxicity Value
Section(s):	3.1, 3.2
References:	New procedure.
Data Requirements:	Toxicity data are available on a mixture that is judged as sufficiently similar to the mixture of concern in the environment. No data are available on the mixture of concern. Examples of such data are human epidemiologic data from an occupational setting, human data from a clinical study, or animal toxicology data on the complex mixture.
Strategy of Method:	Estimate dose-response toxicity value using data on the sufficiently similar mixture as a surrogate for data on the mixture of concern, using the same procedures as those used for single chemicals.
Ease of Use:	Calculations are simple.
Assumptions:	Composition of the sufficiently similar mixture is functionally the same as what is found in the environment. Test data are adequate to account for all sensitive endpoints. Similarity judgment across the mixtures must be made and supported.
Limitations:	Availability of data is limited.
Uncertainties:	Scientific judgments of sufficient similarity, chemical composition and stability of the two mixtures; toxicologic relevance of the laboratory data to the environmental mixture.

User-Fact Sheet:
Comparative Potency

The user of this Guidance document can use Figure 2-1 to determine that the data available are on a group of similar mixtures. Then, a procedure is suggested for using a comparative potency approach to estimating a cancer slope factor as encapsulated in the following user-information fact sheet.

Approach:	Comparative Potency
Type of Assessment:	Dose-Response Toxicity Values for Cancer, Genetic Toxicity
Section(s):	3.1, 3.3
References:	Used for combustion mixtures (Lewtas, 1985, 1988; Nesnow, 1990).
Data Requirements:	Method requires short-term data on several similar mixtures including the mixture of concern and at least one data point from a chronic *in vivo* study on one of these mixtures. Examples of such data are *in vitro* mutagenicity assays and chronic rodent bioassays.
Strategy of Method:	Estimate dose-response value using relationships across similar mixtures and similar assays to extrapolate to a value for the mixture of concern.
Ease of Use:	Calculations involve some statistical modeling and toxicologic judgement. Method is data intensive with short-term assay data required.
Assumptions:	Assumes the potency change for similar mixtures across assays is the same for all similar mixtures. Test data are adequate to account for all sensitive endpoints. Similarity judgment across the mixtures must be made and supported.
Limitations:	Availability of data is limited.
Uncertainties:	Scientific judgments of sufficient similarity relative to chemical composition and toxicologic activity of the mixtures.

Lewtas, J. 1985. Development of a comparative potency method for cancer risk assessment of complex mixtures using short-term *in vivo* and *in vitro* bioassays. Toxicol. Ind. Health. 1:193-203.

Lewtas, J. 1988. Genotoxicity of complex mixtures: Strategies for the identification and comparative assessment of airborne mutagens and carcinogens from combustion sources. Fund. Appl. Toxicol. 10:571-589.

Nesnow, S. 1990. Mouse skin tumours and human lung cancer: Relationships with complex environmental emissions. In: Complex Mixtures and Cancer Risk. IARC Scientific Publ. 104:44-54.

User Fact-Sheet:
Geographic Site-Specific Assessments

The user of this Guidance document can follow Figure 2-1 to determine that the data available are on a group of similar mixtures. Then, a procedure is suggested for estimating risk from exposure to the mixture by using an Geographic Site-Specific Assessment, as detailed in the following user-information fact sheet.

Approach:	Geographic Site-Specific Assessment
Type of Assessment:	Risk Characterization for any Toxic Endpoint
Section(s):	3.1, 3.4
References:	Used for cancer assessment of PCBs (U.S. EPA. 1996)
Data Requirements:	Method requires both toxicity and exposure data on the mixture's components.
Strategy of Method:	Toxicity data on the commercial mixture are used to estimate a range of toxicity values that are then adjusted for alterations in the mixture's composition due to environmental factors to produce a risk estimate for the total mixture.
Ease of Use:	Complicated to use. Data intensive.
Assumptions:	Requires the user to make assumptions about the fate and transport of groups of chemicals.
Limitations:	Some data restricted by similarity. Restricted to specific conditions. Limited by data quality.
Uncertainties:	Scientific judgment of fate and transport. Accuracy of exposure data.

U.S. EPA. 1996. PCBs: Cancer Dose-Response Assessment and Application to Environmental Mixtures. National Center for Environmental Assessment, Washington, DC. EPA/600/P-96/001F.

User Fact-Sheet:
Hazard Index

The user of this Guidance document can follow Figure 2-1 to determine that the data available are on the components of the mixture of concern and that there is evidence of toxicologic similarity of the components. Then, a procedure is suggested for estimating a Hazard Index, an indication of risk from exposure to the mixture, as encapsulated in the following user-information fact sheet.

Approach:	Hazard Index
Type of Assessment:	Risk Characterization for any Toxic Endpoint
Section(s):	4.1, 4.2
References:	Used in Superfund site assessments (U.S. EPA, 1989).
Data Requirements:	Method requires both toxicity and exposure data on the mixture's components. Good dose-response data are needed, such as what is available on IRIS (U.S. EPA, 2008).
Strategy of Method:	Scale individual component exposure concentrations by a measure of relative potency (typically, divide by a Reference Dose/Concentration (RfD/C)) for components with a similar mechanism-of-action. Add scaled concentrations to get an indicator of risk from exposure to the mixture of concern.
Ease of Use:	Easy to calculate.
Assumptions:	Applies dose addition which carries with it assumptions of a common mode-of-action and similarly shaped dose-response curves across the components. The common mode-of-action assumption can be met by using a surrogate of same target organ.
Limitations:	Exposure data must be at relatively low levels (near no-adverse-effect levels) at which interaction effects are not expected. RfD/C values across components vary in their uncertainty, so other measures of potency may be more appropriate.
Uncertainties:	Similarity of mechanism-of-action. Accuracy of exposure data.

U.S. EPA. 1989. Risk Assessment Guidance for Superfund. Vol. 1. Human Health Evaluation Manual (Part A). EPA/540/1-89/002.

U.S. EPA. 2008. Integrated Risk Information System (IRIS). Online. National Center for Environmental Assessment, Washington, DC. http://www.epa.gov/iris.

User Fact-Sheet:
Relative Potency Factors

The user of this Guidance document can follow Figure 2-1 to determine that the data available are on the components of the mixture of concern and that there is evidence of toxicologic similarity of the components. Then, a procedure is suggested for estimating risk from exposure to the mixture by using Relative Potency Factors, as encapsulated in the following user-information fact sheet.

Approach:	Relative Potency Factors
Type of Assessment:	Dose-Response Assessment for any Toxic Endpoint
Section(s):	4.1, 4.4
References:	New Procedure (Hertzberg et al., 1999)
Data Requirements:	Method requires both toxicity and exposure data on the mixture's components. Toxicity data are missing for some components.
Strategy of Method:	Scale component exposure concentrations relative to potency of an index chemical (typically the best studied component) following expert committee consensus. Add scaled concentrations. Use dose-response curve of index chemical to generate response estimate for sum of scaled concentrations.
Ease of Use:	Complicated to use. Requires some statistical modeling and judgment of relative potency factors.
Assumptions:	Based on dose addition which carries with it assumptions of same mode-of-action and similarly shaped dose-response curves across the components. The common mode-of-action assumption can be met using a surrogate of toxicologic similarity, but for specific conditions (endpoint, route, duration).
Limitations:	Limited by data quality and similarity. May not have data from all routes of exposure of interest. Same mode-of-action across components may not be known.
Uncertainties:	Judgment of relative potency factors. Similarity of toxicologic action. Missing data on some components.

Hertzberg, R.C., G. Rice and L.K. Teuschler. 1999. Methods for health risk assessment of combustion mixtures. In: Hazardous Waste Incineration: Evaluating the Human Health and Environmental Risks, S. Roberts, C. Teaf and J. Bean, Ed. CRC Press LLC. p. 105-148.

User Fact-Sheet:
Toxicity Equivalence Factor

The user of this Guidance document can follow Figure 2-1 to determine that the data available are on the components of the mixture of concern and that there is evidence of toxicologic similarity of the components. Then, a procedure is suggested for estimating risk from exposure to the mixture by using Toxicity Equivalence Factors, as encapsulated in the following user-information fact sheet.

Approach:	Toxicity Equivalence Factors
Type of Assessment:	Dose-Response Assessment for any Toxic Endpoint
Section(s):	4.1, 4.4
References:	Used for dioxins and furans (U.S. EPA, 1989)
Data Requirements:	Method requires both toxicity and exposure data on the mixture's components. One well studied chemical.
Strategy of Method:	Scale component exposure concentrations relative to potency of an index chemical (a well studied component) following expert committee consensus. Add scaled concentrations. Use dose-response curve of index chemical to generate response estimate for sum of scaled concentrations.
Ease of Use:	Complicated to use. Data intensive. Requires some statistical modeling and judgment of toxicity equivalence factors.
Assumptions:	Based on dose addition which carries with it assumptions of same mode-of-action and similarly shaped dose-response curves across the components.
Limitations:	Rare data. Restricted by strong similarity so few chemical classes will quality. Applied to all endpoints and exposure routes. Same mode-of-action across components is established.
Uncertainties:	Judgment of toxicity equivalence factors. Accuracy of exposure estimates.

U.S. EPA. 1989. Interim Procedures for Estimating Risks Associated with Exposures to Mixtures of Chlorinated Dibenzo-p-dioxins and -dibenzofurans (CDDs and CDFs) and 1989 update. Risk Assessment Forum. EPA/625/3-89/016. March.

User Fact-Sheet:
Response Addition

The user of this Guidance document can follow Figure 2-1 to determine that the data available are on the components of the mixture of concern and that there is evidence of toxicologic independence of action. Then, a procedure is suggested for estimating risk from exposure to the mixture by using Response Addition, as encapsulated in the following user-information fact sheet.

Approach:	Response Addition
Type of Assessment:	Risk Characterization for any Toxic Endpoint
Section(s):	4.1, 4.5
References:	Used extensively for cancer. Used in Superfund site assessments (U.S. EPA, 1989).
Data Requirements:	Method requires both toxicity data (measured in percent responding) and exposure data on the mixture's components. Good dose-response data are needed, such as what is available on IRIS (U.S. EPA, 2008).
Strategy of Method:	Risk of an effect is estimated for each component using its dose-response curve at the component's exposure concentration. Component risks are added, using the independence formula, to yield a risk estimate for the total mixture for the specific exposure.
Ease of Use:	Easy to calculate.
Assumptions:	Assumes toxicologic independence of action. Assumes interactions are not significant at low exposures.
Limitations:	Limited to low exposure concentrations. Slight overestimate of mixture's upper bound on risk when adding individual component upper bound estimates. Restricted to independence of action.
Uncertainties:	Independence of action. Accuracy of exposure data. Individual risk estimates may vary in quality.

U.S. EPA. 1989. Risk Assessment Guidance for Superfund. Vol. 1. Human Health Evaluation Manual (Part A). EPA/540/1-89/002.

U.S. EPA. 2008. Integrated Risk Information System (IRIS). Online. National Center for Environmental Assessment, Washington, DC. http://www.epa.gov/iris.

User Fact-Sheet:
Interaction-based Hazard Index

The user of this Guidance document can follow Figure 2-1 to determine that the data available are on the components of the mixture of concern and that interactions data are available. Then, a procedure is suggested for estimating risk from exposure to the mixture by incorporating information on binary combinations of the components using an Interaction-based Hazard Index, as encapsulated in the following user-information fact sheet.

Approach:	Interaction-based Hazard Index
Type of Assessment:	Risk Characterization for any Toxic Endpoint
Section(s):	4.1, 4.3
References:	New procedure. (Hertzberg et al., 1999)
Data Requirements:	Method requires both toxicity and exposure data on the mixture's components, and interactions data on at least one pair of components.
Strategy of Method:	Scale component exposure concentrations by a measure of relative potency (typically, divide by a Reference Dose/Concentration (RfD/C)) for components with a similar mechanism-of-action. Modify this term with data on binary interactions. Add scaled/modified concentrations to provide an indicator of risk from exposure to the mixture of concern.
Ease of Use:	Complicated to use.
Assumptions:	Assumes binary interactions are the most important. Assumes interaction magnitude is not dose dependent, but depends on component proportions.
Limitations:	Limited interactions data are available. Model with relative proportions is untested. Interaction magnitude is often a default because of lack of measurement data.
Uncertainties:	Binary interactions used to represent the interactions for the whole mixture. Accuracy of exposure data. Accuracy of default for interaction magnitude.

Hertzberg, R.C., G. Rice and L.K. Teuschler. 1999. Methods for health risk assessment of combustion mixtures. In: Hazardous Waste Incineration: Evaluating the Human Health and Environmental Risks, S. Roberts, C. Teaf and J. Bean, Ed. CRC Press LLC. p. 105-148.

Hertzberg, RC, LK Teuschler. 2002. Evaluating Quantitative Formulas for Dose-Response Assessment of Chemical Mixtures. *Environmental Health Perspectives*. 110(6):965-970.

Cumulative Risk Assessment and Chemical Mixture Definitions

Consistent and clear terminology is critical to the discussion of cumulative risk assessments. U.S. EPA's *Concepts, Methods and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document* (2007) presents a listing of key terms that are useful for understanding CRA. These are presented in Table 1 below. U.S. EPA's *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures* (2000) presents a number of definitions to articulate the differences among the many terms used to describe chemical mixtures and the types of interactions that may occur among chemicals. Two tables from that document are presented here. Table 2 presents chemical mixtures definitions in terms of specific criteria including the complexity of the mixture, similarity of biologic activity, similarity of chemical structure or mixture composition, the environmental source of the mixture, toxic endpoint, etc. Table 3 provides definitions for terms that are used to describe various types of toxicologic interactions including forms of additivity, antagonism, synergism and other toxicologic phenomena. Tables 2 and 3 can be used by the risk assessor to classify available toxicity and exposure data in order to choose from among the risk assessment methods for chemical mixtures.

Table 1
Key Terms for Cumulative Health Risks
(Source U.S. EPA, 2007)

Aggregate exposure	Combined exposure to one chemical; can be from multiple sources or pathways
Cumulative risk	Combined risk from exposures to multiple chemicals or stressors; exposures may be aggregate
Effect	Health endpoint estimated from toxicity studies (first-observed is critical effect; secondary effect seen at higher doses)
Exposure pathway	A complete pathway includes (1) source and mechanism of release, 2) contaminant fate & transport (through environmental media), (3) point of receptor contact with the source or affected medium and (4) exposure route
Exposure route	How a contaminant gets inside a person (e.g., via inhalation, ingestion, or dermal absorption)
Environmental interaction	One chemical acting on another to influence fate or transport
Joint toxicity	Toxic action exerted by two or more chemicals acting together
Toxicological interaction	Joint toxicity that is greater or less than expected under additivity (note: forms of additivity include summing of doses, risks or biological measurements across chemical components of a mixture)
Receptor population	Group actually or potentially exposed
Source	Origin of contaminant (e.g., a landfill)

Table 2 Definitions of Chemical Mixtures (Source U.S. EPA, 2000)
Chemical Mixture Any set of multiple chemical substances that may or may not be identifiable, regardless of their sources, that may jointly contribute to toxicity in the target population. May also be referred to as a "whole mixture" or as the "mixture of concern."
Components Single chemicals that make up a chemical mixture that may be further classified as systemic toxicants, carcinogens, or both.
Simple Mixture A mixture containing two or more identifiable components, but few enough that the mixture toxicity can be adequately characterized by a combination of the components' toxicities and the components' interactions.
Complex Mixture A mixture containing so many components that any estimation of its toxicity based on its components' toxicities contains too much uncertainty and error to be useful. The chemical composition may vary over time or with different conditions under which the mixture is produced. Complex mixture components may be generated simultaneously as by-products from a single source or process, intentionally produced as a commercial product, or may co-exist because of disposal practices. Risk assessments of complex mixtures are preferably based on toxicity and exposure data on the complete mixture. Gasoline is an example.
Similar Components Single chemicals that cause the same biologic activity or are expected to cause a type of biologic activity based on chemical structure. Evidence of similarity may include similarly shaped dose-response curves, or, log-probit dose-response curves for quantal data on the number of animals (people) responding and same mechanism of action or toxic endpoint. These components are expected to have comparable characteristics for fate, transport, physiologic processes and toxicity.
Similar Mixtures Mixtures that are slightly different, but are expected to have comparable characteristics for fate, transport, physiologic processes and toxicity. These mixtures may have the same components but in slightly different proportions, or have most components in nearly the same proportions with only a few different (more or fewer) components. Similar mixtures cause the same biologic activity or are expected to cause the same type of biologic activity due to chemical composition. Similar mixtures act by the same mechanism of action or affect the same toxic endpoint. Diesel exhausts from different engines are an example.
Chemical Classes Groups of components that are similar in chemical structure and biologic activity, and that frequently occur together in environmental samples, usually because they are generated by the same commercial process. The composition of these mixtures is often well controlled, so that the mixture can be treated as a single chemical. Dibenzo-dioxins are an example.

Table 3
Definitions of Toxicologic Interactions between Chemicals*
(Source: U.S. EPA, 2000)

Additivity When the "effect" of the combination is estimated by the sum of the exposure levels or the effects of the individual chemicals. The terms "effect" and "sum" must be explicitly defined. Effect may refer to the measured response or the incidence of adversely affected animals. The sum may be a weighted sum (see "dose addition") or a conditional sum (see "response addition").
Antagonism When the effect of the combination is less than that suggested by the component toxic effects. Antagonism must be defined in the context of the definition of "no interaction", which is usually dose or response addition.
Chemical Antagonism When a reaction between the chemicals has occurred and a new chemical is formed. The toxic effect produced is less than that suggested by the component toxic effects.
Chemical Synergism When a reaction between the chemicals has occurred and a different chemical is formed. The toxic effect produced is greater than that suggested by the component toxic effects, and may be different from effects produced by either chemical by itself.
Complex Interaction When three or more compounds combined produce an interaction that cannot be assessed according to the other interaction definitions.
Dose Additivity When the effect of the combination is the effect expected from the equivalent dose of an index chemical. The equivalent dose is the sum of component doses scaled by their potency relative to the index chemical.
Index Chemical The chemical selected as the basis for standardization of toxicity of components in a mixture. The index chemical must have a clearly defined dose-response relationship.
Inhibition When one substance does not have a toxic effect on a certain organ system, but when added to a toxic chemical, it makes the latter less toxic.
Masking When the compounds produce opposite or functionally competing effects at the same site or sites, so that the effects produced by the combination are less than suggested by the component toxic effects.
No Apparent Influence When one substance does not have a toxic effect on a certain organ or system, and when added to a toxic chemical, it has no influence, positive or negative, on the toxicity of the latter chemical.

Table 3 (cont.)
Definitions of Toxicologic Interactions between Chemicals*

No Observed Interaction When neither compound by itself produces an effect, and no effect is seen when they are administered together.
Potentiation When one substance does not have a toxic effect on a certain organ or system, but when added to a toxic chemical, it makes the latter more toxic.
Response Additivity When the response (rate, incidence, risk or probability) of effects from the combination is equal to the conditional sum of component responses as defined by the formula for the sum of independent event probabilities.
Synergism When the effect of the combination is greater than that suggested by the component toxic effects. Synergism must be defined in the context of the definition of "no interaction", which is usually dose or response addition.
Unable to Assess Effect cannot be placed in one of the above classifications. Common reasons include lack of proper control groups, lack of statistical significance, and poor, inconsistent or inconclusive data.

*Based on definitions in U.S. EPA (1990). These definitions of interaction refer to the influence on observed toxicity, without regard to the actual mechanisms of interaction.

Further Information on Cumulative Risk Assessment

More information is available at:

ATSDR's Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures. 2004. Online. http://www.atsdr.cdc.gov/interactionprofiles/ipga.html

ATSDR's Interaction Profiles for Toxic Substances. 2008. Online. http://www.atsdr.cdc.gov/interactionprofiles/ Interaction Profile Guidance. 2001. Online. http://www.atsdr.cdc.gov/interactionprofiles/interaction_profile_guidance.pdf

California EPA's Cumulative Impacts and Precautionary Approaches http://oehha.ca.gov/ej/index.html

National Academy of Science's National Research Council's Report on Phthalates and Cumulative Risk Assessment. Research Brief. Online. http://dels.nas.edu/dels/rpt_briefs/phthalates_final.pdf

National Academy of Science's National Research Council's Report on Science and Decisions Advancing Risk Assessment. Research Brief. Online. http://dels.nas.edu/dels/rpt_briefs/IRA_brief_final.pdf

NIOSH Mixed Exposures Team Research Agenda. 2004. Online. http://www.cdc.gov/niosh/docs/2005-106/

NoMiracle (Novel Methods for Integrated Risk Assessment of Cumulative Stressors in Europe) Online. http://nomiracle.jrc.ec.europa.eu/default.aspx

U.S. EPA's Office of Science Policy Cumulative Risk Assessment Program http://www.epa.gov/osa/spc/2cumrisk.htm

U.S. EPA. 2003. Framework for Cumulative Risk Assessment. Online. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=54944

U.S. EPA. 2007. Concepts, Methods and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document. Online. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=190187

U.S. EPA's Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures. 2000. Online. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=20533

U.S. EPA's Information on Assessing Pesticide Cumulative Risk (Office of Pesticide Programs) Online. http://www.epa.gov/pesticides/cumulative/

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