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GUIDELINES FOR CUMULATIVE RISK ASSESSMENT PLANNING AND PROBLEM FORMULATION

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GLOSSARY OF KEY TERMS

The terms in this glossary were selected to ensure consistent meaning when used in these Guidelines. The EPA recognizes that definitions continue to evolve and may be updated in future EPA resources. This glossary was created for the Guidelines for Cumulative Risk Assessment Planning and Problem Formulation, is not a comprehensive list of risk assessment terms, and might not represent how the terms are defined in specific EPA programs.

Adverse outcome pathway. A conceptual framework that portrays existing knowledge about biological events that could lead to an adverse outcome in health effects in human populations and ecosystems (U.S. EPA, 2022a).

Agent. A chemical, physical, or biological entity that contacts a receptor (U.S. EPA, 2019).

Aggregate exposure. The sum of exposures to a single stressor from all sources by multiple routes over multiple periods (U.S. EPA, 2019).

Conceptual model. A diagram or written description of the predicted key relationships (e.g., known, predicted, and assumed causal relationships) between the stressor(s) (or agents) and the assessment endpoint(s) for a risk assessment (Linder & Sexton, 2011; Suter, 1999).

Cumulative exposure. An accounting of exposures to multiple stressors and sources by multiple pathways and routes over multiple periods (Zartarian & Schultz, 2010).

Cumulative impacts. The totality of exposures to combinations of chemical and nonchemical stressors and their effects on health, well-being, and quality-of-life outcomes (U.S. EPA, 2022c).

Cumulative impacts assessment. The process of accounting for cumulative impacts in the context of problem identification and decision-making. Cumulative impacts assessments consider exposures to both chemical and nonchemical stressors at each life stage throughout the life course and apply to individuals, geographically defined groups, or definable population groups (U.S. EPA, 2024).

Cumulative risk assessment. An analysis, characterization, and possible quantification of the combined risks to health and/or the environment from multiple agents and/or stressors (U.S. EPA, 2003b).

Exposure. The contact between an agent and the external boundary (exposure surface) of a receptor for a specific duration (U.S. EPA, 2019).

Environmental justice. The fair treatment and meaningful involvement of all people regardless of race, color, national origin, or income with respect to the development, implementation, and enforcement of environmental laws, regulations, and policies (U.S. EPA, 2010).

Exposure-response modifier. Any condition or state that could alter a receptor's (individual- or group-level) exposure to a chemical or nonchemical agent (single or multiple) and/or could alter a physiological response following contact with these agents.

Health impact assessment. A systematic process using an array of data sources and analytical methods to determine the potential effects of proposals on the health of a population and the distribution of those effects within the population. HIA provides recommendations on monitoring and managing those effects (NRC, 2011b).

Initiating factor. A condition involving more than one chemical or agent that prompts a cumulative risk assessment, such as (1) multiple sources/releases, (2) measured or inferred chemical concentrations, or (3) illness in a given population (U.S. EPA, 2007a).

Lifestage. Temporal stages of life that have distinct anatomical, physiological, and behavioral or functional characteristics that contribute to potential differences in vulnerability to environmental exposures (U.S. EPA, 2006c).

Nonchemical stressor. A stressor that is not based on chemical exposure, which could include biological or physical factors and activities that directly or indirectly adversely affect health or increase vulnerability to chemical stressors. The term is often used to refer to psychological or social stressors that might also act as an exposure-response modifier to other stressors (Tulve et al., 2016; U.S. EPA, 2003b).

Receptor. Any biological entity (e.g., human, human population, lifestage within a human population) that receives an exposure or dose (U.S. EPA, 2019).

Stressor. Any physical, chemical, biological, or psychosocial agent that can induce an adverse response.

Stakeholder. (1) Individuals or representatives from organizations or interest groups that have a strong interest in the Agency's work and policies (U.S. EPA, 2014b) and (2) anyone who has a "stake" in a risk assessment or risk management decisions.[1]

Vulnerability. Characteristics of individuals or populations that place them at increased risk of an adverse health effect (U.S. EPA, 2019). Any conditions that increase the likelihood and/or consequences of exposure to a stressor(s) in an identifiable group of receptors; the intrinsic predisposition or extrinsic condition of an exposed receptor (person, community, population, ecologic entity) to suffer from external stresses and perturbations. Vulnerability is based on variations in disease susceptibility, psychological and social factors, exposures, and adaptive measures to anticipate and reduce future harm and to recover from an insult (adapted from NRC, 2009).

[1] Adapted from PCCRARM (1997), Vol. 1, p. 15, text for stakeholder engagement: "A stakeholder is anyone who has a 'stake' in a risk management situation."

ACRONYMS AND ABBREVIATIONS

CEQ	Council on Environmental Quality
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CIA	cumulative impact assessment
CMG	Common Mechanism Group
CRA	cumulative risk assessment
CVD	cardiovascular disease
DAG	Directed Acyclic Graph
DBP	disinfection by-product
DQO	data quality objective
EFSA	European Food Safety Authority
EPA	U.S. Environmental Protection Agency
FQPA	Food Quality Protection Act
HAP	hazardous air pollutant
HI	hazard index
HIA	Health Impact Assessment
HQ	hazard quotient
IOM	Institute of Medicine
IPCS	International Programme on Chemical Safety in the World Health Organization
NAAQS	National Ambient Air Quality Standards
NEJAC	National Environmental Justice Advisory Council
NRC	National Research Council
OAR	Office of Air and Radiation
OAR-TTN	Office of Air and Radiation–Technology Transfer Network
OP	organophosphate
OPP	Office of Pesticide Programs
PCCARM	Presidential Congressional Commission on Risk Assessment and Risk Management
RAF	Risk Assessment Forum
RAGS	Risk Assessment Guidance for Superfund
RME	reasonable maximum exposure
SARA	Superfund Amendments and Reauthorization Act
WHO	World Health Organization
WoE	weight of evidence

PREFACE

Cumulative risk assessment (CRA) is an analytical approach to understanding the health effects of exposure to multiple environmental agents and/or stressors and other stressors that could confer or exacerbate vulnerabilities in an affected population. Risk assessment is a dynamic practice with established procedures and methods that evolve with experience and the advance of new scientific capability. Risk assessment informs risk management but is distinct from risk management decisions at the U.S. Environmental Protection Agency (hereafter referred to as the "EPA"), which are guided by statutes and regulations. To successfully use CRA, an understanding is needed of when and how the approach can be applied. This document (hereafter referred to as the "Guidelines") describes steps for the planning and problem formulation of CRAs and offers guidance for when such assessments might be appropriate. It updates and supersedes the 1997 *Guidance on Cumulative Risk Assessment, Part 1, Planning and Scoping* and builds on the 2003 *Framework for Cumulative Risk Assessment*. Emphasis is placed on providing a uniform, yet flexible, CRA planning and problem formulation approach for risk assessment at the EPA. These Guidelines are not prescriptive and do not impose any requirement for use by the EPA or any federal, state, or Tribal agency.

The need to characterize human health and environmental risks posed by exposures to multiple stressors was first articulated as EPA-wide policy in a 1997 memorandum (U.S. EPA, 1997a). The memorandum directed "each office to take into account cumulative risk issues in scoping and planning major risk assessments." Subsequent CRAs conducted on drinking water disinfection by-products (U.S. EPA, 2000a) and classes of pesticides (U.S. EPA, 2006e, 2006f, 2007b) illustrate major risk assessments incorporating CRA methods. Statutes like the 1996 Food Quality Protection Act (FQPA)[2] need to be taken into consideration when preparing CRAs because they stipulate provisions that delineate assessment requirements for certain chemicals.

These Guidelines build on the experience and knowledge of the EPA in conducting human health and ecological risk assessments and have also been shaped by recommendations from the National Research Council (NRC), the National Environmental Justice Advisory Council (NEJAC), and EPA's Children's Health Protection Advisory Committee,[3] among others. The Guidelines address public health and environmental health concerns arising from sequential and multiple exposures to multiple stressors. NRC articulates the importance of more generally incorporating CRA in EPA decision-making, citing two primary justifications: (1) "consideration of other compounds and other factors may be necessary to inform the decision," even if the regulatory decision of interest addresses a single chemical with a single route of exposure; and (2) "the types of questions that are increasingly being asked of the EPA require the tools and concepts of cumulative risk assessment" (NRC, 2009). NRC observes that CRA will provide the EPA with a "broader and more comprehensive understanding of the complex interactions between chemicals, humans, and the environment" (NRC, 2012).

These Guidelines lay the foundation for considering current and anticipated future cumulative risk analytical methods. They provide recommendations to aid Agency risk assessors in developing a CRA analysis plan but do not provide direction on which analytical methods to use for conducting CRAs. These Guidelines are intended for use with other EPA guidelines, such as the *Guidelines and Supplementary Guidance for Assessment of Chemical Mixtures* (U.S. EPA, 1986b, 2003c), the *Framework for Human Health Risk Assessment to Inform Decision Making* (U.S. EPA, 2014b), and the

[2] The statutory requirement for pesticide cumulative risk assessment is specifically defined by the 1996 Food Quality Protection Act (FQPA) as a consideration of potential human health risks from all pathways of dietary and nondietary exposures to more than one pesticide acting through a common mechanism of toxicity.

[3] See two letters from J. Routt Reigart, MD, Chair of the Children's Health Protection Advisory Committee, dated September 26, 2000 (https://www.regulations.gov/document/EPA-HQ-OA-2022-0552-0022) and August 9, 2002 (https://www.regulations.gov/document/EPA-HQ-OA-2022-0554-0006).

Guidelines for Human Exposure Assessment (U.S. EPA, 2019). The Guidelines were prepared by senior risk assessors and managers from across the EPA and coordinated through EPA's Risk Assessment Forum.

These Guidelines are not prescriptive, instead offering considerations and recommendations to EPA risk assessors regarding best practices for the CRA's initial phase of planning and problem formulation. The risk analysis and characterization phases of the assessment are not addressed in these Guidelines and are typically guided by the statute or authority under which they are conducted. The Guidelines do not impose any requirement for their use by the EPA or any federal, state, or Tribal agency.

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CHAPTER 1. INTRODUCTION

Cumulative risk assessment (CRA) is an analysis, characterization, and possible quantification of the combined risks to health or the environment from multiple agents or stressors (U.S. EPA, 2003b). In describing CRA, we begin with a focus on the purposes for which CRA may be useful. All environmental risk assessments endeavor to estimate a likelihood of harm arising from *exposure* to *stressors.* The primary distinguishing factor between CRA and other risk assessments is that CRA is an assessment of the probability of harm from exposure to *multiple agents and/or stressors*. CRA is responsive to the EPA's mission, as well as national policy, regulations, and statutes, including several executive orders.[4] Together, they direct agencies of the federal government, as appropriate and consistent with applicable law, to address multiple and cumulative exposures, recognize effects on vulnerable populations, recognize the value of Indigenous Knowledge, and evaluate disproportionate and adverse human health and environmental effects (including risks).

These Guidelines describe considerations for evaluating when CRA is both suitable and feasible, as well as steps to plan a CRA when those conditions are met, consistent with applicable law. These Guidelines were designed to adapt to the differing and evolving needs of risk managers at EPA program offices and regions based on differing initiating factors, statutory authority, program objectives, and availability of data and analytical methods. The Guidelines provide a strategy that emphasizes planning the CRA to consider the need(s) of the risk management decision. Depending on the purpose, problem, or question, CRAs can take many different forms and may be conducted under various environmental statutes. Examples include community-scale risk assessments, national-scale standards setting and chemical reviews, and prioritization of actions. Therefore, no single set of criteria can be applied to determine when a CRA is appropriate. That determination is necessarily tailored to the purpose for which a CRA is proposed, considering statutory authority, and decided by risk assessors and decision-makers. These Guidelines are *not prescriptive*, instead offering considerations and recommendations to EPA risk assessors regarding best practices for the CRA's initial phase of planning and problem formulation. The risk analysis and characterization phases of the assessment are not addressed in these Guidelines and are typically guided by the statute or authority under which they are conducted. As with other risk assessments, a CRA should not be conflated with a risk management decision but is appropriately used as scientifically defensible evidence to inform decisions. However, other factors also come into play in decision-making. Depending on the situation, a CRA may not always be the most appropriate or suitable approach. When a CRA helps address a risk management question and is within statutory mandates, it may be appropriate to consider conducting a CRA.

The elements of CRAs discussed here are: the initiating factor, iterative scoping of the study, problem formulation, and steps for preparation of the analysis plan (U.S. EPA, 2014b). The subsequent analysis plan will specify the methods and data to estimate and characterize risks to the target receptor(s) from multiple agents of concern. These Guidelines focus on human health outcomes, but many of the planning recommendations are generally applicable to CRAs that integrate human health and ecology.[5] Evaluation of both human health and ecological endpoints is important for understanding risk for groups who may have a greater focus on integrating ecological resources (e.g., cultural and subsistence users of ecological resources including Tribes and Indigenous Peoples). The EPA has a policy of considering and incorporating Indigenous Knowledge, as appropriate, per the *Guidance for Federal Departments and*

[4] Some executive orders and memorandums include: *Executive Order 12898 – Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations* (EOP, 1994); *Executive Order 13985 – Advancing Racial Equity and Support for Underserved Communities Through the Federal Government* (EOP, 2021); *Executive Order 14091– Further Advancing Racial Equity and Support for Underserved Communities Through the Federal Government* (EOP, 2023a); *Executive Order 14096 – Revitalizing Our Nation's Commitment to Environmental Justice for All* (EOP, 2023b); *Executive Order 13045 – Protection of Children From Environmental Health Risks and Safety Risks* (EOP, 1997); *Implementation of Guidance for Federal Departments and Agencies on Indigenous Knowledge* (CEQ, 2022b).

[5] See EPA's web page on Ecological Risk Assessment (https://www.epa.gov/risk/ecological-risk-assessment).

Agencies on Indigenous Knowledge.[6] Tribes should be, and are, considered subject matter experts of their own lifeways and environment, and their science should be considered an aspect of "best available science."

A defining feature of CRAs, given the current state of practice, is the approach for combining exposures to multiple stressors that can result in common adverse health outcomes. The National Research Council (NRC), in *Science and Decisions: Advancing Risk Assessment* (2009), notes that many risk assessment applications in the EPA and elsewhere "are often centered on evaluating risks associated with individual chemicals in the context of regulatory requirements or isolated actions…." NRC states that there is concern "among stakeholder groups (especially communities affected by environmental exposure) that such a narrow focus does not accurately capture the risks associated with the exposure(s) driving the CRA, given simultaneous exposure to other multiple chemical and nonchemical stressors and other factors that could influence vulnerability." This concern can potentially be addressed by CRAs, which may be implemented when there is adequate information to identify the relevant exposure-risk relationships for multiple chemical and nonchemical stressors, as well as the means to identify those most important to health outcomes. This approach is consistent with the existing risk assessment paradigm that relies upon scientifically rigorous methods for assessing hazard and exposure and the resulting adverse outcomes. The wide range of conditions and circumstances that might result in consideration of a CRA necessitates that planning and problem formulation guidelines be equally broad in consideration of the factors that may be relevant to the assessment. The diversity of initiating factors may result in the call for a CRA under various federal authorities or from other governmental entities or the public.

Because of the complexity of properly identifying and evaluating multiple agents in a CRA, a "systems approach" for planning and problem formulation is useful. The systems approach seeks to examine "a problem holistically, include[ing] all the drivers and stressors that affect it and the dimensions that frame it, and integrate[s] information from human health and ecological sciences and the social sciences to formulate sustainable solutions…" (Burke et al., 2017). The systems approach Burke et al. described for problem formulation is consistent with existing best practices and includes as examples the conceptual model of Suter (2006) and information important to consider during problem formulation, which the EPA describes in its *Framework for Human Health Risk Assessment to Inform Decision Making* (U.S. EPA, 2014b). Also important in the systems approach is engaging assessment users and stakeholders early in the process so all useful information sources are identified and all parties fully understand the problem or question and the system boundaries under investigation.[7] The systems approach is also described in the *total environment framework* (Tulve et al., 2016). An application of this framework illustrates the interrelationships between inherent characteristics, activities, and behaviors, as well as stressors from the built, natural, cultural, and social environments that influence children's health and well-being as they progress through various stages of development (Barros et al., 2018a; Barros et al., 2018b; Lichtveld et al., 2018; Nilsen et al., 2020a; Nilsen et al., 2020b; Nilsen & Tulve, 2020; Ruiz et al., 2016).

A second defining feature of CRAs is that the problem formulation can start with either the stressor(s) or the adverse human health or environmental outcomes of interest in the receptor(s). Traditionally, EPA risk assessments start with an examination of exposure to stressors, with the intent to estimate the effect of such exposures on human health or the environment. However, a CRA problem formulation can also begin with an adverse outcome (e.g., cancer, neurotoxicity) experienced by a receptor (e.g., organism, community[8]) and then seek to examine exposures to possible stressors causing the adverse outcome (see

[6] See *Indigenous Traditional Ecological Knowledge and Federal Decision Making* (CEQ, 2021); *Guidance for Federal Departments and Agencies on Indigenous Knowledge* (CEQ, 2022a); *Implementation of Guidance for Federal Departments and Agencies on Indigenous Knowledge* (CEQ, 2022b).

[7] See EPA's web page on its draft Meaningful Engagement Policy (https://www.epa.gov/environmentaljustice/epas-meaningful-engagement-policy).

[8] Receptors, as used in these Guidelines, do not include molecular receptors and are focused on higher levels of organization.

APPENDIX C, Figure C-1. Conceptual Model for Factors Influencing the Risk of Cardiovascular Disease).

CRA is one among a variety of assessment methods undertaken to inform risk and other management decisions protective of environmental and public health. In addition to risk, other management decision contexts may include prioritizing stressors for attention and program design, identifying communities disproportionately affected by pollution and other stressors, determining enforcement priorities, or setting regulatory standards. Understanding the purpose of an assessment is fundamental to its design. Clarifying the management decision context and the information necessary to support it, as well as data quality, is the first step in determining whether a CRA may be suitable, and if so, determining an assessment design. This step is described as "fit for purpose," in EPA's *Framework for Human Health Risk Assessment to Inform Decision Making* (U.S. EPA, 2014b) (see Figure 1). This step is common to all assessment processes because the assessor should understand the strengths and limitations of the assessment frameworks potentially being used to address the risk management decision (NRC, 2009). Some agencies use the National Academies of Sciences, Engineering, and Medicine (NASEM) recommended phrase "intended purpose and context of use" to communicate the fit for purpose concept (NASEM, 2023). In the current practice of risk management at the EPA, analysis relating stressor exposures to specific effects or changes in primary or target exposure-response relationships for the CRA is often employed to support decisions on environmental and human health standards and regulations. These Guidelines largely conform to this practice and provide approaches for considering multiple chemical and nonchemical exposure and response modifiers as part of CRA problem formulation and planning. The background and history of CRA development at the EPA, as well as CRA applications, are discussed in APPENDIX A. APPENDIX B describes key Agency documents informing CRA, with tables highlighting contributions from the EPA (Table B-1) and other source documents (Table B-2), to improve CRA planning and problem formulation. Together, they provide useful background for planning a CRA. Figure 2 highlights some of the CRA publication milestones.

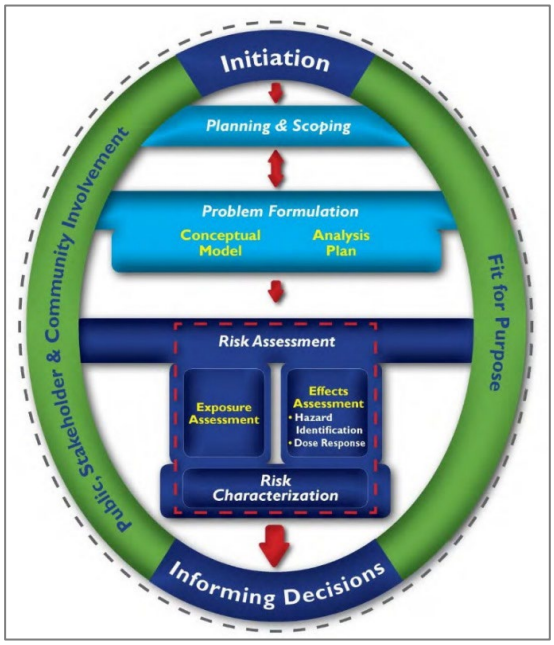

Figure 1. Framework for Human Health Risk Assessment

Source: U.S. EPA (2014b).

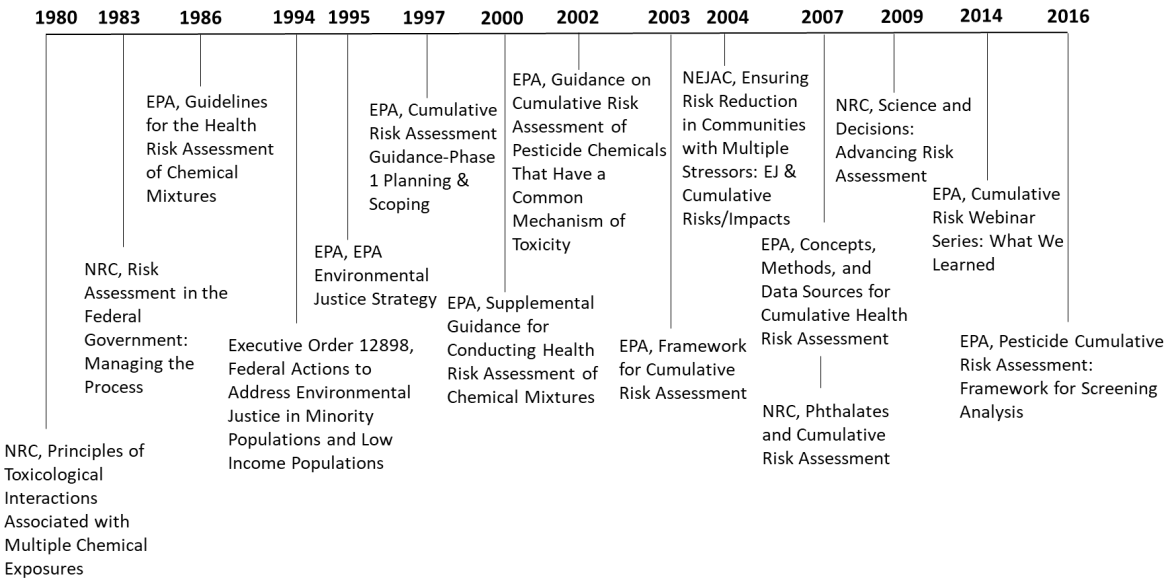

Figure 2. Timeline of CRA Publication Milestones [Selected Milestones]

1.1. Early Considerations for Planning and Scoping in Cumulative Risk Assessment

Early considerations in scoping a CRA could include public health needs and the concerns of communities or Tribes and Indigenous Peoples and statutory or other requirements; an anticipated time frame for addressing community concerns; and risk management needs. These considerations may need to be approached in an iterative way, allowing for possible reassessment of some aspects of the CRA throughout the process.

Whether CRA is a suitable and feasible approach for informing a risk management decision should be determined as early in the assessment process as possible. The determination rests on whether CRA is a good fit for the risk management question (fit for purpose) and whether the available data, analytical methods, and resources will support the needs of the assessment. The decision, which can involve stakeholder input, can be considered a two-step process:

1. Suitability – Examining whether a CRA is a good match for the risk or other management question (i.e., is it suitable? see Sections 2.3 and 2.4).
2. Feasibility – Determining whether data, analytical methods, time, and other resources are sufficient to conduct a CRA (i.e., is it feasible? see Section 2.6).

Determining whether CRA is a suitable approach begins with considering the initiating factors and risk management question relative to the resources and data available to address them. There may be various initiating factors for a CRA. Potential examples include possible exposure to multiple pollutants, chemical concentrations above levels of concern (individually or collectively), or a documented community illness with a known or suspected connection to pollution, which have been linked to numerous variables that can contribute to adverse health outcomes (U.S. EPA, 2007a).

If it is determined that CRA is a suitable assessment approach, several screening considerations are recommended for evaluating whether CRA is feasible:

- Sufficient data exist or may be reasonably obtained to inform the assessment with adequate consideration of uncertainty (see Sections 2.6 and 3.4).
- Methods are adequate to analyze the data and to integrate them into the risk characterization with consideration of uncertainty.
- Time, staff, and financial resources are sufficient to successfully conduct the assessment.

The current practice of CRA seeks quantitative estimates of risk that are based on an understanding of how multiple stressors jointly contribute to one or more common adverse health outcomes, indicated by common mechanisms of toxicity, common key events, or converging adverse outcome pathways, and to account for uncertainties related to the relationship between stressors and adverse outcomes. These quantitative methods increase our understanding about toxicological action and resulting adverse health outcomes from multiple stressors.

CRA is appropriate when the decision context is well matched to an assessment that is informed by this kind of information. Chemical class (or group) reviews, for example, are good candidates for this kind of analysis. Community-based CRAs may also be undertaken when the stressors of concern are well characterized, and sufficient data can be obtained to provide for an analysis of the relationship between stressors, exposure, and health outcomes.

Some decision contexts may present questions that extend beyond what can be answered with dose-response stressor and exposure information. Examples include concentrated burdens of multiple and different stressors lacking health effects data or concerns of disproportionate and adverse human health and environmental effects among populations. There are also analytical challenges stemming from when populations of concern are subject to less well-understood nonchemical stressors (e.g., poor nutrition or limited access to health care) that might exacerbate an adverse response to known stressors and result in greater vulnerability (or less resilience) than the general population. In these cases, there may be uncertainty about which stressors are important and how to incorporate them into a risk analysis. A qualitative or semiquantitative characterization of suspected stressors that lack data needed for quantitative risk analysis can nonetheless improve understanding of the full range of potential stressors contributing to adverse health outcomes. An evaluation of when and how to incorporate them into an assessment is case dependent and should follow a determination by the CRA team using an appropriate weight-of evidence (WoE) evaluation (see WoE discussion in Section 3.2.4).

To ensure CRA is an appropriate fit for purpose tool, it is important to understand when and how it can be productively applied relative to other approaches, including but not limited to cumulative impact assessment (CIA) and health impact assessment (HIA). Each approach may employ a variety of methods to provide information to decision-makers about health outcomes associated with exposures to multiple chemical and nonchemical stressors. Methods employed are not exclusive to an assessment approach and can be used across different approaches. Determinations about which approaches and analytical methods to use depend on factors such as statutory requirements, the scope of an assessment, types of data needed and available, and applicability for the evaluation and needs of the decision-maker. Risk assessment is specifically used to inform risk management decisions. However, any of these approaches could be used to help address environmental management questions related to disproportionate and adverse human health and environmental effects, community action plans or other community-based needs, and other environmental management considerations if the analytical method is warranted given the decision-making context. More than one approach may be used in combination. Assessors need to exercise judgment in determining when to use CRA, CIA, or another approach for evaluating exposures to multiple stressors for a specific purpose. Assessors can refer to EPA's *Interim Framework for Advancing Consideration of Cumulative Impacts* for additional information on the matter (U.S. EPA, 2024).[9]

Risk assessments have traditionally been conducted on specific stressors with known adverse health outcomes. CRA may be planned around stressors but can also focus on receptors and adverse outcomes as the risk management question. NRC's report on phthalates (NRC, 2008a) and the European Union's NoMiracle project (Løkke, 2010) illustrate the use of CRA to evaluate receptors of concern. A major

[9] See EPA's website for the Interim Framework for Advancing Consideration of Cumulative Impacts: https://www.epa.gov/cumulative-impacts/interim-framework-advancing-consideration-cumulative-impacts.

conclusion of the NoMiracle project highlighted the importance of CRA when focused on receptors: "…it gradually became clear that the current approach in coping with chemical mixtures focusing on 'the chemical' and 'chemical cocktails' should be replaced by a focus on the biological organismal receptor, e.g., on the organism (humans or other species), the population or the ecosystem being exposed to a more definite cocktail of stressors" (Løkke, 2010). Similarly, NRC's *Phthalates and Cumulative Risk Assessment* (NRC, 2008a) report was initiated because "studies show widespread human exposure to multiple phthalates and indicate that effects on the development of the reproductive system of laboratory animals occur at much lower doses than were predicted in earlier studies." In this context, the EPA asked NRC to review independently the health effects of phthalates.

As the practice of CRA continues to evolve, an increasing number of toxicological and epidemiological studies link nonchemical stressors to population vulnerabilities in many contexts that may be relevant to a risk management decision (Payne-Sturges et al., 2018). When there is evidence of a relationship between the stressor and the health outcome, that evidence can be incorporated into the assessment in multiple (or a variety of) ways (e.g., when the suspected stressors demonstrate stressor estimates of risk are difficult to quantify but show other qualitative or semiquantitative relationships). These Guidelines provide recommendations for documenting quantitative and qualitative information in the risk characterization (see Sections 2.6 and 3.5). Additionally, methods for merging quantitative and qualitative information are discussed in the *Framework for Cumulative Risk Assessment* (U.S. EPA, 2003b) and elsewhere in peer-reviewed literature (e.g., Schäfer et al., 2023).

1.2. Organization of This Document

These Guidelines provide considerations and strategies for CRA planning and problem formulation, which are necessary steps in the advancement of CRA from a concept to a decision-relevant tool (Sexton, 2015). These Guidelines comprise three sections: this introduction, a second section on CRA planning and scoping, and a third section on CRA problem formulation. The scoping step in the planning phase identifies the significant factors in the assessment and should determine whether CRA is the right approach for conducting the assessment. The steps for scoping the assessment presume a risk management question suited to CRA. The problem formulation section describes steps for developing the conceptual model that provides an initial understanding of relationships among factors in the assessment. The problem formulation statement provides a precise description of how the proposed risk assessment serves the risk management decision. Problem formulation results in an analysis plan, which describes the methods necessary to conduct the analysis.

Although steps are defined sequentially for ease of communication, the process can involve simultaneous steps or a different sequence. Steps also might be repeated in an iterative approach. The scoping and problem formulation phases are mutually informative, as greater detail and more information advance the assessment. Factors important to consider are listed in many of the sections. Strategic questions associated with some sections are highlighted in shaded boxes.

These Guidelines recommend a tiered or phased process for matching the design of a CRA to the level of risk management needed (see Section 2.5). The intent of tiering or phasing the analysis is to tailor the level of effort to the purpose of the risk assessment. The incremental process of gathering information typical of tiering and phasing reinforces the recursive process between problem formulation and the other steps in planning the CRA.

Text Box 1.
Cumulative Risk Assessment Planning Milestones

1. Initiating factors (Section 2.1.)
2. Identification of stakeholders (Section 2.2.)
3. Statement of purpose (Section 2.3.)
4. Evaluation of "fit for purpose" (Section 2.4.)
5. Scoping summary statement (Section 2.4.)
6. Conceptual model (Section 3.2.)
7. Weight of evidence evaluation (Section 3.2.4.)
8. Analysis plan (Section 3.3.)

These Guidelines identify eight milestones in planning the CRA (Text Box 1). Each milestone is an appropriate point at which the CRA team may confirm its planning progress and consider whether any changes would be appropriate (perhaps on the basis of new information).

CHAPTER 2. CUMULATIVE RISK ASSESSMENT PLANNING AND SCOPING

CRA design involves defining and preparing a risk-related problem for evaluation. CRA planning and scoping generate the initial definition of the problem for assessment. Planning and scoping help to organize issues and participants in advance of problem formulation and the development of a technically oriented conceptual model and the preliminary analysis plan for CRA.

Problem formulation and development of a conceptual model and preliminary analysis plan for CRA are considered parts of the planning process but are organized separately in these Guidelines (Chapter 3). In practice, however, problem formulation occurs iteratively with other planning and scoping considerations. This chapter discusses eight topics for CRA planning and scoping:

- Decision context and initiating factors (Section 2.1.)
- Participant and stakeholder involvement (Section 2.2.)
- Statement of purpose (Section 2.3.)
- Scoping objectives, boundaries, and constraints (Section 2.4.)
- Tiering and phasing the assessment (Section 2.5.)
- Data quality, needs, and availability (Section 2.6.)
- Project and risk management considerations (Section 2.7.)
- Peer review (Section 2.8.)

The approach to CRA planning in these Guidelines is consistent with the vision for risk assessment that NRC's Committee on the Institutional Means for Assessment of Risks to Public Health advances in its report, *Risk Assessment in the Federal Government: Managing the Process* (NRC, 1983).

2.1. Decision Context and Initiating Factors

Risk assessments, including CRAs, are generally performed within a decision-making context to inform regulatory actions, to address a health concern, or to comply with legal requirements or align with broad EPA priorities, such as children's health, environmental justice,[10] and sustainability (EOP, 1997; U.S. EPA, 2014b 2021a). This context and the information or technical factors leading to a decision to consider CRA are termed "initiating factors." Identification of CRA initiating factors is generally the beginning of the CRA planning phase. Consistent with explanations in EPA's *Framework for Human Health Risk Assessment* (U.S. EPA, 2014b) and NRC's *Science and Decisions* (NRC, 2009), initiating factors provide the rationale for CRA. In addition to supporting EPA regulatory requirements and policy commitments, the decision to conduct a CRA may stem from the input of stakeholders, including government and Tribal representatives, academia, industry, and concerned citizens or organizations. Initiating factors can relate to environmental justice concerns, specific stressors (sources), or population exposures (receptors); they can also be specific to a location or situation. Initiating factors help define the assessment in terms of geographic area(s) and population(s) or receptor(s) to be evaluated, relevant stressors and effects, and the time frame in which results are needed. Clarity on initiating factors is helpful for determining whether CRA will be a suitable approach to inform the management decision. However, the variability of initiating factors and decision-making contexts does not allow for a definitive

[10] Environmental justice means the just treatment and meaningful involvement of all people, regardless of income, race, color, national origin, Tribal affiliation, or disability, in agency decision-making and other Federal activities that affect human health and the environment so that people: are fully protected from disproportionate and adverse human health and environmental effects (including risks) and hazards, including those related to climate change, the cumulative impacts of environmental and other burdens, and the legacy of racism or other structural or systemic barriers; and have equitable access to a healthy, sustainable, and resilient environment in which to live, play, work, learn, grow, worship, and engage in cultural and subsistence practices. See the EPA web page on Environmental Justice definitions for more information: https://www.epa.gov/environmentaljustice/learn-about-environmental-justice#definitions.

decision criterion to initiate a CRA. A determination to initiate a CRA builds on early planning steps and an evaluation of the match of available information for risk analysis to inform the decision context.

Examples of initiating factors include one or more of the following:

Statutory Provisions. Statutes might require or pertain to CRA. For example, the Food Quality Protection Act (FQPA) of 1996[11] specifies CRA for certain pesticide assessments.

Community Concern. Communities can play a role in initiating CRA by identifying ecological or human health conditions of concern, such as exposure or vulnerabilities from multiple factors (e.g., nonchemical stressors, age) and exposure to combined (local or national) multiple pollutant sources or releases not addressed by single-pollutant or single-source assessments.

Future Changes in the Community/Environment, Permitting, Upfront Assessment. Anticipated changes in a community or environment might be a precondition for a project or activity (e.g., environmental review requirements associated with rezoning proposals).

Evidence of Human Illness/Ecosystem Stress. Increased or elevated prevalence of human illness (or the observation of personal or local increases) in a community or an ecosystem could motivate consideration of CRA.[12] Available data supporting multiple chemical exposures leading to specific disease outcomes could also motivate CRA. An example is highlighted in an NRC report stating: "… EPA could evaluate combined exposures to lead, methylmercury, and polychlorinated biphenyls because all contribute to the cumulative risk of cognitive deficits associated with IQ reductions in children, although the deficits are produced by different mechanisms of action...." (NRC, 2008a).

Elevated Stressor Levels. Measured or potential elevations in pollutant concentrations could motivate CRA (e.g., metrics such as those included in EPA's *Report on the Environment* (U.S. EPA, 2020c) or *America's Children and the Environment* (U.S. EPA, 2013)).[13] Research suggests an association between proximal human exposures to chemicals and the production of high-volume chemicals and accidental releases and that "where chemical production volumes are so high (i.e., they are produced or imported into the U.S. in quantities of 500 tons per year or greater)…human exposures should be expected" and should "trigger additional scrutiny and potential interventions" (Vandenberg et al., 2023).

Evidence of Widespread Exposure to Chemical(s) of Concern in a Population. NRC recommends conducting a CRA when there is substantial evidence supporting multiple chemical exposures in the human population (e.g., biomonitoring data) (NRC, 2008a). In some instances, coordination with other entities (e.g., other federal agencies, state and local government, other organizations) may be appropriate.

Social and Economic Concerns about Natural Resource Conservation. Environmental conservation concerns, such as sustaining cultural and subsistence practices, could lead to requests for CRA.

Useful descriptions of CRA initiating factor(s) are concise statements of what the initiating factor(s) are: how, when, and by whom they were brought forward for evaluation; human or ecological population(s)/receptor(s) potentially affected; any specific contaminants or other stressors of concern; temporal scales and geographic areas of concern; and anticipated environmental impacts or health effects that might need evaluation.

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[11] See the EPA's Summary of the Food Quality Protection Act (https://www.epa.gov/laws-regulations/summary-food-quality-protection-act).

[12] Community concerns that environmental exposures are contributing to illness and that single-agent and/or single-source assessments do not adequately reflect risks from the combination of stressors and sources (as well as vulnerabilities) are conditions that can lead to a community's request for a CRA.

[13] Updates to *America's Children and the Environment* occurred in 2015, 2017, 2018, and 2019. See https://www.epa.gov/americaschildrenenvironment/basic-information-about-ace.

2.2. Participant and Stakeholder Involvement

The EPA's *Framework for Human Health Risk Assessment to Inform Decision Making* defines stakeholders as "…individuals or representatives from organizations or interest groups that have a strong interest in the Agency's work and policies." It also identifies internal stakeholders, such as EPA offices and external stakeholders, which can include the public, affected industries, public health or environmental organizations, and other governmental agencies such as Tribes, states, and municipalities (U.S. EPA, 2014b).

The Presidential/Congressional Commission on Risk Assessment and Risk Management (PCCRARM) uses another definition also worth noting: "A stakeholder is anyone who has a 'stake' in a risk management situation" (PCCRARM, 1997). This broad stakeholder definition recognizes that even those unaware of risk assessment/risk management activities such as CRA might have a "stake" in or be affected by such work. The Commission considered the "Problem/Context" stage of its process—roughly equivalent to planning, scoping, and problem formulation in CRA—to be crucial. The Commission emphasized "active stakeholder involvement at this particular stage [as] the most critical element of the decision-making process." Determining who is "at the table" during CRA design is a consideration that has consequences for all subsequent steps in the CRA process.

The levels of public participation, stakeholder negotiation, community outreach, Tribal consultation,[14] and capacity building vary depending on the activity and program requirements (U.S. EPA, 2001b, 2014b). Applicable laws, regulations, and the domain of other agencies affect what may and may not be done in participatory processes and how agencies with authority to act may use the results of such processes. Even when process flexibility is constrained by legal mandates, the CRA team can have a robust discussion of stakeholder participation and involvement (NRC, 2008b). When engaging with federally recognized Tribes, the EPA uses the Tribal consultation process to provide an opportunity for meaningful dialogue and input when EPA actions or decisions may affect Tribes (U.S. EPA, 2023c).[15]

The range of circumstances motivating or initiating CRA can be broad, and stakeholder involvement can be greatly determined by initiating factor(s). For example, stakeholders concerned about local environmental conditions could seek to initiate a CRA process. In such a case, stakeholder involvement and participation can influence EPA's risk assessment or CRA design; however, the extent and timing of such involvement can vary.[16] As stated in the Agency's *Framework for Human Health Risk Assessment to Inform Decision Making* (U.S. EPA, 2014b), the appropriate stakeholder involvement process will depend on the specifics of the situation: "…The timing, frequency and level of community involvement will depend on several factors, including regulatory requirements, the nature of the decision and community interest." Public, stakeholder, and community involvement, when appropriate, should be considered part of the risk assessment and decision-making processes. A key principle of community engagement is to be clear about the purposes or goals of the engagement and the populations or communities to be engaged (ATSDR, 2011). Other examples of how to engage communities and public stakeholders can be found in Appendix 2 of the EPA's *Meaningful Involvement Policy*[17] and in the EPA's *Stakeholder Involvement &*

[14] https://www.epa.gov/tribal/consultation-tribes

[15] Tribal consultation is a process to ensure meaningful and timely input by Tribal officials. In addition, the Agency's network of Tribal Partnership Groups (https://www.epa.gov/tribal/partnerships-tribes) facilitates the exchange of technical information and communication between Tribes and the EPA. For example, the National EPA-Tribal Science Council works to integrate and increase tribal involvement in the EPA's scientific activities, while the National Tribal Toxics Council provides Tribal input on issues related to toxic chemicals and pollution prevention.

[16] A request for a CRA can be made by anyone. However, for the EPA to initiate a CRA in response, it would need to conform with statutory or program guidelines and procedures and have management approval. While this document is written in particular for EPA use and application under regulatory authorities, the principles may be useful to other authorities, such as Tribal, state, and local governments.

[17] See the EPA's web page on its draft Meaningful Engagement Policy (https://www.epa.gov/environmentaljustice/epas-meaningful-engagement-policy).

Public Participation at the U.S. EPA: Lessons Learned, Barriers, & Innovative Approaches (U.S. EPA, 2001d). Key questions and considerations may include:

- Who are the stakeholders?
- What and when are the opportunities for stakeholder involvement?
- What communication materials are needed to effectively engage stakeholders?
- What mechanisms, including data-sharing agreements, will be most effective for engaging different stakeholders?

Those conducting the CRA (e.g., the EPA, contractors, subject matter experts) can be called CRA participants or the CRA team. The composition of the CRA team depends on the nature of the problem. The level of complexity of a risk assessment and the context for its conduct often dictate a multidisciplinary approach. Legal experts, Tribal program managers, and policymakers also might be called on to contribute to risk assessment planning and scoping. Depending on the context and the process by which the risk assessment is conducted, specific expertise might be needed to develop specialty tools, data, or analyses. Other team participants can provide information on project management issues, including funding levels and sources, staffing, contractor requirements, and any need for interagency agreements (U.S. EPA, 2003c).

2.3. Statement of Purpose

Following identification of initiating factors and stakeholders/participants, a purpose statement (see Text Box 2[18]) should be confirmed with all involved parties. Depending on the context of the assessment, this statement could be a formal or informal step, but written documentation is recommended. A statement of purpose could also take the form of a relevant framework for a conceptual model, which also could become an important part of the analysis plan. In general, the purpose should be stated in concise and direct terms, clearly identifying what the CRA is intended to accomplish or produce. This statement, which may be written as a specific risk question, is used to identify what will be needed to accomplish the desired outcome or product of the CRA. Topics such as resource and data availability, CRA scope, and risk management options are relevant to the CRA purpose statement and should be discussed *before* it is completed. Because the statement of purpose provides direction for subsequent steps in the CRA and likely is referred to repeatedly, the discussion should be as precise as possible and clearly understood. At a minimum, the statement should be expected to clarify the initiating factor(s) and the risk management decision the CRA is intended to inform. It can be sufficiently detailed to provide an initial framework for construction of a conceptual model. This step provides an initial indication of the suitability and feasibility of the CRA and the extent to which it can address the risk management decision.

Text Box 2.
Hypothetical Cumulative Risk Assessment Statement of Purpose

A Tribe experiences ongoing air and water pollution released from two nearby facilities. The purpose of a cumulative risk assessment would be to evaluate whether these exposures are affecting the health of the community through estimating emission rates of air and water pollutants from the two facilities. As part of this assessment, potential concerns that would be particularly relevant for the Tribe could be considered: contaminated fish, which makes up half of their normal dietary protein intake; contaminated water, which is not just a dietary intake exposure but used for cultural practices such as steam baths and sweat lodges; and higher rates of asthma or respiratory issues among Tribal children. Additional consideration could also include nonchemical stressors. If the Tribe agrees to share further information pertaining to unique lifeways, this could also be considered in the evaluation.

[18] Tribal lifeways are inclusive of, but not limited to, economic, cultural, ceremonial, recreational, and subsistence practices. It is characterized by an EPA Partnership Group, the National Tribal Toxics Council. https://nttc.sfo3.cdn.digitaloceanspaces.com/Docs/NTTC-Understanding_Tribal_Exposures_to_Toxics-2015-06-19.pdf

2.4. Scoping Cumulative Risk Assessment Objectives, Boundaries, and Constraints

Scoping of a risk assessment's general objectives, boundaries, and constraints provides a foundation for problem formulation (U.S. EPA, 2014b). Scoping represents the CRA team's initial "big picture," first-draft statement of the key considerations, topics, or elements the assessment will address and begins with consideration of whether the CRA is fit for purpose—the suitability and feasibility of CRA to address the risk management decision. Scoping incorporates as many issues and concerns as the team believes relevant to the assessment's success. It describes the risk problem and how the CRA will address and inform that problem. In scoping the assessment, decision managers, stakeholders, and relevant technical experts work as a team informed by stakeholder input to discuss key considerations of the subject CRA. Because the scope of a CRA may cut across the legal domains of multiple statutes and regulatory agencies, it can involve issues and topics that are outside the expertise of the EPA risk assessors and regulators (e.g., HIPAA) (Sexton, 2015). The CRA team should seek appropriate additional expertise as necessary. Scoping often concludes with a scoping summary statement.

Fit for Purpose. A well-designed scoping process ensures the CRA will meet the intended purpose(s) as specified in the statement of purpose and will inform decision-making. As discussed in Section 1.1, the evaluation early in the assessment planning process of whether a CRA is a suitable and feasible assessment approach that will inform its purpose is referred to as fit for purpose. The EPA introduced the concept of fit for purpose for human health risk assessment to help ensure assessment products were properly designed to inform the risk management decisions for which they were conducted (U.S. EPA, 2014b). Consideration of fit for purpose is an articulation of the risk management needs early in the scoping process and the questions to be informed by the risk assessment. Attention is given to this concept through focused planning and problem formulation, and its confirmation throughout the process to ensure the assessment is generating the information that will inform the risk management decision. An initial evaluation of fit for purpose follows the statement of purpose and constitutes a determination of whether a CRA can inform a risk management decision.

Overarching questions when evaluating the CRA's suitability and feasibility using a fit for purpose approach—the answers to which will improve scientific understanding of the problem—include:

- How will the assessment inform choices among risk management options?
- Will the risk assessment need to change or expand to differentiate among risk management options?
- Does the risk assessment design meet the objectives, and will it have the attributes identified in the problem formulation step?
- Does the assessment address the initial objectives, and is it consistent with the attributes identified in problem formulation? Or, if the initially identified objectives or attributes have been modified, does the assessment incorporate the modifications?
- If the assessment requires peer review, is the review consistent with the current EPA peer-review policy (e.g., *Peer Review Handbook, 4th Edition*), and have the issues raised during peer review been addressed adequately?
- How will the results of the risk assessment be communicated to the risk managers and stakeholders (from U.S. EPA, 2014b)?

Other important scoping considerations in this section (below and in Table 1) may also guide the evaluation of whether the CRA is fit for purpose.

Potential Statutory and Regulatory Provisions. Risk assessment could be affected by statutory or regulatory mandates administered by the EPA or local, state, Tribal, and other federal agencies. Such mandates can affect how the CRA is conducted (e.g., by constraining the assessment's scope or the way appropriated funds can be spent). The CRA team should refer to the relevant EPA authority other federal agency, or Tribal, state, and local authorities for statute and regulation information.

Supportive Policy/Executive Orders. Relevant scientific background and reasoning for a CRA can be noted in some relevant policies and directives, which can be considered in planning and scoping any risk assessment, including a CRA. For example, the *Policy on Children's Health* (U.S. EPA, 2021a) describes the EPA's policy to protect children from environmental exposures by consistently and explicitly considering early-life exposures and lifelong health in all human health decisions.[19] More policies and executive orders can be relevant to supporting CRA planning and scoping.[20]

History of the Issue(s). The history of a particular environmental issue might be extensive and need documentation to set context and boundaries for the CRA. Identifying stakeholders who have been previously concerned or involved or communities that are directly affected by the issue could be important. Event history and potential legacy pollution might be useful information in describing the initiating factor(s), assembling a planning team, and obtaining and organizing information for the CRA. The contributing pollutants, regulatory history (existing laws and regulations), and assessment history (conducted by other EPA programs and other organizations) are also important to identify and consider.

Populations of Interest. As part of CRA scoping, characteristics of any population of interest in the CRA need to be defined and would include identification of worker/occupational nonusers, consumers and bystanders, fenceline communities, Tribal and Indigenous Peoples, and other populations of interest. Within each population of interest could be individuals with increased exposures or vulnerabilities, which could result in increased consequences from exposure.

It is important for a CRA to consider groups of individuals or communities within the general identified study population who, due to vulnerabilities, may be at greater risk than the general population of adverse health effects from exposure to stressors. Vulnerability can stem from intrinsic factors (e.g., preexisting disease, lifestage, reproductive status, age, sex, genetic traits) or extrinsic factors (e.g., social determinants of health such as food insecurity, geography, poverty, socioeconomic status, racism, discrimination, cultural and subsistence practices, workplace) when identifying subpopulations of concern.[21] A goal of the Agency is to address age- and sex-specific issues, using age- and sex-differentiated data in Agency risk assessments and risk management decisions, whenever appropriate, and when relevant information is available (U.S. EPA, 1995b, 1997c, 2021a).

Differences in vulnerability may be explained by an analysis of toxicokinetic or toxicodynamic differences across lifestages or populations (e.g., across humans and animals, across animal species, across sexes or lifestages). Individual and social factors that may increase vulnerability to exposure-

[19] This Policy recognizes that such considerations may be qualitative when data are unavailable to support quantitative assessment. It states in part: "In implementing this policy, the EPA will identify and integrate data to conduct risk assessments of children's health to inform decisions. To the extent that relevant data is available, a quantitative risk assessment will be conducted. When quantitative information is not available but risks to children may exist, a qualitative risk assessment will be performed. In certain circumstances, assessment of aggregate and cumulative exposures may be necessary to properly characterize risks to children."

[20] Another recent policy example that may be relevant to CRA planning and scoping is Executive Order 13985 on Advancing Racial Equity and Support for Underserved Communities Through the Federal Government, which directs all agencies of the federal government to "pursue a comprehensive approach to advancing equity for all, including people of color and others who have been historically underserved, marginalized, and adversely affected by persistent poverty and inequality." A third example of a major policy directive to consider is Executive Order 14096, which requires the EPA to specifically "take steps to address disproportionate and adverse human health and environmental effects (including risks) and hazards unrelated to federal activities, including those related to climate change and cumulative impacts of environmental and other burdens on communities with environmental justice concerns."

[21] EPA programs and some regions rely on the Integrated Risk Information System (IRIS) for toxicity values for human health. IRIS noncancer reference values include the application of uncertainty factors that address interindividual differences in variability and susceptibility (e.g., addressing differences in response due to lifestage, sex, or genetic predisposition). Similarly, some IRIS toxicity values for cancer recommend the application of age-dependent adjustment factors to address an assumption of increased early-life susceptibility when there is sufficient support for a mutagenic mode of action. Such decisions are dependent on the chemical-specific evidence available when the assessment was developed.

related health effects include, genetic or epigenetic variability, age or developmental lifestage, health status, behaviors or practices, and social determinants of health (see Table 1 and APPENDIX D). Empirical data supporting such vulnerabilities may be absent, and incorporation of these considerations may be dependent on modeling.

Nonchemical stressors are an umbrella category of factors that can independently influence the risk of adverse health effects or may do so in combination with another stressor(s). Nonchemical stressors may directly affect physiological stress or contribute to physiological dysregulation and damage, which can be measured as allostatic load.[22] For CRA, nonchemical stressors are most likely to be considered for their role as potential exposure-response modifiers to chemical stressors (see Section 3.5). Limited experience with incorporating nonchemical stressors (e.g., allostatic load) in risk analysis may challenge the CRA team to identify appropriate methods consistent with data quality guidelines for the assessment. Incorporating nonchemical stressors in a CRA can be complicated by uncertainties in evaluating exposure to them, and their evaluation, potential health consequences, potential modification of the effects of or by other stressors (e.g., chemical exposures) and variation in individual (or community-scaled) vulnerabilities. When a lack of methods for assessing and quantifying such stressors limits their incorporation into an analysis plan, the conceptual model can be used to flag them for further study or note that any relevant qualitative information be included in the risk characterization for consideration by risk managers. Methods to incorporate such information qualitatively or quantitatively (when possible) may be available in peer-reviewed literature and could be considered during CRA scoping. The EPA may develop additional guidance to incorporate such information in the future.

Output from CRA scoping includes a documentation of findings (e.g., a scoping summary statement) that outlines general objectives, constraints, and boundaries of the CRA. Such documentation allows a common understanding of the scoping results across the team and will provide the foundation upon which further planning and problem formulation proceeds. The CRA scoping output also formalizes the earlier determination of whether CRA is a suitable approach for informing the risk management decision in the fit for purpose determination. Following this related discussion, the CRA team determines whether the available information supports continuation of the CRA with possible consideration of tiering or phasing (Moretto et al., 2017; U.S. EPA, 2016b). This phase is similar to the "gatekeeper step" implemented prior to problem formulation described and recommended by Moretto et al. (2017). The purpose of this step is to ensure all chemicals of potential concern are identified and grouped so the likelihood of common toxicity and co-exposure can be given initial evaluation by the CRA team and a determination made whether further effort for a CRA is appropriate (Embry et al., 2014; Moretto et al., 2017). The initial evaluation can vary in scope and level of detail based on the project. If a CRA is determined to be unsuitable, an explanation for the record of why the CRA is not considered appropriate to inform the risk or other management decision should be prepared and communicated to the risk manager or other decision-maker. A CRA might not be appropriate if there is not enough information available on stressors that have been identified by the CRA team. Similarly, if the scoping indicates there is no potential for adverse health risk, a full CRA may not be necessary (see Section 2.5).

Table 1 summarizes possible scoping considerations discussed throughout this document. Some of the examples listed are aspirational in nature and may not be feasible within current CRA practice. The CRA team should follow the data quality objective (DQO) process when scoping a CRA (see Section 2.6).

Table 1. Possible Considerations for Cumulative Risk Assessment
This table is not intended to be a checklist but provides possible considerations during the problem formulation of a CRA.

[22] Allostatic load represents the physiological consequences of chronic exposure to fluctuating or heightened neural or neuroendocrine response that results from repeated or chronic stress (Juster et al., 2010). Cardiovascular, metabolic, and inflammatory responses are also specified (Rodriquez et al., 2019).

Overall Considerations	Description or Example	Relevant Subsection in the Guidelines
Overall CRA purpose	The CRA purpose describes objectives, what is being evaluated, and limits of the CRA. See more in the CRA statement of purpose (2.3)	Section 2.3.
General scope of the assessment	Determine whether it is stressor- or receptor-oriented Identify geographic scale, population(s) of interest, and temporal boundaries Identify hazards/health outcomes and endpoints	Section 2.4.
Potential stressors and health outcomes evaluated in the assessment	Multiple stressors (i.e., chemical exposures, nonchemical stressors) Dose-response factors and related issues (e.g., modes/mechanisms of action and adverse outcome pathways) Exposure routes and pathways, including spatial, temporal, "background" exposures, pollutant modeling, or monitoring	Section 3.2. (conceptual model)

Potential Case-Specific Considerations for CRA	Description or Example	Relevant Subsection in the Guidelines
Biology and genetic variability	Different population characteristics based on genetic differences that may affect response to stressors (including epigenetics and genetic diseases), sex, anatomical and physiological traits, lifestage (age or life course (e.g., women of childbearing age, infants, fetuses, children, people >age 65+), in utero, adolescence, or pregnancy), health status (preexisting conditions or disease, such as psychosocial stress, elevated body mass index, frailty, nutritional status (e.g., food deserts), chronic disease)	Section 2.4. (Population of Interest) and 3.2.2.
Lifestyle and cultural practices	Diet, smoking, alcohol consumption, pica and other mouthing behaviors in children, subsistence, or recreational hunting and fishing	Section 2.4. (Population of Interest) and 3.2.2.
Social determinants of health-related and vulnerabilities	Social determinants of health include economic stability (e.g., steady income), education access and equality, health care access and equality, neighborhood and built environment (e.g., housing conditions conducive to flooding, pests, or allergens; housing status; access to transportation), social and community context (e.g., social, economic, and political inequality), cultural and subsistence practices, education, nutritional status, environmental justice factors (e.g., communities with potentially disproportionately high exposures to stressors), legacy pollution, or other conditions contributing to potential and disproportionate vulnerabilities in the potentially affected population[23] Examples of indicators for social determinants of health include educational status, income status, occupation, race/ethnicity, and geography (e.g., urban/rural) Social determinants of health could have direct impacts on health outcomes of interest or act as exposure-response modifiers and could therefore affect the conceptual model or analysis plan	Section 3.2.2. (Receptors of Potential Interest) and Appendix D
Analyses specific to an assessment	Topics of potential interest and accompanying rationale (e.g., effects of climate change) Sensitivity analyses Previous or targeted uncertainty and variability analyses Analytical resources required or available, such as data or models Subsequent conceptual model and analysis plan development Tribal lifeways (inclusive of, but not limited to, economic, cultural, ceremonial, recreational, and subsistence practices)[24] Consideration of internal/external peer review Relationships among potential assessment endpoints and risk management options	Various sections (e.g., Section 2.8., Section 3.4.)

[23] Adapted from the Office of Disease Prevention and Health Promotion's Social Determinants of Health web page (https://health.gov/healthypeople/priority-areas/social-determinants-health).

[24] Examples of Tribal lifeways and risk assessment can be found in "Paper on Tribal Issues Related to Tribal Traditional Lifeways, Risk Assessment, and Health & Well Being: Documenting What We've Heard" (National EPA-TSC, 2006).

Potential Case-Specific Considerations for CRA	Description or Example	Relevant Subsection in the Guidelines
	Risk assessment products (quantitative and qualitative) for risk management decision-making Economic analyses Alternative assessment analyses	
Project management	Source(s) of funding Availability of CRA team members Legal constraints Other resource and data limitations Schedule for completion Community/stakeholder consultation board Data sharing agreements	Section 2.7.

Adapted from U.S. EPA (1997c, 2014b).

2.5. Tiering and Phasing the Assessment

Tiering and phasing are complementary processes that can contribute to a flexible CRA design and may be employed to assist with planning and scoping the assessment. They are optional strategies that can help "to balance resources against the desire to reduce uncertainty in the assessments" (Menzie et al., 2007). Both tiering and phasing are iterative process considerations that begin with planning and involve a sequential execution of the analysis plan. Tiering is focused on a stepwise process to evaluate risk and the adequacy of data to meet the purpose of the CRA, whereas phasing is focused on the identification and prioritization of stressors to address the risk management decision. Both processes use an iterative, stepwise methodology to prioritize stressors and exposures and to determine an appropriate level of analysis commensurate with the risk decision being informed (Meek et al., 2011). Tiering and phasing are complementary, as they consider different aspects of how the iterative inquiry can be conducted.

Text Box 3.
Tiers for Cumulative Risk Assessment Analysis

Tier 0 – This tier is advisable when screening-level assumptions of exposure and hazard indicate very low or no risk, and simple semiquantitative estimates of summed combined exposures for the stressor group may provide sufficient analysis. Semiquantitative estimates are based on limited data and a few very simple conservative (i.e., more health-protective) assumptions. Any information on the stressor group, such as biological mode of action and estimates of exposure, would be compared with more robust quantitative estimates for chemicals with similar profiles to provide a crude quantified estimate of risk. With the use of conservative scenarios if the result is no or low risk, Tier 0 may provide sufficient risk characterization. Alternatively, further assessment at the Tier 1, 2, or 3 level may be indicated.

Tier 1 – This tier also provides an estimate typically based on conservative scenarios (i.e., more health-protective), layering on additional information about the stressor group, such as deterministic exposure estimates for all components of that group (this can be based on measured or modeled data). Results might suffice for comparison with a measure of hazard to determine whether further assessment is necessary.

Tier 2 – In this tier, deterministic estimation of exposure* is refined by incorporating increasing numbers of measured values. Exposure scenarios will be more tailored to the specific situation to provide better detail. Models might incorporate additional parameters, and although estimates are still considered conservative (i.e., more health-protective), they are believed to be more realistic, incorporating more data. Multiple sources often are taken into account by summation.

Tier 3 – This tier is the most thorough and will likely employ probabilistic estimates* of exposure, taking into account all available exposure data and applying exposure factors. This approach requires representative information on exposure for the scenarios of interest for the relevant populations and across populations. Models at this level of complexity often include multiple-source exposures.

*Deterministic assessments use single values or point estimates as inputs to the exposure equation. Health-protective assessments typically use a deterministic approach with default high-end point estimates (conservative). Deterministic assessments might also use central tendency values to estimate "typical" exposure. A probabilistic assessment uses distributions of data from which multiple points are selected as inputs to the exposure equation over the course of multiple simulations. As a result, the output of a probabilistic assessment is a distribution of potential exposure values. Probabilistic approaches are generally used only for higher-tier assessments. See: Exposure Assessment Tools by Tiers and Types – Deterministic and Probabilistic Assessments (https://www.epa.gov/expobox/exposure-assessment-tools-tiers-and-types-deterministic-and-probabilistic-assessments).

As described by Meek et al. (2011).

The objective of tiering is to optimize the efficiency of the risk analysis by first assessing apparent margins of low hazard or exposure based on conservative (i.e., more health-protective) assumptions or scenarios.[25] Subsequent tiers incorporate more rigorous analysis with additional data that are based on initial indications of possible hazard and risk from exposure (see Text Box 3). The Tier 0 assessment requires the least labor, data, and analysis. It is an accounting of semiquantitative estimates of hazard and exposure under conservative (i.e., more health-protective) and relatively simple assumptions. The EPA's *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity* supports a tiering strategy and recognizes that not all CRAs will require the same scope or depth and that some groups "will require only screening level assessment to decide whether to invest resources in collecting and analyzing data for a more extensive cumulative risk assessment" (U.S. EPA, 2002a). The purpose of this initial analysis tier is to assess whether initiating factors reveal cause for concern and justify the need for a CRA. Care is necessary at Tier 0 to include all identified stressors for which there is some rationale to combine effects that could result in a common adverse health outcome. If the results of the initial tier analysis indicate a risk level that is potentially of concern or the need for additional information to clarify potential risk, subsequent analytical tiers are conducted as necessary—each progressively more refined, reducing uncertainty, but increasingly more resource and data intensive. The interplay between the CRA planning phase and the execution of the risk analysis phase in tiers demonstrates how the tiering process informs the level of effort associated with the risk analysis. Higher tiers are executed as necessary to discover and demonstrate potential relationships between stressors and outcomes, including when additional research is necessary . At any tier, the outcome of analysis can be:

- There is sufficient information to proceed with risk characterization;

[25] Screening-level assumption of exposure refers to upper-bound limits of exposure and duration. When used in risk assessment, they are intended to ensure that as much risk as possible is taken into account.

- Additional data are needed but not available; decision for no further action; or
- Additional data are needed and possible to obtain; decision for further assessment (a higher tier).

The phased approach described by Menzie et al. (2007) emphasizes examination of stressor and pathway combinations thought likely to have the most significant outcomes (see Text Box 4). In this phased approach, a conceptual model is initially developed to prioritize the relative importance of the various stressors. This conceptual model for the CRA documents the various exposure pathways and interrelationships and can be used to indicate the relative importance of various stressor/pathway combinations. Inclusion of all identified stressors, to the extent possible at this phase, is necessary both for identifying sources within the EPA's authority, as well as for consideration in tiering the risk assessment. While all identified stressors and pathways can be represented in the conceptual model, resources should be directed to understanding the stressor and pathway combinations considered to have the greatest potential effects. "In this way, it is possible to simultaneously capture the breadth of the problem and [focus] on its key aspects" (Menzie et al., 2007). The phased approach to prioritizing the evaluation of combined effects from multiple stressors is useful for bounding the scope of the CRA, which is particularly important when the assessment includes exposure-response modifier interactions with the primary stressors. Importantly, while the *prioritization* of stressors, exposure pathways, and interrelationships is vital for bounding the CRA analysis plan, the full constellation of considerations remains documented in the conceptual model and can be referenced to guide additional analysis as required (e.g., vulnerable populations are identified). Stressors or other agents that might be important, but for which there are insufficient data for the analysis or for which risk management options are not effective (see Section 2.7), can be documented and forwarded to the risk characterization step for discussion as uncertainties or qualitative considerations. Those descriptions may be used to inform risk management decisions or to identify areas for further research.

The phased approach begins with a simple but comprehensive analysis of key stressors identified in the conceptual model. Central to the phased approach is a focus on the key considerations in the evaluation (see Table 1). This focus requires an initial effort to prioritize the relative importance of the various stressors. Exposure pathways and interrelationships identified in the conceptual model can be used to indicate the relative importance of stressor and pathway combinations and point toward situations in which risk management interventions might have the greatest potential for risk reduction.

Text Box 4.
Elements in a Cumulative Risk Assessment Phased Approach

- Develop a conceptual model sufficient to delineate the problem; include all relevant stressors and describe how they might act in combination.
- Screen stressors to arrive at an appropriate and manageable number for the problem; this step is a focusing exercise. Other stressors and pathways can be represented in the conceptual model, but resources are directed to understanding the stressor and pathway combinations considered to have the greatest potential effects. Retain screened stressors on a watch list for subsequent checks after more information is developed.
- Evaluate the individual effects of individual stressors to determine whether any predominantly contribute to (or could contribute to) the effect(s) of interest.
- Evaluate the collective effects of stressors without yet considering the potential for interactions (e.g., synergism or antagonism) and identify the potential for stressor or effect overlap (e.g., based on common properties or temporal and spatial links).
- Evaluate the combined effects of stressors, taking into account potential interactions and considering qualitative to quantitative methods, depending on the information available. Key to the iterative process is revisiting these steps at intermediate stages throughout the assessment to ensure that contributing stressors, influencing factors and effect endpoints are integrated so that combined effects and primary risk contributors can be well characterized to the level that existing knowledge allows.

Adapted from Menzie et al. (2007).

A focus on the interactions emphasized in the phasing process can also be applied to a CRA that is receptor focused (e.g., vulnerable communities). The granularity of the process steps identified in Text Box 4, which depict the phased approach, may also be useful for informing the tiered approach described in Text Box 3.

Tiering, phasing, or both may be helpful process steps when a screening-level effort is indicated as an initial scoping step or when the envisioned CRA might be so complex that identifying priority focus areas would help bound the study scope and make the analysis more manageable.[26, 27]

Depending on the circumstances, the initial scoping of the CRA and fit for purpose evaluation may serve as part of an initial screening-level step (comparable to Tier 0) for evaluating the suitability of CRA to address the risk management question, although the approaches used to evaluate the suitability of CRA may differ somewhat across EPA programs (see Text Box 3). In all cases, the screening-level step examines the available data to determine the extent to which they would inform the CRA's intended purpose (the management decision) and whether they would warrant a CRA. If the CRA team makes a positive determination—that the available data suggest the potential to sufficiently address the fit for purpose determination and support a cumulative risk analysis approach—further tiering or phasing of the CRA may be appropriate.

2.6. Data Quality, Needs, Availability

The decision to use CRA is based on a purposeful evaluation of whether it is an appropriate strategy to inform the risk management question. DQOs are established for EPA projects and are used to evaluate suitability of data or information to inform management decisions.[28] Consistent with the DQO process, planning and scoping for a CRA should consider the data, analytical methods, and available resources to conduct the CRA to determine whether they are sufficient to meet the risk management goals. The decision to proceed with a CRA should ultimately be contingent on meeting DQO criteria.

During planning and problem formulation, an initial assessment of the availability of assessment methods, data, and resources is assembled (discussed further below) within an outline of the general science approaches considered for the various evidence streams supporting the risk evaluation (i.e., chemistry, fate, release, exposure, hazard), along with a description of the reasonably available information and conceptual models. This evaluation process begins in the scoping stage through development of a scoping summary statement (see Section 2.4). The evaluation of data, methods, and resources is refined and further clarified during problem formulation and development of the conceptual model and then finalized for the risk analysis plan.

[26] An example of tiering can be found in the Office of Pesticide Program's *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis,* which describes such an initial tiering step (U.S. EPA, 2016b): "The screening analysis for CRA described in this guidance begins with an evaluation of the toxicological knowledgebase available on a particular group of pesticides derived from experimental toxicology studies submitted for pesticide registration and from the scientific literature. If the toxicological characterization of potential for common mechanism suggests a candidate common mechanism group (CMG) may be established, then a screening-level toxicology and exposure analysis may be conducted to provide an initial screen for multiple pesticide exposure" (U.S. EPA, 2016b).

[27] The EPA's *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* (U.S. EPA, 2016b) also cites the Meek et al. (2011) description of the World Health Organization (WHO) International Programme on Chemical Safety (IPCS) framework for assessment of exposure to multiple chemicals, which describes a screening approach involving tiered analysis with increasing levels of refinement (see Text Box 3). The WHO/IPCS screening approach is more generic than that described in the EPA's Framework.

[28] The DQO process provides a standard working tool for risk assessors, project managers, and planners to develop DQOs for determining the type, quantity, and quality of data needed to reach defensible decisions or make credible estimates (U.S. EPA, 2006d).

Availability of Assessment Methods. Methods for chemical additivity are widely accepted (e.g., U.S. EPA, 1986b, 2000b, 2023a); therefore, CRAs with chemicals that are toxicologically similar[29] have been successfully conducted and subsequently used by the EPA in decision-making. At the time of this publication, there were few CRAs demonstrating how to incorporate nonchemical stressors or chemicals that are not necessarily toxicologically similar but act on a common outcome. However, when there are data on nonchemical stressors that will support their inclusion in the risk analysis, then they should be incorporated into the CRA plan. If the toxicological action is not understood, then alternative approaches, such as response addition, may capture the possible risk modifier. When methods are not available to incorporate data into the risk analysis directly, two alternative approaches are available to the CRA team:

- Include this information as relevant context during risk characterization; or
- Include this information in an alternative assessment framework provided to the risk manager.

Availability of Information. To conduct a CRA, the team needs to determine the data required for the specific needs of the assessment (e.g., monitoring data or modeling results, dose- or exposure-response information), the availability of the data, and the data quality. If the preferred data are unavailable, then consideration is given to whether new data can be collected, and it may be appropriate for the CRA team to relay the need for data to an appropriate authority so such needs can be included in future Agency projects or grant programs. In some instances, the absence of necessary data, such as exposure data, might preclude the assessment or necessitate data collection (or modeling) before the assessment can proceed. Selecting the analysis methods for a risk assessment then entails choosing the appropriate methods for using the available or anticipated new data.

Availability of Resources. Because CRAs might be designed to capture complex assessments of multiple chemical and nonchemical stressors, they can be resource intensive. The CRA team, in consultation with risk managers, needs to consider required resources for the CRA (e.g., budget, technical support, time) in planning and scoping.

The information available to determine whether to proceed with the CRA might be insufficient until the scoping of the assessment is fully conducted. As stated above, the determination might need to be revisited during problem formulation—for example, during analysis plan development—to confirm that data and analytical methods are sufficient to meet the required level of confidence to inform the risk management decision. Always central to the decision is whether the adequacy of the analysis will serve the purpose for which the assessment is performed (WHO/IPCS, 2009c). Following the provisional decision to proceed with CRA planning, new information might necessitate adjustments in the scope, conceptual model, or analysis plan. This possibility is built into the CRA planning process through two strategies:

- Recursive and iterative consideration of the relationships among stressors, and among stressors and receptors, can be appropriate during the planning, analysis, and characterization phases of the overall assessment. This process can help revise and refine the CRA team's understanding of the significant stressors and their relationship to the receptors of concern. When appropriate, iteration enables previous decisions to be revisited when new information suggests reconsideration.
- A phased or tiered approach to the risk analysis is recommended to manage resources efficiently when informing the risk management decision (see Section 2.5).

[29] Toxicological similarity infers a general knowledge about the action of a chemical or a mixture and is used as an overarching term with a wide range of reference, including mechanism of action, target organ (e.g., enzyme changes in the liver), adverse outcome pathways, and in silico tools such as structure-activity or read-across analyses (Williams et al., 2021). Similarity judgments can be tailored to both the specific goals of the risk assessment and the availability of information (U.S. EPA, 2000d, 2023a).

The scope of a CRA should consider all relevant pathways and routes, aggregate and background exposures, data quality, and nonchemical stressors that are exposure-response modifiers—including vulnerabilities that are due to social and economic factors. The EPA's well-established Quality System (U.S. EPA, 2020d) emphasizes that a critical analysis of available and relevant environmental data is crucial, including monitoring and modeling results (U.S. EPA, 2002b), and discusses important aspects of data quality relevant to the CRA. Important considerations for data quality include the extent to which the scientific and technical approaches are reasonable and consistent with the intended application, the tolerance for potential decision errors, requirements for precision, and the use of secondary data collected for purposes other than the planned assessment. Similar to single-chemical risk assessments, additional types of scientific expertise and planning methods may be required to ensure the CRA analysis is feasible and the results are relevant to the risk management decision (NRC, 2009; Sexton, 2015).

Because numerous datasets of varying quality are possible for any risk assessment, a CRA could be subject to conditions in which data analysis should be prioritized or triaged to maintain the integrity of the assessment, as is proposed in the phasing discussion (see Section 2.5). The scope of the CRA, including the required level of rigor of the assessment (e.g., screening-level versus more refined analysis), could also influence data quality needs.

2.7. Project and Risk Management Considerations

As recommended elsewhere in these Guidelines, consideration of risk management options is an important iterative element of CRA. Project management and resource needs should receive particular attention during the planning and problem formulation phases of a CRA.

Risk Management Issues. NRC's 2009 *Science and Decisions: Advancing Risk Assessment* emphasized the importance of considering risk management options in the design of risk assessments, including CRA (NRC, 2009). Care always should be taken to prevent biasing or manipulating the risk assessment to serve a preconceived risk management strategy and, at the same time, ensure consideration of risk management possibilities in the design of risk assessments (U.S. EPA, 2014b).

Risk managers need the ability to compare different management alternatives, using constraints they identify and describe, to better understand the trade-offs associated with selecting one alternative over another and to understand uncertainties. Some risk management issues that might be included in planning a CRA are:

- Relevant regulatory considerations (e.g., program-specific guidance influencing CRA scope); and
- Technical feasibility of alternative interventions that might reduce stressor levels to different extents, introduce new stressors, or be completed more quickly than other intervention(s).

With CRA, there may be numerous risks to remediate, resolve, or otherwise manage. If the CRA team is asked to evaluate articulated risk management options, the CRA conceptual model is expected to base the comparison of risks among these options on the stressors identified in the problem definition and the characteristics of the target population, among any other pertinent factors. The goal of this CRA is to assess and compare risks for each of the risk management options that might be implemented to reduce the cumulative human health risk(s) associated with a scenario.

Consistent with long-standing Agency practices and recommendations from NRC, the EPA ensures that risk assessments are not directed or unduly influenced by risk managers (NRC, 2009). There are two purposes for considering possible risk management input in the analysis design:

1. To identify a subset of stressor(s) or health outcome(s) on which the CRA would potentially focus in a systematic and transparent manner. Other stressors or health outcomes that overlap with the problem definition, but are not the target of remedy, could be eliminated from the CRA if they do not contribute to the cumulative risk. Because CRA may involve cutting across multiple media, statutes, and governmental authorities, any design that limits analysis of stressors and adverse health outcomes to individual programs should be carefully considered.

2. To adjust the conceptual model. Adjustments to, or addition/elimination of stressors and health outcomes initially identified may be necessary based on new information or a determination of insignificance. Similarly, additional risk management options may be identified for evaluation (or a previously evaluated option may need to be eliminated due to no longer being viable).

Decisions about narrowing the evaluation of stressors or outcomes or changing the conceptual model should be part of the CRA communication plan to ensure stakeholders have the opportunity to understand and provide input. Finally, any stressors and vulnerability factors that were screened out because they were unaffected by the intervention(s) could be reintroduced into the CRA analysis to evaluate whether and how they affect the health outcomes evaluated in the CRA.

Project Management Issues. Because the nature of a CRA can be complex, the use of project management approaches and tools is advisable. Development of a project management plan in the planning phase can ensure the CRA achieves all project goals within the given constraints, including defined risk management objectives, schedule, quality, and budget. Including monitoring and control steps in the project management plan, as feasible, might help ensure that resources and other possible limiting factors are addressed in a timely manner. If risk or decision managers are not members of the CRA team, they should routinely be consulted to ensure the CRA remains responsive to the risk management question or problem that initiated it.

2.8. Peer Review

Peer review of the CRA may be considered as a final step but can be conducted at any time in the process that it is determined to be helpful. Key peer review opportunities exist at the completion of the conceptual model or analysis plan, upon completion of the risk analysis, or upon full completion of the CRA. Peer review should be performed consistent with the EPA's peer-review policy and Peer Review Handbook (U.S. EPA, 2015a). Consideration of the following elements of the CRA may be appropriate:

- The purpose and scope, which outlines objectives, constraints, boundaries, and scale of the CRA and provides the foundation upon which the CRA proceeds.
- The conceptual model, which illustrates the environmental health issue(s) motivating the CRA and presents the rationale for selecting the assessment elements from sources to effects and risk metrics, serving as a foundation for the CRA analysis plan.
- The CRA analysis plan, which provided the technical work plan for the risk analysis steps and specified data/inputs, methods/models, and outputs/risk metrics.
- Data from the risk analysis and the risk characterization.

An independent peer review of the identification of constraints, boundaries, and other challenges to conducting the CRA may help ensure quality robustness for the assessment: consideration of relevant stressor-stressor and stressor-receptor relationships, identification of potential exposure-response modifiers, and recognition of strengths and weaknesses of proposed analytical methods. Acknowledging that CRA has limitations is appropriate, whether related to data quantity, quality, or availability; analytical methods; or resources. Peer review offers an opportunity to independently validate the CRA design to inform the risk management decision and identify any potential weaknesses that might require the attention of risk managers. Strategies for choice of peer-review mechanism should consider opportunities to engage affected communities, especially for reviews of the conceptual model and risk characterization.

Independent reviews can be formal for elements supporting major CRAs or relatively informal for CRAs of limited scope. Reviewers should be independent from the members of the CRA team. Independent review benefits the CRA process by identifying potential challenges, constraints, disagreements, and uncertainties that might arise.

CHAPTER 3. PROBLEM FORMULATION

CRA problem formulation is a technical process that identifies the major factors to be considered in the CRA. Problem formulation develops an operational CRA analytical structure by producing a conceptual model and analysis plan. The conceptual model illustrates the associations among stressors, exposure pathways, receptors (exposed lifestages and populations) and assessment endpoints that will be addressed in the CRA. The analysis plan, building on the conceptual model, describes the approach for conducting the risk assessment: design, methods, key inputs, and intended outputs. Together, the conceptual model and analysis plan, informed by stakeholder discussion as appropriate, reflect the purpose for conducting the assessment and the considerations identified in the initial scoping (e.g., through a scoping summary statement).

3.1. Examining Risk Management Options Based on the Initiating Factor

Dialogue and consultation between risk assessors and managers whose decisions will be informed by the CRA is important to ensure the CRA is tailored to support risk-based decision-making. Input from risk managers continues throughout planning and problem formulation to help the CRA team identify the information and assessment methods that will support decision-making.

The following questions (adapted from U.S. EPA (2014b) and NRC (2009)) can be used in consultation with risk managers to determine an assessment's fit forpurpose determination:

- Does the assessment provide adequate information to inform the choice(s) among risk management options?
- Will the risk assessment need to be modified or expanded to inform evaluation of risk management options?
- What level of uncertainty and variability analysis is appropriate and acceptable in the assessment?

Consulting with risk managers during the problem formulation stage of a CRA affords an opportunity to focus the assessment on the question(s) that the decision-maker needs to have answered. The consultation might include obtaining insight on how to narrow the focus to fewer or more readily addressed stressors. The CRA team may consider risk management options during the problem formulation step so the focus is on stressors that might be most responsive to risk management strategies (Solomon et al., 2016). Consulting with risk managers also helps ensure the level of complexity and uncertainty is sufficient to discriminate among risk management options but avoids expending resources when analyses do not significantly contribute to informing decision-making. Continued dialogue with the risk managers may lead to the identification of countervailing risks associated with the risk management option.

3.2. Conceptual Model

Conceptual models are pictorial or written depictions of the pathways connecting stressors to health outcomes in a population of interest (Linder & Sexton, 2011; Menzie et al., 2007). The pathways can represent known, predicted, or assumed relationships. Conceptual models consist of two principal components: (1) a set of risk hypotheses that describe predicted relationships among stressor, exposure, and health endpoints or responses, along with the rationale for their selection; and (2) a diagram that illustrates the relationships presented in the risk hypotheses (U.S. EPA, 2014b). Conceptual models are used to inform technical work products (i.e., the analysis plan), and may incorporate the following considerations:

- The rationale for selecting the sources, stressors, exposure pathways, receptors, exposed populations, assessment endpoints, and risk metrics.[30]
- The basis for the conceptual model development.

[30] For example, cases of disease or disease incidence, hazard quotient, magnitude of effect, and margin of exposure.

- The scientific and resource (including temporal) implications of additional data gathering.

Development of the conceptual model may rely on a variety of data sources to hypothesize known or suspected stressors, cumulative combinations among them, and resulting adverse health outcomes. Data sources may include published studies, toxicological data, and stakeholder input. For purposes of risk assessment, conceptual models are usually developed by risk assessors, with consideration of input from stakeholders, such as a relevant government, Tribal authority, community representative, or other experts whenever appropriate. Conceptual model development is iterative, and models are updated when new data become available that alter the original model. The inputs and outputs for a conceptual model may be represented using directed acyclic graphs (DAGs). DAGs are visual representations of assumptions about the underlying causal structure that generate observable data. DAGs can be used to identify confounders and modifiers for a given exposure-response relationship. This information can be used to determine whether the available data are appropriate and sufficient to obtain risk estimates for the population(s) of interest (Brewer et al., 2017).

The complexity of the conceptual model depends on the complexity of the problem and the scope of the risk assessment. The complexity might be related to the number of stressors, exposure pathways, or assessment endpoints; the nature of effects; and the characteristics of the exposed populations or lifestages. Conceptual models can be particularly useful when addressing multiple, diverse activities potentially contributing to cumulative risk to receptors of concern (Suter, 1999). A CRA conceptual model uses available evidence and hypotheses to "draw a picture" of the environmental health issue generating concern and motivating a CRA.[31] The visual representation of the conceptual model is a diagram that could include the following types of elements: sources, stressors, exposure and outcome pathways, receptors, endpoints, and risk metrics (Figure 3).

The sources of stressors relevant to a CRA might include point/nonpoint sources. Natural sources and other background sources (e.g., upwind or upstream) might also be appropriate to consider in combination with a stressor of concern. Examples of stressors of concern include chemicals, physical stressors, biological stressors, and psychosocial factors.

Routes of exposure relevant to humans and other animal species include ingestion, dermal uptake, inhalation, and vector transfers (e.g., mosquitoes). Exposure to some nonchemical stressors might not involve a traditional environmental pathway. They may also influence responses to biological, physical, and chemical stressors. Environmental pathways of exposure, particularly along food chains, might include the processes of bioaccumulation and biomagnification.

[31] See U.S. EPA (2006a) Exhibit 3-1, p. 63; Exhibit 4-7, p. 134.

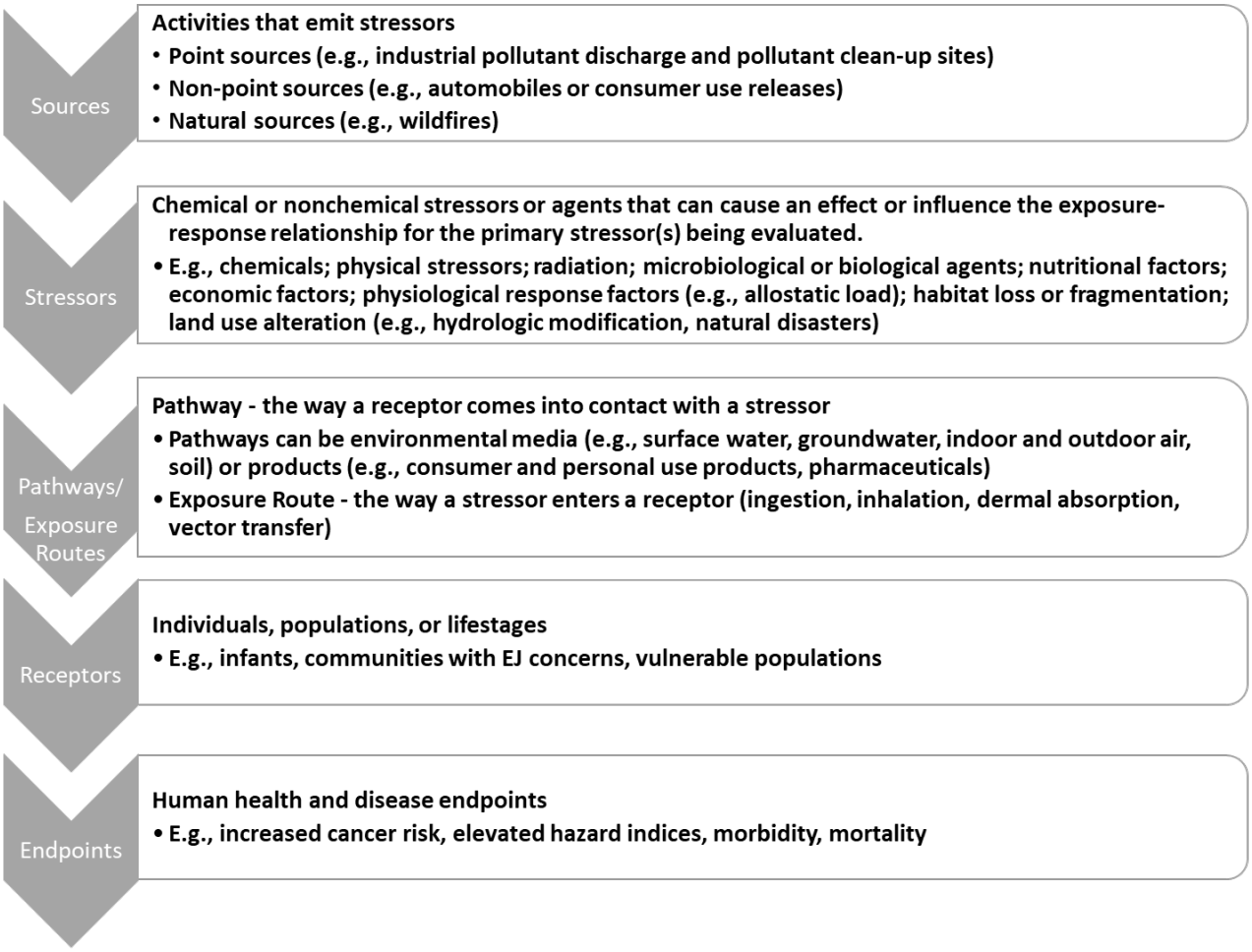

Figure 3. Elements of a Conceptual Model[32, 33]

Receptor definitions range from target organs to individuals and populations and may focus on certain subpopulations or lifestages. Assessment endpoints could be human or ecological effects or both. For example, developmental deficits or loss of species diversity could be based on findings from animal studies, ecotoxicological studies, clinical studies, or sociological or epidemiological data. Risk metrics are important because they provide a means to quantify risk, such as disease incidence, hazard quotient, magnitude of effect, and margin of exposure.

The additional factors described below might be important to consider in conceptual model development.

Exposure context and characteristics. Frequency, duration, intensity, and overlap of exposure intervals for a stressor or mixtures of stressors are important in considering the time frame of the stressor-response relationships. Exposures could be acute, subchronic, chronic, delayed, intermittent, or a combination for multiple stressors. Notably, the same level of exposure can have different effects depending on timing, due in part to differing windows of susceptibility for specific health outcomes. This context can be especially important for early-life exposures and when considering cumulative exposure (e.g., consumption of contaminated food products associated with Tribal lifeways or other subsistence-reliant

[32] Figure 3 illustrates the conventional stressor-to-receptor model. As discussed in Section 1.1., CRA can also be conceptualized as a receptor-(adverse outcome)-to-stressor problem, as depicted in Appendix Figure C-3.
[33] The phrase "communities with environmental justice concerns" is used by the EPA's Office of Environmental Justice and External Civil Rights (OEJCER) (https://www.epa.gov/environmentaljustice/learn-about-environmental-justice).

populations) for specified time periods.

Availability of information from different evidence streams. Toxicology, epidemiology, field studies, Indigenous Knowledge, and other related evidence might be available for consideration in conceptual model development. A literature review should be performed to gather this evidence and, together with a priori knowledge, input from stakeholders (including Tribes), expert opinion, and other assumptions, which can contribute to development of the conceptual model. An initial evaluation of evidence relating exposure to outcome will facilitate a description and characterization of the strength of that evidence. This evaluation contributes to an initial WoE for the relationships of interest, which will be useful in deciding which relationships to include in the conceptual model.

Timing of exposure when combining stressors. Careful consideration of relationships important to characterizing cumulative risks might necessitate inclusion of temporal relationships between stressors, including exposures occurring during early-life stages or multigenerational exposures. Potential exposure-response modifiers, biases, and confounders are additional factors that may be important to consider in a conceptual model when examining the relationship between a stressor and a receptor (Christensen et al., 2015). Detailed causal models could be used to identify biases and confounders and subsequently might inform revision of pathways in the conceptual model. Confirming that the conceptual model includes assessment endpoints related to risk management objectives and options is also important.

Conceptual models identify and display relationships between various stressors (or factors) and endpoints for use in developing the risk analysis plan. They may also include factors and endpoints that will not be analyzed in the risk assessment but that are important in the overall decision-making process. For example, although a risk assessment for a particular stressor might focus on exposure pathways or media relevant to the regulatory decision being faced (e.g., ingestion of drinking water), the conceptual model may also describe the contribution from other pathways (e.g., inhalation of an airborne chemical), thus ensuring appropriate characterization of and context for the assessment results (U.S. EPA, 2014b). In addition to the hazard and exposure analysis, the risk characterization may incorporate factors qualitatively that are important in the overall decision-making process due to vulnerability or risk management considerations. Input from stakeholders can also provide valuable information for development of the model. With incorporation of multiple stressors and data streams, there is likely to be variability in data quality resulting in increased or unforeseen uncertainties. It is important to identify these uncertainties and variabilities in the conceptual model so that they are appropriately considered throughout the CRA process and addressed in risk characterization. Completion of the conceptual model and analysis plan can provide an opportunity for scientific review and stakeholder involvement (see U.S. EPA, 2014b, Section 2.1.4).

Consulting higher-level conceptual frameworks, or theoretical frameworks as illustrated in the generic model shown in Figure 4, may help to contextualize causal pathways for complicated relationships (Gee & Payne-Sturges, 2004; Linder & Sexton, 2011; Morello-Frosch & Shenassa, 2006; Schulz et al., 2005; Sexton & Linder, 2010). Figure 4 highlights higher-level relationships between generalized factors for both community- and individual-level vulnerabilities that may be relevant to a risk management problem. Other examples of conceptual models specific to human health are provided in Section 2.2.2 of the EPA's CRA Framework (U.S. EPA, 2003b) and the *Risk Assessment Guidance for Superfund* (RAGS). RAGS Part A, Exhibit 4-1 provides the elements of a conceptual evaluation model (U.S. EPA, 1989). RAGS Part D, Table 1 provides an approach for planning and scoping to create a conceptual model (U.S. EPA, 2001b). Appendix A of the *Soil Screening Level Guidance* provides methods, summary sheets, and other information that might be useful in constructing a conceptual model (U.S. EPA, 1996a).

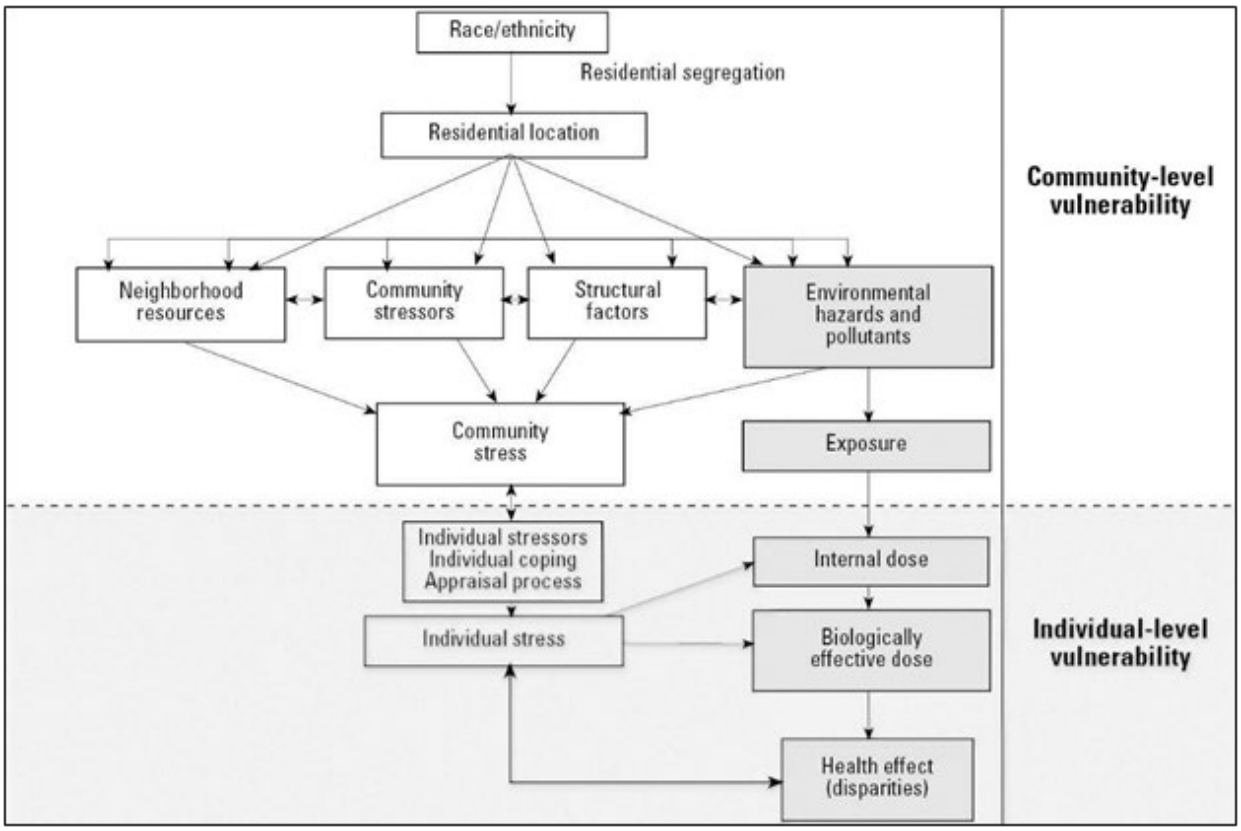

Figure 4. Example of a Generalized Conceptual Model Evaluating Cumulative Risk and the Exposure-Disease Paradigm

Reprinted with permission from Gee and Payne-Sturges (2004).

A more detailed example of a response-based conceptual model (cardiovascular disease, CVD) is provided in APPENDIX C. Developing a conceptual model can be an iterative process. As elements are added or considered for addition, the CRA team may gain new understanding of relationships between model elements, necessitating a revision of the conceptual model. The final conceptual model will be the culmination of the iterative process and should represent features of both a scientific hypothesis and a work plan. It should directly inform development of an analysis plan by describing key inputs, methods, and analytical outputs of the assessment, and include risk metric(s). As described in the Agency's *Framework for Cumulative Risk Assessment*, the conceptual model should capture the rationale for risk management decisions and should be used as a risk communication tool (U.S. EPA, 2003b). In some cases (e.g., in a major assessment of pollutants with controversial or novel methods or scoping issues), conceptual models might be submitted for review, leading to possible additional iterations.

Table 2 summarizes a stepwise strategy for incorporating factors in planning and problem formulation with different alternatives (stressor-, receptor-, vulnerability-based approach) that depend on differences in the initiating factor. Step 1 is relevant particularly to conceptual model development, whereas subsequent steps 2 and 3 might also serve to inform model development through evaluation of stressors. Selection of the approach should align with the context and scope of the risk assessment (e.g., a regulatory standard, a community-based assessment).

Table 2. Outline for a Stepwise Approach to Cumulative Risk Assessment Planning and Problem Formulation

Step	Stressor-Based Approach	Effects-Based Approach	Vulnerability-Based Approach
1. Develop a conceptual model describing relationships between stressors and adverse health effects. Identify common receptors and endpoints.	Identify receptors and endpoints that stressors affect, both individually and in combination.	Specify and characterize adverse health outcomes of concern, and assign possible stressors based on dose-response and exposure data.	Identify the vulnerable population(s), community, or lifestage prior to developing the model, along with adverse health effects of concern.
2. Screen stressors.	Determine which stressors need to be included in the assessment and which might act in combination.	Identify a manageable number of priority stressors that can be linked to effects and can characterize the problem adequately.	Identify stressors affecting the population/community/lifestage to establish priorities that should be included in the analysis.
3. Evaluate the effect of stressors on critical endpoints.	Evaluate (1) individual effects of stressors and (2) combined effects of combinations of stressors, including relevant psychosocial stressors.	Evaluate individual effects of individual stressors to determine whether one or a few stressors are predominant in any adverse health outcomes.	Evaluate individual and combined effects of important stressors to determine whether one or a few stressors are predominant in any adverse health outcomes .

Table is based on concepts adapted from Sexton (2015).

3.2.1. Consideration of Stressors

CRAs consider human health or ecological effects following exposures to *multiple* stressors. During problem formulation and consistent with the question(s) the CRA needs to answer, an initial approach to evaluating potential stressors is developed. If the initiating factors stem from adverse outcomes noted in receptors, stressors might not be explicitly identified initially. Such circumstances require an initial inquiry of the receptor and adverse outcome(s), followed by an investigation of potential stressors based on available source and exposure data. The problem formulation reflects this inquiry and can address human health risk, ecological risk, or a combination thereof. A preliminary phasing of stressor evaluation, as discussed in Section 2.5 and Text Box 4, should be considered when numerous stressors are identified for evaluation.

Stressors typically considered in CRA can be chemical, biological, physical, or psychosocial. Described in more detail in Section 3.2.3 and Section 3.2.4, these stressors often are grouped on the basis of mechanism, temporal occurrence, health endpoint, or some other commonality. Stressors and their source(s) are identified in the context of potentially affected populations or ecosystems, potential stressor effects, and protective factors that might alter responses to stressors. A unique aspect of CRA is that it includes the consideration that receptors can be exposed to multiple stressors via multiple exposure pathways from various environmental media. For example, a local subsistence diet, as is common among Tribal populations, may result in bioaccumulation of contaminants for that population. Importantly, exposures might not be associated with traditional environmental media (e.g., air, soil, or water) in some cases but could be associated with nonchemical stressors (e.g., psychosocial, socioeconomic, temperature, or habitat). Increasingly, physical factors associated with climate change may be considered important dose-response modifiers or stressors.[34, 35]

[34] See How Climate Change Affects Human Health (https://www.epa.gov/climateimpacts/climate-change-and-human-health#how).
[35] See EPA's Impacts of Climate Change web page (https://www.epa.gov/climatechange-science/impacts-climate-change).

In cases involving multiple chemical stressors, potential interactions among chemicals might need to be considered.[36] When available, information from various in vivo and in vitro test systems can be used to elucidate and characterize the interactions and can provide important insights at different levels of biological organization. For evaluating chemical mixtures, the EPA typically assumes the chemicals are toxicologically similar if the chemicals have a common mode of action or if they affect a common target organ or elicit a common effect. Such mixtures are typically evaluated using methods that assume dose addition. For exposures to chemicals that elicit a common outcome but are not toxicologically similar, the EPA has employed methods that are not based on dose addition, such as response addition as well as other methods that use elicitation of a common outcome as discussed in EPA documents (e.g., U.S. EPA, 1986b, 2000d, 2023a).

Epidemiological studies are a potential source of data for informing CRAs. Epidemiological studies might encompass both chemical and nonchemical stressors and might evaluate the ways in which possible relationships among stressors could affect human health and ecological outcomes. Because stressors can vary together in the environment, covariance measures might be used to examine interactions/interdependencies among them, such as how changes in levels of one stressor are associated with changes in levels of another. Other disciplines and areas of research, such as microbiology, public health, sociology, health psychology, health geography, exposomics, in situ toxicity testing, or in silico toxicology (including virtual and complex tissue models that resemble an organ in vivo), also might contribute to identification of stressors of concern for CRAs.

3.2.2. Receptors of Potential Interest

Identifying receptors of potential interest could be targeted based on the initiating factor (e.g., geographic, receptor, or stressor based). As described in the EPA's CRA resource document (U.S. EPA, 2007a), the initiating factor for a CRA can influence whether the study boundary or the population is defined first. For example, the initial population of concern could be a Tribe or a community in a larger city or county, including any identified vulnerable population groups. The initial description of the study area and population of concern may be considered preliminary and may change during the course of the risk assessment.

Factors potentially important to consider in characterizing receptors for a CRA are described in Text Box 6. Selection of these factors to be included in the CRA will depend on the purpose and scope of the assessment.

Exposure-Response Modifiers. Numerous conditions or factors, termed exposure-response modifiers, can contribute to altered levels of exposure or altered risk of a health effect occurring at a given level of exposure to an environmental pollutant (Text Box 5). Examples of human health exposure-response modifiers include genetics, sex, preexisting disease, altered physiological functions, psychosocial stress, and lifestages (Sexton & Linder, 2011). Chemical and nonchemical stressors that are not the primary stressor(s) in a CRA may also operate as exposure-response modifiers. Behavioral variability,

Text Box 5.
Exposure-Response Modifiers and Stressors

In this document, an exposure-response modifier is characterized as a condition or state (e.g., sex, lifestage, socioeconomic status), whereas a stressor is characterized as a physical, chemical, biological, or psychosocial agent (see Glossary), referred to in this document as nonchemical stressors. The terms can be somewhat interchangeable, and in some cases, exposure-response modifiers and nonchemical stressors (e.g., low socioeconomic status) might appear to overlap. The nature and circumstances of the CRA, however, will inform determination of the appropriate characterization as either an exposure-response modifier or a nonchemical stressor. It is possible for a factor to be both an exposure-response modifier and a nonchemical or chemical stressor.

Vinikoor-Imler et al. (2014).

[36] Interaction through additivity of dose is of primary interest; however, the potential for other interactions should be considered, such as synergism, antagonism, and masking (see U.S. EPA, 2000d).

such as occupation or hand-to-mouth activity, can modify exposure. An example of an environmental exposure-response modifier is pH, which can affect metal bioavailability. Exposure-response modifiers can alter an exposure or a response negatively or positively. Some factors can also insulate or reduce the deleterious effects of stressors or reduce exposure and function as protective agents. In these Guidelines, however, exposure-response modifiers are discussed largely in terms of vulnerability factors (see further discussion in APPENDIX D).

Exposure-response modifiers associated with a community or a Tribe are the conditions or circumstances that shape where people are born, live, work, grow, learn, play, and age. These community-level conditions or circumstances are also known as the social determinants or social causes of health (CSDH, 2008; Solar & Irwin, 2010). Examples include housing, education, food access or security, income, transportation, physical and social environmental conditions, and health care access (CSDH, 2008; U.S. HHS, 2020).

Text Box 6.
Factors to Consider in Characterizing Receptors

- Relevant level of organization: Receptors can be organized at the organism, community, population, ecosystem, or other appropriate level.
- Level of exposure: Differential exposures to primary stressors of concern can be due to geographic area, length of exposure (including multigenerational), lifestage, sex, racial or ethnic group, economic status, housing type, proximity to exposure sources, or dietary and lifestyle/cultural factors, etc.
- Exposure-response modifiers:
    - Factors that might increase or influence vulnerability or resilience: Greater vulnerability response to the primary stressors of concern could develop as a result of the presence of social or individual factors that either influence exposure or response or both. Examples include low socioeconomic status, food insecurity, poor housing quality, lack of access to health care, preexisting disease, lifestage, occupation (e.g., farmworkers) and sex.
    - Factors that might increase resilience in the population: Examples include access to health care, positive social climate, and food security.
    - Landscape or geographic concerns: Watersheds, aquifers, airsheds, regional ecosystems, and recreational lands might influence exposure and outcomes in the receptor group.

At the *individual* level, exposure-response modifiers include individual behaviors and practices and individual characteristics such as nutritional status, genetics, epigenetics, preexisting disease, and lifestage that could affect exposure and response to stressors. These individual attributes are also referred to as individual determinants of health. Social determinants can influence health through direct and indirect impacts on individual determinants and through multiple pathways and vice versa (deFur et al., 2007). Vulnerability is a differentiating factor for how individuals, communities, populations, or organisms experience adverse effects related to exposure to environmental stressors (deFur et al., 2007). Therefore, if a CRA is initiated to address the needs of one or more vulnerable populations or lifestages, it should identify pertinent exposure-response modifiers to incorporate vulnerability into the conceptual model and identify whether and how to include this information in analysis and decision-making stages.

3.2.3. Adverse Effect and Exposure Stressor Groups

Multiple approaches are available for grouping effects or exposures for evaluation. Some grouping approaches are based on statutory requirements (e.g., FQPA), whereas others have been developed for particular risk assessment efforts. In selecting a risk assessment method for chemical mixtures, an important initial step is evaluation of data quality (U.S. EPA, 2000d). The EPA's *Supplementary Guidance for Conducting Health Risk Assessments of Chemical Mixtures* emphasizes consideration of

whether data suggest the stressors are acting by similar toxicological processes and whether they can be grouped by emissions source, chemical structure, or biological activity (U.S. EPA, 2000d).

Several approaches or criteria have been described for grouping chemical stressors on the basis of toxicology (Moretto et al., 2017), including common adverse health outcomes or similar modes or mechanisms of action among a group of chemicals. Numerous other considerations also can be used to identify a preliminary list of stressor groupings (see below). Subsequent determination of stressor grouping for the purpose of assessing risk of particular health or environmental outcomes could be based on methods for additivity of hazard from mixtures and determination of response modification, if any.

Considerations for grouping stressor or effects include:

- Environmental medium (e.g., air, soil, water)
- Duration (e.g., acute, chronic, subchronic)
- Source of emissions/releases
- Co-occurrence in the same geographic location
- Functional use
- Chemical structure
- Timing of exposure (e.g., early lifestage and stressor exposure or overlapping exposure to the chemicals in the mixture exhibiting a common adverse outcome, an overlap in the duration of the health effect as a consequence of one chemical exposure and subsequent exposures by a second chemical, or other types of overlap based on the toxicokinetics or toxicodynamics of the chemicals)
- Mode of action (e.g., dose addition might be applied to chemical groups determined to have similar modes of action)
- Outcome (e.g., morbidity and mortality, neurotoxicity, cancer, respiratory irritation, development, reproduction)
- Receptor vulnerabilities, human or ecological, including level of biotic or abiotic organization and evidence for vulnerability in the target population

3.2.4. Integration of Data for Examining Stressor-Response Relationship(s)

The scope of CRA scientific inquiry is articulated in the problem formulation and is focused on the stressors that are of greatest importance for the assessment's intended purpose. Therefore, a strategy is needed to develop the evidence base of key stressor-response relationships. Strategies for assembling data and information can be more or less formalized but need to describe what evidence is included (or excluded), rationales for inclusion, and the extent to which evidence supports possible answers to a scientific question (EFSA Scientific Committee, 2017). This process has been commonly termed a "WoE strategy," and this phrase is used in these Guidelines to refer to this process.

For CRA, the WoE strategy should identify possible stressor-response relationships and exposure-response modifiers for consideration in the conceptual model. The results can be expressed qualitatively or quantitatively, depending on the information available and the needs of the CRA.

This strategy begins with identifying available sources of evidence (e.g., through a literature search or, when few published data are available, a survey of community-identified stressors). Evidence might be available from a variety of disciplines, including toxicology, epidemiology, clinical research, sociology, ecology, or spatial analyses. Different disciplines use different mathematical and statistical techniques, with varying degrees of applicability to the population(s) of interest. Consequently, the WoE and data quality assessment should be tailored to arrive at the best possible explanation for the scientific questions formalized in the CRA problem formulation and conceptual model. This point is especially important when there are nonquantifiable agents or factors that are considered by the CRA team or stakeholders to be consequential to the CRA. The WoE documentation becomes the record identifying and justifying the

decision to include or exclude factors in the analysis plan or, alternatively, the decision to instead consider and discuss factors in the risk characterization. The World Health Organization (WHO) defines WoE as "a process in which all of the evidence considered relevant for a risk assessment is evaluated and weighted" (WHO/IPCS, 2009b). The EPA's Integrated Risk Information System (IRIS) program characterizes evidence synthesis and integration within a larger framework of systematic review (U.S. EPA, 2022d).[37] The *ORD Staff Handbook for Developing IRIS Assessments* (IRIS Handbook) notes that the term "evidence integration" is analogous to "weight of evidence" used in some other assessment processes. Other methods and approaches for weighing evidence of various types, in various contexts, and for various purposes are available (Linder et al., 2010; Linkov & Satterstrom, 2006; Weed, 2005), as are other frameworks for integrating and evaluating evidence from multiple disciplines (Adami et al., 2011; European Food Safety Authority [EFSA] Scientific Committee, 2017; Levy, 2008; Stahl & Cimorelli, 2020). Moretto et al. (2017) described use of evidence tables to present the strength of evidence or uncertainty associated with grouping for additivity analysis. The EPA's Quality System (U.S. EPA, 2020d) is available for data quality assessment. The EPA's CADDIS (Causal Analysis/Diagnosis Decision Information System), its accompanying text, *Ecological Causal Assessment* (Norton et al., 2014), and the Agency's *Weight of Evidence for Ecological Assessment* (U.S. EPA, 2016c) provide techniques and resources for weighing evidence for ecological receptors. WoEs are demonstrated in the existing EPA CRAs (U.S. EPA, 2006b, 2006e, 2006f, 2007b, 2009) and in other guidance documents (U.S. EPA, 1994, 1998a, 2005).

The evidence for a stressor-response relationship need not be conclusive for it to be documented in problem formulation. Uncertainty might call for including the possible link between stressor and receptor in the conceptual model or analysis plan. There, it could direct additional studies toward the uncertain relationship or, in the absence of sufficient data to form a conclusion, flag the uncertain relationship for consideration by the risk manager later in the risk characterization phase. The data available to support the pathways in the conceptual model also might be highly variable. For example, some relationships might be flagged in the WoE because they are important to stakeholders, but no empirical data have yet been collected to support stakeholder concerns. The CRA team should expect stakeholders to have diverse opinions on possible causality or dose-response modifiers.

When available and appropriate, the incorporation of biomonitoring data may provide useful measures of internal doses reflective of exposures via multiple pathways and multiple different chemicals operating by the same exposure-to-effect pathway. Biomonitoring data may also provide information regarding potential exposure disparities among diverse demographics, such as race or income, and may help establish baseline exposure conditions in a population. Capturing all identified dose/exposure-response ideas for consideration and possible evaluation is appropriate and, particularly in community-based CRAs, important for acknowledging stakeholders' concerns.

Community observations can provide significant and practical insights into the problem and assumptions made. They can also provide evidential weight for practical and relevant decision-making. Community observations might include an understanding of the relative contribution of stressors to effects (even if only qualitatively). For example, noise as a physical stressor is generally understood to be worse the louder it is, especially if baseline or ambient noise is close to the threshold for ear damage (U.S. EPA, 2020a). No empirical data specific to a particular anthropogenic activity are needed for analysts to agree on this understanding, and inclusion of the relationship in a WoE could be entirely appropriate.

Response- or receptor-initiated CRAs might identify speculative links between outcomes and possible stressors. Because the information available to develop the initial conceptual model is preliminary, it may

[37] In the IRIS program, evidence integration is defined as the "Integration of animal and human evidence synthesis judgments to draw an overall conclusion(s) that incorporates inferences drawn on the basis of information on the human relevance of the animal evidence, cross-stream coherence across the human and animal evidence, susceptibility, and biological plausibility/MOA."

not be sufficient to characterize stressor-response relationships. Subsequent analysis and iterations of the conceptual model should reflect ongoing assessment of stressor-response and modifier relationships on the basis of additional information. Such information, however, might or might not be relevant to the effects, endpoint, or receptors of concern identified in the conceptual model. The CRA team's judgment should determine whether inclusion of a stressor-response or modifier relationship in the conceptual model is warranted. Even if the potential relationship is not ultimately evaluated in the analysis phase of the assessment, capturing the community stakeholders' concerns may be important to reflect issues important to the stakeholders and their participation in the CRA process and may also be useful in the characterization phase for consideration by the risk manager or decision-maker.

Evidence evaluation to assess the strength of causal relationships is an essential consideration in CRAs because of their scope and complexity. Because sources of evidence might be available from multiple disciplines, the evaluation of the data required for a CRA should consider WoE both within and across evidence streams—e.g., epidemiology, toxicology, and mechanistic studies. To consider exposure-response modifiers, such as psychological or socioeconomic stressors, a multidisciplinary team with expertise in many areas is required to provide a clear "delimitation of the analysis" so the results meaningfully inform the analysis plan (Solomon et al., 2016).

Study quality, key elements of which can vary by type of study, should be considered when evaluating the evidence. Data completeness also might require consideration, such as the breadth of toxicity endpoints or dose-response data availability for individual components in a chemical mixture. For epidemiological studies, the WoE evaluation might include evaluation of group characteristics, ability to control for potential confounders and other sources of bias or temporal relationships, comparability of exposure to multiple stressors, and disease in the population of interest. Such evaluation is done both for individual studies and across the body of evidence from multiple studies and may be guided by considerations such as those outlined in the IRIS Handbook (U.S. EPA, 2022d) or the *Preamble to the Integrated Science Assessments* (U.S. EPA, 2015b). Both the IRIS Handbook and the Preamble provide frameworks for synthesizing evidence within a body of evidence (such as all epidemiology studies) and integration of evidence across evidence streams (such as epidemiology, toxicology, and mechanistic studies).

As in other risk assessments, important considerations for CRAs include the extent to which the scientific and technical approaches are reasonable and consistent with the intended application, the tolerance for potential decision errors, precision requirements, and the use of secondary data collected for purposes other than the planned assessment. The required level of rigor of the assessment (e.g., screening-level versus a more robust analysis) can influence data quality needs. The WoE will support or be used to revise a risk hypothesis and will provide the evidence base necessary to develop plans for the analysis phase. Evidence evaluation and data quality assessment requirements should be considered throughout the CRA to ensure the product is fit for purpose.

3.3. Analysis Plan

Analysis plan development is the final stage of planning and problem formulation and generates the technical work plan for subsequent analytical steps. The analysis plan clearly specifies which analyses will be done and with which methods (e.g., models) and inputs, who will conduct these activities, and on what schedule. It addresses conceptual model elements and includes the CRA's purpose, scope, methods, DQOs, data needed for collection or analysis models using these data, and a description of how data gaps/uncertainty will be addressed. The conceptual model may be packaged in the same document as the analysis plan. Important in developing the analysis plan is to coordinate with the appropriate program(s) to ensure any existing guidance, guidelines, policies, and procedures are followed.

The analysis plan, tailored to the specific CRA, describes how the CRA proposes to address the scientific questions highlighted in the conceptual model. No "one size fits all" model is proposed. The analysis plan needs to be responsive to the conceptual model elements. It needs to specify a receptor, outcomes/metrics

evaluated for the receptor, stressors/stressor groups and stressor sources for the outcome, the exposure data for the stressors, and dose-response methods for the outcome and its associated stressors. A description of the evidence related to the elements and pathways included in the conceptual model can inform development of the analysis plan, an initial appraisal of uncertainties, and identification of any additional data gathering activities needed before risk characterization. Systematic review or other WoE methods may be an appropriate approach for some or all of these elements as a way to identify, organize, and synthesize information. The IRIS Handbook outlines one approach to incorporating systematic review methods in human health risk assessment (U.S. EPA, 2022d).

The elements described below should be considered for inclusion in the analysis plan:[38]

CRA Purpose and Scope. A description of the CRA question that risk managers need to answer (and potential risk management options) and an outline of the general objectives, constraints, and boundaries of the assessment (identified in Section 2.4 as a "scoping summary statement").

Data Compilation/Collection. A description of the initial WoE[39] as it pertains to the conceptual model pathways includes an appraisal of uncertainties and any data collection needs to "operationalize" the conceptual model for chemical and nonchemical stressors (e.g., soil sampling, meteorological data, air monitoring). Some data, particularly for nonchemical stressors, might be qualitative or only relatively scalable (Meadows, 2008). Depending on the methods selected for the analysis phase of the CRA, such data might or might not be accommodated in the CRA (although it may be included in the risk characterization as an uncertainty). The compatibility of data and methods should be identified as early as possible in the process.

Preliminary or Previous Risk Estimates. The utility of developing preliminary risk estimates that might better inform decisions regarding the scope of the assessment, the level of effort warranted, or risk management options could be considered and is described in Section 2.5. An example is screening out stressors or stressor groups that contribute little or nothing to risk. While "cutoff" values can be identified (e.g., $<10^{-6}$ for cancer, ≤ 0.1 hazard quotient [HQ][40]), interactions with other factors, such as preexisting disease, need to be considered. When preliminary risk estimates result in identifying no risks of concern, even when all stressors, proposed stressor groupings, and chemical mixtures are considered, further evaluation might not be warranted.[41] Such an outcome suggests resources then might be spent in other, more critical CRAs (U.S. EPA, 2016b). Additionally, an existing, previously performed assessment could be available that might provide useful information, including salient details of its analysis approach.

Exposure Assessment. A description of the exposure assessment approach and metrics, including the population that is the subject of the assessment; whether methods or guidance (e.g., from a particular EPA program office) will be used; relevant key definitions; temporal considerations (e.g., only chronic exposure will be evaluated); use of lifestage-specific exposure factors (see U.S. EPA, 2011);[42] monitoring approaches; modeling approaches; key assumptions (e.g., evaluated receptors are "exposed" to modeled

[38] The RISK21 project (https://risk21.org/about-risk21/) of the Health and Environmental Sciences Institute, itself a project of the International Life Sciences Institute (https://ilsi.org/), is a notable resource for identifying questions to develop the analysis plan (Solomon et al., 2016). The CRA team should reference EPA's *Guidance for Quality Assurance Project Plans (QAPPs)* (https://www.epa.gov/quality/guidance-quality-assurance-project-plans-epa-qag-5) when developing a QAPP.

[39] The WoE and other elements of the analysis plan that are developed during problem formulation and scoping may be revised at later stages of the risk assessment process as new information becomes available.

[40] Usually, an HQ ≤ 1 for a single chemical indicates that adverse effects are not likely to occur and is a negligible hazard; however, an HQ ≤ 0.1 is used in screening exposure to multiple chemicals.

[41] The CRA team should contextualize cumulative risk assessments within the full scope of stressors as holistically as possible, especially when vulnerable communities constitute part or all of the population of interest. The process should also consider the uncertainties associated with data limitations (e.g., when stressors may be left out due to a lack of data).

[42] The *Exposure Factors Handbook* is being updated by chapter (see U.S. EPA (2011) updated chapters, available at https://www.epa.gov/expobox/about-exposure-factors-handbook).

or monitored concentrations for certain exposure durations); exposure factors by activity; land use—current and future; cultural and subsistence practices; and associated variabilities and uncertainties. The exposure metrics should relate to those identified for effects/outcomes.

Effects/Outcomes Assessment. A description of adverse effect/outcome metrics to be used for stressor exposures in evaluated receptors (e.g., cancer potency estimates for quantitative dose-response CRA) and qualitative CRA risk descriptions (e.g., low/medium/high) also might be described. Potential sources of dose-response data include chemical assessments from the EPA's IRIS database, physical stressor assessments (e.g., noise) developed by the U.S. National Institute for Occupational Safety and Health, and the peer-reviewed literature.

Data Quality and Relevance. A discussion of DQOs and needs (U.S. EPA, 2020d) relevant for the subject CRA should be included. Such descriptions might include robustness of the experimental design for an epidemiological study, statistical strength, spatial and temporal scales, target receptor specificity, and other issues specific to the CRA. The primary goal of the Quality Program[43] is to ensure that environmental data are of sufficient quantity and quality to support their intended use. In addition, the relevance and appropriateness of the data (which includes quality and uncertainty analysis) relative to the specific CRA question need to be determined. The discussion should address the evaluation of data quality for existing data, including the DQOs.

Identification and Selection of CRA Techniques/Methods to Apply to Integrated Stressor Groups. A description of risk assessment methods and procedures that might be used to conduct CRA (e.g., methods described in *U.S. EPA Mixtures Guidance* and related documents (U.S. EPA, 1986b, 2000d, 2023a); *Pesticides Cumulative Risk Assessment* (U.S. EPA, 2002a); *Risk Assessment Guidance for Superfund* (U.S. EPA, 2001b, 2001c); *Office of Air and Radiation–Technology Transfer Network (OAR-TTN) Fate, Exposure, and Risk Analysis*[44]).

Characterization of Baseline Conditions. A description of the characterization of the baseline ("before") population or ecosystem in a CRA can allow evaluation of "before/after" scenarios. For example, measures included in ecosystem health indicators in study area streams prior to construction of a new roadway could be compared with predictions of changes both during and after construction. This element could take the form of a comparison among risk scenarios or options to inform risk management decisions when appropriate.

Risk Characterization/Risk Description Plan. The plan for characterizing risk, with attention to the context and purpose for the assessment. For example, why the CRA is being conducted, what question(s) the CRA is designed to answer, what it includes and excludes, and, if available, preliminary risk estimates or comparative risk estimates. A discussion should be included on how the CRA will approach uncertainty analysis (e.g., qualitatively, quantitatively) and whether sensitivity analysis is possible or planned for any individual or combined input variables. Important limitations and assumptions of the planned analysis should also be presented.

Cost Estimates. Anticipated or estimated costs for conducting the CRA, including staffing and expertise needed and a plan for how costs will be paid.

Schedule. An estimated schedule for conducting the CRA may be provided.

[43] The EPA's Quality Program manages the collection, production, evaluation, and use of environmental information. The primary goal of the Quality Program is to ensure that the Agency's environmental information is of sufficient quantity and quality to support the intended use (https://www.epa.gov/quality/about-epas-quality-program).
[44] See the EPA's Air: Fate, Exposure, and Risk Analysis web page (https://www.epa.gov/fera).

3.4. Uncertainties and Variability

CRA requires consideration of uncertainty and variability in terms of both source identification and analysis approach. CRAs address multiple stressors that could be dissimilar and rely on a variety of sources of quantitative or qualitative data. These attributes can complicate the evaluation of variability and uncertainty in CRA.

Potential sources of variability and uncertainty in all CRA phases (exposure assessment, effects assessment, risk characterization) to be considered, especially if further study of particular aspects of variability or uncertainty, is required to support decision-making, including:

- Scenario uncertainty resulting from errors, typically of omission, that stem from incorrect or incomplete specification of the cumulative risk scenario to be evaluated (e.g., all relevant stressors have not been or cannot be identified)
- Consistency of the overall database for estimating risks associated with important adverse outcomes
- Variability in exposure characterization (e.g., different durations of exposure, differences in exposures based on lifestage, activity patterns, dietary preferences)
- Dose metric(s) used for dose-response modeling, route-to-route extrapolation, or extrapolation to humans; relevant issues include the strength of evidence associating a dose metric with critical effects, strength of evidence for human relevance of the dose metric (if based on an animal study), and whether extrapolation to humans relies on chemical-specific evidence or default allometric relationships
- Human toxicokinetic and toxicodynamic variability
- Model uncertainty attributable to the use of empirical and mechanistic models
- Statistical uncertainty, as characterized by the model-estimated confidence interval, which is generally due to variability associated with the particular data set
- Input or parameter uncertainty from any errors in characterizing the empirical values used as inputs to any model used (e.g., engineering, physical, chemical, biological, or behavioral variables)
- Uncertainty as to whether relationships in the conceptual model are causal and due to lack of or gaps in data; gaps in data should be considered alongside information from available evidence in making a determination about the extent of uncertainty in the conceptual model

Early consideration should be given to the approach, methods, and metrics that will be used to evaluate variability and uncertainty. These approaches might be quantitative or qualitative, and they address data evaluation, procedures, measures, methods, and models used in the CRA. The extent to which variability and uncertainty can be evaluated and characterized in the CRA also should be considered. Depending on the availability of suitable information and the targeted needs of individual CRAs, qualitative discussion and syntheses of uncertainty might be enhanced by quantitative analyses, including sensitivity analyses for decisions (e.g., selection of study populations, dose metrics, or model parameters). Modeling uncertainty using ranges or probability distributions could also be useful when data are adequate.

In developing the approach to address variability and uncertainty for the CRA, the purpose and context for the assessment, as well as the timeline and resources, should be considered. The variability and uncertainty analysis should be appropriate for the decision context (IOM, 2013).

Resources for characterizing uncertainty and variability include the following:

- *Guiding Principles for Monte Carlo Analysis* (U.S. EPA, 1997d)
- *Science Policy Council Handbook: Risk Characterization* (U.S. EPA, 2000b)
- *Process for Conducting Probabilistic Risk Assessment. Part A of Vol. III of Risk Assessment Guidance for Superfund* (U.S. EPA, 2001c)

- *An Examination of Risk Assessment Principles and Practices* (U.S. EPA, 2004a)
- *A Framework for Assessing Health Risk of Environmental Exposures to Children* (U.S. EPA, 2006c)
- *Guidelines for Human Exposure Assessment* (U.S. EPA, 2019)
- ExpoKids: Children's Aggregate Exposure Visualization Tool[45]
- *Risk Assessment Forum White Paper: Probabilistic Risk Assessment Methods and Case Studies* (U.S. EPA, 2014c)

3.5. Next Steps in Cumulative Risk Assessment

These Guidelines provide a generalized approach to the planning and problem formulation of a CRA. Following completion of the risk analysis, there are two additional steps that may be tailored for completion of the CRA:

- Risk characterization
- Risk communication

Risk characterization integrates and interprets the results of the analysis phase. It describes the qualitative or quantitative risk assessment results; lists key assumptions, limitations, variability, and uncertainties associated with those results; and discusses the application of the results for risk management decisions (U.S. EPA, 2003b). It is also appropriate for the CRA team to consider whether information in the risk characterization may be usefully shared with other governmental agencies that are positioned to address identified risks or exposure-response modifiers. There are many different assessment processes conducted by federal agencies for chemicals found in the environment, workplace, consumer products, hazardous waste sites, food, or cosmetics. Most serve to provide public health guidance or recommendations, and opportunities exist for collaboration and coordination through risk assessment (Shaffer, 2021).

Risk characterization information may be channeled into *risk communication*. Although communication begins early in the CRA planning process, the risk communication step requires that decision-makers have a thorough understanding of the risk characterization; however, risk characterization is not synonymous with risk communication (U.S. EPA, 2014b). Because the risk characterization may be technical and complex, communication tools with summarized levels of detail may be developed for risk communication. These communication tools are often a set of documents tailored to meet the needs of different stakeholders and audiences (e.g., *Superfund Community Involvement Handbook* (U.S. EPA, 2020e)). In addition to meeting the requirements of the risk management decision, risk communication materials and tools may also be tailored to provide information to the public—including individuals, groups, and other institutions—about not only the cumulative risks identified, but also how people can mitigate risks through behavioral changes, protective actions, and joint problem solving.

[45] See the EPA's ExpoKids: Children's Aggregate Exposure Visualization Tool (https://www.epa.gov/expobox/expokids-childrens-aggregate-exposure-visualization-tool).

REFERENCES

Adami, H. O., Berry, S. C., Breckenridge, C. B., Smith, L. L., Swenberg, J. A., Trichopoulos, D., Weiss, N. S., & Pastoor, T. P. (2011). Toxicology and epidemiology: Improving the science with a framework for combining toxicological and epidemiological evidence to establish causal inference. *Toxicological Sciences*, *122*(2), 223-234. https://doi.org/10.1093/toxsci/kfr113

ATSDR (Agency for Toxic Substances and Disease Registry). (2004). *Guidance manual for the assessment of joint toxic action of chemical mixtures*. U.S. Department of Health and Human Services. https://stacks.cdc.gov/view/cdc/6935

ATSDR (Agency for Toxic Substances and Disease Registry). (2011). *Principles of community engagement: Second edition* (NIH Publication No. 11-7782). U.S. Department of Health and Human Services. https://www.atsdr.cdc.gov/community-engagement/php/about/index.html

Barrett, E. S., & Padula, A. M. (2019). Joint impact of synthetic chemical and non-chemical stressors on children's health. *Current Environmental Health Reports*, *6*(4), 225-235. https://doi.org/10.1007/s40572-019-00252-6

Barros, N., Tulve, N. S., Bailey, K., & Heggem, D. T. (2018a). Outdoor air emissions, land use, and land cover around schools on tribal lands. *International Journal of Environmental Research and Public Health*, *16*(1), Article 36. https://doi.org/10.3390/ijerph16010036

Barros, N., Tulve, N. S., Heggem, D. T., & Bailey, K. (2018b). Review of built and natural environment stressors impacting American Indian/Alaska-Native children. *Reviews on Environmental Health*, *33*(4), 349-381. https://doi.org/10.1515/reveh-2018-0034

Brewer, L. E., Wright, J. M., Rice, G., Neas, L., & Teuschler, L. (2017). Causal inference in cumulative risk assessment: The roles of directed acyclic graphs. *Environment International*, *102*, 30-41. https://doi.org/10.1016/j.envint.2016.12.005

Burke, T. A., Cascio, W. E., Costa, D. L., Deener, K., Fontaine, T. D., Fulk, F. A., Jackson, L. E., Munns, W. R., Jr., Orme-Zavaleta, J., Slimak, M. W., & Zartarian, V. G. (2017). Rethinking environmental protection: Meeting the challenges of a changing world. *Environmental Health Perspectives*, *125*(3), A43-A49. https://doi.org/10.1289/ehp1465

Callahan, M. A., & Sexton, K. (2007). If cumulative risk assessment is the answer, what is the question? *Environmental Health Perspectives*, *115*(5), 799-806. https://doi.org/10.1289/ehp.9330

CEQ (Council on Environmental Quality). (2021). *Indigenous traditional ecological knowledge and federal decision making*. Executive Office of the President, Office of Science and Technology Policy. https://www.whitehouse.gov/wp-content/uploads/2021/11/111521-OSTP-CEQ-ITEK-Memo.pdf

CEQ (Council on Environmental Quality). (2022a). *Guidance for federal departments and agencies on indigenous knowledge*. Executive Office of the President, Office of Science and Technology Policy. https://www.whitehouse.gov/wp-content/uploads/2022/12/OSTP-CEQ-IK-Guidance.pdf

CEQ (Council on Environmental Quality). (2022b). *Implementation of guidance for federal departments and agencies on indigenous knowledge*. Executive Office of the President, Office of Science and Technology Policy. https://www.whitehouse.gov/wp-content/uploads/2022/12/IK-Guidance-Implementation-Memo.pdf

Christensen, K., Christensen, C. H., Wright, J. M., Galizia, A., Glenn, B. S., Scott, C. S., Mall, J. K., Bateson, T. F., Murphy, P. A., & Cooper, G. S. (2015). The use of epidemiology in risk assessment: Challenges and opportunities. *Human and Ecological Risk Assessment*, *21*(6), 1644-1663. https://doi.org/10.1080/10807039.2014.967039

CSDH (Commission on Social Determinants of Health). (2008). *Closing the gap in a generation: Health equity through action on the social determinants of health. Final report of the Commission on Social Determinants of Health*. World Health Organization. http://apps.who.int/iris/bitstream/10665/43943/1/9789241563703_eng.pdf

deFur, P. L., Evans, G. W., Cohen Hubal, E. A., Kyle, A. D., Morello-Frosch, R. A., & Williams, D. R. (2007). Vulnerability as a function of individual and group resources in cumulative risk assessment. *Environmental Health Perspectives*, *115*(5), 817-824. https://doi.org/10.1289/ehp.9332

EFSA Scientific Committee. (2017). Scientific opinion: Guidance on the use of the weight of evidence approach in scientific assessments. *EFSA Journal*, *15*(8), Article e04971. https://doi.org/10.2903/j.efsa.2017.4971

Embry, M. R., Bachman, A. N., Bell, D. R., Boobis, A. R., Cohen, S. M., Dellarco, M., Dewhurst, I. C., Doerrer, N. G., Hines, R. N., Moretto, A., Pastoor, T. P., Phillips, R. D., Rowlands, J. C., Tanir, J. Y., Wolf, D. C., & Doe, J. E. (2014). Risk assessment in the 21st century: Roadmap and matrix. *Critical Reviews in Toxicology*, *44*(Suppl. 3), 6-16. https://doi.org/10.3109/10408444.2014.931924

EOP (Executive Office of the President). (1994). Executive Order 12898: Federal actions to address environmental justice in minority populations and low-income populations. *Federal Register*, *59*(32), 7629-7633. https://www.epa.gov/laws-regulations/summary-executive-order-12898-federal-actions-address-environmental-justice

EOP (Executive Office of the President). (1997). Executive Order 13045: Protection of children from environmental health risks and safety risks. *Federal Register*, *62*(78), 19885-19888. https://www.epa.gov/laws-regulations/summary-executive-order-13045-protection-children-environmental-health-risks-and

EOP (Executive Office of the President). (2021). Executive Order 13985: Advancing racial equity and support for underserved communities through the federal government. *Federal Register*, *86*(14), 7009-7013. https://www.federalregister.gov/documents/2021/01/25/2021-01753/advancing-racial-equity-and-support-for-underserved-communities-through-the-federal-government

EOP (Executive Office of the President). (2023a). Executive Order 14091: Further advancing racial equity and support for underserved communities through the federal government. *Federal Register*, *88*(35), 10825-10833. https://www.federalregister.gov/documents/2023/02/22/2023-03779/further-advancing-racial-equity-and-support-for-underserved-communities-through-the-federal

EOP (Executive Office of the President). (2023b). Executive Order 14096: Revitalizing our nation's commitment to environmental justice for all. *Federal Register*, *88*(80), 25251-25261. https://www.federalregister.gov/documents/2023/04/26/2023-08955/revitalizing-our-nations-commitment-to-environmental-justice-for-all

Fox, M. A., Brewer, L. E., & Martin, L. (2017). An overview of literature topics related to current concepts, methods, tools, and applications for cumulative risk assessment (2007-2016). *International Journal of Environmental Research and Public Health*, *14*(4), Article 389. https://doi.org/10.3390/ijerph14040389

Gallagher, S. S., Rice, G. E., Scarano, L. J., Teuschler, L. K., Bollweg, G., & Martin, L. (2015). Cumulative risk assessment lessons learned: A review of case studies and issue papers. *Chemosphere*, *120*, 697-705. https://doi.org/10.1016/j.chemosphere.2014.10.030

Gee, G. C., & Payne-Sturges, D. C. (2004). Environmental health disparities: A framework integrating psychosocial and environmental concepts. *Environmental Health Perspectives*, *112*(17), 1645-1653. https://doi.org/10.1289/ehp.7074

Ginsberg, G. L., Dietert, R. R., & Sonawane, B. R. (2014). Susceptibility based upon chemical interaction with disease processes: Potential implications for risk assessment. *Current Environmental Health Reports 1*(4), 314-324. https://doi.org/10.1007/s40572-014-0030-z

Hibbert, K., & Tulve, N. S. (2019). State-of-the-science review of non-chemical stressors found in a child's social environment. *International Journal of Environmental Research and Public Health*, *16*(22), Article 4417. https://doi.org/10.3390/ijerph16224417

IOM (Institute of Medicine). (2013). *Environmental decisions in the face of uncertainty*. The National Academies Press. https://doi.org/10.17226/12568

Juster, R. P., McEwen, B. S., & Lupien, S. J. (2010). Allostatic load biomarkers of chronic stress and impact on health and cognition. *Neuroscience and Biobehavioral Reviews*, *35*(1), 2-16. https://doi.org/10.1016/j.neubiorev.2009.10.002

Kashuba, R., Menzie, C., & Martin, L. (2021). Risk of cardiovascular disease is driven by different combinations of environmental, medical and behavioral factors: Building a conceptual model for cumulative risk assessment. *Human and Ecological Risk Assessment*, *27*(7), 1902-1925. https://doi.org/10.1080/10807039.2021.1925083

Kasperson, J. X., Kasperson, R. E., & Turner, B. L., 2nd (Eds.). (1995). *Regions at risk: Comparisons of threatened environments*. United Nations University Press.

Kasperson, R. E., Dow, K., Archer, E. R. M., Caceres, E., Downing, T. E., Elmqvist, T., Eriksen, S., Folke, C., Han, G., Iyengar, K., Vogel, C., Wilson, K. A., & Ziervogel, G. (2005). Vulnerable peoples and places. In R. M. Hassan, R. J. Scholes, & N. Ash (Eds.), *Ecosystems and human well-being: Current state and trends: Findings of the Condition and Trends Working Group* (pp. 146-162). Island Press.

Levy, J. I. (2008). Is epidemiology the key to cumulative risk assessment? *Risk Analysis*, *28*(6), 1507-1513. https://doi.org/10.1111/j.1539-6924.2008.01121.x

Lichtveld, K., Thomas, K., & Tulve, N. S. (2018). Chemical and non-chemical stressors affecting childhood obesity: A systematic scoping review. *Journal of Exposure Science and Environmental Epidemiology*, *28*(1), 1-12. https://doi.org/10.1038/jes.2017.18

Linder, S. H., Delclos, G., & Sexton, K. (2010). Making causal claims about environmentally induced adverse effects. *Human and Ecological Risk Assessment*, *16*(1), 35-52. https://doi.org/10.1080/10807030903459288

Linder, S. H., & Sexton, K. (2011). Conceptual models for cumulative risk assessment. *American Journal of Public Health*, *101*(Suppl. 1), S74-S81. https://doi.org/10.2105/ajph.2011.300318
Linkov, I., & Satterstrom, F. K. (2006). Weight of evidence: What is the state of the science? *Risk Analysis*, *26*(3), 573-575. https://doi.org/10.1111/j.1539-6924.2006.00756.x
Løkke, H. (2010). Novel methods for integrated risk assessment of cumulative stressors — Results from the NoMiracle project. *Science of The Total Environment*, *408*(18), 3719-3724. https://doi.org/10.1016/j.scitotenv.2010.05.009
Meadows, D. H. (2008). *Thinking in systems: A primer*. Chelsea Green Publishing.
Meek, M. E., Boobis, A. R., Crofton, K. M., Heinemeyer, G., Raaij, M. V., & Vickers, C. (2011). Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework. *Regulatory Toxicology and Pharmacology*, *60*(2 Suppl.), S1-S14. https://doi.org/10.1016/j.yrtph.2011.03.010
Menzie, C. A., MacDonell, M. M., & Mumtaz, M. (2007). A phased approach for assessing combined effects from multiple stressors. *Environmental Health Perspectives*, *115*(5), 807-816. https://doi.org/10.1289/ehp.9331
Morello-Frosch, R., & Shenassa, E. D. (2006). The environmental "riskscape" and social inequality: Implications for explaining maternal and child health disparities. *Environmental Health Perspectives*, *114*(8), 1150-1153. https://doi.org/10.1289/ehp.8930
Morello-Frosch, R., Zuk, M., Jerrett, M., Shamasunder, B., & Kyle, A. D. (2011). Understanding the cumulative impacts of inequalities in environmental health: Implications for policy. *Health Affairs*, *30*(5), 879-887. https://doi.org/10.1377/hlthaff.2011.0153
Moretto, A., Bachman, A., Boobis, A., Solomon, K. R., Pastoor, T. P., Wilks, M. F., & Embry, M. R. (2017). A framework for cumulative risk assessment in the 21st century. *Critical Reviews in Toxicology*, *47*(2), 85-97. https://doi.org/10.1080/10408444.2016.1211618
NASEM (National Academies of Sciences, Engineering, and Medicine). (2017). *Using 21st century science to improve risk-related evaluations*. The National Academies Press. https://doi.org/10.17226/24635
NASEM (National Academies of Sciences, Engineering, and Medicine). (2023). *Building confidence in new evidence streams for human health risk assessment: Lessons learned from laboratory mammalian toxicity tests*. The National Academies Press. https://doi.org/10.17226/26906
National EPA-TSC (Tribal Science Council). (2006). *Paper on tribal issues related to tribal traditional lifeways, risk assessment, and health & well being: Documenting what we've heard* (EPA/620/R-06/004). U.S. Environmental Protection Agency. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P1006LIF.txt
NEJAC (National Environmental Justice Advisory Council). (2004). *Ensuring risk reduction in communities with multiple stressors: Environmental justice and cumulative risks/impacts*. U.S. Environmental Protection Agency. https://www.epa.gov/sites/production/files/2015-04/documents/ensuringriskreducationnejac.pdf
Nilsen, F. M., Frank, J., & Tulve, N. S. (2020a). A systematic review and meta-analysis investigating the relationship between exposures to chemical and non-chemical stressors during prenatal development and childhood externalizing behaviors. *International Journal of Environmental Research and Public Health*, *17*(7), Article 2361. https://doi.org/10.3390/ijerph17072361
Nilsen, F. M., Ruiz, J. D. C., & Tulve, N. S. (2020b). A meta-analysis of stressors from the total environment associated with children's general cognitive ability. *International Journal of Environmental Research and Public Health*, *17*(15), Article 5451. https://doi.org/10.3390/ijerph17155451
Nilsen, F. M., & Tulve, N. S. (2020). A systematic review and meta-analysis examining the interrelationships between chemical and non-chemical stressors and inherent characteristics in children with ADHD. *Environmental Research*, *180*, Article 108884. https://doi.org/10.1016/j.envres.2019.108884
Norton, S. B., Cormier, S. M., & Suter, G. W., 2nd (Eds.). (2014). *Ecological causal assessment*. CRC Press. https://doi.org/10.1201/b17603.
NRC (National Research Council). (1980). *Principles of toxicological interactions associated with multiple chemical exposures*. The National Academies Press. https://nap.nationalacademies.org/catalog/20435/principles-of-toxicological-interactions-associated-with-multiple-chemical-exposures
NRC (National Research Council). (1983). *Risk assessment in the federal government: Managing the process*. The National Academies Press. https://doi.org/10.17226/366
NRC (National Research Council). (1993). *Pesticides in the diets of infants and children*. The National Academies Press. https://doi.org/10.17226/2126
NRC (National Research Council). (1996). *Understanding risk: Informing decisions in a democratic society*. The National Academies Press. https://doi.org/10.17226/5138

NRC (National Research Council). (2006). *Fluoride in drinking water: A scientific review of EPA's standards*. The National Academies Press. https://doi.org/10.17226/11571
NRC (National Research Council). (2007). *Toxicity testing in the 21st century: A vision and a strategy*. The National Academies Press. https://doi.org/10.17226/11970
NRC (National Research Council). (2008a). *Phthalates and cumulative risk assessment: The tasks ahead*. The National Academies Press. https://doi.org/10.17226/12528
NRC (National Research Council). (2008b). *Public participation in environmental assessment and decision making*. The National Academies Press. https://doi.org/10.17226/12434
NRC (National Research Council). (2009). *Science and decisions: Advancing risk assessment*. The National Academies Press. https://doi.org/10.17226/12209
NRC (National Research Council). (2011a). *Improving health in the United States: The role of health impact assessment*. The National Academies Press. https://doi.org/10.17226/13229
NRC (National Research Council). (2011b). *Sustainability and the U.S. EPA*. The National Academies Press. https://doi.org/10.17226/13152
NRC (National Research Council). (2012). *Exposure science in the 21st century: A vision and a strategy*. The National Academies Press. https://doi.org/10.17226/13507
Payne-Sturges, D. C., Korfmacher, K. S., Cory-Slechta, D. A., Jimenez, M., Symanski, E., Carr Shmool, J. L., Dotson-Newman, O., Clougherty, J. E., French, R., Levy, J. I., Laumbach, R., Rodgers, K., Bongiovanni, R., & Scammell, M. K. (2015). Engaging communities in research on cumulative risk and social stress-environment interactions: Lessons learned from EPA's STAR program. *Environmental Justice*, *8*(6), 203-212. https://doi.org/10.1089/env.2015.0025
Payne-Sturges, D. C., Scammell, M. K., Levy, J. I., Cory-Slechta, D. A., Symanski, E., Carr Shmool, J. L., Laumbach, R., Linder, S., & Clougherty, J. E. (2018). Methods for evaluating the combined effects of chemical and nonchemical exposures for cumulative environmental health risk assessment. *International Journal of Environmental Research and Public Health*, *15*(12), Article 2797. https://doi.org/10.3390/ijerph15122797
PCCRARM (Presidential/Congressional Commission on Risk Assessment and Risk Management). (1997). *Framework for environmental health risk management: Final report. Volumes 1 and 2* (EPA/950/R-97/011). U.S. Environmental Protection Agency. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=9101K1C3.txt
Rodriquez, E. J., Kim, E. N., Sumner, A. E., Nápoles, A. M., & Pérez-Stable, E. J. (2019). Allostatic load: Importance, markers, and score determination in minority and disparity populations. *Journal of Urban Health*, *96*(Suppl. 1), 3-11. https://doi.org/10.1007/s11524-019-00345-5
Ruiz, J. D. C., Quackenboss, J. J., & Tulve, N. S. (2016). Contributions of a child's built, natural, and social environments to their general cognitive ability: A systematic scoping review. *PLoS One*, *11*(2), Article e0147741. https://doi.org/10.1371/journal.pone.0147741
Ryan, P. B., Burke, T. A., Cohen Hubal, E. A., Cura, J. J., & McKone, T. E. (2007). Using biomarkers to inform cumulative risk assessment. *Environmental Health Perspectives*, *115*(5), 833-840. https://doi.org/10.1289/ehp.9334
Schäfer, R. B., Jackson, M., Juvigny-Khenafou, N., Osakpolor, S. E., Posthuma, L., Schneeweiss, A., Spaak, J., & Vinebrooke, R. (2023). Chemical mixtures and multiple stressors: Same but different? *Environmental Toxicology and Chemistry*, *42*(9), 1915-1936. https://doi.org/10.1002/etc.5629
Schulz, A. J., Kannan, S., Dvonch, J. T., Israel, B. A., Allen, A., 3rd, James, S. A., House, J. S., & Lepkowski, J. (2005). Social and physical environments and disparities in risk for cardiovascular disease: The Healthy Environments Partnership conceptual model. *Environmental Health Perspectives*, *113*(12), 1817-1825. https://doi.org/10.1289/ehp.7913
Segal, D., Lin, Y. S., Ginsberg, G., & Sonawane, B. (2015). A conceptual framework for evaluating the interaction of a chemical and nonchemical stressor in human health risk assessments: A case study for lead and psychosocial stress. *Human and Ecological Risk Assessment*, *21*(7), 1840-1868. https://doi.org/10.1080/10807039.2014.992852
Sexton, K. (2015). Cumulative health risk assessment: Finding new ideas and escaping from the old ones. *Human and Ecological Risk Assessment*, *21*(4), 934-951. https://doi.org/10.1080/10807039.2014.946346
Sexton, K., & Hattis, D. (2007). Assessing cumulative health risks from exposure to environmental mixtures—three fundamental questions. *Environmental Health Perspectives*, *115*(5), 825-832. https://doi.org/10.1289/ehp.9333

Sexton, K., & Linder, S. H. (2010). The role of cumulative risk assessment in decisions about environmental justice. *International Journal of Environmental Research and Public Health*, *7*(11), 4037-4049. https://doi.org/10.3390/ijerph7114037

Sexton, K., & Linder, S. H. (2011). Cumulative risk assessment for combined health effects from chemical and nonchemical stressors. *American Journal of Public Health*, *101*(Suppl. 1), S81-S88. https://doi.org/10.2105/ajph.2011.300118

Shaffer, R. M. (2021). Environmental health risk assessment in the federal government: A visual overview and a renewed call for coordination. *Environmental Science and Technology*, *55*(16), 10923-10927. https://doi.org/10.1021/acs.est.1c01955

Simmons, J. E., Teuschler, L. K., Gennings, C., Speth, T. F., Richardson, S. D., Miltner, R. J., Narotsky, M. G., Schenck, K. D., Hunter, E. S., 3rd, Hertzberg, R. C., & Rice, G. (2004). Component-based and whole-mixture techniques for addressing the toxicity of drinking-water disinfection by-product mixtures. *Journal of Toxicology and Environmental Health, Part A*, *67*(8-10), 741-754. https://doi.org/10.1080/15287390490428215

Solar, O., & Irwin, A. (2010). *A conceptual framework for action on the social determinants of health: Social determinants of health discussion paper 2 (policy and practice)*. World Health Organization. http://apps.who.int/iris/bitstream/10665/44489/1/9789241500852_eng.pdf

Solomon, K. R., Wilks, M. F., Bachman, A., Boobis, A., Moretto, A., Pastoor, T. P., Phillips, R., & Embry, M. R. (2016). Problem formulation for risk assessment of combined exposures to chemicals and other stressors in humans. *Critical Reviews in Toxicology*, *46*(10), 835-844. https://doi.org/10.1080/10408444.2016.1211617

Stahl, C. H., & Cimorelli, A. J. (2020). *Environmental public policy making exposed: A guide for decision makers and interested citizens*. Springer. https://doi.org/10.1007/978-3-030-32130-7

Suter, G. W., 2nd. (1999). Developing conceptual models for complex ecological risk assessments. *Human and Ecological Risk Assessment*, *5*(2), 375-396. https://doi.org/10.1080/10807039991289491

Suter, G. W., 2nd. (2006). *Ecological risk assessment* (2nd ed.). CRC Press. https://doi.org/10.1201/9781420012569

Teuschler, L. K., Rice, G. E., Wilkes, C. R., Lipscomb, J. C., & Power, F. W. (2004). A feasibility study of cumulative risk assessment methods for drinking water disinfection by-product mixtures. *Journal of Toxicology and Environmental Health, Part A*, *67*(8-10), 755-777. https://doi.org/10.1080/15287390490428224

Tulve, N. S., Ruiz, J. D. C., Lichtveld, K., Darney, S. P., & Quackenboss, J. J. (2016). Development of a conceptual framework depicting a child's total (built, natural, social) environment in order to optimize health and well-being. *Journal of Environment and Health Sciences*, *2*(2), 1-8.

U.S. EPA (U.S. Environmental Protection Agency). (1986a). *Guidelines for mutagenicity risk assessment* (EPA/630/R-98/003). Risk Assessment Forum. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=23160

U.S. EPA (U.S. Environmental Protection Agency). (1986b). *Guidelines for the health risk assessment of chemical mixtures* (EPA/630/R-98/002). Risk Assessment Forum. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=22567

U.S. EPA (U.S. Environmental Protection Agency). (1989). *Risk assessment guidance for Superfund: Volume I: Human health evaluation manual (part A)* (EPA/540/1-89/002). Office of Emergency and Remedial Response. https://www.epa.gov/risk/risk-assessment-guidance-superfund-rags-part

U.S. EPA (U.S. Environmental Protection Agency). (1991a). *Guidelines for developmental toxicity risk assessment* (EPA/600/FR-91/001). Risk Assessment Forum. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=23162

U.S. EPA (U.S. Environmental Protection Agency). (1991b). *Risk assessment guidance for Superfund: Volume I - Human health evaluation manual (part B, development of risk-based preliminary remediation goals)* (EPA/540/R-92/003). Office of Emergency and Remedial Response. https://www.epa.gov/risk/risk-assessment-guidance-superfund-rags-part-b

U.S. EPA (U.S. Environmental Protection Agency). (1994). *Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry* (EPA/600/8-90/066F). Office of Research and Development. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=71993

U.S. EPA (U.S. Environmental Protection Agency). (1995a). *Environmental justice strategy: Executive Order 12898*. Administration and Resources Management, Office of Environmental Justice. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=40000AEB.txt

U.S. EPA (U.S. Environmental Protection Agency). (1995b). *Policy on evaluating health risks to children*. https://www.epa.gov/children/epas-policy-childrens-health

U.S. EPA (U.S. Environmental Protection Agency). (1996a). Attachment A: Conceptual site model summary. In *Soil screening guidance: User's guide* (2nd ed.). (EPA/540/R-96/018). Office of Solid Waste and Emergency Response. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=100027WI.txt

U.S. EPA (U.S. Environmental Protection Agency). (1996b). *Guidelines for reproductive toxicity risk assessment* (EPA/630/R-96/009). Risk Assessment Forum. https://www.epa.gov/risk/guidelines-reproductive-toxicity-risk-assessment

U.S. EPA (U.S. Environmental Protection Agency). (1997a). *Cumulative risk assessment guidance–Phase I planning and scoping (Memorandum, July 3)*. https://www.epa.gov/sites/production/files/2015-01/documents/cumulrisk.pdf

U.S. EPA (U.S. Environmental Protection Agency). (1997b). *Ecological risk assessment guidance for Superfund: Process for designing and conducting ecological risk assessments* (EPA 540-R-97-006). Solid Waste and Emergency Response. https://semspub.epa.gov/work/HQ/157941.pdf

U.S. EPA (U.S. Environmental Protection Agency). (1997c). *Guidance on cumulative risk assessment. Part 1. Planning and scoping*. Science Policy Council. https://www.epa.gov/risk/guidance-cumulative-risk-assessment-part-1-planning-and-scoping

U.S. EPA (U.S. Environmental Protection Agency). (1997d). *Guiding principles for Monte Carlo analysis* (EPA/630/R-97/001). Risk Assessment Forum. https://www.epa.gov/risk/guiding-principles-monte-carlo-analysis

U.S. EPA (U.S. Environmental Protection Agency). (1998a). *Guidelines for ecological risk assessment* (EPA/630/R-95/002F). Risk Assessment Forum. https://www.epa.gov/risk/guidelines-ecological-risk-assessment

U.S. EPA (U.S. Environmental Protection Agency). (1998b). *Guidelines for neurotoxicity risk assessment* (EPA/630/R-95/001F). Risk Assessment Forum. https://www.epa.gov/risk/guidelines-neurotoxicity-risk-assessment

U.S. EPA (U.S. Environmental Protection Agency). (1998c). *Methodology for assessing health risks associated with multiple pathways of exposure to combustor emissions* (EPA/600/R-98/137). Office of Research and Development, National Center for Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=55525

U.S. EPA (U.S. Environmental Protection Agency). (1999). *Guidance for identifying pesticide chemicals and other substances that have a common mechanism of toxicity*. https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/guidance-identifying-pesticide-chemicals-and-other

U.S. EPA (U.S. Environmental Protection Agency). (2000a). *Conducting a risk assessment of mixtures of disinfection by-products (DBPs) for drinking water treatment systems* (EPA/600/R-03/040). Office of Research and Development, National Center for Environmental Assessment. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=57054&CFID=80080479&CFTOKEN=68320311

U.S. EPA (U.S. Environmental Protection Agency). (2000b). *Risk characterization handbook* (EPA 100-B-00-002). Office of Research and Development, Office of Science Policy. https://www.epa.gov/risk/risk-characterization-handbook

U.S. EPA (U.S. Environmental Protection Agency). (2000c). *Stressor identification guidance document* (EPA/822/B-00/025). Office of Water, Office of Research and Development. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=20685

U.S. EPA (U.S. Environmental Protection Agency). (2000d). *Supplementary guidance for conducting health risk assessment of chemical mixtures* (EPA/630/R-00/002). Risk Assessment Forum. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=20533

U.S. EPA (U.S. Environmental Protection Agency). (2001a). *General principles for performing aggregate exposure and risk assessments*. Office of Pesticide Programs. https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/general-principles-performing-aggregate-exposure

U.S. EPA (U.S. Environmental Protection Agency). (2001b). *Risk assessment guidance for Superfund: Volume I: Human health evaluation manual (part D, standardizing planning, reporting, and review of superfund risk assessments)* (Publication 9285.7-47). Office of Emergency and Remedial Response. https://www.epa.gov/risk/risk-assessment-guidance-superfund-rags-part-d

U.S. EPA (U.S. Environmental Protection Agency). (2001c). *Risk assessment guidance for Superfund: Volume III - Part A, process for conducting probabilistic risk assessment* (EPA 540-R-02-002; OSWER 9285.7-45). Office of Emergency and Remedial Response. https://www.epa.gov/risk/risk-assessment-guidance-superfund-rags-volume-iii-part

U.S. EPA (U.S. Environmental Protection Agency). (2001d). *Stakeholder involvement & public participation at the U.S. EPA: Lessons learned, barriers, & innovative approaches* (EPA-100-R-00-040). Office of Policy,

Economics, and Innovation. https://www.epa.gov/sites/default/files/2015-09/documents/stakeholder-involvement-public-participation-at-epa.pdf
U.S. EPA (U.S. Environmental Protection Agency). (2002a). *Guidance on cumulative risk assessment of pesticide chemicals that have a common mechanism of toxicity*. Office of Pesticide Programs. https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/guidance-cumulative-risk-assessment-pesticide
U.S. EPA (U.S. Environmental Protection Agency). (2002b). *Lessons learned on planning and scoping for environmental risk assessments* (EPA/600/R-02/802). Office of Science Policy. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P1008PP7.txt
U.S. EPA (U.S. Environmental Protection Agency). (2003a). *Developing relative potency factors for pesticide mixtures: Biostatistical analyses of joint dose-response* (EPA/600/R-03/052). Office of Research and Development, National Center for Environmental Assessment. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=66273&CFID=80059878&CFTOKEN=47378702
U.S. EPA (U.S. Environmental Protection Agency). (2003b). *Framework for cumulative risk assessment* (EPA/630/P-02/001F). Risk Assessment Forum. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=30004TJH.txt
U.S. EPA (U.S. Environmental Protection Agency). (2003c). *Public involvement policy of the U.S. Environmental Protection Agency* (EPA 233-B-03-002). Office of Policy, Economics, and Innovation. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=40000P9G.txt
U.S. EPA (U.S. Environmental Protection Agency). (2004a). *An examination of EPA risk assessment principles and practices: Staff paper prepared for the U.S. Environmental Protection Agency by members of the Risk Assessment Task Force* (EPA/100/B-04/001). Office of the Science Advisor. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=100045MJ.txt
U.S. EPA (U.S. Environmental Protection Agency). (2004b). *Risk assessment guidance for Superfund: Volume I: Human health evaluation manual (part E, supplemental guidance for dermal risk assessment)*. Office of Superfund Remediation and Technology Innovation. https://www.epa.gov/risk/risk-assessment-guidance-superfund-rags-part-e
U.S. EPA (U.S. Environmental Protection Agency). (2005). *Guidelines for carcinogen risk assessment* (EPA/630/P-03/001F). Risk Assessment Forum. https://www.epa.gov/risk/guidelines-carcinogen-risk-assessment
U.S. EPA (U.S. Environmental Protection Agency). (2006a). *Air Toxics Risk Assessment reference library: Volume 3: Community-scale assessment* (EPA-452/K-06-001C). Office of Air Quality Planning and Standards. https://www.epa.gov/sites/production/files/2013-08/documents/volume_3_communityassess.pdf
U.S. EPA (U.S. Environmental Protection Agency). (2006b). *Cumulative risk from chloroacetanilide pesticides*. Office of Pesticide Programs. https://web.archive.org/web/20150417192548/http://epa.gov/pesticides/cumulative/chloro_cumulative_risk.pdf
U.S. EPA (U.S. Environmental Protection Agency). (2006c). *A framework for assessing health risk of environmental exposures to children* (EPA/600/R-05/093F). Office of Research and Development, National Center for Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=158363
U.S. EPA (U.S. Environmental Protection Agency). (2006d). *Guidance on systematic planning using the Data Quality Objectives Process: EPA QA/G-4* (EPA/240/B-06/001). Office of Environmental Information. https://www.epa.gov/quality/guidance-systematic-planning-using-data-quality-objectives-process-epa-qag-4
U.S. EPA (U.S. Environmental Protection Agency). (2006e). *Organophosphorus cumulative risk assessment – 2006 update*. Office of Pesticide Programs. https://yosemite.epa.gov/oarm/alj/alj_web_docket.nsf/Filing+Additional+Attachments/55EB8690337D456185258A0C00440F0F/$File/RX%2018%20Revised%20Organophosphorous%20Pesticide%20Cumulative%20Risk%20Assessment.pdf
U.S. EPA (U.S. Environmental Protection Agency). (2006f). *Triazine cumulative risk assessment*. Office of Pesticide Programs. https://archive.epa.gov/pesticides/reregistration/web/pdf/triazine_cumulative_risk.pdf
U.S. EPA (U.S. Environmental Protection Agency). (2007a). *Concepts, methods, and data sources for cumulative health risk assessment of multiple chemicals, exposures and effects: A resource document* (EPA/600/R-06/013F). Office of Research and Development, National Center for Environmental Assessment. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=190187

U.S. EPA (U.S. Environmental Protection Agency). (2007b). *Revised N-methyl carbamate cumulative risk assessment*. Office of Pesticide Programs. https://archive.epa.gov/pesticides/reregistration/web/pdf/nmc_revised_cra.pdf
U.S. EPA (U.S. Environmental Protection Agency). (2009). *Integrated Science Assessment for particulate matter* (EPA/600/R-08/139F). Office of Research and Development, National Center for Environmental Assessment. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=216546
U.S. EPA (U.S. Environmental Protection Agency). (2010). *EPA's action development process: Interim guidance on considering environmental justice during the development of an action*. https://www.epa.gov/environmentaljustice/interim-guidance-considering-environmental-justice-during-development-action
U.S. EPA (U.S. Environmental Protection Agency). (2011). *Exposure factors handbook: 2011 edition* (EPA/600/R-09/052F). Office of Research and Development, National Center for Environmental Assessment. https://cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=236252
U.S. EPA (U.S. Environmental Protection Agency). (2013). *America's children and the environment: Third edition* (EPA 240-R-13-001). https://www.epa.gov/sites/production/files/2015-06/documents/ace3_2013.pdf
U.S. EPA (U.S. Environmental Protection Agency). (2014a). *Cumulative risk webinar series: What we learned* (EPA/600/R-14/212). https://www.epa.gov/sites/production/files/2015-10/documents/cra-webinar-summary.pdf
U.S. EPA (U.S. Environmental Protection Agency). (2014b). *Framework for human health risk assessment to inform decision making* (EPA/100/R-14/001). Office of the Science Advisor, Risk Assessment Forum. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P100IEKK.txt
U.S. EPA (U.S. Environmental Protection Agency). (2014c). *Risk assessment forum white paper: Probabilistic risk assessment methods and case studies* (EPA/100/R-14/004). Office of the Science Advisor, Risk Assessment Forum. https://www.epa.gov/scientific-leadership/risk-assessment-forum-white-paper-probabilistic-risk-assessment-methods-and
U.S. EPA (U.S. Environmental Protection Agency). (2015a). *Peer review handbook: 4th edition* (EPA/100/B-15/001). Science and Technology Policy Council. https://www.epa.gov/scientific-leadership/peer-review-handbook-4th-edition-2015-0
U.S. EPA (U.S. Environmental Protection Agency). (2015b). *Preamble to the Integrated Science Assessments* (EPA/600/R-15/067). Office of Research and Development, National Center for Environmental Assessment. https://cfpub.epa.gov/ncea/isa/recordisplay.cfm?deid=310244
U.S. EPA (U.S. Environmental Protection Agency). (2016a). *EJ 2020 Action Agenda: The U.S. EPA's environmental justice strategic plan for 2016 - 2020*. https://www.epa.gov/environmentaljustice/ej-2020-action-agenda-epas-environmental-justice-strategy-0
U.S. EPA (U.S. Environmental Protection Agency). (2016b). *Pesticide cumulative risk assessment: Framework for screening analysis*. Office of Pesticide Programs. https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/pesticide-cumulative-risk-assessment-framework
U.S. EPA (U.S. Environmental Protection Agency). (2016c). *Weight of evidence for ecological assessment* (EPA/100/R-16/001). Office of the Science Advisor, Risk Assessment Forum. https://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=P100SFXR.txt
U.S. EPA (U.S. Environmental Protection Agency). (2019). *Guidelines for human exposure assessment* (EPA/100/B-19/001). Risk Assessment Forum. https://www.epa.gov/risk/guidelines-human-exposure-assessment
U.S. EPA (U.S. Environmental Protection Agency). (2020a). *Clean Air Act title IV - Noise pollution*. Retrieved May 20, 2020 from https://www.epa.gov/clean-air-act-overview/clean-air-act-title-iv-noise-pollution
U.S. EPA (U.S. Environmental Protection Agency). (2020b). *Cumulative Risk Assessment 2012 webinar series*. Retrieved May 20, 2020 from https://archive.epa.gov/ncer/multimedia/videos/web/html/cumulative-risk/webinar/2012/index.html
U.S. EPA (U.S. Environmental Protection Agency). (2020c). *EPA's Report on the Environment (ROE)*. Retrieved May 20, 2020 from https://www.epa.gov/report-environment
U.S. EPA (U.S. Environmental Protection Agency). (2020d). *How EPA manages the quality of its environmental data*. Retrieved May 20, 2020 from https://19january2021snapshot.epa.gov/quality_.html
U.S. EPA (U.S. Environmental Protection Agency). (2020e). *Superfund community involvement handbook* (OLEM 9230.0-51). Office of Superfund Remediation and Technology Innovation. https://semspub.epa.gov/work/HQ/100002505.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2021a). *2021 Policy on children's health: October 5, 2021*. Office of the Administrator. https://www.epa.gov/sites/default/files/2014-05/documents/1995_childrens_health_policy_statement.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2021b). *List of alternative test methods and strategies (or new approach methodologies [NAMs]). Second update: February 4th, 2021*. Office of Chemical Substances and Pollution Prevention. https://www.epa.gov/sites/default/files/2021-02/documents/nams_list_second_update_2-4-21_final.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2022a). *Adverse Outcome Pathway Database (AOP-DB)*. Retrieved 2022 from https://www.epa.gov/healthresearch/adverse-outcome-pathway-database-aop-db

U.S. EPA (U.S. Environmental Protection Agency). (2022b). *Chemical safety for sustainability: Strategic research action plan: Fiscal years 2023–2026* (EPA/600/R-22/238). Office of Research and Development. https://www.epa.gov/system/files/documents/2022-10/CSS%20FY23-26%20StRAP_EPA-ORD_October%202022_508.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2022c). *Cumulative impacts research: Recommendations for EPA's Office of Research and Development* (EPA/600/R-22/014a). https://www.epa.gov/system/files/documents/2022-09/Cumulative%20Impacts%20Research%20Final%20Report_FINAL-EPA%20600-R-22-014a.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2022d). *ORD staff handbook for developing IRIS assessments* (EPA/600/R-22/268). Office of Research and Development, Center for Public Health and Environmental Assessment. https://iris.epa.gov/Document/&deid=356370

U.S. EPA (U.S. Environmental Protection Agency). (2023a). *Advances in dose addition for chemical mixtures: A white paper* (EPA/100/R-23/001). Risk Assessment Forum. https://assessments.epa.gov/risk/document/&deid%3D359745

U.S. EPA (U.S. Environmental Protection Agency). (2023b). *EPA legal tools to advance environmental justice: Cumulative impacts addendum* (Publication No.: 360R22002). Office of General Counsel. https://www.epa.gov/system/files/documents/2022-12/bh508-Cumulative%20Impacts%20Addendum%20Final%202022-11-28.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2023c). *EPA policy on consultation with Indian tribes*. https://www.epa.gov/system/files/documents/2023-12/epa-policy-on-consultation-with-indian-tribes-2023.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2024). *Interim framework for advancing consideration of cumulative impacts*. https://www.epa.gov/system/files/documents/2024-11/epa-interim-cumulative-impacts-framework-november-2024.pdf

U.S. HHS (U.S. Department of Health and Human Services). (2020). *Healthy People 2020: Social determinants of health*. Retrieved April 14, 2020 from https://web.archive.org/web/20200414105159/https://www.healthypeople.gov/2020/topics-objectives/topic/social-determinants-of-health

Vandenberg, L. N., Rayasam, S. D. G., Axelrad, D. A., Bennett, D. H., Brown, P., Carignan, C. C., Chartres, N., Diamond, M. L., Joglekar, R., Shamasunder, B., Shrader-Frechette, K., Subra, W. A., Zarker, K., & Woodruff, T. J. (2023). Addressing systemic problems with exposure assessments to protect the public's health. *Environmental Health*, *21*(Suppl. 1), Article 121. https://doi.org/10.1186/s12940-022-00917-0

Varshavsky, J. R., Rayasam, S. D. G., Sass, J. B., Axelrad, D. A., Cranor, C. F., Hattis, D., Hauser, R., Koman, P. D., Marquez, E. C., Morello-Frosch, R., Oksas, C., Patton, S., Robinson, J. F., Sathyanarayana, S., Shepard, P. M., & Woodruff, T. J. (2023). Current practice and recommendations for advancing how human variability and susceptibility are considered in chemical risk assessment. *Environmental Health*, *21*(Suppl. 1), Article 133. https://doi.org/10.1186/s12940-022-00940-1

Vinikoor-Imler, L. C., Owens, E. O., Nichols, J. L., Ross, M., Brown, J. S., & Sacks, J. D. (2014). Evaluating potential response-modifying factors for associations between ozone and health outcomes: A weight-of-evidence approach. *Environmental Health Perspectives*, *122*(11), 1166-1176. https://doi.org/10.1289/ehp.1307541

Weed, D. L. (2005). Weight of evidence: A review of concept and methods. *Risk Analysis*, *25*(6), 1545-1557. https://doi.org/10.1111/j.1539-6924.2005.00699.x

Weiss, B., & Bellinger, D. C. (2006). Social ecology of children's vulnerability to environmental pollutants. *Environmental Health Perspectives*, *114*(10), 1479-1485. https://doi.org/10.1289/ehp.9101

WHO/IPCS (World Health Organization/International Programme on Chemical Safety). (2009a). *Assessment of combined exposures to multiple chemicals: Report of a WHO/IPCS international workshop on aggregate/cumulative risk assessment*. World Health Organization. https://iris.who.int/handle/10665/44113

WHO/IPCS (World Health Organization/International Programme on Chemical Safety). (2009b). *Principles and methods for the risk assessment of chemicals in food* (Environmental Health Criteria 240). World Health Organization. https://apps.who.int/iris/bitstream/handle/10665/44065/WHO_EHC_240_eng.pdf?sequence=152

WHO/IPCS (World Health Organization/International Programme on Chemical Safety). (2009c). *Principles for modelling dose–response for the risk assessment of chemicals* (Environmental Health Criteria 239). World Health Organization. http://apps.who.int/iris/bitstream/10665/43940/1/9789241572392_eng.pdf

Williams, A. J., Lambert, J. C., Thayer, K., & Dorne, J. L. C. M. (2021). Sourcing data on chemical properties and hazard data from the US-EPA CompTox Chemicals Dashboard: A practical guide for human risk assessment. *Environment International*, *154*, Article 106566. https://doi.org/10.1016/j.envint.2021.106566

Zartarian, V. G., & Schultz, B. D. (2010). The EPA's human exposure research program for assessing cumulative risk in communities. *Journal of Exposure Science and Environmental Epidemiology*, *20*(4), 351-358. https://doi.org/10.1038/jes.2009.20

APPENDIX A. EVOLUTION OF CUMULATIVE RISK ASSESSMENT AT THE EPA

A.1. Background and History

The EPA Administrator's 1997 memo on *Cumulative Risk Assessment Guidance – Phase I Planning and Scoping* first established cumulative risk assessment (CRA) policy at the EPA. Referencing the 1997 CRA Guidance, the Administrator directed "each office to take into account cumulative risk issues in scoping and planning major risk assessments and to consider a broader scope that integrates multiple sources, effects, pathways, stressors and populations for cumulative risk analyses in all cases for which relevant data are available" (U.S. EPA, 1997a). The 1997 CRA Guidance states:

> EPA's risk assessment emphasis has shifted increasingly to a more broadly based approach characterized by greater consideration of multiple endpoints, sources, pathways, and routes of exposure; community-based decision making; flexibility in achieving goals; case-specific responses; a focus on all of the environmental media; and significantly, holistic reduction of risk. This more complex assessment involves cumulative risk assessment (U.S. EPA, 1997c).

A major impetus for the 1997 CRA Guidance was Executive Order 12898, Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations (EOP, 1994). Provisions of the order included development of Agency implementation strategies and a requirement in the Research, Data Collection, and Analysis section, that "Environmental human health analysis, whenever practicable and appropriate, shall identify multiple and cumulative exposures." Subsequently, in the EPA's *Environmental Justice Strategy: Executive Order 12898*, the Agency specified that as a component of sound science for contributing to environmental justice, "EPA will evaluate the current state of knowledge in exposure and cumulative risk fields, and then identify data gaps and research needs" (U.S. EPA, 1995a).

The EPA's Science Policy Council and Risk Assessment Forum led the work on cumulative risk identified in the EPA's Environmental Justice Strategy, integrating it with the Agency's ongoing assessment of risk from chemical mixtures research. A milestone in this effort was the 2003 *Framework for Cumulative Risk Assessment*, which helped advance CRA development by clarifying basic concepts and objectives. The two main purposes of the 2003 Framework are (1) to offer a simple, flexible structure for designing, conducting, and evaluating CRA at EPA; and (2) to construct basic principles around which later guidelines might be organized (U.S. EPA, 2003b). An important contribution of the 2003 Framework was to define the terms "cumulative risk" and "cumulative risk assessment" in a way that is generally accepted (Sexton, 2015).

The 2003 Framework specifies three discrete but overlapping assessment phases: (1) planning, scoping, and problem formulation (assessment design); (2) analysis; and (3) risk characterization. The assessment phases specified in the 2003 CRA Framework were also adopted by the *Framework for Human Health Risk Assessment* (U.S. EPA, 2014b). These Guidelines draw on and are consistent with both earlier publications. Planning and scoping define both the process for conducting the risk assessment and its general scope, whereas problem formulation identifies major factors considered in a specific assessment to inform its technical approach (U.S. EPA, 2014b).

The 2003 Framework states that the analysis phase produces risk results associated with multiple chemical or nonchemical stressors to which study population(s) might be exposed (U.S. EPA, 2003b). The risk characterization phase puts analysis findings and risk estimates into perspective in terms of significance, reliability, and overall confidence. Risk characterization also evaluates whether the assessment met the goals and objectives it initially set forth.

Distinguishing between a chemical- or stressor-focused assessment approach and a "receptor-focused" assessment approach was central to the 2003 Framework. When the effects on the receptor are the initiating factor for the assessment, the importance of the organism's (or population's) interactions with stressors or agents (which could include factors that affect or mitigate the exposure or response to stressors) is explicitly recognized. For example, as Weiss and Bellinger (2006) point out in the context of developmental neurotoxicity, "…toxicity is not simply an inherent property of the toxicant but derives from an assortment of jointly acting variables bound implacably into the individual…." In a CRA context, this could mean that "receptor" properties such as stressor vulnerability, background exposure, and exposure history can be modifying factors. Evaluating the importance of such factors to the system being assessed is a major challenge in CRA problem formulation.

The EPA has maintained an active CRA research and study program since the publication of the 2003 Framework that informed development of these Guidelines (U.S. EPA, 2003b). The 2007 CRA resource document, *Concepts, Methods and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects*, is an important reference for CRA planning and problem formulation. It describes and explains strategies such as the consideration of initiating factors for a CRA to organize population characterization, data collection, and assessment planning and how to implement chemical grouping to facilitate toxicity analysis (U.S. EPA, 2007a). Grouping stressors to simplify analysis is recommended as a critical component of the CRA planning process to design a tractable study and to target resources properly.

Building on the method for grouping stressors, the EPA's *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* (U.S. EPA, 2016b) provides guidance on how to screen groups of pesticides for cumulative evaluation during Registration Reviews.[46] A screening analysis is used to determine whether the available toxicological data for a group of chemicals suggest that a common mode of action[47] can be established. If so, a screening-level toxicological and exposure analysis is used to provide an initial determination of whether further assessment is necessary. The Pesticide CRA Framework implements a tiering strategy to identify risks effectively and to use resources efficiently. Tiering a CRA, discussed further in Section 2.5, is an important planning method for targeting priority stressors and matching appropriate assessment efforts to the risk management decision.

The EPA supported a series of grants exploring methods to address nonchemical stressors in CRA (Payne-Sturges et al., 2015) and commissioned a series of issue papers that investigated a range of CRA themes, including combined health effects from multiple stressors, incorporating vulnerability into CRA, assessing environmental mixtures, and using biomarkers to inform CRA (Callahan & Sexton, 2007; deFur et al., 2007; Menzie et al., 2007; Ryan et al., 2007; Sexton & Hattis, 2007). Those sources provided important background to support the development of these Guidelines.

Gallagher et al. (2015) examined CRAs in case studies and issue papers (including those cited above) written by or commissioned for the EPA between 2000 and 2007 and concluded the following:

- A tiered approach can be valuable to CRA because it focuses resources on the most important factors in a CRA.
- The spatial scale of a CRA influences data needs, model choice, and the utility of the information for comparing risk management options.
- Consideration of population vulnerabilities is necessary.
- Early and regular communication with stakeholders is important.
- The use of iterative processes (e.g., continued reexamination of assessment goals, verifying that

[46] The Pesticide CRA Framework is an extension of two prior documents: *Guidance for Identifying Pesticide Chemicals and Other Substances That have a Common Mechanism of Toxicity* (U.S. EPA, 1999) and *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity* (U.S. EPA, 2002a).
[47] A common mode of action is a CRA requirement of the Food Quality Protection Act but not for other EPA programs.

the necessary data and methods are available) is beneficial to the CRA process.

The EPA presented a CRA series of 15 public webinars between August 2012 and December 2013, featuring EPA grant awardees and other scientists studying CRA methods. A list of topics and recordings of the webinars is available in the EPA's archive (U.S. EPA, 2020b). The summary of conclusions from the webinar series (U.S. EPA, 2014a) provides useful perspective when planning a CRA. These conclusions include:

- Complexity of Vulnerability and Nonchemical Stressors. Extensive studies show associations between disadvantaged communities and suboptimal health. Examination of how to include social stressors in CRA has led to epidemiological studies receiving greater emphasis in CRA as an approach to assessing the relative contribution of different stressors and potential interactions between chemical and social stressors.

- Epidemiological Methods, Effect Modifiers, and Dose-Response Curves. Evidence continues to emerge that social conditions can amplify the effect of environmental agents on health and can contribute to health disparities. These social conditions can be incorporated quantitatively in CRA as effect modifiers in the dose-response assessment if data exist to support the relationship.

- Statistical Models. CRA at community levels is challenged by the limited availability of relevant exposure and health data at the appropriate geographic scale. Statistical models can be useful tools for evaluating cumulative exposures and risks. An example is a regression model based on National Health and Nutrition Examination Survey (NHANES) biomonitoring data that could predict the effect of exposures on common health endpoints in communities.

- Mapping and Screening for Cumulative Burden (Indices). Geographic information system mapping of multiple pollution sources overlaid with demographics information that incorporates indicators of population vulnerability and nonchemical stressors can help identify vulnerable populations that also have high environmental hazard burdens. Visualization of areas of overlap can be useful in planning a CRA. Mapping approaches for cumulative burden have been used as a proxy for cumulative impacts, identifying overburdened populations and helping to prioritize areas for further analysis.

- Legal/Decision Frameworks. Risk assessors have expressed concern that CRA requires considering every possible stressor in the assessment. Concerns about the limitations of statutory authority for the use of CRA in decision-making also exist. Statutes may impose a general provision on the Agency to "protect human health and the environment," which could support the use of cumulative risk in a decision. For this, the EPA should be able to demonstrate that (1) its CRA approach and its use of the results are scientifically reasonable (appropriate use of data and assumptions) and (2) the Agency considered all factors the statute requires.

- Differing Meanings of CRA/Use of Terms (Impacts, Risks, Levels, Effects). Participants in the discussion observed many and divergent understandings of "cumulative." The insight gained is that a cumulative assessment need not necessarily provide a bright line for risk or a single number. "Cumulative" can be described in multiple ways—as impacts, levels, risks, and effects, both quantitatively and qualitatively, and on different spatial and temporal scales—and all are useful for informing different decisions.

The National Research Council (NRC) helped shape risk assessment policy at the EPA, beginning with the seminal 1983 publication, *Risk Assessment in the Federal Government: Managing the Process* (NRC, 1983), widely known as the "Red Book" in the risk assessment community, that led to formalization of the EPA's use of risk assessment to underpin risk management supporting regulations. Before the Red Book, NRC took on the challenge of characterizing *Principles of Toxicological Interactions Associated*

with Multiple Chemical Exposures in 1980 for the U.S. Coast Guard, where there was concern for marine inspectors exposed to multiple different chemicals during their workdays. This NRC report laid out the basis for CRA with an examination of "the mechanisms of toxicological interactions in terms of the toxicokinetic and toxicodynamic factors that are involved" (NRC, 1980). The study of "sites and mechanisms at which and through which toxicological interactions can occur" (NRC, 1980) dominated NRC's inquiries into risk assessment through its publication of *Toxicity Testing in the 21st Century* (NRC, 2007). In 2008, NRC examined a specific class of chemicals in *Phthalates and Cumulative Risk Assessment: The Tasks Ahead* (NRC, 2008a). NRC examined the utility of a CRA for phthalates and made recommendations for how a CRA could be undertaken. In 2009, with publication of *Science and Decisions*, NRC enhanced the visibility of public health perspectives, following the observation that:

> …there is increasing concern among stakeholder groups… that such a narrow (individual chemical) focus does not accurately capture the risks associated with exposure, given simultaneous exposure to multiple chemical and nonchemical stressors and other factors that could influence vulnerability.

NRC further inquired about the limitations of mechanistic toxicology and concluded that "Without additional modifications, risk assessment might become irrelevant in many decision contexts, and its application might exacerbate the credibility and communication gaps between risk assessors and stakeholders" (NRC, 2009). NRC then noted key differences between the CRA paradigm and traditional human health risk assessments:

- CRA is not necessarily quantitative.
- CRA extends beyond chemicals to include psychosocial, physical, and other factors.

In *Sustainability and the U.S. EPA,* NRC acknowledged that the limitations of risk assessment to adequately approach complex issues such as characterizing sustainability:

> …has led to approaches to widen the risk paradigm, to include the context in which the analysis is performed, the early consideration of a broad range of decision options, and the cumulative threats of multiple social, environmental, and economic stressors to health and the environment (NRC, 2011b).

NRC has asserted that standard risk-based regulatory approaches have limitations. Limitations include difficulty in dealing with complex problems that are not readily addressed by analyses that seek to "simplify the multidimensionality of the risk or make sense of the uncertainty" (NRC, 1996) or that require a volume of information and analyses that far outstrip the resources available to provide them (NRC, 2006). NRC has stated that CRA provides the EPA with a "broader and more comprehensive understanding of the complex interactions between chemicals, humans, and the environment" (NRC, 2012). NRC has asserted throughout numerous publications addressing risk management and environmental decision-making that CRA should be implemented in a way that is responsive to community needs and extends beyond chemical toxicology to incorporate psychosocial, physical, and other factors. NRC's observation is consistent with the assertions of environmental justice advocates who encourage the EPA to recognize the need for more comprehensive assessments in communities burdened by elevated levels of multiple environmental stressors from multiple sources, where populations could be at risk because they are highly exposed to numerous environmental as well as psychosocial stressors. These populations might be more vulnerable to such stressors due to other socioeconomic conditions (NEJAC, 2004).[48]

[48] These communities are sometimes called "environmental justice communities." Environmental justice advocates have focused attention on the need for increased understanding of population vulnerabilities and increased stakeholder involvement in the risk assessment process.

NRC's evolving perspective on risk assessment mirrors the EPA's progress in development of the CRA Guidelines. A conundrum is created when the need to keep risk assessment relevant to public and environmental health realities requires a broader inquiry that includes qualitative factors not easily incorporated into the risk assessment paradigm. This challenge is resolved in part through characterizing the different types of information needed to meet various purposes served by different types of assessments. The extent and scope of quantitative analyses in an assessment will vary depending on the objectives of a management decision. For example, establishing pollutant release limits generally requires quantitative analysis but may benefit from information that is not easily quantifiable or traditionally part of the risk management paradigm. The 2003 Framework for CRA recognized the utility of nonquantitative information; accordingly, these Guidelines provide for the consideration of such information within the constraints of the risk management decision.

A.2. Examples of CRA at the EPA

EPA programs have pioneered CRA applications. Past use of CRA at the EPA offers examples of when a CRA can be useful.[49] The Office of Water/Office of Ground Water and Drinking Water in conjunction with the Office of Research and Development undertook the cumulative assessment of drinking water disinfection by-products (DBPs) that identified potential adverse outcomes (U.S. EPA, 2000a). DBPs are classes of chemicals that can form during the treatment of drinking water and could present human health risks for developmental and reproductive effects and cancer. The assessment supported development of the Stage 1 and Stage 2 rules regulating disinfectant/disinfection by-products using an approach to CRA in which DBPs with a common response were summed to establish acceptable exposure levels. The approach developed for conducting such assessments was to construct physiologically based pharmacokinetic (PBPK) models to estimate internal dose from exposure to two classes of DBPs (Simmons et al., 2004; Teuschler et al., 2004).

The EPA's Office of Land and Emergency Management and regional risk assessors routinely conduct site-specific human and ecological risk assessments under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA), also known as "Superfund," as amended by the Superfund Amendments and Reauthorization Act (SARA), the Resource Conservation and Recovery Act, and other statutory authorities. The site-specific risk assessments generally consider elements of cumulative risk when evaluating exposure, calculating risk, and performing risk characterization. Exposure assessments typically quantify all possible routes reasonably expected to occur at a site. The Superfund risk assessments are based on an estimate of the reasonable maximum exposure (RME) expected to occur under both current and future land-use conditions consistent with the EPA's *Risk Assessment Guidance for Superfund* (RAGS), published in several specific guidance documents.[50] The RME is defined as the highest exposure that is reasonably expected to occur at a site. RMEs are estimated for each exposure pathway. If a population is exposed via more than one pathway, the combination of exposures across pathways also should represent an RME. The exposure assessment considers all RME individuals who may be exposed now or in the future, including residents, workers, trespassers, and others depending on the nature of contamination at the Superfund site and potential exposures. RME assessments for the RME individual use a combination of upper-bound and central tendency estimates of exposure parameter values for both an adult and a child. The combination of parameter estimates is designed to be protective of the RME individuals exposed at the site. For screening and related efforts, the most sensitive receptor typically is chosen, and cultural and lifestyle-specific exposures are considered when indicated. The dose-response relationship(s) of chemicals present in mixtures might be evaluated using hazard index or relative potency methods and cancer risks from exposures to site-related multiple chemicals and multiple

[49] *EPA Legal Tools to Advance Environmental Justice: Cumulative Impacts Addendum* (U.S. EPA, 2023b) is a compilation of legal authorities available to the EPA for identifying and addressing cumulative impacts and cumulative risks on communities with environmental justice concerns and other underserved populations.

[50] See the EPA's Risk Assessment Guidance for Superfund (RAGS): Part A web page (https://www.epa.gov/risk/risk-assessment-guidance-superfund-rags-part).

pathways. OLEM generally does not consider the impact of nonchemical stressors in human health risk assessment (radiological risks are an exception); ecological risk assessments, however, do occasionally consider nonchemical stressors (e.g., habitat impairment).

Within the EPA's Office of Chemical Safety and Pollution Prevention, the Office of Pesticide Programs (OPP) has conducted CRAs for pesticides with a common mechanism of toxicity, as stipulated by the Food Quality Protection Act of 1996 (FQPA). The first pesticide group for which OPP conducted a CRA was the organophosphate (OP) pesticides group. Variations in toxicity among OP pesticides were considered by assigning each pesticide in the group a relative potency factor, relative to an index OP. Using a similar methodology, OPP also completed CRAs for triazines, chloroacetanilides, pyrethroids, and *N*-methyl carbamates using established OPP cumulative guidance. These guidance documents and OPP's experience with conduct of CRAs on pesticide groups were used to develop *Pesticide Cumulative Risk Assessment: Framework for Screening Analysis* (U.S. EPA, 2016b), discussed above.

The EPA's Office of Air and Radiation (OAR) uses CRA to support decisions in the regulation of hazardous air pollutants (HAPs) and in reviews of some National Ambient Air Quality Standards (NAAQS). For example, in the HAP program, cumulative assessments of cancer risk and noncancer hazard associated with exposures to multiple HAPs emitted from stationary emission sources inform regulatory decisions on source category-specific emission standards for HAPs (also called air toxics). Cumulative cancer risk is estimated as the sum of all individual HAP cancer risk estimates. For assessment of cumulative noncancer hazard, target organ-specific hazard indices are estimated. OAR's nonregulatory Annual Air Toxics Update, performed to inform programmatic priorities, does the same for multiple stationary and mobile sources of HAPs. Additionally, CRAs have been performed to inform decisions on some of the individual NAAQS. The NAAQS, as single pollutant-based standards for ambient air, reflect consideration of the cumulative concentrations of various precursor or constituent chemicals in ambient air, which result from emissions from many sources. In the case of risk assessments for fine particulate matter, the assessment is of the whole mixture of fine particulate matter and reflects cumulative health risk associated with all particulate substances in ambient air that fall into the particle size class of interest. Cumulative ecological risk assessment has also been performed to inform NAAQS decisions (e.g., in assessing ecological risk associated with the co-occurrence in ambient air of multiple oxides of sulfur and nitrogen).

A.3. Looking Ahead toward CRA Advances

Advances in CRA methodologies are occurring primarily in two areas: (1) adverse outcome pathways and common mode of action and (2) the combined effects of chemical and nonchemical stressors (Fox et al., 2017).

The first area of advancement is in assessing the effects of chemical mixtures that share common modes of action or that cause common adverse outcomes. In this area, two primary models are used for predicting effects from exposure to mixtures of chemicals: dose addition and response addition (NRC, 1993, 2008a; U.S. EPA, 1986b, 2000d, 2002a, 2003a, 2023a). The EPA updated and provided detailed models for examining additivity of chemical mixtures in *Advances in Dose Addition for Chemical Mixtures: A White Paper* (U.S. EPA, 2023a). The second area of advancement in CRA methods is in evaluating the combined effects of chemical and nonchemical stressors (NRC, 2009; U.S. EPA, 1997c; 2003b). Methods for evaluating the combined effects of chemical and nonchemical stressors have been proposed, and approaches are being developed (Barrett & Padula, 2019; Hibbert & Tulve, 2019; Payne-Sturges et al., 2018; Varshavsky et al., 2023). A particular challenge is how to incorporate mechanistic and mode of action information for the combination of chemical and nonchemical stressors that impact communities and associated uncertainties, as well as the evaluation of differential vulnerability. The EPA stated it will "Increase understanding of the factors that influence environmental health disparities, and develop methods and data to assess adverse and cumulative risks" to strengthen the scientific foundation for considering the factors important to incorporating environmental justice in decision-making (U.S.

EPA, 2016a). As scientific innovation advances with new analytical methods, a corresponding growth occurs in the types and complexity of cumulative assessment problems that can be analyzed. The use of new approach methods,[51] such as high-throughput screening systems and global gene-expression analysis, in assessing cumulative risk brings substantial new methodological capacity to CRA and broadens its potential application. *Using 21st Century Science to Improve Risk-Related Evaluations* (NASEM, 2017) described how these methods are developing rapidly. The EPA's development and implementation of such methods are in part described in the *Chemical Safety for Sustainability Strategic Research Action Plan* (U.S. EPA, 2022b) and *List of Alternative Test Methods and Strategies (or New Approach Methodologies)* (U.S. EPA, 2021b). These Guidelines anticipate the evolution of CRA analysis methods to include an ever wider range of possible stressors and exposure-response modifiers.

[51] In a risk assessment context, new approach methods (NAMs) are defined as any technology, methodology, approach, or combination thereof that can provide information useful for risk assessment (including hazard assessment, dose-response assessment, and exposure assessment) without the use of traditional test animals (e.g., rats, mice), including in silico, in chemico, in vitro, and ex vivo approaches.

APPENDIX B. CUMULATIVE RISK ASSESSMENT FOUNDATIONAL DOCUMENTS

Table B-1 provides a list of EPA publications that are foundational to the evolution of the field of cumulative risk assessment (CRA) planning and problem formulation in chronological order and a brief description of their relevance. Table B-2 serves the same function but highlights foundational publications from the National Research Council (NRC) and other non-EPA sources.

Table B-1. EPA Publications Relevant to Cumulative Risk Assessment Planning and Problem Formulation[a]

EPA Publication	Relevance to CRA Planning and Problem Formulation
Guidelines for the Health Risk Assessment of Chemical Mixtures (U.S. EPA, 1986b)	Indicates scoping inputs from internal and external inputs, describes problem (significant data gaps), terminology, and conceptual approach for addressing gaps to support decision needs.
Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures (U.S. EPA, 2000d)	Builds on previous context, identifying data requirements: mixture of concern, similar mixture, components.
Conducting a Risk Assessment of Mixtures of Disinfection By-Products (DBPs) for Drinking Water Treatment Systems (U.S. EPA, 2000a)	Includes scoping and problem formulation by scientific experts, including assessing the state of toxicity and exposure data, conducting an initial example assessment to guide the more detailed follow-on, and gaining inputs and insights via a targeted workshop.
Risk Assessment for Superfund Sites (RAGS) (U.S. EPA, 1989)	Oriented to CERCLA requirements, focusing on environmental contaminants (notably chemicals and radionuclides); reflects the National Contingency Plan, which includes distinct stakeholder involvement requirements; describes project scoping process and remedial investigation/feasibility study goal (of which baseline health risk assessment is a part), project planning, conceptual model, and data quality; outlines a tiered approach from initial screening to more detailed assessment. Superfund Guidance is available at: https://www.epa.gov/risk/risk-assessment-guidance-superfund-rags-part .
Guidelines for Ecological Risk Assessment (U.S. EPA, 1998a)	First EPA report to articulate problem formulation—what is at risk, what needs to be protected—as one of three main phases, the other two being analysis (exposure and toxicity) and risk characterization; emphasizes conceptual model and iterating throughout the process; outlines stressor identification, including ways to think about nonchemical stressors.
Guidance on Cumulative Risk Assessment. Part 1. Planning and Scoping (U.S. EPA, 1997a, 1997c)	Encourages early and continued planning and scoping; describes process for engaging stakeholders and others, including experts; urges identifying these at the outset: overall purpose and risk management objectives, scope, participants and roles, resources, conceptual model, analysis plan.
Lessons Learned on Planning and Scoping for Environmental Risk Assessments (U.S. EPA, 2002b)	Uses examples to reinforce importance of formal planning and dialogue from outset; conceptual models help outline stressor-effect relationships, program-regulatory activities; encourages considering same sources.
General Principles for Performing Aggregate Exposure and Risk Assessments (U.S. EPA, 2001a)	Oriented to FQPA requirements; identifies scope as overall framework and principles focusing on exposure to a single chemical by multiple pathways and routes; places emphasis on quality evaluations of available data from multiple sources.
Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity (U.S. EPA, 2002a)	Oriented to FQPA requirements, pesticides with a common mechanism of toxicity; emphasizes importance of determining need for/capability to perform a CRA at outset and identifying CRA objectives; notes that not all CRAs need be of the same depth and scope; considers both screening-level and refined or detailed assessments.
Framework for Cumulative Risk Assessment (U.S. EPA, 2003b)	Flexible structure to anchor program-specific guidance; identifies CRA components, terms, technical and coordination issues, with planning and scoping as a key early step to gain consensus on CRA goals; includes principles for stakeholder involvement.

EPA Publication	Relevance to CRA Planning and Problem Formulation
A Framework for Assessing Health Risk of Environmental Exposures to Children (U.S. EPA, 2006c)	Examines the impact of potential exposure to stressors during developmental lifestages and subsequent lifestages while emphasizing the iterative nature of the analysis phase with a multidisciplinary team; outlines the framework in which mode of action(s) (MOAs) can be considered across lifestages; is based on existing approaches adopted in the Framework on Cumulative Risk Assessment and identifies existing guidance, guidelines, and policy papers that relate to children's health risk assessment emphasizes the importance of an iterative approach between hazard, dose response, and exposure analyses; includes discussion of principles for weight-of-evidence consideration across lifestages for the hazard characterization database.
Concepts, Methods, and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects (U.S. EPA, 2007a)	Emphasizes early planning and scoping, decision-focused stakeholder involvement; problem formulation and conceptual model; introduces initiating factors to determine whether CRA is appropriate, what key data are needed; addresses data quality.
Framework for Human Health Risk Assessment to Inform Decision Making (U.S. EPA, 2014b)	Clarifies the many decisions needed in this step, the risk management focus, and stakeholder involvement; aggregates exposure issues and some toxicity issues such as influence of population characteristics.
Pesticide Cumulative Risk Assessment: Framework for Screening Analysis (U.S. EPA, 2016b)	Provides guidance on how to screen groups of pesticides for cumulative evaluation using a two-step approach, beginning with the evaluation of available toxicological information and, if necessary, followed by a risk-based screening approach; an example of tiering, the incremental approach to determining which level of effort is required to assess risks cost effectively.

[a]Acronyms: CERCLA = Comprehensive Environmental Response, Compensation, and Liability Act, as amended; FQPA = Food Quality Protection Act of 1996.

Guidelines for the Health Risk Assessment of Chemical Mixtures (U.S. EPA, 1986b, 2000d)
The 1986 mixture risk guidelines are notable for their brevity (25 pages), as the detailed procedures were intentionally left to the EPA's program offices to address legislation-specific guidance. (Note that the Superfund guidance summarized in the document's Section 1.4.1.4 was the earliest and most extensive program guidance that addressed mixtures). The 1986 mixture guidelines included some general concepts of dose and response addition, and they recommended the dose-additive hazard index (HI) for assessing the potential for noncancer effects and response addition for estimating cancer risk. These guidelines also identified cautions about potential impacts of missing information, including toxicological interactions.

The 2000 supplement greatly expands on those concepts and methods, primarily regarding dose-response assessment, introducing the interaction-based HI as a way to incorporate known toxicological interactions quantitatively. The most important contribution of both documents to CRA is the encouragement to account for toxicological interactions among chemicals (including a default five-fold interaction magnitude when specific data are absent), to use qualitative or subjective analyses when necessary (e.g., the weight-of-evidence scheme for interactions, the quality scores for data on exposure, toxicity, and interactions) and to prefer the use of scenario-specific information (e.g., exposure and toxicity information on the mixture of concern instead of its component chemicals).

The 2000 supplement extensively discussed concepts and terminology, including several applications of dose addition based on the available information, including toxicity equivalence factors, relative potency factors, and HI. These documents led to the adoption of dose addition as the primary default approach for mixtures of chemicals causing similar effects, promoting Agency-wide consistency of the approach's use when interaction data are absent. Another program-specific application published that year is the report on drinking water disinfection by-product (DBP) mixtures (U.S. EPA, 2000a), which applied and extended the potency factor approach to a cumulative relative potency factor to integrate data on mode of action and multiroute exposures over physiologically relevant time frames.

Risk Assessment Guidance for Superfund (RAGS) (U.S. EPA, 1989)
The EPA's Superfund office developed a set of guidance documents for human and ecological risk assessments at waste sites on the National Priorities List to address the mandate of the 1980 Comprehensive, Environmental Response, Compensation, and Liability Act (CERCLA), as amended by the 1986 Superfund legislation. This suite of documents has been adopted for many other applications, including operational facilities. Tiering is a key concept of RAGS, with analyses ranging from screening level to detailed, depending on the operable units addressed and needs of a given decision. The initial guidance focused on human health, and subsequent documents have added concepts and approaches to the portfolio of available methods (e.g., ecological, dermal exposures, toxicity value selection, inhalation).

The conceptual model is a central element of the RAGS exposure assessment, with direct and indirect exposures considered across multiple pathways involving multiple chemicals (including radionuclides). Environmental fate, such as partitioning and transformation over time, can be very important, depending on the nature of the contaminants (e.g., volatile compounds versus metals). Per supplemental guidance (U.S. EPA, 2002a), the concentration term typically reflects the 95% upper confidence limit of the arithmetic average based on existing measurements, with modeling conducted to predict future concentrations as indicated by the scenarios being assessed.

The RAGS approach for developing preliminary remediation goals (U.S. EPA, 1991b) considers multiple chemicals in multiple media and generally uses default assumptions to assess several standard exposure scenarios (including hypothetical residential use). A subsequent RAGS document (Part E), released in 2004 (U.S. EPA, 2004b), addressed dermal exposures to contaminants in soil, sediment, and water. This document addresses a relatively limited set of organic compounds (those with dermal absorption fractions exceeding a threshold level), considers the cumulative amount available over a time profile to support permeability coefficients, and calls for using gastrointestinal absorption data to adjust for systemic toxicity when dermal data are unavailable. The original RAGS approach for assessing joint toxicity of multiple chemicals reflected the method outlined in the 1986 mixtures guidelines, with the HI approach used to assess the potential for noncancer effects and response addition applied for cancer risk. This approach was subsequently updated electronically to incorporate the mixtures supplement (U.S. EPA, 2000d). Pathway-specific risks and/or HIs are summed to produce combined risk and combined HI estimates for each scenario. If the combined HI exceeds the target level of one, it is commonly segregated by endpoint to address organ- or system-specific differences. Risk assessments conducted for these cleanup sites (and other applications that follow RAGS) typically use reference values developed by the EPA in accordance with several toxicity guidelines, notably for mutagenic (U.S. EPA, 1986a), developmental (U.S. EPA, 1991a), reproductive (U.S. EPA, 1996b), and neurotoxic endpoints (U.S. EPA, 1998b), as well as for cancer (U.S. EPA, 2005).

Other RAGS documents have further expanded the scope of tools for assessing disparate risk, including the 2001 guidance for probabilistic risk assessment that focuses on Monte Carlo approaches to quantify variability and uncertainty in risk estimates (although not specific to CRAs) and the supplemental guidance (U.S. EPA, 2001c) for assessing health risk from inhalation exposures. The latter explicitly discusses estimating aggregate and cumulative risk for multiple chemicals and exposure routes, noting the importance of indicating whether the assumption of independent action underlying the default additive approach is valid (i.e., "no synergistic or antagonistic interactions and all chemicals produce the same effect, i.e., cancer"). Further, this document introduces an approach for considering different exposure periods—acute, subchronic, and chronic—indicating that in general (1) hazard estimates from multiple acute events should be summed only when the exposures occur simultaneously; (2) when a series of acute events occur, the highest single exposure concentration should be compared with the relevant reference value; (3) distinct HIs should be calculated for each exposure period; and (4) if the HI exceeds the threshold level, the assessor should segregate it by target organ. These guidelines also explicitly call for placing susceptibilities in context within the risk characterization section; receptor characteristics such as

age, disease, sex, and genetic characteristics are included, and two examples are discussed (children and workers).

Standard default exposure assumptions are provided on the following web page: https://www.epa.gov/risk/update-standard-default-exposure-factors.

In addition, Superfund risk assessment guidance is available at: https://www.epa.gov/risk/risk-assessment-guidance-superfund-rags-part.

Guidelines for Ecological Risk Assessment (U.S. EPA, 1998a)
The 1998 EPA ecological risk guidelines and two related documents—the 1997 ecological risk guidance for Superfund (U.S. EPA, 1997b) and the stressor identification guidance from 2000 (U.S. EPA, 2000c)—provide much of the basis for CRA by addressing combinations of dissimilar stressors over varying time frames and with multiple measurable endpoints for adverse impacts. The guidelines also articulated a three-phased structure for risk assessment: problem formulation, analysis, and risk characterization (shown in Figure 1-1 of the 1998 EPA ecological risk guidelines), and they highlight the importance of involvement by risk managers in the risk assessment process. To accommodate data of widely differing quality and type, the ecological risk methods allow for both qualitative and quantitative analyses and characterizations. Problem formulation in particular is emphasized, as is the need for iterating throughout the assessment process. "Successful completion of problem formulation depends on the quality of three products: assessment endpoints, conceptual models, and an analysis plan. Because problem formulation is an interactive, nonlinear process, substantial reevaluation is expected to occur during the development of all problem formulation products..." (U.S. EPA, 1998b). With details provided for construction of conceptual models and specific guidance on stressor identification, these three documents address many of the difficult areas of cumulative risk analysis and provide a valuable foundation upon which CRA methods can be developed for human health risk as well as for joint impacts on health and ecosystems.

CRA Planning and Scoping (U.S. EPA, 1997c, 2002b)
Two documents, the 1997 *Guidance on Cumulative Risk Assessment, Part 1, Planning and Scoping* and the 2002 *Lessons Learned on Planning and Scoping for Environmental Risk Assessments*, focus on the initial steps in the CRA process. The first brief guidance is designed to raise awareness and promote dialogue on CRAs, and it describes a process for engaging assessors, managers, and stakeholders. The intent is to help assessors and managers plan and document the scope of a given CRA and consider appropriate participants and their roles (technical, advisory, or stakeholder, as determined by the risk manager), as well as information sources. It considers multiple stressors or agents, multiple sources, media, pathways, routes of exposure, and multiple endpoints. Emphasis is placed on community-based decision-making, flexibility in achieving goals, case-specific responses or approaches, and holistic reduction of risk. While acknowledging data limitations, this initial guidance focused on integrating human health and ecological effects from synthetic chemicals, radiation, and biological stressors in the environment, with a longer-term plan to address further issues.

Additional concerns related to social, economic, behavioral, or psychological stressors are mentioned, but because relevant data on psychosocial influences were limited, the focus is on the other stressors. Vulnerable populations are emphasized, notably children and sex-related differences in both vulnerability and exposure. A key theme is involving stakeholders and others (including economists and other social scientists) in planning and scoping and throughout the risk assessment and risk management process (e.g., to provide input to the decision-maker(s)). The aim is for technical experts and management to work as a team, informed by stakeholder input, beginning with early planning and scoping. Such a coordinated process would increase the likelihood of the analysis addressing the risk management needs and the risk managers understanding the strengths and limitations of the analysis.

The integration of environmental risks includes dialogue on the given assessment, definition of the main CRA term(s), products needed to make a risk decision, tentative budget and schedule, and planned approach. Implementation tasks include:

- Define purpose and management objectives
- Determine scope, problem statement, participants, and resources for the CRA
- Identify questions to answer, technical approach, conceptual model, and plan
- Outline six risk dimensions: sources (point, nonpoint, natural), stressors, pathways and exposure routes, population(s) (human, ecological, landscape/geography), endpoints (human, ecological), time frames (acute, chronic, subchronic, intermittent)

The second report supplements the 1997 *Guidance on Cumulative Risk Assessment, Part 1* document, using case studies to illustrate organizing principles for identifying participants, bounding the problem, developing a conceptual model, and planning the analysis for a CRA. It aims to reinforce the importance of formal planning and dialogue prior to conducting complex cumulative assessments and to provide case study "lessons learned" for those planning an assessment. Case studies included pesticide registration, water permit conditions for a concentrated animal feeding operation, a citizen petition-based cumulative risk initiative under the Toxic Substances Control Act, EPA's National Air Toxics Assessment for national screening of hazardous organics in urban air, and a screening-level surface impoundment study for cumulative risk from hazardous constituents in wastewater treatment ponds. This report shows that (1) early stakeholder input can help focus the analysis and improve confidence in the decision-making process, and (2) planning and scoping help ensure the CRA better informs a risk manager's decisions. The other findings emphasized communication, notably:

- Involving the decision-maker (e.g., risk manager) throughout the process helps ensure that the products will meet the decision needs.
- Involving stakeholders at the beginning helps identify public health endpoints to study.
- Providing a clear set of definitions of key terms facilitates consensus.
- Obtaining clear, objective resource commitments and estimated schedules from risk managers contributes to identifying the scope and detail of an assessment.
- Having conceptual models helps identify relationships between stressors-effects and programs-regulatory activities.
- Explaining the uncertainties is important to build trust, credibility, and support for the decision-making process.

Multi-pathway Combustor Emissions (U.S. EPA, 1998c)
This methodology document updates previous reports on indirect exposures to chemicals in incinerator emissions. It is intended to apply to aggregate (direct and indirect) exposures "resulting from atmospheric pollutants that are emitted from a stationary combustion source, transferred through the atmosphere, and deposited downwind to environmental media and biota." Because direct exposure data for all pathways are rarely available, the document discusses the use of data and models to estimate uptake and transfer of atmospheric agents through the terrestrial or aquatic food chains. Aggregate exposures could occur through many routes, including inhalation; ingestion (e.g., of tap water, produce, livestock, fish, and breast milk); and dermal contact with soil and water contaminated by aerial deposition. Most of this report presents mathematical models for estimating average daily route-specific exposures. Combinations across pathways and routes are estimated by summing the absorbed daily doses or by summing the oral equivalent daily doses. Cross-route conversion is identified as an uncertainty and recommended only for dermal-to-oral exposures and only under certain conditions.

This document is one of the first EPA methodology reports to incorporate different factors for children versus adults to estimate daily intake. The final chapter (Risk Assessment) presents several advances relevant to cumulative risk. One is the recommendation to align the dose-response data with the exposure

duration being addressed, including using mixture dose-response data when appropriate. A second is to recognize the likelihood of multiple sources, not just incinerators, and multiple chemicals, so that "cumulative exposure" is defined as the total exposure (single chemical or multiple stressors, including nonchemical pollutants) resulting from all sources through multiple routes over the interval of interest. Finally, this report emphasizes the additional uncertainties associated with multi-pathway exposures, including the possible interactions in exposure (one chemical affects the fate and transport of another) and uptake (two chemicals compete for the same metabolic pathway or toxicodynamic process). Considerable attention is paid to various methods of characterizing variability and uncertainty. Because this report is not an Agency-wide or program-specific guidance per se, it has had limited application beyond combustor emissions. Nevertheless, its impact on cumulative risk methods has been significant.

Cumulative Risk Assessment of Pesticide Chemicals (U.S. EPA, 2001a, 2002a)
In response to the Food Quality Protection Act (FQPA) of 1996, the Office of Pesticide Programs (OPP) began conducting CRAs to evaluate potential human health risks arising from combined exposures to pesticides in classes that act through a common mechanism of toxicity. The primary methods are presented in OPP's *Guidance for Identifying Pesticide Chemicals and Other Substances That Have a Common Mechanism of Toxicity* (U.S. EPA, 1999)*, General Principles for Performing Aggregate Exposure and Risk Assessments* (U.S. EPA, 2001a), and *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity* (U.S. EPA, 2002a). The major contribution to cumulative risk methods concerns the extreme detail and care in addressing multi-pathway exposure. Methods are also presented for combining inputs across multiple data types that have varying quality and different metrics. For example, using monitoring data along with both probabilistic and deterministic models, the exposure estimates reflect combined exposure pathways and routes separated by time, geographic scale, and populations of concern. The methods used for toxicity or dose-response assessments are not much changed from previous EPA approaches; they involve calculating relative potency factors and determining risk by dose addition (the total margin of exposure used with pesticides is conceptually similar to the HI).

These extensive and detailed guidance documents articulate several additional important methodological changes relevant to CRA. The determination regarding which pesticides constitute a common mechanism group is an important toxicological advance. The dose-response assessment considers a single uncertainty factor for the chemical group instead of multiple uncertainty factors for the individual chemicals in that group, reducing the potential for a poorly studied chemical (with a very large uncertainty factor) to drive the calculation of the mixture risk. The potential application of a 10-fold safety factor for children (a potentially vulnerable population) is a consideration specifically identified in the FQPA. These methods have been applied to several pesticide classes, providing valuable examples of CRAs derived from complex information resources.

Framework for Cumulative Risk Assessment (U.S. EPA, 2003b)
This flexible framework defines a general structure and components for a CRA, laying out three basic phases of the process (shown in Figure 1–3 of the framework): (1) planning, scoping, and problem formulation; (2) analysis; and (3) risk characterization. It also describes several technical and coordination issues and defines many terms relevant to CRA. In addition, the framework suggests some analytical methods, techniques for analyzing and interpreting data, and other options and tools for carrying out a full CRA. The steps outlined in this CRA Framework are consistent with those of the ecological risk guidelines. While the first phase is expanded to include planning, scoping, and problem formulation, the description is similar to the problem formulation step in the ecological risk guidelines but includes additional detail.

Concepts, Methods, and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document (U.S. EPA, 2007a)
This report is designed as a resource for the EPA and other organizations to use in identifying elements of and implementing CRAs. It focuses on two areas: (1) concepts concerning CRA initiating factors, along with procedures for data collection and organization; and (2) technical approaches for assessing and characterizing health risks associated with a subset of cumulative risk issues (multiple chemicals, exposures, effects), with examples pertaining to contaminated sites, drinking water, and ambient air. Some of the emphasis areas and innovations proposed in this document include:

- Developing a description of CRA initiating factors and procedures for population characterization, data collection, and organization based on these factors.
- Implementing chemical grouping as a potentially helpful way to scope analyses into manageable pieces to be assessed as chemical mixtures with co-occurring exposures.
- Indicating approaches and data sources for evaluating the timing of exposures, including discussions of kinetics and dynamics.
- Integrating internal dose measurements to account for multiple-route exposures.
- Further developing the quantitative method for the interaction-based HI, first introduced in the EPA's 2000 mixtures guidance document.
- Extending the relative potency factor method to cumulate across exposure routes, an approach first presented in the report on drinking water disinfection by-product (DBP) mixtures.
- Integrating outputs from multiple-effects modeling (illustrated using a categorical regression model) with the HI and response-addition models to express risks.
- Providing added detail on the cumulative HI approach used by the Superfund Program, including discussions of the impacts for risk characterization.
- Presenting a method for cumulative risk characterization that considers factors unique to the conduct of a CRA, including the recognition of uncertainties in cumulative dose-response and exposure assessment.
- Generally emphasizing close integration of exposure and dose-response analysis, a recommendation presented in earlier EPA reports, including the methods document on combustor emissions.

This report showed that resources exist for performing some types of CRAs. One important section considers how to decide whether a CRA is needed; a table is included that compares CRA with classic single-chemical, source-based risk assessment. In addition to an extensive glossary, this report also includes multiple tables and figures to explain and illustrate various concepts and issues and an appendix (toolbox) with tables and internet links of informational resources covering key aspects of a CRA, including environmental and health data, predictive modeling and analysis methods, and risk communication techniques.

Framework for Human Health Risk Assessment to Inform Decision Making (U.S. EPA, 2014b)
The goal of this report is to disseminate information to EPA staff and managers, external stakeholders, and the public on the general process for conducting human health risk assessments. As such, it focuses on the context, utility, and planning for risk assessment rather than on providing details for conducting the assessment. With this orientation, it identifies CRA as an overarching EPA interest and notes that "combining" does not necessarily mean the risks being assessed should be added; rather, it indicates that some analysis should be conducted to determine how those risks from various agents or stressors interact. This report highlights two main points from the 2003 CRA Framework (see Sections 1.4.1.7 and 1.2.1). The first is the importance of planning, scoping, and problem formulation in designing a risk assessment that will address a specific need and purpose, which means that the characteristics of a given assessment will depend on the specific scientific needs and risk management decisions being addressed, which might not necessarily require a quantitative assessment of cumulative risks. The second point is the importance

of involving the public, especially stakeholders and the community being assessed. This involvement is emphasized as a key element of risk assessment and an integral part of CRA and environmental justice actions. Some specifics about the CRA process are contained in the section on planning and scoping, mainly summarizing concepts presented in the 2003 CRA Framework. The report also identifies examples of different CRAs for different situations, with links to several EPA reports related to aggregate (multi-pathway) risks and cumulative risk (including many reports summarized in this appendix).

Pesticide Cumulative Risk Assessment: Framework for Screening Analysis Purpose (U.S. EPA, 2016b)

This guidance was developed to assist scientists and decision-makers in screening pesticides for potential common mechanism groups (CMGs) and conducting screening-level CRAs. The document provides guidance for screening available information to identify groups of pesticides that might have a common mechanism of toxicity (candidate CMGs). This document follows up on previous guidance documents the Office of Pesticide Programs developed, including *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity* (U.S. EPA, 2002a), which describes the steps used in conducting CRA on pesticide chemicals. The 2002 CRA guidance provides methods resulting in a highly refined CRA but requires an extensive number of resources and large amounts of toxicology and exposure data and might involve sophisticated modeling. The level of refinement provided by that approach is not necessary or even feasible, however, for all existing pesticide classes. The 2002 CRA guidance notes that not all cumulative assessments need to be of the same depth and scope and that determining the need for a comprehensive risk assessment by considering the exposure profile is important.

The screening-level assessment described in this document applies more conservative approaches and health-protective overestimates of toxicity and/or exposure than would a refined CRA conducted using the 2002 CRA guidance. The screening analysis for CRA described in this guidance begins with an evaluation of the toxicological knowledgebase available.[52] If the toxicological characterization of potential for a common mechanism suggests a candidate CMG can be established, a screening-level toxicology and exposure analysis could be conducted to provide an initial screen for multiple pesticide exposure. This framework methodology was developed as an initial screening tier for pesticide CRAs and, in this respect, illustrates the tiering strategy recommended in this Guidelines document for CRA planning and problem formulation.

Table B-2. National Research Council and Other Publications Relevant to Cumulative Risk Assessment Planning and Problem Formulation

Publication	Relevance to CRA Planning and Problem Formulation
Risk Assessment in the Federal Government: Managing the Process (NRC, 1983)	Describes the four basic elements of risk assessment (hazard identification, exposure assessment, dose-response assessment, risk characterization); suggests a good risk assessment should include nonchemical factors, such as characteristics of the exposed population and other variables that might affect response.
Understanding Risk: Informing Decisions in a Democratic Society (NRC, 1996)	Emphasizes an analytical-deliberative process with problem formulation as a "paramount consideration."
Framework for Environmental Health Risk Management, Risk Assessment and Risk Management in Regulatory Decision-Making (PCCRARM, 1997)	Identifies the need to address multiple-issue situations with multisource, multimedia, multichemical, and multi-risk characteristics and the need to be sensitive to societal constraints (e.g., political, social, legal, cultural); advocates involvement of stakeholders throughout the risk assessment process and recommends development and adoption of a common metric for comparing and assessing diverse health effects.

[52] An example is a screening analysis of a particular group of pesticides that would be derived from experimental toxicology studies submitted for pesticide registration evaluation, as well as from the scientific literature.

Publication	Relevance to CRA Planning and Problem Formulation
Guidance Manual for the Assessment of Joint Toxic Action of Chemical Mixtures (ATSDR, 2004)	Presents detailed qualitative methods for evaluating toxicological interactions, including a structured weight-of-evidence approach that has spawned similar schemes for evaluating interactions between chemicals and other stressors; advocates evaluation of uncertainties, health implications of other medical and toxicological factors and sensitive populations, community-specific health outcome data, and consideration of community health concerns.
Ensuring Risk Reduction in Communities with Multiple Stressors: Environmental Justice and Cumulative Risks/Impacts (NEJAC, 2004)	Recommends a community-based collaborative problem-solving model for addressing cumulative risks and impacts and the aligning of response to community and risk assessment goals; includes case studies and lists of tools for screening and assessment.
Phthalates and Cumulative Risk Assessment. The Tasks Ahead (NRC, 2008a)	Recommends inclusion in the CRA of all chemicals with common adverse outcomes instead of limiting to chemicals grouped by mechanistic similarity.
Science and Decisions: Advancing Risk Assessment (NRC, 2009)	Advocates assessment of combined risks posed by aggregate exposure to multiple agents or stressors, including lifestyle, vulnerability, and background risk factors; recommends developing simplifying tools and databases for screening assessments, including stakeholder-run assessments, and aligning the assessment effort with the decision alternatives.
Risk Assessment of Combined Exposures to Multiple Chemicals: A WHO/IPCS Framework (WHO/IPCS, 2009a)	Presents a tiered approach to CRA, moving from simplest, conservative screening or priority-setting evaluations to detailed, predictive biomathematical models; urges matching the effort (thus the tier) with the extent of understanding and precision required for the risk management decision.
Improving Health in the United States: The Role of Health Impact Assessment (NRC, 2011a)	Links health with multiple types of decisions, personal and societal, allowing evaluation of positive and negative impacts of various regulatory decisions on different communities with varying characteristics.
Environmental Decisions in the Face of Uncertainty (IOM, 2013)	Identifies a wide variety of uncertainty approaches and recommends that the effort to analyze specific uncertainties through probabilistic risk assessment or quantitative uncertainty analysis be guided by the ability of those analyses to affect the environmental decision; urges development of new graphic methods for communication of cumulative risk uncertainties to the public.

APPENDIX C. EXAMPLE OF A RESPONSE-BASED CONCEPTUAL MODEL

This appendix provides a more detailed example of a response-based conceptual model (cardiovascular disease [CVD]) as shown in Figure C-1. The development of this conceptual model for factors influencing the risk of CVD is detailed in Kashuba et al. (2021), but a brief description is included here as an example. Subject matter experts in fields including medicine (specifically cardiology), epidemiology, biostatistics, toxicology, and human health risk assessment participated in model development. The conceptual model was constructed following four major steps, with indication of corresponding location in Figure C-1:

1. (*Bottom*) Begin with the health endpoint—CVD.
2. (*One level up*) Review the literature to identify the major proximal biological mechanisms considered to contribute collectively or individually to CVD.
3. (*Across the top*) List major stressor categories that are related (directly or indirectly) to the biological mechanisms identified in step 2.
    a. A literature search was performed to identify common, predominant factors and topics associated with CVD as a starting point for discussion with experts. Search terms used were purposely broad: "causes of cardiovascular disease" and "factors associated with cardiovascular disease."
    b. The results of the literature search were organized and presented to experts for discussion and included studies that quantified the relationship between identified risk factors and CVD. Studies were excluded if no data supported the postulated relationship.
4. The stressors identified in step 3 were grouped and related to each other through expert review of the literature and discussion. Note that this was an iterative process; original stressor classifications were often revisited and amended; nodes were added and deleted, condensed, and expanded; and the existence and directionality of relationships were revised. Stressors were grouped into the following categories:
    a. (*Far left*) Immutable risk factors (e.g., sex, genetics, age) – In a risk assessment and management context, information on these immutable factors can serve to broaden understanding of vulnerability within the population and the need for focused risk management.
    b. (*Far right*) Potentially modifiable risk factors – These represent opportunities wherein risk management has the potential to be effective in decreasing risk through prevention and intervention. Such risk-reducing options are also included in the conceptual model.
        i. (*Right*) Risk-increasing behaviors – Examples include sedentary lifestyle, smoking, diet, and alcohol.
        ii. (*Near left*) Environmental exposures – Includes exposure with both direct and indirect influence on CVD risk; consider other stressors associated with CVD, such as lead and cadmium (which water hardness might influence), arsenic, and halogenated organic compounds.

iii. (*Near right*) Other medical issues and conditions – Arrows indicate direction of relationships and may be bidirectional (if CVD and the medical issue affect each other).

iv. (*Top*) Nonproximal stressors – Factors that do not directly cause CVD but do modify the magnitude of direct stressors (e.g., socioeconomic influences).

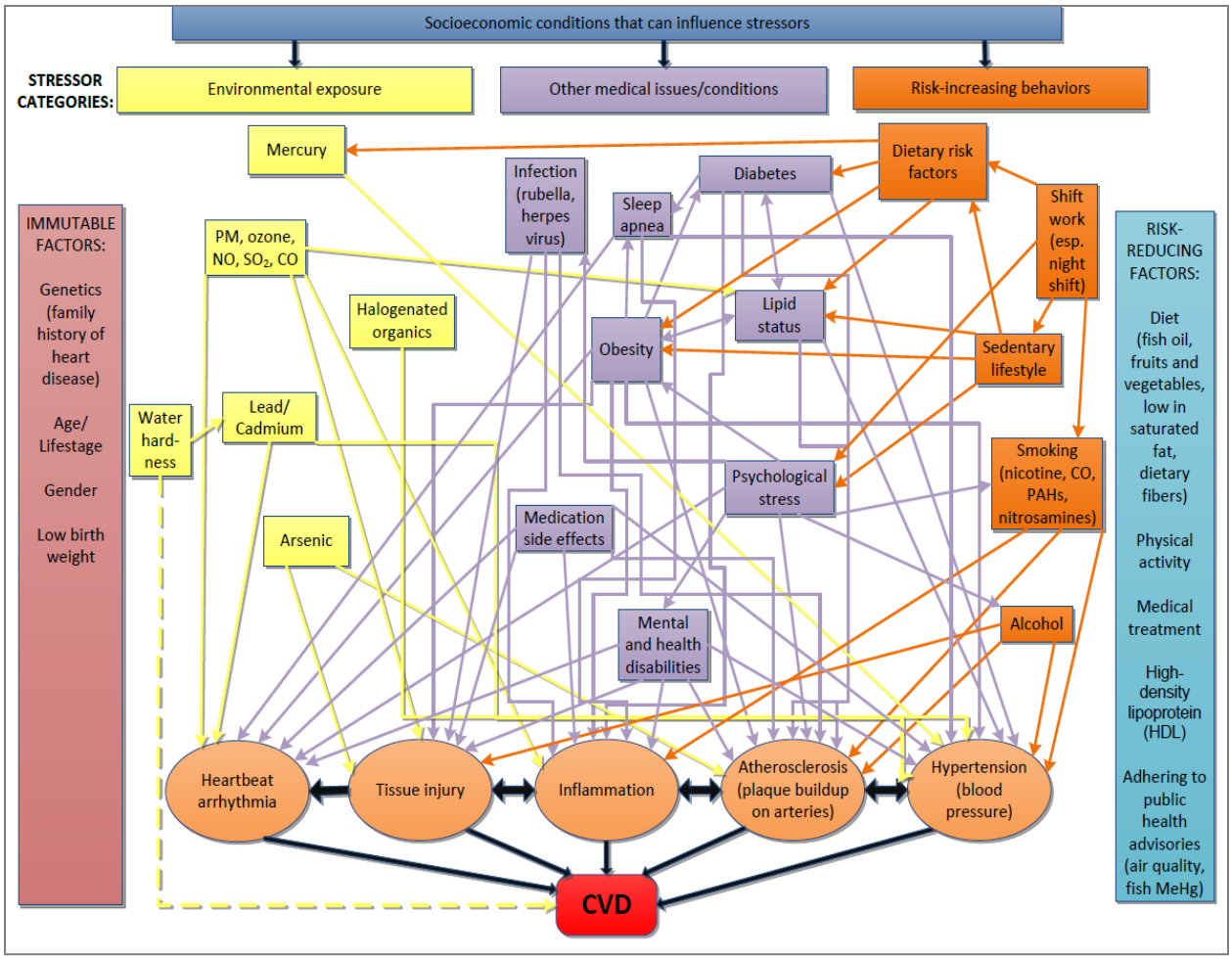

Figure C-1. Conceptual Model for Factors Influencing the Risk of Cardiovascular Disease

CVD = cardiovascular disease.
Prepared for the EPA by Charlie Menzie and Roxolana Kashuba, Exponent.

APPENDIX D. EXPOSURE-RESPONSE MODIFIERS

It has been well characterized that many conditions or factors can contribute to altered levels of exposure or altered risk of a health effect occurring at a given level of exposure to an environmental pollutant. Within the scientific literature, there is a large degree of variability in how these conditions or factors are referred to, but they generally encompass exposure disparities, social vulnerabilities, and biological vulnerability (Morello-Frosch et al., 2011). For simplicity, in these Guidelines, conditions or factors that alter a receptor's exposure or response to an environmental pollutant are referred to as exposure-response modifiers.

In these Guidelines, exposure-response modifiers are discussed largely in terms of vulnerability factors. Vulnerability in CRA is a multidimensional concept. Kasperson et al. described vulnerability as a product of exposure, resistance (ability to withstand impacts), and resilience (ability to recover from exposure to a stressor) (Kasperson et al., 1995). The National Environmental Justice Advisory Committee similarly defines vulnerability as "a matrix of physical, chemical, biological, social, and cultural factors which result in certain communities and subpopulations being more susceptible to environmental toxins, being more exposed to toxins, or having compromised ability to cope with and/or recover from such exposure" (NEJAC, 2004). This definition explicitly names categories/types of vulnerability factors that are important determinants of the environmental health of an individual or a community. It refers to the intrinsic predisposition of an exposed element (individual, community, population, or ecological entity) to be affected by external stresses and perturbations and the element's ability to recover from such stresses (resilience). It is based on variations in disease vulnerability, psychological and social factors, exposures, and adaptive measures to anticipate and reduce future harm and to recover from an insult (Kasperson et al., 1995; Kasperson et al., 2005; NRC, 2009).

Vulnerability is a differentiating factor for how individuals, communities, populations, or organisms experience adverse effects related to exposure to environmental stressors. The presence of a vulnerability factor or condition in an assessment can increase the health impact of exposure to environmental stressors (deFur et al., 2007). Although the identification of vulnerable human populations often focuses on individual conditions or factors that can contribute to increased exposures or health risks from environmental pollutants, such factors do not occur in isolation. Instead, vulnerabilities likely emerge from a combination of multiple factors or conditions, including both chemical and nonchemical stressors, at both the community and individual levels. Vulnerability factors can be differentially experienced across social groups in any given population. This differential experience underscores environmental justice concerns and uneven distribution of the health-supporting and health-degrading aspects of social determinants of health (e.g., access to health care and healthy foods, increased exposure to multiple pollution sources) among different social groups (e.g., by race and class).

As described above, vulnerability can be driven by exposure to a single community- or individual-level factor or from the complex interactions between multiple factors at multiple levels and environmental exposures. Figure D-1 models the risk paradigm, with stressors on the left affecting receptors in the middle, and with outcomes on the right. The pathways through which vulnerability factors may operate as exposure-response modifiers are denoted with dashed arrows. The bidirectional arrows indicate the dynamic interactions between environment and receptor and the impact of an outcome on the subsequent vulnerability of a receptor.

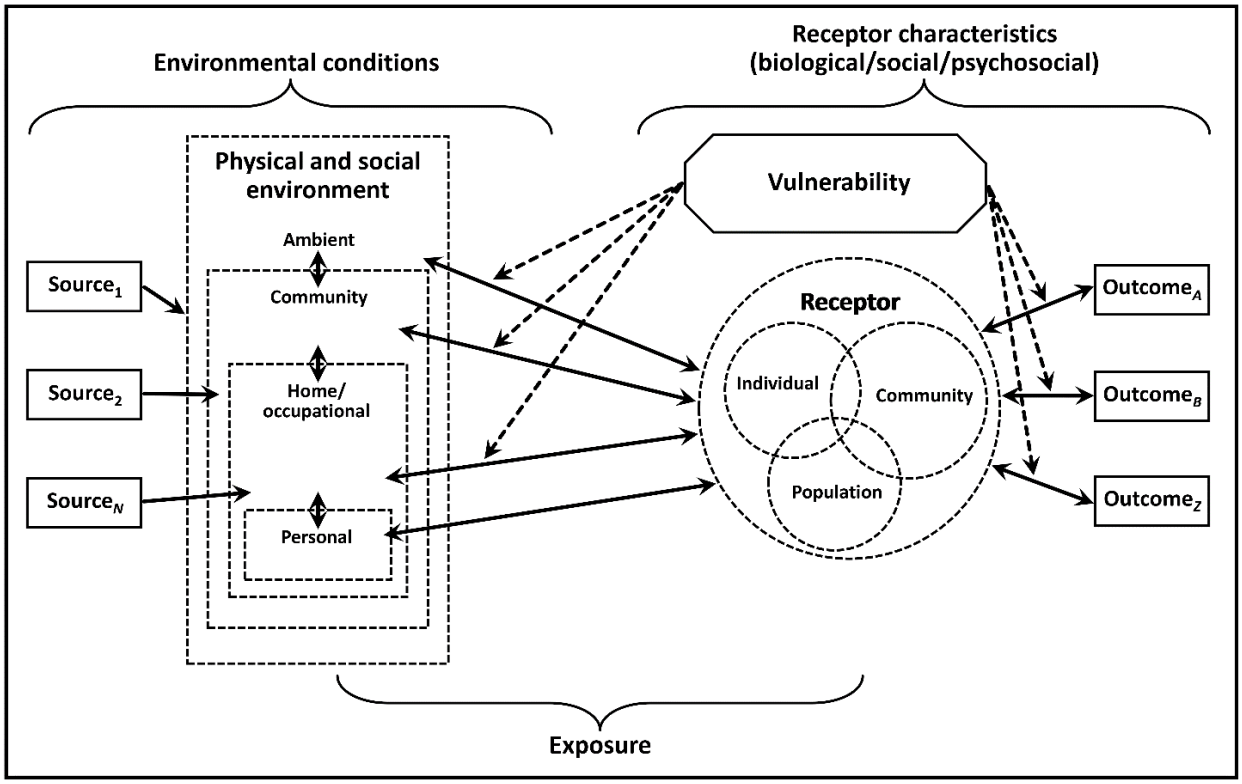

Figure D-1. Vulnerability Factor Categories, Interactions, and Pathways in Exposure-Response Relationships

Source: deFur et al. (2007).

While the focus of discussion has been on human populations, ecological receptors can also exhibit traits or behaviors that could affect their ability to respond to stressors or could reduce their resilience. Examples of vulnerable ecological populations include wetland communities stressed by human development and an endangered species stressed by land-use alterations. A CRA would note, for example, that for Tribal and Indigenous Peoples and some rural communities, ecological stress may be linked to human stress as well as to food security and malnutrition.

Vulnerability factors can influence the exposure-response relationship in one or more ways, irrespective of whether they primarily operate intrinsically (i.e., via preexisting or genetic conditions, as identified in Figure D-2) or extrinsically through their effects on external conditions):

- Changing the contact (greater or lesser) with a stressor in the environment.
- Changing internal levels (increase or decrease) of a stressor once contact has occurred such that for the same amount of external exposure, a vulnerable person has different (higher or lower) internal levels of the stressor or its toxic form, which could emerge through influences on toxicokinetic processes (absorption, distribution, metabolism, and excretion).
- Altering how a given internal level of the stressor affects target tissues and organs by influencing toxicodynamic processes such as DNA repair, which serves to change processes that impose tolerance and resilience and thus affects the occurrence or the severity of disease.
- Influencing disease pathways, the stressor changes (potentiates or reduces) the adverse outcomes associated with exposure.

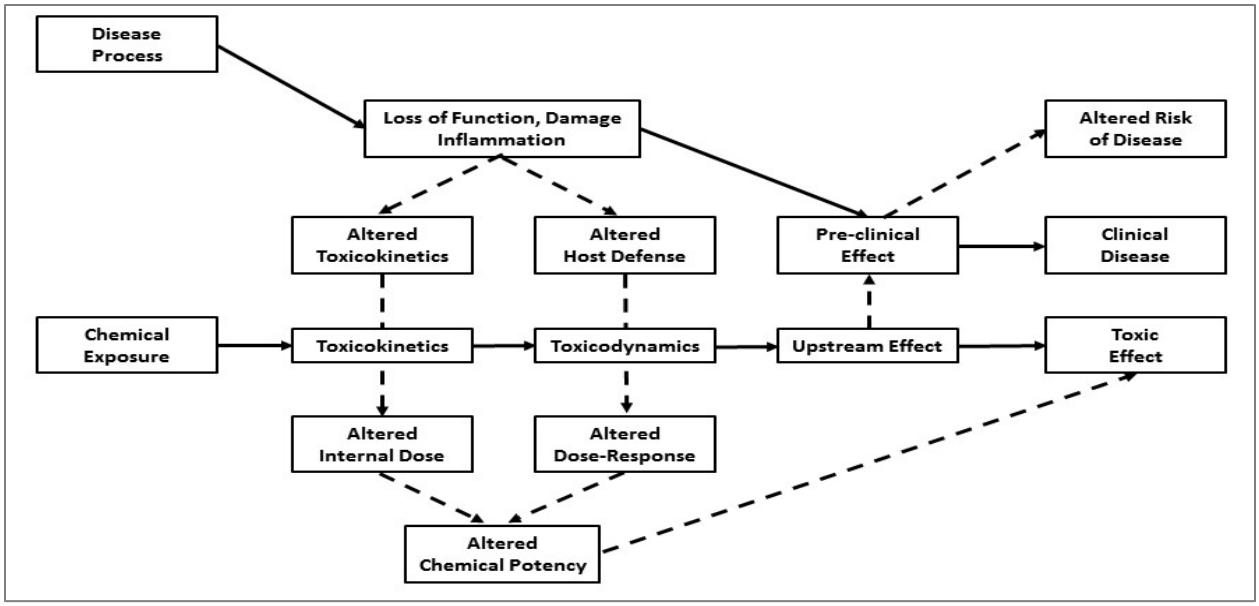

Figure D-2. Key Intrinsic Events in Exposure-Response Relationships

Source: Ginsberg et al. (2014).

In CRA, understanding how vulnerability factors might influence the assessment is critical during problem formulation. Vulnerability factors should be evaluated as "exposure modifiers" or "response modifiers," recognizing that the pathway to modification could occur via influences on conditions extrinsic or intrinsic to the individual.

deFur et al. (2007) and Ginsberg et al. (2014) offer helpful frameworks for examining vulnerability in this regard (see Figure D-1 and Figure D-2). The framework of deFur et al. emphasizes the need to clarify the relationships among the various factors and their roles in affecting vulnerability (deFur et al., 2007) – the influence of vulnerability factors on exposure-response relationships should be evaluated in terms of the relationships and interactions among the vulnerability factors, identified stressors, and outcomes of interest.

The Ginsberg et al. (2014) framework emphasizes delineation of key intrinsic events in the exposure-response relationship to understand vulnerability. This framework approaches vulnerability through the lens of the effect of preexisting disease on toxicokinetics and toxicodynamics, although its main constructs are applicable to other vulnerability factors. Three pathways are proposed:

- Altered chemical processing by disease in ways that materially change the internal dose;
- Weakened host defense mechanisms that impair tolerance; and
- Altered disease pathways that the disease process also affects.

Segal et al. (2015) proposed a framework for integrating the effect of a single nonchemical stressor within the context of a risk assessment for a single-chemical stressor (Figure D-3). The approach considers the nonchemical stressor as a modifier of response. The framework offers a method for considering a vulnerability factor in a one-chemical risk assessment and thus has some utility in thinking about assessments of cumulative risks for chemical and nonchemical stressor combinations.

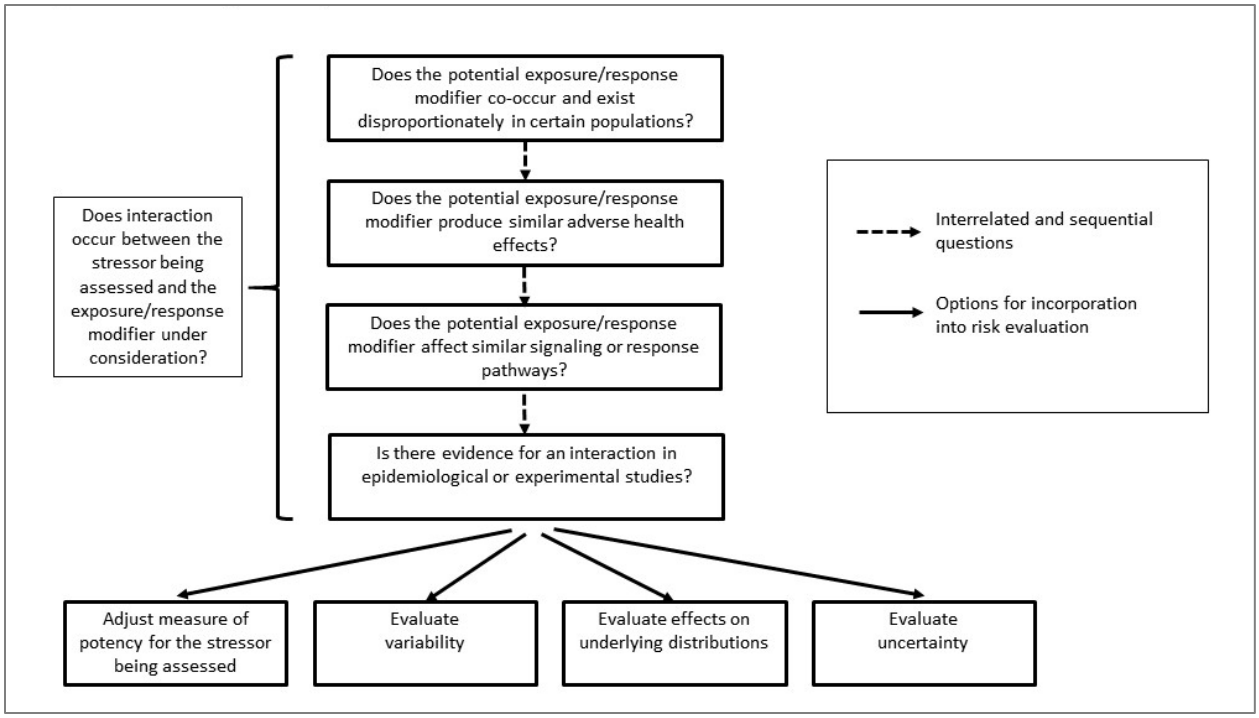

Figure D-3. A Framework for Incorporating Nonchemical Stressors into Risk Assessments

Adapted from Segal et al. (2015).

Considering the social determinants of health augments the set of vulnerability factors typical in risk assessment, such as lifestage and preexisting disease. In traditional risk assessments, social and individual determinants other than stressors being assessed might be integrated into risk assessments as vulnerability factors. In CRA scenarios, however, it is plausible that a primary/target stressor could also operate as a vulnerability factor, modifying how one or more other stressors in the mix lead to adverse health outcomes. Thus, a vulnerability factor may be considered an "exposure modifier," a "response modifier," or both.

Such exposure-response modifiers can be integrated into risk assessment frameworks such as Segal et al. (2015).

Integrating Vulnerability into Problem Formulation. A systematic approach is necessary for identifying and examining evidence of vulnerability during problem formulation. This ensures the CRA team is aware of key vulnerability considerations in the assessment and can develop well-informed hypotheses about important risk and adverse outcomes for the assessment. The following questions are suggested to inform the integration of vulnerability in the hypotheses for the assessment and in the development of a conceptual model for the assessment:

- What factors (external to the set of stressors that are the focus of the CRA) are potential modifiers of exposure or response for one or more stressors in the CRA? This inquiry can be initiated from the toxicological and epidemiological data for stressors. For example, if Chemicals A, B, and C are the focus of a CRA, what factors might modify exposure or response to one or any combination of A, B, and C?

    - Is there a factor/set of factors (chemical, biological) or condition(s) that can modify the exposure and/or response of A, B, or C or any combination thereof? For this discussion, refer to these other factors/conditions as "E" and "F."
    - What type of evidence is available to support this finding of exposure or response modification—toxicological, epidemiological?
    - Is the information sufficient to estimate differentiated dose-response assessments for each chemical, A, B, or C?

- If data suggest exposure or response modification, what is the extent to which these factors (E or F) co-occur with the stressors (A, B, or C) in the population of interest?
- Given available data, what are plausible ways in which these factor(s) might increase or decrease exposure or response?

In addition to approaching the identification of vulnerability factors through existing epidemiological and toxicological data specific to the stressors in the assessment (A, B, and C), it may be helpful or necessary to identify potential vulnerability factors by researching conditions that are characteristic of or important to the population(s) of interest. This inquiry should be a routine step during communication with stakeholders. By identifying community-level characteristics and concerns, the CRA team will be able to better scrutinize the epidemiological and toxicological literature further for information that might inform potential exposure-response modification by these factors. Consistent with the U.S. Department of Health and Human Services' *Healthy People 2020 Social Determinants of Health Framework* (U.S. HHS, 2020), the CRA team should consider the following questions:

- To what extent do one or more issues within one or more categories of social factors (e.g., food insecurity as an economic stability issue) co-occur with stressors A, B, or C in the population?
    - Do populations with higher exposures to A, B, or C experience greater food insecurity (food insecurity becomes a potential E or F)?
    - Is exposure to an economic stability issue (e.g., food insecurity) prevalent in the population that is the focus of the CRA?
- To what extent are one or more economic stability issues prevalent among populations that experience the health outcomes linked with exposure to stressors A, B, or C?
    - Is the economic stability issue prevalent in the population that is the focus of the CRA?
- Do the epidemiological and toxicological data offer information to indicate whether these economic stability issues might modify exposure or response?
- What are plausible pathways (given available data) through which an economic stability issue might modify exposure or response?

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