Integrating Chemical and Non-Chemical Stressors in Cumulative Risk Assessment

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Introduction

As defined by the U.S. Environmental Protection Agency (EPA), cumulative risk assessment involves "an analysis, characterization, and possible quantification of the combined risks to health or the environment from multiple agents or stressors" [1]. This definition is deliberately wide-ranging, encompassing a variety of contexts in which consideration of individual chemicals in isolation would not provide sufficient information for making decisions. These circumstances would include settings in which environmental justice concerns are paramount, as ignoring multiple stressors could lead to insufficient emphases on highly burdened communities, as well as settings in which health risks would be underestimated or otherwise mischaracterized by focusing narrowly on individual chemicals. Consideration of chemical mixtures is one element of cumulative risk assessment, but this process goes well beyond multi-chemical exposures and considers the influence of non-chemical stressors. Cumulative risk assessment also involves an orientation toward populations rather than chemicals, although this could include local or national-scale assessments, assessments that focus on general populations versus distributions of subpopulations, retrospective or prospective characterizations, and evaluations of current disease burdens or the benefits of future risk management strategies. In addition, the definition of cumulative risk assessment listed above would theoretically encompass ecological risk assessment, although most of the emphasis to date using the term cumulative risk assessment has been on human health outcomes. We focus on human health cumulative risk assessment in this white paper, although we also consider the implications of ecological stressors and ecosystem services along with other non-chemical stressors on health outcomes.

The rapidly growing interest in characterizing the combined effects of chemical and non-chemical stressors on health outcomes has stemmed from a few key observations. First, chemical and important non-chemical stressors often are spatially correlated, clustered in lower income communities along highways or industrial corridors [2]. Second, there is growing epidemiological and toxicological evidence that chronic psychological stress (driven by poverty, exposure to violence and other community-scale non-chemical stressors) may alter individuals' susceptibility to environmental pollution [3-7]. This heightened susceptibility is believed to be mediated through a suite of immune, endocrine and metabolic changes that occur under chronic stress, a condition collectively referred to as allostatic load [8]. Together, these observations suggest that the communities with the highest exposures also may be the most susceptible [9]. Thus, disentangling the effects of highly correlated social and environmental exposures, and identifying their potential interactions (synergies or antagonisms) are increasingly becoming research and policy priorities, recognized as critical toward identifying and protecting susceptible populations as well as reducing health disparities [10].

In parallel, there has been growing recognition that a variety of ecosystem services are critically important in a broad societal context [11] and can have important direct and indirect influences on health and well-being [12-14]. Studies have shown improved health in places with more access to, and availability of, green space [15, 16], and there are numerous other examples where aspects of the local environment can influence chemical exposures or vulnerability to the effects of these chemicals. Broadly, health may be influenced by a multitude of non-chemical stressors and other factors, and the challenge before EPA is to determine appropriate methods and frameworks to characterize health risks due to joint exposures to chemical and non-chemical stressors.

Within this white paper, we focus on the specific question of how non-chemical stressors can be systematically and rigorously included in cumulative risk assessments given data and analytical limitations, and EPA's traditional focus on chemical stressors (noting the regulatory authority that emphasizes individual chemicals). There clearly are numerous additional areas in which methodological advancement would be required, but a systematic approach by which non-chemical stressors can be included could be generalized to a variety of stressors and contexts.

Also of note is that EP pursues voluntary partnerships and activities related to cumulative risk that support outside Federal, tribal, state, local and non-governmental organizations. These efforts can be especially important not only for cumulative assessment but also to address environmental justice. Although the National Environmental Justice Advisory Council, the NRC, and other EPA reviews and internal efforts have moved EPA toward cumulative risk, it is worth recognizing that the main drivers with the Agency may not be specific directives in statutes or regulations at this point in time. Prior to considering the current state of the science with respect to inclusion of non-chemical stressors in cumulative risk assessment, it is important to carefully define what is (and is not) meant by non-chemical stressors in this context. EPA defines a stressor as "any physical, chemical, or biological entity that can induce an adverse response" [1]. Importantly, the definition also emphasizes that stressors may not cause harm directly, but instead may increase vulnerability to harm by other stressors. Examples of non-chemical stressors mentioned in the Framework for Cumulative Risk Assessment include (but are not limited to):

- lack of health care
- personal activities (such as smoking and diet)
- natural phenomena (such as forest fires and floods)

- biological pathogens
- psychosocial stress
- noise
- heat

EPA's definition further includes current physical and mental health status, past exposure histories, and level of income and community property values, among other factors. Beyond these listed examples, there are numerous other non-chemical stressors that could fit the definition listed above, including ecological amenities or degradation of ecological amenities. Based on the definition and examples, the working definition of non-chemical stressor in this white paper would be any exposure in the physical or social environment that can impact human health through pathways other than those traditionally included in health risk assessment. By this definition, nearly any risk factor (or stressor) for environmental quality or human health could conceivably be included in cumulative risk assessment—any individual risk assessment, however, would clearly require a more narrow focus. The challenge, therefore, lies in determining the appropriate subset of non-chemical stressors for consideration within a given cumulative risk assessment, as well as the appropriate methodology for doing so. Whether or not the assessment is motivated by observed disease patterns, clusters of stressors, identified sources within a community or other factors, the assessment ultimately will begin with a process of determining which chemical and non-chemical stressors to incorporate formally into the analysis. As discussed in more detail within this white paper, the planning and scoping phase at the start of a cumulative risk assessment is critical in determining the range of inputs (e.g., stressors, exposure pathways, population characteristics) and the approach to be utilized in the assessment.

These and other questions related to cumulative risk assessment were addressed in multiple recent NRC reports, providing some key insights and helping to focus on the salient methodological questions within this white paper. In *Science and Decisions* [17], the committee's statement of task included providing recommendations for approaches to characterize cumulative risk from multiple stressors. The recommendations found in *Science and Decisions* were tied closely to two primary themes of the overall report: (1) conducting analyses that are appropriate given the risk management context; and (2) developing new approaches for dose-response modeling that take account of the influence of background exposures and vulnerable population characteristics. On the former point, the committee indicated that risk assessment (and therefore cumulative risk assessment) should be considered primarily as a tool to inform choices among various risk management options, where the assessment can be planned only with knowledge of the decision context. More specifically, a series of diagnostic questions should be asked prior to planning a risk assessment, including the goals of the assessment, the timing when the analysis would need to be completed, and the candidate risk management options. On the latter point, the committee concluded that the current approach for non-cancer risk assessment was uninformative in many decision contexts and did not recognize that significant background exposures to other chemicals and processes can lead to low-dose linear effects for toxicants commonly considered to have thresholds. The committee proposed a new unified approach for dose-response modeling that would be applicable to both cancer and non-cancer endpoints and would recognize the influence of the array of stressors people face in their communities.

Both of these concepts played a central role in the recommendations in *Science and Decisions* regarding cumulative risk assessment and the inclusion of non-chemical stressors.

Broadly, the committee recognized that individual chemical risk assessments already were time-consuming and complex, so that expanding the scope of risk assessments to address numerous stressors simultaneously could rapidly become intractable. However, the committee specifically cited the omission of non-chemical stressors as the major limitation of cumulative risk assessment practice to date, which generally has considered only chemical mixtures or other multi-chemical exposure scenarios. Although the omission of non-chemical stressors was attributable in part to data limitations and to EPA's traditional emphasis, the committee thought that it was important to develop strategies to include non-chemical stressors, given the stated definition and end uses of cumulative risk assessment. The *Science and Decisions* committee did not offer specific guidance on which non-chemical stressors were and were not appropriate to include, but instead proposed multiple strategies by which this decision could be made on a case-by-case basis.

One strategy to include non-chemical stressors involved developing default approaches to modeling non-chemical stressor exposures in the absence of data on specific populations, similar to defaults that exist in the realm of chemical stressors. Another specific recommendation was to determine the stressors that are associated strongly with socioeconomic status (SES) and other demographic variables. Although variables such as SES may be either distal or proximal causes of health outcomes, SES indicators are readily available from public databases and may serve as reasonable proxies for specific non-chemical stressors in some carefully considered circumstances and locales. Finally, the committee recommended further research to enhance insight about mode of action among non-chemical stressors. We expand upon these recommendations from *Science and Decisions* later in the white paper.

The committee also recommended strategies to streamline the analytical process and allow for the inclusion of non-chemical stressors. One suggestion was to develop simpler screening-level techniques across multiple dimensions of the risk assessment. For example, the committee cited the use of intake fractions or look-up tables for concentration effects as approaches to approximate population exposures or maximum impacts, respectively. These methods would have greater uncertainty but a sufficiently strong scientific foundation to allow for sequential model refinements to be appropriately targeted. In addition, the committee recommended that analysts adopt a risk management orientation coupled with the new non-cancer dose-response paradigm. Adapting an approach used in ecological risk assessment [18], the committee proposed that cumulative risk assessments initially develop conceptual models for the stressors that could be influenced by risk management efforts, considering mode of action, background exposures to chemical and non-chemical stressors that could influence the same health outcome, and a vulnerability assessment that considers key disease processes in the at-risk population. After initial screening using epidemiological and toxicological evidence, the committee recommended that the assessment focus principally on stressors that contribute to endpoints of interest for risk management options and are either differentially affected by control strategies or influence the benefits of stressors that are differentially affected. All other stressors contribute more generally to the consideration of background exposures and the possible shape of the dose-response function, but may not need to be evaluated formally.

Although this proposed structure potentially can help to systematize the cumulative risk assessment process, significant questions remain to be addressed. For example, this process involves a judgment about whether background exposures are significant enough to linearize an otherwise non-linear mode of action. In other words, a chemical may be hypothesized to have a

threshold within non-cancer risk assessment for individuals exposed only to that chemical. In the presence of other stressors, however, the threshold may not exist at a population level, and it may be more appropriate to assume a linear dose-response function (see the section on *Dose-Response Modeling* for more detail). Making this judgment clearly would require a systematic approach to evaluate a large amount of information, including insight about stressor exposure patterns that typically may not be available. In addition, the *Science and Decisions* framework proposed that cumulative risk assessments should consider the main effects of individual stressors first and interactions only if simple sensitivity analyses show that the conclusions can be influenced by the presence of interactions. However, it is possible for some stressors to influence health outcomes only among a subpopulation or in the presence of another stressor, in which case exploring these interactions would be necessary prior to screening out any exposures. More generally, as this proposed framework has not yet been applied to a specific case study, it is difficult to know whether it would successfully allow for the efficient inclusion of a significant number of chemical and non-chemical stressors.

Another key theme in *Science and Decisions* was the necessity of developing insight about cumulative risks in human health risk assessment by examining approaches in ecological risk assessment and social epidemiology. For some time, ecological risk assessments have focused on a defined geographic location and considered the influence of all stressors on the ecosystem, often by using a rank-oriented approach that does not include all of the elements of quantitative risk assessment. Although it would be preferable to have an approach that yields quantitative risk outputs (or, at a minimum, reflects insight about both exposure and toxicity), simpler tools may capture a wider array of stressors and offer insight about optimal risk management strategies or domains in which more analysis would be needed to arrive at risk

management decisions. For example, the relative-risk model (RRM) cited in *Science and Decisions* has been used in ecological risk assessments to evaluate risks across numerous stressors, developing a broad conceptual model and using stakeholder input as well as scientific evidence to rank sources, exposure modifiers, habitats, and other key components of ecological impacts. The rankings do not directly correspond with quantitative risk outputs, but the process allows for triaging and determination of the stressors most likely to contribute to the outcomes of interest.

Similarly, social epidemiologists have developed simple cumulative risk models to represent the influence of joint exposures to multiple physical and social environmental stressors that could be adapted for human health risk assessment. For example, as described in *Science and Decisions*, studies have used scoring systems to determine how many of an array of physical and social risk factors are at least one standard deviation above the mean value, with the sum of these dichotomous variables used as the exposure metric [19]. The concept of allostatic load has been developed to reflect the cumulative burden of stress, where the outcome measure has been defined by the number of risk factors for which the individual is above a certain point in the population distribution [8]. As with ecological risk assessment, adopting these metrics would be useful only if they included key attributes necessary for risk assessment (e.g., capturing exposure magnitude and duration, population distributions, and health-relevant outcomes). However, strategies such as these may represent the only way to proceed with cumulative risk assessments as envisioned.

Finally, another key recommendation from *Science and Decisions* (both in the context of cumulative risk assessment and more generally) had to do with increased opportunity for stakeholder involvement. *Science and Decisions* did not provide extensive discussion on this

topic, in part because many prior National Research Council (NRC) reports and EPA guidance documents had specifically focused on how to increase stakeholder participation in risk assessments. What *Science and Decisions* emphasized was that cumulative risk assessment provided a natural vehicle for increased stakeholder participation, given the emphasis on the planning and scoping process and the community orientation in a subset of cumulative risk assessments. The important role and position of population and community analysis in cumulative risk assessment makes the process of stakeholder input arguably more important than in traditional risk assessments.

Furthermore, if the framework for risk-based decision-making proposed within *Science and Decisions* were adopted, an orientation toward developing solutions to significant environmental problems in communities would naturally lead to more active engagement. It is likely that a wider array of stakeholders would be able to offer substantive suggestions for risk management than for the analytical components of the risk assessment. The committee therefore concluded that EPA needed to plan (and budget) for public and stakeholder involvement; facilitate involvement by providing information that could be readily interpreted by the public, and engage with the public and other stakeholders throughout the cumulative risk assessment process. The stakeholder involvement process in cumulative risk assessment needs to be included at the outset, and not as an afterthought. In this way, the assessment can be more open, transparent, and perspectives and inputs from the community can be incorporated from the planning and scoping phase onwards.

Another NRC report, *Phthalates and Cumulative Risk Assessment: The Task Ahead* [20] addressed the question of cumulative risk assessment, focusing on the specific topic of phthalates, while raising concepts applicable in a variety of contexts. The committee concluded

that a focus on "mode of action" (defined following the EPA report in 2005 [21] as a sequence of key events and processes, starting with interaction of an agent with a cell, proceeding through operational and anatomical changes, and resulting in an adverse effect) within cumulative risk assessment was overly narrow, as health outcomes may be influenced by stressors across multiple pathways and with varied mechanisms. Therefore, they recommended a focus on "common adverse outcomes," which they defined as health outputs that can be manifested regardless of pathway. This is consistent with the broader vision of cumulative risk assessment and with the focus of *Science and Decisions*. For the specific example of phthalates, the committee suggested that a variety of stressors that could influence male sexual differentiation should be evaluated jointly, even if they do not operate on the same mechanistic pathway as phthalates. Although all of the candidate stressors that the committee proposed be considered along with phthalates were chemicals (i.e., polybrominated diphenyl ethers [PBDEs], polychlorinated biphenyls [PCBs], and azole fungicides), the concept could be applied broadly to a variety of stressors. The committee also concluded that the current approaches for cumulative risk assessment are overly restrictive regarding when it is appropriate to use dose-addition (in which one assumes that the toxicity of the mixture can be characterized by the sum of the individual constituent toxicities). If this committee's suggestions were adopted, it would lead to a more expansive approach for cumulative risk assessment, with more chemical and non-chemical stressors being simultaneously evaluated and a greater likelihood that health effects would be predicted in a multi-stressor context.

In summary, recent advisory committee reports reinforce the value of cumulative risk assessment for EPA and suggest some viable approaches for conducting more informative

analyses that incorporate non-chemical stressors, but some significant questions remain unresolved:

- How does cumulative risk assessment best use insight from both toxicology and epidemiology, given that the former generally lacks information about non-chemical stressors and lifestyle factors, and the latter lacks evidence for the vast majority of chemicals? Similarly, can either toxicology or epidemiology adequately inform questions of the distribution of vulnerability in the population, given the relatively homogeneous populations in toxicology and challenges in determining effects across numerous subpopulations in epidemiology?
- How can exposures to non-chemical stressors be appropriately and jointly quantified, given relatively little data beyond simple demographic information in most settings? Can defaults be established that are both meaningful and can be interpreted identically in a variety of settings?
- Can a cumulative risk assessment meaningfully include both chemical and non-chemical stressors when risk management decisions by EPA invariably emphasize chemical stressors? Is the process different if a non-chemical stressor happens to be influenced by risk management activities (e.g., if cleaning up a pollution source in a community alleviates psychosocial stress)?
- Should there be any limits on what stressors EPA should consider within cumulative risk assessment? Are all lifestyle factors and non-chemical stressors potentially relevant? Can complex amenities (e.g., ecosystem services, which entail multiple factors acting through both physical and psychosocial pathways) be reasonably disaggregated for meaningful incorporation into human health risk assessment?

- Should the primary orientation of human health cumulative risk assessment be to predict apical endpoints typically used for risk management decisions? To what extent can insights from evaluations of cellular-level responses from *in vitro* testing be incorporated into the prevailing risk management paradigm?

In this white paper, we focus on strategies for inclusion of non-chemical stressors in human health cumulative risk assessment. The paper has been constructed following the standard steps of a human health risk assessment, though noting that this does not mean that each of these steps need to be followed sequentially and linearly, although some planning and scoping is important at the beginning. We begin by discussing the planning and scoping phase of the analysis, building on previously proposed frameworks to delineate the contexts in which non-chemical stressors should and should not be included in cumulative risk assessments, as well as strategies for their inclusion. We then consider the hazard identification step, as an initial qualitative determination of the stressors under consideration in the analysis. We discuss available databases and metrics that could allow for characterization of exposure to non-chemical stressors, considering theoretical ideal parameters as well as proxy measures or default assumptions that could be used in the absence of detailed population-specific data. For dose-response modeling, we present strategies that could be used for either epidemiological or toxicological evidence, with a broad-based discussion regarding similarities and differences from the chemical mixtures problem. We briefly address risk characterization, as a step that synthesizes evidence across outcomes from a *stressor-based* cumulative risk assessment, or appropriately contextualizes the findings from an *effects-based* cumulative risk assessment. We present three illustrative case examples to reinforce the viability of including non-chemical stressors using either toxicological or epidemiological evidence and to present approaches by

which community characteristics can be incorporated. We conclude by identifying significant data and methodological gaps that could be addressed by targeted research.

Planning and Scoping

A critical initial step in any cumulative risk assessment involves planning and scoping/problem formulation. This process was described in detail within the EPA Framework for Cumulative Risk Assessment [1] and was expanded upon in *Science and Decisions*. Rather than describe these processes in detail, we focus herein on the specific question of how EPA can most appropriately determine the non-chemical stressors to include within a given cumulative risk assessment. We recognize that EPA does not have regulatory authority over most non-chemical exposures, and most voluntary or informational activities center on the chemical stressors central to the Agency's mission. That said, we aim to provide guidance that will enable EPA to examine chemical pollutant exposure in context—that is, with an understanding that a single pollutant impacts upon health outcomes as only one part in a richer physical and social environment in which individuals live, work and play.

A general approach for planning and scoping in the context of cumulative risk assessment was proposed by Menzie [18] and expanded upon by *Science and Decisions* [17]. In Menzie, the initial step of the cumulative risk assessment process involves building a conceptual model. How this conceptual model is developed depends largely on whether the assessment is effects-based or stressor-based. For an effects-based assessment, which is motivated by observed or anticipated effects of concern (e.g., a cancer cluster, elevated asthma rates), the conceptual model determines the subset of stressors that could be plausibly associated with the outcome of interest [22]. An analyst would then conduct a screening assessment to determine the subset of stressors that

might merit further consideration and then would proceed to the other steps of the risk assessment. Of note, this process is far more likely to be iterative than linear; an initial conceptual model might be refined by looking in more detail at the results of screening-level exposure and dose-response assessment, which could lead to more refined risk modeling. In a stressor-based cumulative risk assessment, which is motivated by the presence of a defined set of stressors, a conceptual model is constructed similarly, but considers multiple potential effects from those stressors. The screening assessments in this case involve both screening the candidate list of stressors and determining the most relevant set of outcomes. In community-driven assessments, such as voluntary efforts or the EPA CARE partnerships (epa.gov/care), both effects and stressors may be identified as of interest and the stressors may be underlying sources (roadway, disposal site, factory), as well as individual chemicals of concern [23].

The modification proposed in *Science and Decisions* was to use not only general scientific insight and stakeholder feedback to develop the conceptual model and analysis plan, but also to use a risk management framework to focus on those stressors and effects most relevant to a defined decision. As described in the Introduction above, this requires an upfront consideration of candidate risk management options and the stressors they would influence, along with an evaluation of other stressors with similar mode of action. An expanded version of this paradigm would use common adverse outcomes rather than mode of action, but ultimately still would use the risk management context to focus the analysis.

Broadly, whether EPA follows the *Science and Decisions* process for planning and scoping or a process more closely following Menzie [18] depends in part on the desired end use of cumulative risk assessment. If the goal is to characterize existing circumstances for a specific application, then the risk management orientation is less salient and the process of determining

appropriate stressors to include could follow Menzie [18]. If the goal is to use cumulative risk assessment in the service of specific risk management decisions, following the process proposed in Table 7-1 of *Science and Decisions* could make the analysis more manageable. Broadly, because cumulative risk assessment with multiple chemical and non-chemical stressors has the capacity to expand beyond the capabilities of technical resources and knowledge, one of the essential elements in the planning and scoping phase is focusing and defining the nature and breadth of the effort, to define a manageable and interpretable suite of stressors to be explored. We suggest careful attention to elucidating the hypothesized pathway(s) through which each proposed stressors acts (and interacts), and a description of the data resources available to characterize exposures and effects (whether quantitative or qualitative). A clear conceptual model that includes both proximal and distal effects and describes pathways and evidence for causality will be at the heart of any planning and scoping process. We return to this idea throughout the white paper, as the conceptual model may rely on hazard identification, screening-level exposure assessment, and preliminary interpretation of dose-response evidence.

A few refinements beyond previously proposed structures for planning and scoping would be warranted. First, it should be recognized that there are two key dimensions across which cumulative risk assessments are conducted, generally based on the situation that led to the need for the assessment. The first involves bottom-up (stressor-based) versus top-down (effects-based) assessments. A stressor-based assessment might be initiated when there is a known source/stressor, such as an emission source or discharge pipe. As described above, an effects-based assessment would be motivated by a known problem/effect, such as a disease cluster. The second key dimension involves whether the assessment is oriented toward a specific community or is motivated by general population concerns. A community-based assessment might be

initiated by a defined subpopulation (i.e., low-income children in a specific community), and would involve some additional elements in the planning and scoping phase. This includes an explicit characterization of the community including its demographics, geographic boundaries, health—unique or specific characteristics that need to be carried through the entire assessment. In this context, it also is valuable to specifically characterize sensitive subpopulations to be evaluated within the analyses. Although this process could occur in a stressor-based or effects-based assessment as well, some of those assessments may be less grounded in community characteristics.

Although there are a number of cumulative risk assessment applications with a potential community orientation, one important context is communities proximate to contaminated sites that are regulated under Superfund law, the Resource Conservation and Recovery Act, Formerly Used Defense Sites, and others regulated under specific laws or programs. Communities near contaminated sites often have other health concerns and multiple relevant non-chemical stressors. The community of Midlothian, TX, was one of the case examples in the EPA 2003 Cumulative Risk Assessment Framework [1] and is representative of such communities. These communities face the combined (multiple) stresses of industrial chemicals, poverty, low SES, disenfranchisement, health issues and other challenges.

Case studies developed within the environmental justice context may be helpful in describing community characteristics and community responses to environmental stressors. Publications such as *Unequal Protection: Environmental Justice & Communities of Color* [24], *Confronting Environmental Racism: Voices from the Grassroots* [2], and *Sacrifice Zones: The Front Lines of Toxic Chemical Exposure in the United States* [25] present a variety of environmental justice case studies. The text describing these situations is general and often does

not present quantitative or qualitative data. The case studies do, however, provide a community and cultural context for the case. Additionally, receptor-based or community-based stressors often are identified by community members as concerns in case studies.

These case studies, at the very least, describe community demographics, including racial demographic profiles and income information. Some studies, however, such as the Sumter, AL, case study presented in Chapter 7 of *Confronting Environmental Racism* [2], provide more detailed descriptions of site demographics and community perceptions. Although site-specific case studies of environmental justice issues do not provide in-depth analysis of community-based stressors, the information may provide a general context for further community-based research. An example case is presented in the last section of this report, indicating the information that might comprise a community characterization, with consideration given to health and psychosocial risk factors.

In summary, the planning and scoping phase is a central component of any cumulative risk assessment, as described and proposed previously. In the context of including non-chemical stressors, a risk management orientation can help to reduce the list of candidate stressors to consider. In the absence of a risk management orientation, a systematic approach to developing a conceptual model and conduct iterative screening analyses would be most likely to yield an analysis that is manageable in scope and content.

Hazard Identification

The initial step in any human health risk assessment generally is hazard identification, defined in the Red Book [26] as "the process of determining whether exposure to an agent can cause an increase in the incidence of a health condition." This step is a qualitative synthesis of

available evidence to determine whether there is sufficient information to determine a causal association between the exposure and outcome of interest.

The process would be similar in the context of human health cumulative risk assessment, but there are some important distinctions. First, the process of developing a conceptual model for the cumulative risk assessment implicitly includes the hazard identification step, so it is not necessarily a stand-alone activity. In addition, the hazard identification process would differ somewhat depending on whether the cumulative risk assessment was stressor-based (bottom-up) or effects-based (top-down). In a stressor-based cumulative risk assessment, the hazard identification process involves evaluating a candidate list of stressors and determining which are appropriate for inclusion. The stressors could be considered individually without interactions, as has been performed in many health risk assessments to date. However, it also is of interest to include stressors that modify only the health risks of another stressor, or stressors that could significantly modify exposures or doses of a chemical or non-chemical stressor determined to be hazardous. For example, suppose that a cumulative risk assessment of pyrethroid pesticides was being conducted. Piperonyl butoxide often is included with pyrethroid pesticides as a synergist that increases the potency of pyrethroids [27]. A hazard identification step narrowly focused on piperonyl butoxide as an individual agent could conclude that it is unlikely to contribute to health effects of interest, but its ability to modify the risks of pyrethroids indicates that it should be included in a pyrethroid cumulative risk assessment. Similarly, suppose that a cumulative risk assessment of multiple metals was being conducted. Calcium does not have significant independent health risks but could modify the absorbed dose of lead or remobilization of lead from bone [28] and would be appropriate to include. Whether or not these steps are considered as part of hazard identification or the establishment of the conceptual model is less important than

ensuring that a systematic process is followed to determine the appropriate stressors to include. This systematic process should look at an array of chemical and non-chemical stressors to consider which ones are likely to have independent health effects, and which may increase or decrease the risk of stressors with hypothesized health effects.

For an effects-based cumulative risk assessment, the hazard identification process would be slightly different as the health outcome of interest already has been determined, which narrows the list of candidate stressors. The process of systematically examining the epidemiology, toxicology and exposure/dose assessment literature would be analogous to the process for stressor-based cumulative risk assessment. However, rather than a yes/no decision based on the likelihood that health effects or risk/dose modification would be observed, hazard identification in this context also would require an explicit consideration of the adverse outcomes of interest. As proposed in the phthalate NRC report [20] and described above, it would be more appropriate to use a broader construct of common adverse outcomes rather than mode of action in cumulative risk assessment. This would imply both a larger set of stressors under consideration and greater ability to leverage epidemiological or other human evidence in the absence of a precisely defined mode of action.

In summary, hazard identification is a crucial component of any cumulative risk assessment, likely embedded within the planning and scoping phase of the assessment. Hazard identification in cumulative risk assessment would require a somewhat broader set of considerations than hazard identification in single-chemical risk assessment, given the importance of considering effect modifiers or dose modifiers. As this is a qualitative step regarding the strength of available evidence rather than a quantitative modeling step, a variety of

information can be used in deciding which stressors merit inclusion, but the process should be codified to ensure consistency across analyses.

Exposure Assessment

Although much of the discussion about including non-chemical stressors in cumulative risk assessment tends to focus on the dose-response modeling component, characterizing human exposures to non-chemical stressors is a significant and non-trivial step. It is extremely challenging to accurately characterize exposures to chemicals, especially in a community context with consideration of multiple chemicals simultaneously. Non-chemical stressors are even more challenging. Many non-chemical stressors cannot be quantitatively measured or modeled using the same methods used for chemical exposures, and a subset depends on individual perceptions or context. This section briefly addresses four key dimensions of exposure assessment for non-chemical stressors:

1) The need to characterize the mechanism(s) of action and hypothesized pathways of effect to determine the most appropriate form of exposure characterization;

2) The importance of determining the appropriateness of proxy variables for non-chemical stressors, considering the level of operation and conducting validation analyses;

3) The need to consider correlates of exposure and other factors that would allow for appropriate characterization of joint exposures to chemical and non-chemical stressors; and

4) The need to establish default assumptions for exposures to non-chemical stressors in the absence of population-specific exposure data.

Characterizing mechanism(s) of action/pathways of effect

First, exposure characterization for non-chemical stressors is challenging because the same stressor can have multiple pathways of effect. Whereas many chemical stressors influence different organ systems and health outcomes, the pathways for some non-chemical stressors may not even be interrelated, with some exposures operating as both physical and non-physical stressors. Exposure assessment might need to differ depending on the outcome and pathway. For example, traffic is a source of both air pollution and noise, and an exposure metric predictive of air pollution may not be the same as an exposure metric predictive of noise. Similarly, housing characteristics that predict mold exposures may not be those that predict psychosocial stress related to the physical structure of the home. Even in situations with a well-defined empirical exposure measure, that measure may not be relevant to all pathways.

For example, noise can physically damage the inner ear, but also can be a psychosocial stressor. As a physical exposure, noise (really, sound) would be measured in terms of physical characteristics—such as amplitude (decibels) and frequency—using noise monitoring devices. As a psychological stressor, however, noise (i.e., sound which is perceived as annoying) is best measured using questionnaire instruments of noise-related annoyance or disturbance. The distinction is important, because the associated health outcomes, and the physiological pathways towards health outcomes, likely differ (i.e., physical vibration vs. psychological stress). Although these two measures of "noise" may be highly correlated, different characteristics may influence each, and best predict health outcomes; amplitude may predict impacts on sound-related pathways, while periodicity, or timing relative to sleep cycles, may best predict effects along psychosocial pathways.

The appropriate exposure assessment for the former pathway would be direct measures of sound, and the appropriate exposure assessment for the latter pathway would require measures of perceived irritation. Although a direct measure of sound may correlate with perceived irritation, there could be significant exposure misclassification in using this measure directly for the latter pathway. Likewise, heat may physically stress an individual, leading to heat exhaustion or hypertensive outcomes, but heat also is uncomfortable and therefore psychologically taxing on individuals over extended periods (one reason that urban violence increases during the summer). The appropriate exposure measure for the direct physical effects on heat would not be identical to the appropriate measure for the perceived discomfort associated with heat.

A related challenge has to do with the possibility that sources of physical pollution could serve as psychosocial stressors by sending messages to residents about the value of their health and well-being to the larger society [29]. Indeed, it can be difficult to disentangle health effects produced by the physical aspects of air pollution from psychosocial health effects in communities near toxic sites [30, 31]. It is unlikely that exposure assessment for the psychosocial component of air pollution would be similar to the physical measurement of chemical concentrations, as there would not be a one-to-one relationship between the magnitude of concentrations and the resulting community response.

For these reasons, it is crucial for the exposure assessment step to be conducted with knowledge of the dose-response modeling component as well as the hazard identification step. Although it has been argued previously [17] that having exposure assessment be homologous with dose-response modeling is a critical feature of risk assessment in general, this is certainly important for non-chemical stressors in cumulative risk assessment. We recommend that any exposure assessment include a conceptual model of how the exposure would influence health

outcomes either directly or indirectly and therefore why and how the exposure measure being utilized is relevant. Two examples are shown in a subsequent section, wherein the conceptual models include only those stressors of direct interest to each risk assessment, and subsequent analyses strictly follow the hypothesized pathways of effect shown in the conceptual model.

Understanding the pathway of effect is even more challenging for psychosocial stressors, which are hypothesized to act on human health through psychological stress pathways. The same is true for ecosystem services, which are hypothesized to act on human health through multiple pathways, including concentration reduction (e.g., amelioration of heavy metal concentrations in groundwater), exposure modification (e.g., alteration of human activity patterns, through appealing locations for walking or bicycle riding), and reduction of psychological stress and stress-related susceptibility (through recreation and access to quiet space). Below, we briefly describe specific characteristics of these two families of non-chemical stressors. Although there are numerous additional families of non-chemical stressors with significant exposure challenges, these examples are illustrative of the challenges that exist for other non-chemical stressors.

Psychosocial stressors are hypothesized to lead to negative health outcomes directly, or through stress-related alterations in immune, neuroendocrine, or metabolic function, collectively referred to as *allostatic load* [8]. Through these multiple stress-related pathways, chronic stress may serve to damage the individual's health directly, or may alter the individual's susceptibility to exposures in the physical environment, including air pollutants [3] or cold viruses [32].

The psychosocial stressor pathways can be best understood by realizing that psychological stress results when external demands exceed an individual's perceived abilities

and resources to meet those demands [33]. This may be best characterized as a three-phase process:

(1) Stressor (i.e., event, condition or stimuli which poses a challenge),

(2) Appraisal (i.e., an individual's perception or interpretation), and

(3) Response (e.g., psychological and physiological sequelae) [33].

These phases are not independent, and all phases are required to exert a psychological or biological stress response; a stressor perceived as benign or beneficial produces no stress response. Thus, exposure assessment for psychosocial stressors would ideally not simply catalog stressors (e.g., life events, community violence), but would rather emphasize total perceived stress (capturing response to multiple differently appraised stressors), or negative affect (e.g., anxiety, depression) as a cumulative indicator of mental distress and psychosocial stress [34, 35]. In the context of cumulative risk assessment, it can be extremely challenging to quantitatively address either the appraisal or response phase, especially for populations, but it is important to keep in mind these potential modifiers in interpreting exposure measures for psychosocial stress, which may reflect only the first phase. It is a topic of ongoing research to validate the association between community-level stressors (e.g., crime) and individual perceived stress, or to better understand the factors that lead to stronger or weaker associations between stressor indices and mean stress response.

Because of the challenges in understanding individual stress responses from community-level stressor data, there has been increasing interest in developing biomarkers of stress. In theory, a well-characterized biomarker could elucidate the mechanisms of action, lead to more epidemiological/toxicological insight and provide a means of estimating exposures. However,

there are numerous challenges. Stress is, by definition, a non-specific condition that affects a wide range of bodily systems [36] and which may have differing effects in the presence of different co-exposures and pre-existing conditions. As such, physiologic responses to stress vary widely across individuals and types of stressors (e.g., acute vs. chronic stress are physiologically very different), and it is unlikely that a single biomarker—or even a resolved suite of biomarkers—will reliably and meaningfully capture all stress responses.

Nevertheless, much research has been done on the physiology of stress and the search for "biomarkers" of acute and chronic stress. To date, most "biomarkers" identified have been immune or neuroendocrine markers associated with physiological stress responses—e.g., cytokines and glucocorticoids [37]—and an important emphasis has been on distinguishing biomarkers of acute stress (e.g., cortisol as indicator of HPA-axis activity) from those of chronic stress (e.g., endocrine disruption, or NK-κB signaling as an indicator of HPA-axis regulation) [38].

Formerly, corticosteroids (e.g., cortisol) in blood or saliva were emphasized as markers of HPA-axis activity, although stress-related HPA function changes lead to cortisol dysregulation (via glucocorticoid resistance and HPA regulation), not simply increased cortisol production. As such, cortisol can be difficult to interpret and generally better indicates acute, rather than chronic, stress. Recent research emphasizes indicators of glucocorticoid resistance and neuroendocrine signaling [38]. Other evidence suggests that C-reactive protein (CRP) may reasonably capture chronic stress; unfortunately, however, CRP is a non-specific immune marker also elevated in response to air pollution and other exposures [4, 6]. Although no single biomarker is appropriate for all applications [39], suites of physiologic parameters have been developed to represent allostatic load in humans and include indicators of cardiovascular function, metabolism,

cholesterol, glucose metabolism, HPA-axis function and sympathetic nervous system activity [34, 35]. Several studies that document chronic stress effects on cardiovascular risk indicators (abdominal obesity, elevated serum triglycerides, lower levels of high-density lipoprotein (HDL) cholesterol, glucose intolerance, elevated blood pressure) [39], known collectively as "metabolic syndrome," may provide a method for capturing cumulative stress effects on cardiovascular and systemic function.

It is important to recognize that biomarkers representing physiological responses to stress provide insight more relevant to dose-response modeling, or to determination of the mechanism of action, than to exposure assessment per se. There may be particular utility in characterizing some of the above biomarkers for an effects-based cumulative risk assessment, since multiple chemical and non-chemical stressors may influence measures of cardiovascular function or other endpoints. However, at this point in time, these biomarkers of biological stress responses do not directly inform the question of exposure characterization for the at-risk population. Stated another way, following the stressor-appraisal-response model, biomarkers can most readily capture the response, available exposure databases can most readily capture the stressor, but it is arguably the appraisal (the individual's perception or interpretation) that is most specific and germane to the exposure assessment phase of psychosocial stress.

Similar challenges exist in the realm of ecosystem services, which can be characterized in a variety of ways and can influence health through numerous pathways, including influencing air quality [40] or water quality [41], encouraging increased exercise, or providing psychosocial benefits [42, 43]. For those ecological amenities and services that modify exposures in a positive or negative way [41], trapping or releasing toxic chemicals or removing pathogens, the critical issue from an exposure assessment question is whether the exposure model used for the chemical

stressor appropriately takes account of the influence of changing ecological services. In particular, within a risk management paradigm, it would be important to understand whether the various candidate intervention strategies would have a direct or indirect effect on ecosystem services that are hypothesized to influence human exposures to the chemical stressors of interest.

The U.S. EPA has taken steps to research and analyze ecosystem services and amenities by developing tools to enable decision-makers at all levels of governance to proactively conserve ecosystem services. One of these tools is a National Atlas of Ecosystem Services, which is being developed in collaboration with other organizations such as the United States Geological Survey and the National Geographic Society. The Atlas will use the principles of landscape ecology and spatial analyses to display the production and beneficiaries of ecosystem services [44]. A community-scale component of the Atlas, the Urban Atlas, will characterize ecosystem services at fine scales, much as EPA's Community-Focused Exposure and Risk Screening Tool (C-FERST) does for human exposure estimates (e.g., census tract level or finer). The availability of these tools is anticipated to provide databases, sometimes screening-level or geographically specific default-type estimates, to facilitate community-based and community-led assessments.

Other amenities are able to modify human responses via improved health or psychological attitudes and supplying spiritual places or social connections [16, 43]. Influences on psychosocial stress would be addressed following a similar logic as described earlier, and the critical question might be whether characterization of ecosystem services can provide a meaningful proxy for psychosocial stress or other proximal predictors of health outcomes in some contexts. This issue is addressed in the subsequent section.

Green space provides an interesting case example where the relevant approach for characterizing exposure would depend significantly on the health outcome of interest and the hypothesized pathway of effect. For example, studies have shown that a direct relationship exists between an individual's proximity to a park and their physical activity level; one study reported that people living within 10 minutes of a park were more physically active than those who lived farther away [45]. If the health outcome of interest were modified by frequency of exercise, the distance from the nearest green space could be a valuable construct (serving as a proxy for frequency of exercise, which may not otherwise be available). On the other hand, green space also may foster social interaction by providing a central area for community members to interact with one another [46]. This could be manifested through a psychosocial pathway. Also it could be argued that green space would lead to local air pollution reductions [40], potentially influencing the ability of central site air pollution monitors to explain exposure patterns. Under this scenario, it could be necessary to reinterpret or adjust the air pollution epidemiology given differences between the study setting and the local community in urban tree canopies and to explicitly consider the types of trees within the neighborhood.

There are analogous challenges in characterizing exposures to other non-chemical stressors. The universe of potential non-chemical stressors is too extensive to articulate the approaches for each within this white paper, but we recommend that risk assessors formally describe the mechanism(s) of action and systematically examine the dose-response evidence to determine the most relevant exposure assessment approach.

Using proxy variables

As many non-chemical stressors would be difficult to measure or model directly within a cumulative risk assessment, there is often value in constructing proxy variables that would capture geographic and demographic patterns in exposure. As mentioned previously, individual stress responses are often approximated using community-level stressor indices (e.g., census level poverty rates), in part because of the limited individual-level data. However, in many contexts, even characterization of relevant community-level stressors may not be viable, and risk assessors may want to use relatively simple aggregate-level data on SES or other measures as a proxy for psychological stress or other related factors. When doing so, analysts should make sure to describe the hypothesized pathways by which these measures would operate, taking care to differentiate between compositional versus contextual variables. Compositional variables refer to measures that reveal information about the distribution of individuals within a community, whereas contextual variables reveal information about the setting in which individuals live. In other words, a measure of community-level poverty could be considered as a proxy for the likelihood of individual poverty that would directly influence individual health (a compositional variable), or as a measure of collective efficacy, disinvestment in a community, or other features that would impact multiple individuals simultaneously (a contextual variable).

Because there are numerous measures of SES, or socioeconomic position (SEP) and given potential confusion about what these proxy variables mean in the context of cumulative risk assessment, we briefly describe key definitions and concepts. SES/SEP refers to the individual or family's position in a society, particularly in societies wherein economic and cultural factors determine resource access. SES/SEP influences human health through a highly complex mix of social and physical factors accumulating and interacting over the life course.

These factors may include diet and health behaviors, access to health care, working and housing conditions, and many others. The impact of SES/SEP on health has been extensively explored in many settings: using wealth or income as an index of status within and across countries [47], in communities using measurements of perceived social standing [48], and in workplace settings using job grade [5, 49]. Increasingly, psychosocial stress appears to be one extremely important part of SES/SEP effects on health, though SES/SEP should not be considered as synonymous with psychosocial stress.

The differentiation between contextual and compositional variables and the numerous pathways by which SES can operate are important, not only because of the implications for the appropriate structure of epidemiological studies using these proxy variables, but also because there could be different mechanistic pathways at play. For example, the percent of households under the poverty line could be a compositional variable that captures the individual-level likelihood of poor nutrition, inadequate access to health care and so forth. Also it could be a contextual variable that captures attributes of the neighborhood that may be injurious to health. The analyst must specify what constructs proxy variables are meant to represent and through what pathways these constructs are hypothesized to operate.

In addition, wherever possible, validation studies should be performed to ensure that an aggregate-level indicator (especially when used as a compositional variable, a proxy for data on individuals) accurately captures intra-community variability in the construct of interest. For example, use of community crime statistics to proxy for crime-related stress could be validated using intra-community surveys enabling comparison of crime indicators to individual-level reports of perceived stress. Although such validation studies may not be practical for many cumulative risk assessments, having these studies as the gold standard will encourage more

refined stressor characterization and improved understanding of the interpretation of proxy variables for non-chemical stressors, at both the individual and aggregate levels.

Incorporating exposure correlations

As a general point, any exposure characterization within cumulative risk assessment needs to explicitly consider possible correlations among stressor exposures, whether positive or negative. For example, if proximity to major roadways is associated both with increased exposure to traffic-related air pollutants and noise, then the exposure assessment should account for this fact. More complex scenarios could exist, as in the case of radon and smoking, where low-income apartment dwellers would exhibit higher rates of smoking but typically lower concentrations of residential radon [50]. Correlations could exist in the aggregate, for subpopulations, or only as a function of individual behaviors or activities. All of these dimensions should be considered, so that joint exposures to stressors are appropriately characterized.

In cumulative risk assessments of chemical stressors, these correlations are often captured through common exposure models or common behavioral pathways. For example, the organophosphorus cumulative risk assessment [51] used drinking water and food consumption data, coupled with pesticide residue levels, to simultaneously estimate exposures to multiple pesticides. A broader analysis that considered other contaminants in food or drinking water would need to follow a similar exposure modeling paradigm to ensure that the consumption patterns are maintained across stressors. Explicit inclusion of geographic and demographic predictors of food and water consumption, time activity patterns, and other behaviors relevant to

accurate exposure assessment would facilitate appropriate modeling of non-chemical stressor exposures that also may be associated with these predictors.

Establishing default assumptions

As mentioned previously, *Science and Decisions* [17] proposed that cumulative risk assessment needed to establish default assumptions to allow for the inclusion of non-chemical stressors in settings where available information is limited. The analogy in *Science and Decisions* was the Exposure Factors Handbook [52], a detailed document prepared by EPA that provides default distributions for drinking water consumption, breathing rates and a number of additional factors relevant to exposures through all routes. This information may be replaced by population-specific data, where available, but these data-driven defaults can approximate missing information in a variety of contexts.

In the realm of non-chemical stressors, default distributions can be characterized from large-scale population surveys, surveillance data, or the peer-reviewed literature, depending on the stressor of interest. Of particular relevance would be assumptions regarding the distribution of stressors difficult to characterize directly in a cumulative risk assessment, such as psychosocial stress. Understanding the readily available factors that correlate with psychosocial stress and could serve as proxies or predictors would be crucial in conducting assessments that are both meaningful and comparable across applications. *Science and Decisions* recommended that the process of assembling the "Non-Chemical Stressor Exposure Factors Handbook" involve both EPA and other agencies and stakeholders with greater expertise in the specific stressors of interest.

Dose-Response Modeling

As mentioned above, the dose-response modeling component of cumulative risk assessment has received the greatest attention to date, largely because of the significant methodological challenges. Whether epidemiological or toxicological evidence is available, there is a need to systematically analyze the available studies to arrive at appropriate dose-response functions. The issue of dose-response modeling in cumulative risk assessment is similar to the issues confronted for chemical mixtures. In this section, we first discuss current approaches for chemical mixtures and consider the extent to which they apply to a combination of chemical and non-chemical stressors. We then provide a generalized approach by which one could derive dose-response functions from the three broad categories of available evidence: toxicology alone, epidemiology alone, and a combination of epidemiology and toxicology. Although more methodological development clearly would be required within each of these categories, this white paper focuses on the conceptual frameworks necessary to make optimal use of available evidence.

Multiple chemical guidance and non-chemical stressors

For decades, EPA has developed approaches to determine dose-response functions applicable to simultaneous exposure to multiple chemicals. For example, EPA's *Guidelines for Health Risk Assessment of Chemical Mixtures* (1986) [53] describes dose additivity of effects if the chemicals are known to operate under a similar mode of action and cause similar health effects. However, if the chemicals do not operate under the same mode of action, then the default is response additivity. Non-chemical stressors, however, were not explicitly addressed in the Guidelines. In EPA's most recent attempt at guidance on multiple stressor cumulative risk

assessment, *Concepts, Methods, and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document* (2007) [22], multiple chemicals and multiple pathways are examined.

However, the scope of the *Multiple Chemicals, Exposures, and Effects* document does not include non-chemical stressors. The document states that, "this report does address each of the main analysis and characterization steps involved in implementing a cumulative risk assessment and most of the approaches should be applicable to broader types of stressors, complex exposures, interactions, and multiple effects" [22]. Also, EPA's default assumption of dose additivity is further analyzed for the occurrence of toxicological interactions, which include the less than additive (antagonism) and more than additive (synergism) net effects. Because these interactions also occur among non-chemical and chemical stressors, guidance that acknowledges these interactions among chemical stressors furthers the efforts of assessing a multiple stressor environment.

Based on the *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures*, "sufficient similarity" requires that a complex mixture that has been studied be similar to the environmental chemical mixture of concern [54]. For chemicals, this requires inclusion of the same major chemical components in similar proportions, but similarities in health effects and dose-response relationships also are to be considered. For psychosocial stressors, similarities in health effects and their relative degree of effect may fulfill "sufficient similarity" and create groupings of psychosocial stressors (or psychosocial and physical stressors) that could be beneficial to the cumulative risk assessment process. Similar to chemical groupings, psychosocial stressors may be reviewed for their co-occurrence, joint action and mode of action. For these reasons, it was proposed [55] that the conceptual framework for

chemical mixtures could be adapted to combinations of chemical and non-chemical stressors, with a systematic approach to determining which stressors could be reasonably grouped and to determine whether a "mixture" of chemical and non-chemical stressors analyzed in a given study was sufficiently similar to the mixture of interest for the cumulative risk assessment.

The approach used by EPA in the *Multiple Chemicals, Exposures and Effects* document is most readily applicable to those stressors that can be measured in the same fashion as chemicals and that have somewhat similar or analogous fate/transport properties (e.g. radiation and particulate matter), given the emphasis on grouping through standard exposure scenarios and as a function of chemical characteristics and co-occurrence in media. For non-chemical stressors that do not meet these criteria (e.g., biological stressors, psychosocial stress, and ecological amenities), modifications or expansions to the approach would be required for inclusion.

The *Multiple Chemicals, Exposures and Effects* document also suggests that, "The characterization of complex exposures, even to a single chemical, might include well-measured exposures along with those that are conjectural or poorly understood. One option is to present the combined exposures and risks numerically for those aspects that can be quantified and then describe the complete exposure and risks in qualitative terms, estimating the impact on the risk estimate of the missing factors" [22]. Under this guidance, EPA allows for the assessor to incorporate qualitative data into the risk characterization and the result could be used for those psychosocial stressors that exist without quantitative data. Even for those stressors that have quantitative data, a qualitative approach may still be necessary if the numerical data are not robust. Establishing basic positive and negative relationships between psychosocial stressors and the population of concern also may be warranted or necessary. Similar to assessing background levels of a contaminant, establishing the population of concern's variance with regards to large

epidemiological databases may strengthen the risk assessment. As described in more detail in the *Toxicology* section below, understanding background exposures to non-chemical stressors may be key in determining the appropriate dose-response function, even if not all background exposures can be reasonably quantified. A qualitative approach to relevant non-chemical stressor interactions is preferable to their complete absence or relegating them only to the uncertainty analysis. Even for those non-chemical stressors with numerical data, just like chemical data, quantifying uncertainty and variability should still be addressed to the best extent possible.

In summary, several of the existing EPA guidelines on chemical mixtures and multiple chemical exposures may be modified for the benefit of including psychosocial and other non-chemical stressors into cumulative risk assessment. The problem with the existing guidance is in incorporating an assemblage of stressors that are dissimilar, with little knowledge of the interactions among the stressors or the mechanisms of action of the combination. Considering common adverse outcomes rather than common mode of action will be helpful in determining an appropriate list of candidate stressors, but limitations clearly remain. Two situations arise that present particular challenges: combinations of chemicals causing unique responses not seen with the individual stressors; and clusters of stressors, each at low levels, causing adverse effects because of their synergistic, additive or other combined influences.

With more data on the components of the grouped non-chemical stressors, further parsing may allow for calculation by response additivity in situations where assumptions of dose additivity are not warranted. In assuming response additivity of the chemical mixture, Mumtaz noted the importance of "correlated susceptibility" in EPA's chemical mixtures guidance [56], which EPA refers to as the pair wise correlation coefficient. A completely positive correlation of susceptibility results in a hazard index that is simply the highest hazard quotient associated with

the mixture. Characterizing the hazard index of a group of stressors by the highest hazard quotient found in the group may serve to simplify the inclusion of similar, co-occurring non-chemical stressors in cumulative risk assessment.

Developing dose-response functions using toxicology alone

In many cases, only toxicological information will be available for a cumulative risk assessment. When evaluating toxicological evidence, the question of cumulative exposures is salient for both cancer and non-cancer risk assessment. However, following conventional risk assessment practice, non-cancer outcomes are typically assumed to have threshold responses, so that the omission of cumulative exposures could result in a zero risk prediction in a situation where health risks could be present. In contrast, conventional cancer risk assessment (for mutagens and compounds without established modes of action) would quantify risks associated with each individual constituent and assume additivity across risk estimates, and the methodological changes needed to incorporate cumulative exposures into cancer risk assessment may be less daunting than for non-cancer risk assessment. We focus on non-cancer risk assessments in this section, given the salience of the information and the emphasis in *Science and Decisions* on revising the non-cancer dose-response modeling approach, but recognize that analogous issues exist for carcinogens.

For non-cancer risk assessments, non-chemical stressors can be considered in three different places. First, as discussed above, if there is direct toxicological evidence on the non-chemical stressor illustrating a similar mode of action as a chemical stressor, it can be treated similarly to a chemical mixture. An example of this would be rat models of lead and chronic stress [57] or concentrated air pollution and chronic stress [4-6], where the non-chemical stressor

is considered in the same bioassay with a range of well-characterized exposures. As proposed in the NRC report on cumulative risk assessment for phthalates [20], dose-addition can be applied in contexts other than congruent dose-response functions, allowing for a broader set of applications. This report also proposes approaches to establish benchmark dose (BMDL) values for chemical mixtures under an assumption of dose-addition, which can be directly applied to non-chemical stressors as well if the analogous toxicological data are available and if the dose metrics are relevant to human populations. This is a viable approach in selected contexts where exposures to non-chemical stressors can be readily characterized in toxicological studies.

Second, non-chemical stressors also can contribute toward a general understanding of the appropriate conceptual model for stressors that have been evaluated toxicologically. In *Science and Decisions* [17], the committee proposed that the functional form of a dose-response model could only be determined once a series of diagnostic questions were asked, related to the mode of action, relevant background exposures and endogenous processes, and vulnerable populations. Depending on the responses to these questions, the population dose-response function would reflect one of three conceptual models: non-linear responses for individuals with low-dose linear population responses, non-linear responses for individuals with low-dose non-linear population responses and linear responses for individuals with linear responses for the population. Historically, non-cancer responses have been considered in the second category, but the presence of significant background exposures and processes could be sufficient to linearize an otherwise non-linear population dose-response function.

Practically speaking, this means that more general mechanistic knowledge for some non-chemical stressors could inform the shape of the dose-response function for those stressors with adequate toxicological evidence. As a simple example, consider hypertension, where

psychosocial stress, smoking, diet and numerous other non-chemical stressors have been associated with increased risk of hypertension or elevated systolic/diastolic blood pressure, though perhaps not toxicologically in a manner necessary to follow the first approach described earlier. The non-chemical stressors are both associated with the outcome of interest and prevalent in the general population. This would imply that toxicological evidence associating a chemical stressor with blood pressure or hypertension would be assumed to follow the first conceptual model above, with the point of departure (POD) used to develop a slope term and an estimated risk-specific dose. This approach is conceptually viable but has two significant challenges. The first, mentioned earlier, is that it may be unclear whether the background processes are sufficient in magnitude to conclude that a low-dose linear model would be appropriate. Experience with some case studies would help to formalize this step. The second is that one would not be able to quantify the risks attributable to non-chemical stressors incorporated in this manner. Although this would be problematic in contexts where these non-chemical stressors were the targets of risk management efforts, they would only be included in this manner if there were no adequate toxicology or epidemiology, in which case they would be omitted from quantitative analysis regardless of the approach.

Third, non-chemical stressors could be captured within physiologically based pharmacokinetic (PBPK) models that provide insight about how these stressors would influence delivered dose or pharmacodynamic outcomes that could be the endpoints of cumulative risk assessments. For example, organophosphate pesticides have well-established PBPK models that characterize their influence on acetylcholinesterase (AChE) inhibition [58]. Non-chemical stressors could influence the metabolism of organophosphates or the amount of AChE activity. Even when lacking direct toxicological evidence on the influence of these non-chemical stressors

on AChE inhibition, the non-chemical stressors could lead to an adjustment of either the delivered doses from the toxicological study or the interpretation of the pharmacodynamic outcome.

In summary, if the *Science and Decisions* paradigm for non-cancer dose-response modeling were adopted, non-chemical stressors could be systematically introduced in multiple different ways. The first approach described earlier does require quantitative exposure measures in toxicological studies that can be translated to human equivalents, which may not be viable for many non-chemical stressors (those that cannot be incorporated toxicologically, those without quantifiable exposure measures, and those where there is no reasonable approach for animal-human equivalence). The second approach is viable in a broader range of applications, and we recommend that EPA develop some test cases to determine the type of evidence needed to assume a linear versus non-linear population dose-response function. Case examples for which well-vetted epidemiological evidence is also available would be particularly relevant, as this could provide some comparison data. Finally, the third approach could offer a creative mechanism to incorporate non-chemical stressors for compounds with well-established PBPK models.

Developing dose-response functions using epidemiology alone

Given the dearth of epidemiological evidence available for chemical stressors, especially considering numerous chemical stressors in the presence of non-chemical stressors, there will be few situations where adequate and informative epidemiology is available for all relevant stressors. If epidemiology is available for all stressors of interest, developing dose-response functions applicable to cumulative risk assessment can be relatively straightforward, but there

are still key diagnostic questions that need to be answered before dose-response functions can be fully characterized.

First, the ideal evidence would involve studies that included all risk factors simultaneously and reported their dose-response functions derived from multivariate models, controlling for the presence of other risk factors and examining effect modification where relevant. However, this will rarely be the case, both because many epidemiological studies are underpowered for such investigations and because many epidemiological studies do not report this information for all covariates even if available. Extracting dose-response functions for different stressors from different studies, generally from regression models that do not include all relevant stressors, is a viable approach only if it is determined that confounding factors are limited. Because epidemiological studies that do not include all relevant stressors likely omit some candidate confounders by definition, insight regarding the likelihood of significant correlations between exposures can be included based on external evidence and first principles. For example, two pollutants that are both dominant in the indoor environment and highly correlated with air exchange rates would likely be positively correlated, whereas an ambient air pollutant and a pollutant where the food consumption pathway dominates may be less correlated. Combining different studies also requires judgments regarding the distribution of vulnerable individuals in each population and the presence of significant exposures that may modify the associations of interest. In 2008, Levy proposed a framework through which epidemiological evidence could be evaluated for cumulative risk assessment, including examination of the "mixture" of chemical and non-chemical stressors present in individual studies to determine sufficient similarity, explicit consideration of vulnerability attributes and their presence/absence in various studies, and methods to combine evidence across multiple studies [55].

Another complexity arises from epidemiological studies that include socioeconomic and demographic covariates as proxies for a variety of non-chemical and lifestyle risk factors for which exposures could not be readily characterized. For example, SES may be included in a regression model linking lead with IQ decrements, with the idea that SES could proxy for psychosocial stress, nutritional factors, presence of a stimulating home environment, or a number of other risk factors associated with neurodevelopment. Using the findings for SES, either as a main effect or a modifier of the lead-IQ association, would require a careful judgment about what the term is capturing within the study population and whether the same association is present in the population of interest for the cumulative risk assessment. Development of a detailed conceptual model that includes both proximal and distal effects on health, as described earlier, will facilitate this process.

As another example, epidemiological studies are increasingly considering the influence of ecosystem services, which could potentially modify dose-response functions for chemical stressors. Studies have shown that open spaces, particularly parks, encourage physical activity and healthy social interactions among users [59, 60]. A lack of adequate physical activity levels may result in obesity, which in turn is related to a wide variety of health disorders, including cardiovascular disease, type 2 diabetes, gall bladder disease, and certain types of cancer [61-63]. For a measure of open space to be an interpretable effect modifier in the context of cumulative risk assessment, there would need to be a clear and well-documented conceptual model linking open space to the health outcome of interest, and the planning and scoping step would need to describe the rationale for using this proxy variable rather than direct measures of physical activity or obesity. As with SES, ecosystem services interact with people/communities at multiple levels and through multiple mechanistic pathways and could therefore serve as a

valuable proxy variable. In addition, as with various measures of SES, ecosystem services can be construed as either a positive or negative attribute, as studies could analyze the absence of a positive ecosystem feature (loss of green space, loss of flood protection) or the presence of an adverse (deleterious) ecosystem feature (earthquakes and hurricanes).

Combination of epidemiology and toxicology

In many cases, there will be epidemiological evidence for a small number of stressors, toxicological evidence for other stressors, and perhaps a subset of stressors with both toxicological and epidemiological evidence. Developing a systematic approach to incorporate chemical and non-chemical stressors in this context will therefore be key to cumulative risk assessment.

Depending on the nature of the available evidence, a hybrid of the two approaches above would be warranted. In a situation where the preponderance of the evidence is toxicological and the epidemiology is not directly applicable, the more limited epidemiological information could help establish whether the toxicants should be considered as low-dose linear or low-dose non-linear. In situations where multiple compounds are well-characterized toxicologically and at least one is well-characterized epidemiologically, approaches can be used to establish dose equivalence within toxicological studies to allow for interpretation of the epidemiological evidence. For example [64], toxicological studies have linked both toluene and alcohol with similar neurobehavioral effects. Epidemiological evidence is robust for alcohol but not available for toluene. The toxicological studies can be used to estimate the dose of toluene that is functionally equivalent to a dose of alcohol for a defined outcome, and this could be used as a bridge to interpret the alcohol epidemiology with respect to toluene exposure. This clearly

involves a number of assumptions regarding comparable dose-response function shapes, but the approach can be generalized in a variety of ways.

Developing comparable dose-response models across epidemiological and toxicological studies, in a manner that would allow for the models to be quantitatively combined, would only be possible in a limited number of situations. The adverse outcomes would need to be comparable to one another, which may be possible for some physiological measures but would be challenging for outcomes such as asthma attacks, hospitalizations and other common epidemiological endpoints. There would also need to be detailed understanding of the vulnerability characteristics of both the human and animal populations, to ensure that adequate adjustments were made to account for the presumed greater heterogeneity in the human population. It is likely that these criteria would be met very infrequently, so that more often, cumulative risk assessment would be primarily based on either epidemiological or toxicological evidence, using the other to help inform the conceptual model or determination of mode of action.

Risk Characterization

The fourth step of a human health risk assessment is risk characterization, defined [26] as "the process of estimating the incidence of a health effect under the various conditions of human exposure described in exposure assessment. It is performed by combining the exposure and dose-response assessments." The 2003 EPA framework for cumulative risk assessment [1] devoted an entire chapter to risk characterization, and the 2007 resource document [22] discussed risk characterization extensively. We do not reproduce those recommendations in this white paper. Instead, we discuss the following three key dimensions relevant to the question of incorporating non-chemical stressors into cumulative risk assessment:

1) Appropriately conveying health risks attributable to chemical and non-chemical stressors given the risk management context and historical mandate of EPA;

2) For stressor-based cumulative risk assessments, applying methods to integrate across health outcomes to facilitate comparability; and

3) Developing approaches to communicate a blend of quantitative and qualitative insights.

We also discuss two additional concerns relevant to risk characterization and completion of meaningful cumulative risk assessments – characterization of uncertainty and variability (which has been discussed extensively elsewhere), and use of the risk management context to inform the risk characterization phase.

Appropriately conveying health risks

In Chapter 7 of *Science and Decisions* [17], the committee emphasized that cumulative risk assessment is not the same as comparative risk assessment and that the goal of cumulative risk assessment should not be simply to compare impacts attributable to an array of stressors. This recommendation is important particularly because of the inclusion of non-chemical stressors that could include lifestyle factors (e.g., diet, smoking) that could confer significantly greater public health risks than many chemical stressors, but also that are outside of EPA's control. A risk characterization step that focuses on the relative contributions of various chemical and non-chemical stressors to disease burden likely will not serve any realistic risk management decisions at EPA and may offend high-risk communities impacted by multiple important stressors. This extends beyond risk characterization to include aspects of risk communication, which is beyond the scope of this white paper, but it should be noted that research clearly

indicates that attributes such as voluntariness of the risk and ability to control the risk influence risk perception.

Instead, if cumulative risk assessments are structured around the specific risk management decisions as recommended earlier, the risk characterization step can focus on the incremental changes in risk associated with various risk management options. Non-chemical stressors not under EPA's authority could serve as effect modifiers, contributors to background processes, or co-benefits of the intervention strategies.

In cumulative risk assessment applications where a risk management construct is not feasible or reflective of the goals of the analysis, the risk characterization step should still separately describe those stressors that EPA has authority over versus those that are not influenced by any EPA actions. There would be some stressors that are not easily categorized, such as indoor air pollutants that are analyzed by EPA but are not formally regulated. As long as the risk characterization is clear in its description, the categorization is less important than the fact that the cumulative risk assessment is being conducted for purposes other than simple comparisons between individual stressors.

Integrating across health outcomes

A stressor-based cumulative risk assessment often will include an array of health outcomes that can be challenging to directly compare with one another. EPA's C-FERST provides a tangible example of this as it includes health outcomes ranging from lung cancer to asthma to heart attacks. In theory, a comparison across multiple risk management strategies, therefore, could involve tradeoffs between health outcomes. A number of approaches exist for assigning values to different health outcomes, including using quality-adjusted life years

(QALYs), disability-adjusted life years (DALYs), or economic valuation of health outcomes based on willingness to pay or cost-of-illness information. Providing specific recommendations regarding the appropriate approach for assigning values to health outcomes is outside of the scope of this white paper, but there are a few important issues that should be explicitly considered.

First, it should be recognized that any weighting scheme involves some implicit judgments about the relative importance of different subpopulations [65]. For example, as QALYs strictly depend on life expectancy remaining, an ailment or premature death for a young person would have much greater weight than a similar event for an older person. Similarly, the premature death of an individual with pre-existing disease would receive less weight than the premature death of a healthy individual. In contrast, willingness to pay (WTP) estimates will have an ambiguous association with remaining life expectancy, but clearly will increase as a function of wealth, which would not be the case for QALYs. Whether or not these and other assumptions reflect the values of decision-makers and other stakeholders is challenging to understand, and there will clearly be significant heterogeneity across individuals and populations. The key is to recognize that each weighting scheme has different implications and, ideally, an evaluation can be conducted on the sensitivity of risk management decisions to the weighting scheme applied.

Similarly, there may be stakeholders who would apply very different weights to health outcomes, or who would consider any weighting to make the assessments less, rather than more, interpretable. Any cumulative risk assessment should report findings both in the "natural units" of the health outcomes as well as with various weights applied, and ideally, should provide the stakeholders with the ability to apply their own weights easily and determine the implications. If

it is not feasible to provide a spreadsheet or other mechanism for dynamic weighting, a description of the relative weights that would be needed to change risk management conclusions would be helpful (i.e., "If lung cancer were assigned a weight at least X times the weight applied to asthma, then risk management strategy A would be preferred. Otherwise, risk management strategy B would be preferred.").

Blending quantitative and qualitative insights

Although most of the description in this white paper has centered on approaches to quantify exposures and health risks, the definition of cumulative risk assessment clearly states that quantification is not always an essential element. In almost any cumulative risk assessment, there will be a subset of stressors, outcomes, scenarios or other factors that can only be included descriptively, especially non-chemical stressors. Some of these factors will be used to construct the quantitative risk models (i.e., by contributing to insights about the appropriate shape of the dose-response model), but others will not be feasible to include in any quantitative components of the assessment. The risk characterization step, therefore, needs to articulate the quantified health risks and appropriately describe the qualitative elements in a manner that acknowledges the potential salience of the qualitative elements.

This issue has been addressed by the 2003 EPA framework for cumulative risk assessment and other guideline documents for risk characterization. A recent NRC report discussing health impact assessment [66] built on these prior documents emphasized the challenge in providing a blend of quantitative and qualitative information to stakeholders, as there is a tendency to dismiss qualitative information in the presence of quantitative estimates. This report concluded that quantitative information should be presented with detailed

descriptions regarding uncertainty, and qualitative information should be presented in a manner that provides clarity to the audience regarding its utility and potential applicability.

Additional considerations for risk characterization

Any risk characterization needs to include a clear description of both uncertainty and variability. This topic has been discussed extensively elsewhere, including in the 2007 resource document [22], *Science and Decisions*, and numerous guidance documents and reports. We do not reproduce this material herein, but note that there are a few dimensions particularly salient to cumulative risk assessments that include non-chemical stressors. There should be a description of how chemical and non-chemical stressors were placed into groups for risk evaluation; what the salient dimensions of uncertainty and variability were for exposure assessment, including in correlations among exposures and the likelihood of co-exposures; how mode of action or sufficient similarity determinations were made across stressors; and what sources and study types were used to derive dose-response data, with their attendant uncertainties. It should be noted that only a subset of these uncertainty and variability attributes are able to be quantified, so that the risk characterization should include both quantitative and qualitative discussions about uncertainty and variability.

In addition, the risk characterization needs to be relevant to the ultimate decision context, especially in settings where cumulative risk assessment is used to discriminate among risk management options. Risk management will depend on many factors beyond the outputs of the cumulative risk assessment, but the cumulative risk assessment should provide the necessary outputs for the risk management decisions under consideration. In a risk management context, as mentioned previously, EPA risk management teams will often face a situation with non-chemical

stressors that are not under EPA jurisdiction combined with chemical stressors over which EPA has legal authority. Although the risk characterization should necessarily focus on the chemical stressors targeted by risk management efforts, inclusion of the non-chemical stressors could lead to conclusions that health outcomes from chemical stressors will be more severe, justifying more aggressive controls (e.g., lower exposure levels). In some cases, inclusion of non-chemical stressors could justify less aggressive controls (if antagonistic effects are documented). Risk characterization should clearly delineate the influence of inclusion of non-chemical stressors on control decisions, including the sensitivity to key model assumptions. Similarly, more refined characterization of population or community vulnerability may lead to different conclusions about optimal control measures, and the key dimensions and their risk management implications should be clearly described.

In other situations, the inclusion of non-chemical stressors may not alter the risk management decision, but the available evidence of vulnerable subpopulations or interactions may lead to a call for more monitoring of health outcomes or stressor exposures, in situations where future controls may be under consideration. More information on non-chemical/chemical stressor interactions also may be able to clarify the decision options if sufficiently targeted, and the risk characterization should include a description of how insights from the assessment led to iterative refinement of the risk management options under consideration.

ILLUSTRATIVE EXAMPLES

To illustrate some of the approaches for incorporating non-chemical stressors described earlier, we present three brief case examples. The first example draws from the epidemiological literature suggesting significant effect modification of the association between urban air

pollutants and childhood asthma by chronic stressors prevalent in the urban environment, notably exposure to violence (ETV). We describe a process by which cumulative risk assessment could include both of these stressors, with the idea that the logical structure could extend to more stressors within a specific risk management context. The second example relies on toxicological evidence linking both lead and chronic stress with cognitive and neurological outcomes, and highlights some of the ways these data could be analyzed within a cumulative risk assessment. As in the first example, significant expansion would be required to complete a cumulative risk assessment appropriate for risk management decisions, but the case example provides a foundation for these future efforts. The third example presents an approach by which community characteristics can be incorporated.

Example 1: Exposure to violence and urban air pollution: Synergistic exposures impacting childhood asthma

Asthma is a multifactorial illness impacted by a host of social, environmental and genetic risk factors. As such, it serves as an appropriate case study for considering the interplay among two (or many more) risk factors—acting separately or in tandem—towards shaping patterns of asthma etiology and exacerbation in the urban environment.

This example may be conceptualized as part of either a stressor-based or effects-based cumulative risk assessment. For example, an analysis might consider the health benefits of multiple stressors reduced through traffic mitigation efforts, and would need to take into account the modifying influence of key non-chemical stressors. Similarly, an analysis might be focused on geographic areas with elevated asthma prevalence or rates of exacerbation, determining key contributors to these patterns, in which case ETV and air pollution may be important to consider.

Most epidemiological studies that have considered effect modification of chronic stress, to date, have explored exposures to air pollution. This focus is primarily due to concerns not only about spatial correlations between these exposures and resultant confounding factors (e.g., traffic-related air pollution is spatially confounded by traffic-related noise), but also is driven by common mechanistic pathways for key health outcomes. Other physical exposures, however, such as the common cold virus [32], can be conceptualized as environmental exposures, and also have shown synergistic effects with psychological stress in epidemiological studies.

ETV is explored here as only one example of an important urban stressor that may influence susceptibility to physical contaminants, in part because there is a small but growing body of literature documenting the salience of urban violence in modifying pollution health effects. A study of asthmatic children in Boston public housing reported altered response to indoor allergen exposures with caregiver-reported fear of violence [67]. A longitudinal study of childhood asthma etiology in East Boston reported significant associations with nitrogen dioxide (NO_2) exposures, but only among children with above-median prior lifetime exposure to violence [3]. This epidemiological study was modeled in one toxicological study exploring the effect of an aggressor stress (Social Dominance Paradigm), as a modifier of concentrated particulate air pollution (CAPs) effects on respiratory function in rats [4]; the authors reported substantively different responses to CAPs by stress group; with only stressed animals breathing more frequently and shallowly (e.g., hyperventilation), resulting in increased CAPs exposures.

A small number of studies have explored other indicators of chronic stress as modifiers of air pollution effects on asthma outcomes, though issues related to exposure measurement and the relative temporality between stress and pollution exposures have proved challenging [68]. Aside

from the existing epidemiological evidence suggesting a strong effect, there are several reasons why ETV is an appropriate stressor to examine in a cumulative risk assessment context.

1) Most importantly, violence is one of the few stressors that are rarely positively appraised. As described in the **Exposure Assessment** section above, under *Characterizing mechanism(s) of action/pathways of effect*, stress is a construct inherently about individual perception. Unlike ETV, most other stressors may be appraised either positively or negatively by the individual (e.g., one may view losing a job as a good or bad thing, depending on whether one enjoyed the job). A positive appraisal can render the stressor null; as such, most other stressors lend themselves to exposure misclassification. There is little reason, however, that exposure to violence would be characterized as a positive exposure.
2) Outside of the rare instances of physical altercation, most of the impact of "exposure to violence" is through fear, hyper vigilance, or stress-related pathways. (Indeed, the experience of "fear of violence" can vary by gender, age, race, class and other personal and community-level factors.) Because the majority of the exposures occur via psychosocial pathways, unlike other urban community stressors (e.g., housing quality), the hypothesized psychosocial pathway is relatively unconfounded by an inherently co-linear physical exposure.
3) Analyses of spatial patterning in urban exposures suggest that ETV may be less spatially confounded by poverty and other stressors than originally hypothesized [69]. Thus, the health impacts of ETV conceivably can be disentangled from those of SES, which is a much more complicated construct entailing a broad array of physical (e.g., diet) and

psychosocial (e.g., discriminatory experience) exposures, at both the individual and community level and accumulating over the life course, to shape individual health.

4) Crime data, albeit an imperfect community-level indicator of ETV, is collected systematically by every police department nationwide, often according to standard criteria, dependent on the type of crime. Reporting bias is absolutely a challenge—and this bias certainly differs by jurisdiction and type of crime—but the data are collected and available publicly nationwide.

Although the details listed above are specific to ETV, the logic used to validate its inclusion is generalizable. Any non-chemical stressor under consideration for a cumulative risk assessment would need to have a logical exposure metric that can be reasonably and systematically collected, evidence for a causal effect on a defined health outcome, and a systematic determination that the exposure metric is reasonably sensitive and specific for the health outcome in question.

We now explore how one would incorporate the interaction between ETV and air pollution into a cumulative risk assessment. As recommended above, we follow the steps outlined in *Science and Decisions* and the Menzie framework approximately, though noting that we lack a formal risk management context and, therefore, adhere more closely to the Menzie framework.

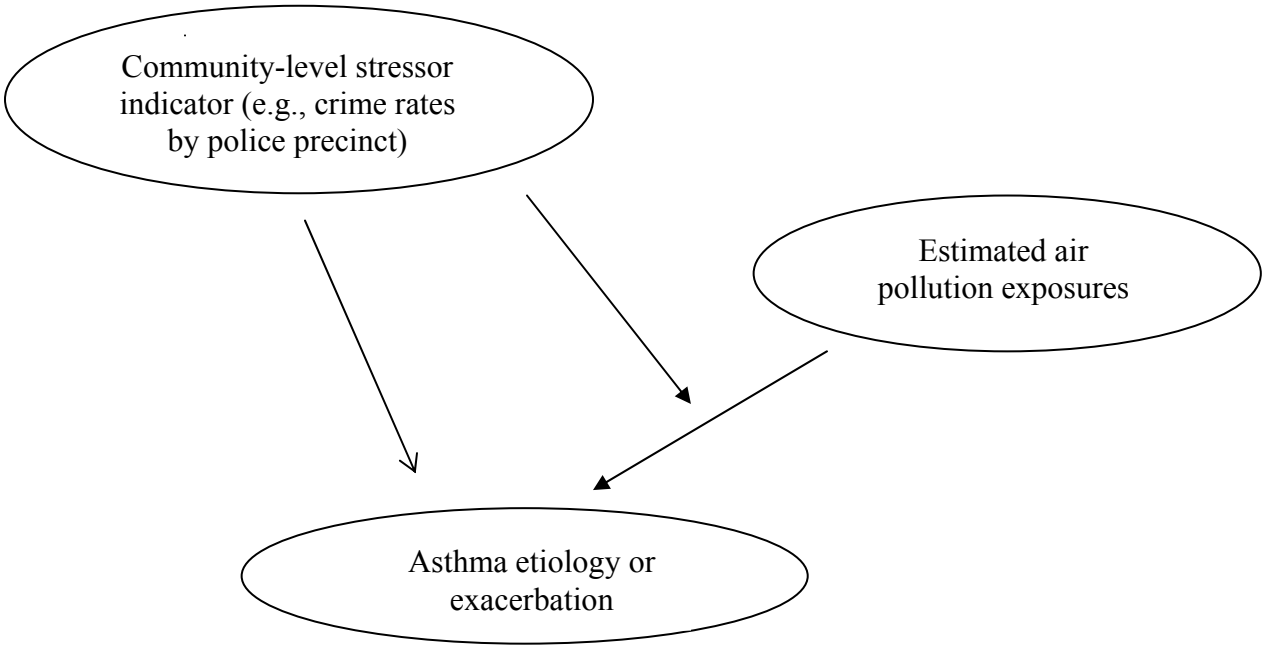
First, we recommend the careful development of a conceptual model depicting the hypothesized relationship among the primary exposures of interest, with attention to modes of action (MOA) or common adverse outcomes.

In the current example, the relatively straightforward conceptual model below captures some of the key hypotheses of interest:

1) A stressor (e.g., ETV) and air pollution exposures may influence separately childhood asthma etiology or exacerbation.

2) Perceived ETV (as a chronic stressor) may, through allostatic load pathways, alter individual susceptibility to air pollution exposures in the progression of asthma.

Notably, many more conceptual diagrams are possible, considering the myriad of exposures that impact upon childhood asthma. Here, we restrict our analysis to the one key exposure (air pollution) and one key hypothesized psychosocial effect modifier (ETV). A typical conceptual model likely would be more complex, with explicit consideration of multiple causal pathways and both proximal and distal risk factors for health.



In the conceptual model above, we allowed for a community-level stressor indicator (e.g., crime rates) to proxy (albeit imperfectly) for individual-level perceived ETV. In conceptual models for analyses in which both community-level and individual-level data are available, it

would be preferable to use the individual data as the primary exposure metric and to explore the community-level indicator as a predictor of the individual-level variable. Alternatively, the community-level variable may be explored as a contextual variable interacting (in a hierarchical model) with the individual-level variable of interest. At this early stage of the cumulative risk assessment, it is useful to determine what readily-available data (normally, community-level data, such as census demographic indicators, community crime data, or indicators of local school quality) are available that may capture the construct(s) of interest as well as the additional data that may need to be collected.

We recommend that each conceptual model be as clear and simple as can reasonably capture the key exposure(s) and pathway(s) of primary interest—even within a cumulative risk assessment that ultimately may include many interacting exposures on a complex disease outcome. Overloading the conceptual model may obscure the specific hypothesized pathways to be tested and lead to overly complicated (and less meaningful) "kitchen-sink" analyses.

The conceptual model—and its incorporated stressors, receptors and endpoints of interest—should be reviewed with stakeholders (e.g., community members, policy makers, researchers and others) within the initial planning and scoping phase. This ideally should include the evidence base used to derive each linkage, the rationale for each exposure proxy derived, and the process by which stressors were included and excluded from the conceptual model. Some of these decisions could be influenced by specific statistical analyses applied to available datasets, but this is more likely to be a process similar to hazard identification, in which evidence for causal linkages is systematically evaluated. Reviewing with a diverse set of stakeholders may be informative particularly in identifying overlooked exposures, modifiers and related health outcomes of interest to the community.

In the case of community-scale exposure metrics (e.g., police precinct crime data) and distributed environmental exposures (e.g., air pollution), it can be valuable to apply spatial methods in Geographic Information Systems (GIS) to evaluate the relative spatial distributions within and between exposures of interest. In the example above, it would be valuable to understand:

1) Spatial (neighborhood-to-neighborhood) variability in crime rates—this extent of spatial "clustering" (or spatial autocorrelation) within a stressor can be formally tested using GIS-based methods such as geographically weighted regression (GWR), or *Local Indicators of Spatial Association (LISA)*. This analysis indicates how each exposure, separately, varies across the region of interest. In an ongoing investigation of social stressor patterning across New York City, investigators find significant spatial variation within all stressors examined, across multiple domains (e.g., economic stressors, crime and violence exposures, resource access, school-based stressors, etc.) [69].

2) Spatial correlations between and among the multiple exposures (e.g., correlation between ETV and air pollution), which can be examined by comparing spatial maps of each stressor and quantified using methods such as spatial simultaneous autoregressive modeling (SAR). This analysis indicates the potential for confounding and/or effect modification between exposures. In New York City, investigators are finding that social stressors vary substantially in their spatial patterning and do not necessarily correlate spatially with poverty, or with air pollution exposures [69].

The framework calls for thoughtful screening of candidate stressors, to arrive at an appropriate and manageable number for the problem at hand. Although we mostly described epidemiological evidence above, the availability of toxicological insight [4-6] enhances the plausibility of the observed association. Beyond determination of causal linkages, this step likely would involve initial screening-level quantification of health risks to determine whether the stressors are significant enough to merit inclusion. In the case of air pollution and ETV, the relative risks from epidemiological studies are high enough, and the exposures sufficiently ubiquitous, to argue for their inclusion. In summary, the final conceptual model is based on epidemiologic and toxicological evidence, screening-level benefit calculations and feedback gained from stakeholders.

For manageability and interpretability, it can be helpful to shape clear mechanistic hypotheses that follow directly from the conceptual model, emphasizing the hypothesized pathways (modes of action/adverse outcomes) depicted for each stressor. To reduce the list of candidate stressors for a community-focused cumulative risk assessment, it may be useful to implement focus groups, open meetings and surveys to elicit those stressors that are deemed most important to the community.

In the example above, we may determine that we are interested solely in community-level stressors, which may act primarily through psychosocial stress pathways and can be captured reasonably through available data. To do so, we first define the construct of interest (e.g., ETV), then catalogue existing data that may reasonably indicate the construct (e.g., felony crimes, murders, robberies, at police precinct geographic levels). A practical limiting factor is that data that reflect the construct must be available throughout the region of interest. Note that it can be practical to avoid those stressors that may act through multiple pathways (e.g., as both a physical

and psychosocial exposure, such as housing quality), to avoid confounding the pathway/mode of action.

The original Menzie 2007 framework calls for the evaluation of the effects of individual stressors, as there may be a predominant stressor that is contributing, or could contribute, to an effect. In our example, this step would consider the epidemiological and toxicological evidence explicitly for the independent effects of ETV and air pollution (and other candidate stressors) on childhood asthma outcomes. Attention would be placed on the relative effect sizes observed for each exposure in the peer-reviewed literature.

To better understand how these steps might occur, it is valuable to consider the logic typically applied in epidemiological studies that evaluate air pollution and ETV. As a general point, it is preferable to determine relative risks from epidemiological studies that consider both stressors simultaneously (whether as main effects or effect modifiers), rather than deriving evidence from different studies. As the number of stressors under study increases, this becomes less practical given statistical power issues in the underlying epidemiology, but appropriately constructed multi-pollutant models are preferred generally, especially when there may be significant confounding or effect modification. The stepwise approach presented by Menzie (first looking at individual effects and then at combined effects) could be interpreted as univariate versus multivariate epidemiological models, but probably is interpreted more appropriately as attribution to individual stressors from multivariate epidemiological models versus the degree to which the combination of stressors explains patterns of outcomes in an effects-based cumulative risk assessment.

Conceptually, the underlying epidemiological models would be primarily of two types:

(1) Asthma outcomes = [best metric(s) of ETV] + confounders

(2) Asthma outcomes = [best metric(s) of air pollution] + confounders

In each case, the list of confounders could include the other stressor (i.e., a single multi-stressor model with both ETV and air pollution), although effect modification likely would not be considered at this stage. Importantly, the best available metrics of each exposure may differ significantly in sensitivity and specificity (if, for example, the best available metric of ETV is a community-level index, and the best available metric of air pollution is a well-calibrated residence-specific model estimate). For this reason, differential exposure misclassification needs to be considered, both when comparing separate models that examine two different exposures on a common health endpoint and when merging both exposure metrics into the same epidemiological model.

At this stage, the underlying epidemiological study often would use GIS methods to visualize and formally assess the spatial relationships between each exposure (stressor) and the health endpoint of interest as described by Menzie [18]. Spatial correlations between each exposure (stressor) of interest and the outcomes of interest are the focus (e.g., correlation between ETV and asthma; correlation between air pollution and asthma). These associations can be examined by comparing spatial maps of each stressor with that of the outcome variable (e.g., asthma hospitalizations), and quantified using SAR or related statistical regression models, which weight observations by their spatial relationship (e.g., nearest-neighbor approaches, or inverse-distance-weighing between areal centroids). This analysis indicates the separate (unadjusted) association between each stressor and the exposure of interest.

The original Menzie framework also calls for the evaluation of the combined effects of the stressors of interest without considering the potential for interactions. The assumption

underlying this step is that each key stressor/exposure of interest carried forward in a cumulative risk assessment should have some significant independent association with the outcome of interest, regardless of the distribution of co-exposures or potential effect modifiers. In some cases, however, this may not be true; in the longitudinal study of childhood asthma etiology cited above [3], significant associations between traffic-related NO_2 exposures and asthma etiology were observed solely among children with above-median ETV. In cases of strong effect modification such as this one, the effect of the physical exposure of interest (air pollution) may be diluted to non-significance, if the sample has a high enough prevalence of low-susceptibility individuals. This concern may be alleviated through sensitivity testing of the modeling process, in which potential modifiers and exposures may be considered iteratively prior to final exclusion from candidacy. The epidemiologic model that would underlie such analyses is:

Asthma = [best metric(s) of ETV] + [best metric(s) of air pollution] + confounders

Simple statistical tools, such as multiple and logistic regression and process models, can be used to explore the contributions of various stressors to the health endpoint of interest.

At this stage, GIS-based spatial approaches can be used to visualize and examine the overlay of stressors with the observed health effects. As above, maps of each exposure and outcome can be compared and formally tested using SAR models for the extent of spatial autocorrelation. A refinement that may be useful at this stage is the composite examination of the combined spatial distributions in ETV and air pollution (or the spatial distribution in a composite index that combines these exposures) against the spatial distribution in the health outcome of interest (e.g., maps of asthma hospitalizations).

Finally, the Menzie framework calls for evaluation of the combined effects of the stressors, with the potential for interactions. Importantly, knowledge reflected in conceptual models should provide a grounding (and some limits on) the consideration of interactions at this stage. The incorporation of too many interactions, or of interactions not supported by a plausible mechanistic pathway, can complicate the analysis, reduce statistical power, and lead to uninterpretable results (especially as the number of stressors under consideration increases).

The epidemiological model that would underlie this analysis is:

Asthma = [best metric(s) of ETV] + [best metric(s) of air pollution]

+ [best metric(s) of ETV] x [best metric(s) of air pollution] + confounders

Long before this stage (preferably at the conceptual model creation), one should be clear about the role of each stressor in the analysis. For example, clear mechanistic hypotheses indicating which stressor is hypothesized to modify each exposure are needed for useful, interpretable epidemiological analyses and related cumulative risk assessment output. Conceivably, this could lead to some stressors being considered only as effect modifiers, because no plausible mechanism exists for a main effect absent another stressor of interest.

If we were extending from the Menzie framework to the *Science and Decisions* framework, most of the logic above would be similar. However, *Science and Decisions* emphasizes the utility of evaluating the benefits of different risk-management options. Although articulating these options is beyond the scope of our simple case example, we note that interventions under consideration by EPA likely would not influence ETV (at least directly). It would be most salient, therefore, to consider the influence of multiple risk management strategies on air pollution exposures, explicitly considering the influence of ETV as an effect

modifier. This would imply that understanding the main effect of ETV is less relevant, although it does contribute to an understanding of background rates of disease and characteristics of high-risk subpopulations. Although this is not an appreciable reduction in effort for a two-stressor analysis, an analysis of numerous stressors would benefit greatly from the analytical boundaries created through an appropriately focused set of risk management options.

Uncertainty analysis is emphasized as a key component of any cumulative risk assessment. For the epidemiology that may underlie a cumulative risk assessment, this goes beyond reported confidence intervals to include sensitivity analyses for the parameters included in the final models. We strongly recommend that any cumulative risk assessment extract information on the sensitivity of epidemiological findings to some key assumptions, whenever such information is reported. Similarly, researchers conducting epidemiological studies aiming to inform cumulative risk assessment should explicitly report such information. Reporting this information is important for a number of reasons. Principally, the available exposure data may be incomplete or biased and capture only a subset of the true range of exposures to any stressors, or mis-classify exposures by community.

Because some important modifiers and predictors may be lost by omitting variables prior to testing interactions (i.e., may miss effects that only become apparent through effect modification), some *sensitivity testing on covariate selection* is needed. This can be done by:

- Swapping order of terms/interactions tested in models
- Identifying key hypothesized predictors and modifiers carried throughout the analysis, regardless of significance

- Using automated variable selection procedures using both predictors and modifiers (e.g., regression trees)
- Using automated variable selection procedures that do not assume linearity or specific interaction structures (e.g., random forest). Tree and RandomForest algorithms also can help to identify underutilized stressor(s) for which data are available, but the relationships of such exposures with the outcome of interest have not been recognized fully in the main model.

Finally, assuming that communities and various stakeholders have been involved in stressor identification steps early in the planning and scoping stages of the cumulative risk assessment, through focus groups and other methods of stakeholder involvement, there remains significant utility in validating that available exposure metrics accurately capture variability in the stressor(s) of interest. An effective way to do so, for aggregate-level indices (e.g. community violence rates) is to implement surveys (questionnaires) on individual's perceived stress to systematically determine: (1) whether community-level indices accurately capture community-to-community variation in mean individual level violence exposures, and (2) to select those aggregate-level metrics that best reflect individual variation in stressor exposures.

In summary, the case example above illustrates that a psychosocial stressor such as exposure to violence can be incorporated reasonably into cumulative risk assessments including air pollution, as there is a biologically plausible linkage with a common adverse outcome (supported by both toxicology and epidemiology), an approach for exposure characterization that involves reasonable proxies from public databases, and empirical evidence supporting main effects and effect modification for both key stressors. Other non-chemical stressors can be evaluated and included through analogous approaches.

Example 2: Lead (Pb) and chronic stress on cognitive and neurological outcomes, with evidence from toxicology

Lead (Pb) is a known neurotoxicant, with well-established impacts on neural development and cognition [70] even at relatively low blood Pb concentrations [71]. More recently, a body of toxicological evidence indicated that animals exposed to chronic stress (i.e., intermittent variable stress or maternal separation from pups) may be more susceptible to the cognitive and neurological impacts of Pb [72]. This work indicated that combined effects of stress and Pb are not limited to early developmental stages; rather, impacts can accumulate throughout the life course and prove non-reversible (e.g., pre-natal maternal stress can produce permanent alteration in HPA-axis function in the offspring). Further, this work found that combined (interactive) effects of Pb and stress can be shown in the absence of an effect of either exposure alone (i.e., a greater-than-additive effect) [73]. This differential susceptibility to metals by chronic stress is shown to occur through permanent alteration of basal corticosterone levels, altered stress responsivity (i.e., permanent change to HPA-axis function), and the production of brain catecholamines. Further, these synergistic effects are not limited to young animals in developmental stages but have been observed in older animals as well. Finally, there is some epidemiological evidence that chronic stress may influence the association between bone Pb (a marker of chronic Pb exposure) and cognitive function in older men [74].

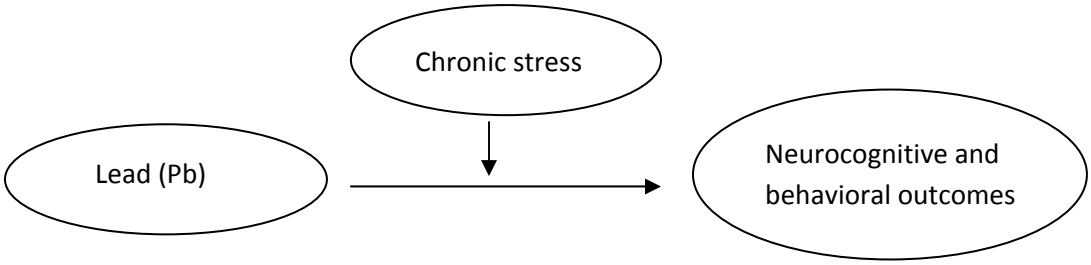
Here, we explore this Pb-stress interaction as one example for incorporating toxicological evidence on non-chemical stressors, as a modifier of the health effects of chemical exposures, into the cumulative risk assessment framework. We chose this example because it is supported by a strong body of toxicological evidence, it illustrates an approach by which a psychosocial stressor can be considered in a toxicological study with subsequent utility in cumulative risk

assessment, and it depicts a clear interaction between chemical and non-chemical exposures. As described above, toxicological evidence for non-chemical stressors can be used in a variety of ways. It can be used to develop dose-response functions analogous to those for the chemical stressors, it can be used to justify the appropriate conceptual model for dose-response modeling, or it can be used to modify the dosimetry or pharmacodynamic outcomes for a chemical stressor. In this case, as the stress is considered categorically (with and without stress) in the core toxicological analyses, the most likely approach would be to use the association between Pb and defined health outcomes among the subpopulation with stress exposures to determine a Point of Departure (POD), and to justify a linear dose-response function from the POD given the likelihood of significant background exposures and vulnerable populations. It should be noted that this "linear" dose-response function refers to the slope at very low dose having a non-zero slope, and that insight about mode of action could lead to alternative low-dose extrapolations (which may be valuable in the case of Pb, which has been shown epidemiologically to exhibit non-zero but non-linear responses at low dose). Conducting this assessment (including deriving POD from the reported toxicological studies) is well beyond the scope of this white paper. Instead, we focus on the conceptual application of the Menzie framework in this context, determining the most relevant approach for stressor inclusion/exclusion and modeling.

Step 1 of the framework calls for a conceptual model for the stressors of primary interest, including an assessment of the hypothesized MOA and identification of the relevant receptors and endpoints affected by these stressors.

In a stressor-based framework such as this one, this first step is somewhat simplified by focusing solely on the stressor(s) of interest, with a clear hypothesis about the MOAs of interest. Here, the researchers have hypothesized quite clearly that chronic stress may—through

physiological pathways including basal corticosterone production, regulation of the HPA-axis, and production of brain catecholamines—alter the observed association between chronic Pb exposures and neurocognitive or behavioral outcomes.



A useful aspect of incorporating toxicological data into a cumulative risk assessment is that toxicological studies offer clear exposure assignment and the ability to remove confounding through randomization and isolation of exposures. As such, the myriad of real-world confounders that may confound associations need not (necessarily) be controlled for in developing toxicological studies. Similarly, the data are easily incorporated into a clear conceptual model, as shown here, although development of the conceptual model would be more challenging in a cumulative risk assessment that included other stressors.

Because of the controlled nature of exposures in the toxicological paradigm, there may or may not be prior dosimetry information detailing whether and how delivered doses relate to normal human exposures. Extrapolation of doses would generally be needed as part of a cumulative risk assessment incorporating toxicological data. This is standard practice for chemical stressors using allometric scaling (or PBPK model outputs) and various adjustment factors for exposure duration. Determining an analogous approach for non-chemical stressors is more difficult. In this example, this could mean re-interpreting the "stress" exposures by considering the most relevant human equivalent and its likely prevalence. Although this

calculation may be infeasible in many contexts, the use of biomarkers of stress (even with their attendant uncertainties) could allow for linkages between animal and human populations. For example, though the toxicological studies listed above focused largely on populations exposed/unexposed to the stress paradigm, they also included measurements of corticosterone. This provides a theoretical vehicle for translation to human populations.

As in the prior example, before moving forward in the cumulative risk assessment process, the conceptual model should be reviewed with varied stakeholders (e.g., community members, policy makers, researchers and others) to improve the initial planning and scoping. Toxicological studies are less likely to be controversial from the perspective of causality, but it will be important to determine the human relevance of the findings and the ability to appropriately estimate the exposures of interest. In addition, because most toxicological studies have considered a limited number of stressors only, it may be informative to the conceptual model, particularly with a diverse set of stakeholders, to identify overlooked exposures, modifiers and related health outcomes of interest to the community. These community-specific confounders and modifiers may alter the true impact of the contaminant of interest on the community's health, accounting for some variation when applying toxicological results in risk applications. One may consider incorporating these additional stressors into the conceptual model, especially if they may confound the health effects of the primary exposure(s) of interest or lead to different conclusions about the appropriate functional form of the toxicologically derived dose-response function.

Finally, GIS and spatial methods may be useful equally in this example as in the prior one. To translate toxicological studies with clear exposure assignment into "real-world" estimations of risk, one must consider the true co-variance in the exposures of interest. To this

end, it can be valuable to apply GIS-based spatial methods to evaluate the relative spatial distributions in markers of Pb exposures (e.g., maps of Pb measurements in outdoor soils, older homes in which Pb remediation has not occurred, blood Pb concentrations from surveillance systems that include geocoded addresses, NHANES data with available geographic specificity) with spatial patterns in survey reports of chronic stress, or community-level stressor exposure indices (e.g., census tract poverty or police precinct crime data). As above, recommended analyses would include within-variable assessment of clustering using measures of *spatial autocorrelation,* and between-variable assessment of *spatial correlations*, using methods such as SAR.

Step 2 of the framework calls for the use of epidemiologic and toxicological evidence and screening-level benefit calculations to provide an initial evaluation of which stressors should be included in the cumulative risk assessment, incorporating stakeholder feedback. In the current example with our focus on two selected stressors, this is less relevant, although it may be useful to determine the health risks of Pb with or without consideration of effect modification due to stress. This step also is important in the event that only toxicological data allow for the inclusion of non-chemical stressors, but epidemiological data exist for chemical stressors. As described in the main text, incorporating a combination of toxicology and epidemiology data can be challenging, but it may be possible in some contexts to construct dose equivalents or use the toxicological insight to better interpret the epidemiological evidence.

Step 3 of the Science and Decisions *framework calls for the evaluation of the benefits of different risk-management options with appropriate characterization of uncertainty.* As in the prior case, we are not examining risk management interventions. Broadly, however, at this stage, one likely needs to shift from a predominantly toxicological focus and consider interpretations

for human communities and the characterization of risk management options. One may consider the potential modifiability of the stressors identified, to determine which, if any, may be amenable to policy or other risk management interventions. Presumably, this would involve multiple alternatives for reducing Pb exposures, most of which are unlikely to influence psychosocial stress.

Step 4 of the Science and Decisions *framework allows for the refinement of the cumulative risk assessment*, *accounting for potential interactions among stressors.* In the example shown here, interactions were considered explicitly from the earliest stage. We generally recommend doing so (or performing sensitivity analysis on omitting stressors, incorporating interactions), if possible, to avoid missing important chemical or non-chemical stressors that may have salience only in a subset of the population (e.g., vulnerable population), and hence would be missed in most univariate (or bivariate) screening analyses that do not consider interactions.

At this stage, it also may be important to consider those interactions not represented in the original conceptual framework. In this example, diet may be a modifier of the effect of Pb on cognitive outcomes; as such, one may want to consider two separate interactions in the ultimate model—one between diet and Pb and the other between stress and Pb.

Example 3: Community Assessment in Cumulative Risk Assessment

As mentioned previously, a key subcategory of cumulative risk assessments involves community-based assessments, in which characterization of the local community and its vulnerability attributes is critical, if challenging. Broadly, such characterization needs to rely on a combination of information gathered from the local community and information available from

public databases and other resources. The former would lead to more specific and realistic characterization, but the latter would be more feasible to incorporate rapidly and would facilitate comparisons across communities using identical databases. Tools such as C-FERST can catalog key community characteristics, including existing exposures and risks, providing a framework within which community-based cumulative risk assessment could be conducted [23, 75]. Although C-FERST cannot be populated with local information for all communities, it provides a common set of data and resources for all communities and can be supplemented with local data and insights where available.

Community-driven cumulative risk assessment can occur in a variety of contexts, but communities housing Superfund sites and other hazardous waste sites may be among the more common settings. A community (or system or receptor) based cumulative risk assessment could start in the absence of any known identified sources of specific stressors, but more often are likely to start in the context of an existing or planned source, such as the Superfund site context, and industrial facility or some proposed construction activity. The cumulative risk assessment process would begin with community (or system) characterization, including vulnerabilities, and existing health, psychosocial issues and concerns. Detailed source identification and stressor analysis would proceed following creation of the conceptual model and initial screening for stressors and effects.

To illustrate the content typical of a community characterization potentially available for cumulative risk assessments, we briefly present information below for the Lower Duwamish River site in Seattle, WA, and the surrounding neighborhoods.

Duwamish Valley Communities

The Duwamish Valley is a largely commercial and industrial area located south of downtown Seattle. The valley lies alongside the Lower Duwamish Waterway, a portion of the Duwamish River that was dredged and straightened by the United States Army Corps of Engineers in the early 1900s to accommodate fishing and shipping activities [76]. The Lower Duwamish Valley is 80 percent of Seattle's industrial land base, and historical and current industrial activity has left soil, groundwater, surface water, air, and sediment contaminated. Therefore, a 5.5-mile portion of the Lower Duwamish Waterway was added to the National Priorities List [77]. Georgetown, South Park, SODO, Delridge/Youngstown, Highland Park, and High Point neighborhoods are located within the Duwamish Valley among the industrial activities [78].

The Duwamish Valley communities are among the lowest income and most racially diverse neighborhoods in Seattle. Forty percent of South Park residents are Latino; other residents largely identify as Asian, African-American, or other non-white races (Pacific Islanders and Native Americans). Forty-four percent of the South Park residents are "white" compared with the Seattle average of 70 percent. Additionally, Duwamish Valley residents speak more than 30 different native languages. South Park, like other Duwamish Valley communities, is home to a large population of people living below the poverty line. In South Park, almost one out of every five children is living in poverty. A considerable homeless population resides along the Lower Duwamish Waterway in camps as well [78].

Members of the Duwamish, Muckleshoot, and Suquamish tribes reside in the Duwamish Valley communities. The Duwamish Tribal Longhouse was constructed in 2009 across the road

from the waterway. The Muckleshoot Tribal Fishery is located on the water, and both the Muckleshoot and the Suquamish Tribes have treaty rights to harvest fish and shellfish from the river [78]. Recreational access areas also have been established in the Valley.

The Agency for Toxic Substances and Disease Registry (ATSDR) conducted a regional modeling and health risk assessment in the area in response to Lower Duwamish Valley community residents voicing concerns over health problems, including cancer, miscarriage and respiratory problems [76]. The report concluded that exposure to chemicals from point sources in the area may result in an increased cancer risk. In addition to experiencing health problems, residents of South Park and Georgetown may be faced with gentrification as business and artist communities continue to grow in these areas [78].

For a cumulative risk assessment, much of this characterization would serve as qualitative descriptors to contextualize the analysis. The more challenging question is whether this community characterization or other related information could provide insight about either exposure or susceptibility factors. For example, detail about local fishing activities of tribes could lead to a more refined characterization of exposure to mercury and other contaminants found in fish. The articulated health concerns, if corroborated by surveillance data, could be helpful in determining vulnerability attributes relevant to the chemical and non-chemical stressors under study. The sociodemographic information is more challenging to directly incorporate, but could be helpful in determining the applicability of epidemiological evidence from studies conducted elsewhere.

Conclusions

Data on non-chemical stressors indicate important effects on health that can interact with chemical stressors in environmental exposure situations. Psychosocial stressors and ecological services and amenities represent two key categories of influences on exposures and/or responses for chemical stressors, with effects at the individual and community level, though other categories exist and cannot be categorically excluded.

Numerous non-chemical stressors could be important to include in cumulative risk assessment, even if they are not under EPA's direct authority, and deciding which non-chemical stressors to include is a key part of the planning and scoping process. Using a risk management framework to guide the analysis is one strategy to limit the number of non-chemical stressors included, coupled with approaches commonly used in ecological risk assessment to focus the analysis on the most important stressors.

The exposure assessment phase of cumulative risk assessment requires increased attention, given both the need to characterize effects of simultaneous exposure to multiple chemical stressors and the need to develop meaningful proxies of exposure to non-chemical stressors that are challenging to characterize directly. Development of a strong conceptual model including proximal and distal effects on health will help in determining the appropriate constructs for the analysis. This step is key, as many non-chemical stressors can influence health through multiple pathways and many proxies for non-chemical stressor exposure can represent multiple stressors.

Dose-response modeling for multiple chemical and non-chemical stressors remains challenging, but significant progress can be made by leveraging approaches used for chemical

mixtures using the new unified model for dose-response modeling proposed in *Science and Decisions* and making optimal use of both toxicological and epidemiological evidence. Non-chemical stressors that cannot be quantitatively incorporated as main effects or effect modifiers may still be valuable in determining the appropriate conceptual model for dose-response assessment.

Our case examples illustrate that it is viable to incorporate selected non-chemical stressors into cumulative risk assessment, using either epidemiological or toxicological evidence. Not all aspects of non-chemical stressor interactions were incorporated into those examples, but similar logic can be applied to other stressors that can potentially modify exposures and/or responses to chemical stressors.

Recommendations

- EPA should formalize the planning and scoping process within cumulative risk assessment, building on the existing approach developed in the 2003 framework for cumulative risk assessment to incorporate insights from ecological risk assessment and an orientation toward risk management decisions where relevant. This should include conceptual model development that incorporates expanded approaches for hazard identification and stressor inclusion/exclusion.

- EPA should adopt an orientation toward common adverse outcomes rather than common mode of action as a basis for characterizing combined effects of chemical and non-chemical stressors.

- The evidence base supporting the influence of psychosocial stressors, ecosystem services and amenities, and other key non-chemical stressors should be systematically described

in a manner conducive to inclusion in human health cumulative risk assessment. This includes an effort to catalog various stressors, their mechanisms of action and their exposure metrics.

- For non-chemical stressors for which empirical evidence of health effects exists but insight about mechanisms(s) of action is limited, primary research should be conducted that would allow for inclusion of these non-chemical stressors into cumulative risk assessments.

- Exposure assessment for non-chemical stressors should be done only after the mechanism(s) of action are formally described and the dose-response evidence is examined, to ensure that stressors are appropriately characterized.

- EPA should develop a non-chemical stressor Exposure Factors Handbook for non-chemical stressor exposures to be characterized in the absence of site-specific data.

- EPA should start to develop multiple case examples illustrating different approaches to cumulative risk assessment for chemical and non-chemical stressors. This includes examples of multiple chemical stressors in the presence of psychosocial stressors and ecosystem amenities. Evidence on pairs of stressors should be expanded to more complicated situations with a longer list of stressors such as multiple chemicals and multiple psychosocial factors.

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