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Is Epidemiology the Key to Cumulative Risk Assessment?

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Although cumulative risk assessment by definition evaluates the joint effects of chemical and nonchemical stressors, studies to date have not considered both dimensions, in part because toxicological studies cannot capture many stressors of interest. Epidemiology can potentially include all relevant stressors, but developing and extracting the necessary information is challenging given some of the inherent limitations of epidemiology. In this article, I propose a conceptual framework within which epidemiological studies could be evaluated for their inclusion into cumulative risk assessment, including a problem formulation/planning and scoping step that focuses on stressors meaningful for risk management decisions, extension of the chemical mixtures framework to include nonchemical stressors, and formal consideration of vulnerability characteristics of the population. In the long term, broadening the applicability and informativeness of cumulative risk assessment will require enhanced communication and collaboration between epidemiologists and risk assessors, in which the structure of social and environmental epidemiological analyses may be informed in part by the needs of cumulative risk assessment.

KEY WORDS: Cumulative risk assessment; environmental epidemiology; vulnerability

1. INTRODUCTION

Cumulative risk assessment, defined by the U.S. Environmental Protection Agency (EPA)[1] as the evaluation of the combined risks from aggregate exposure to multiple agents or stressors (both chemical and nonchemical), has received increasing attention in recent years. However, while the environmental justice community considers vulnerability and the contributions of nonchemical stressors to be central to cumulative risk assessment,[2,3] cumulative risk assessments conducted to date[4,5] focus largely on aggregate exposures to chemicals. This focus is related to the use of toxicological evidence for dose-response assessment, which could not plausibly yield insight about factors such as access to health care or socioeconomic status (SES), both of which are examples of key nonchemical stressors.[1]

Although the lack of sufficient human evidence often necessitates reliance on toxicological evidence, it is noteworthy that epidemiology received little mention in any of the cumulative risk assessment guidance or applications to date. The Framework for Cumulative Risk Assessment[1] provides no guidance for the use of epidemiology and only describes it as an "area of complexity." There is no mention of or reliance on epidemiology in the recent pesticide cumulative risk assessments,[4,5] and a PubMed search conducted in October 2007 found no articles that either used or proposed how to use epidemiological evidence in cumulative risk assessment. Even reports that express concern about social factors and other nonchemical stressors[2,3] make no explicit mention of the role of epidemiology, and publications that consider the role of epidemiology in risk assessment[6–9] do not address cumulative risk.

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At the same time, the epidemiological evidence base increasingly captures issues central for cumulative risk assessment. This includes studies of the joint effects of key chemical and nonchemical stressors[10–12] and evidence of sufficient background exposures, background disease processes, and variability in individual thresholds to imply that low-dose health effects would exist for some outcomes.[13,14]

If cumulative risk assessment is to address the questions that motivated its development, it must make better use of epidemiological findings and insight. In this article, I propose a conceptual framework for the incorporation of epidemiology into cumulative risk assessment, considering the primary limitations of epidemiology in a risk assessment context and proposing a path forward involving more active collaboration between epidemiologists and risk assessors.

2. LIMITATIONS AND ADVANTAGES OF EPIDEMIOLOGY IN CUMULATIVE RISK ASSESSMENT

A number of common issues are raised when considering the role of epidemiology in risk assessment. Causality is always a concern, especially in light of the numerous correlated environmental exposures in many settings.[7] Because of the possibility of confounding as well as variability across studies and populations, multiple studies are often needed to estimate dose-response functions relevant for a defined population. Exposure misclassification could result in biases in the resulting dose-response relationships. For health outcomes associated with chronic exposure, epidemiology requires populations to be exposed for significant periods of time before evidence can be derived, resulting in long time lags between study initiation and completion and limited study availability due to cost and logistical considerations. Epidemiology by definition requires health impacts to occur before risk management measures can be adopted. Finally, the available epidemiological evidence may be derived from occupational settings, creating issues with generalizability to the general public.

Although these are significant concerns, some are mitigated in the most common applications of cumulative risk assessment. The inability of epidemiology to be preventive is not as important if cumulative risk assessment is being used to determine the influence of a subset of stressors to which a population is currently exposed, or the benefits of controlling these stressors, which will be common risk management applications. Although situations in which numerous stressors are highly correlated are problematic for apportioning risk across individual stressors, they are less problematic when trying to define the health effects of bundles of stressors. If five pollutants were perfectly correlated with one another given a common source, it would be impossible for epidemiological studies to disentangle their individual effects, but it would be immaterial for cumulative risk assessment as long as their joint effects could be characterized across different relevant bundles of exposure. As risk management strategies are often source-oriented, evaluations of correlated exposures would be common.

Although variability in population response might imply that multiple epidemiological studies would be needed to determine an appropriate dose-response function, it would also imply substantial uncertainty for toxicologically based risk assessments using default characterization of human heterogeneity, emphasizing the value of epidemiology. Exposure misclassification could be increased by the need to determine exposures for multiple stressors. However, detailed exposure characterization would need to occur in a cumulative risk assessment using toxicological data as well, so enhanced exposure methods are needed regardless of the dose-response approach. In addition, any exposures relevant for a given health outcome would need to be included in an epidemiological study to limit confounding; cumulative risk assessment would simply make use of this information. For this reason, the time and cost of toxicological studies would increase exponentially with the inclusion of numerous stressors, with a lesser increase in effort for an epidemiological study. Applicability of occupational epidemiology to general populations requires further attention given that some dimensions of vulnerability may not be observed in the workplace. The framework proposed below attempts to address this and other issues.

3. FRAMEWORK FOR INCLUSION OF EPIDEMIOLOGICAL EVIDENCE INTO CUMULATIVE RISK ASSESSMENT

For any cumulative risk assessment, there would need to be a systematic process to determine which epidemiological studies (if any) would be suitable for the assessment, and how to incorporate the evidence from these studies. The framework outlined below and presented in Fig. 1 uses as its basis the

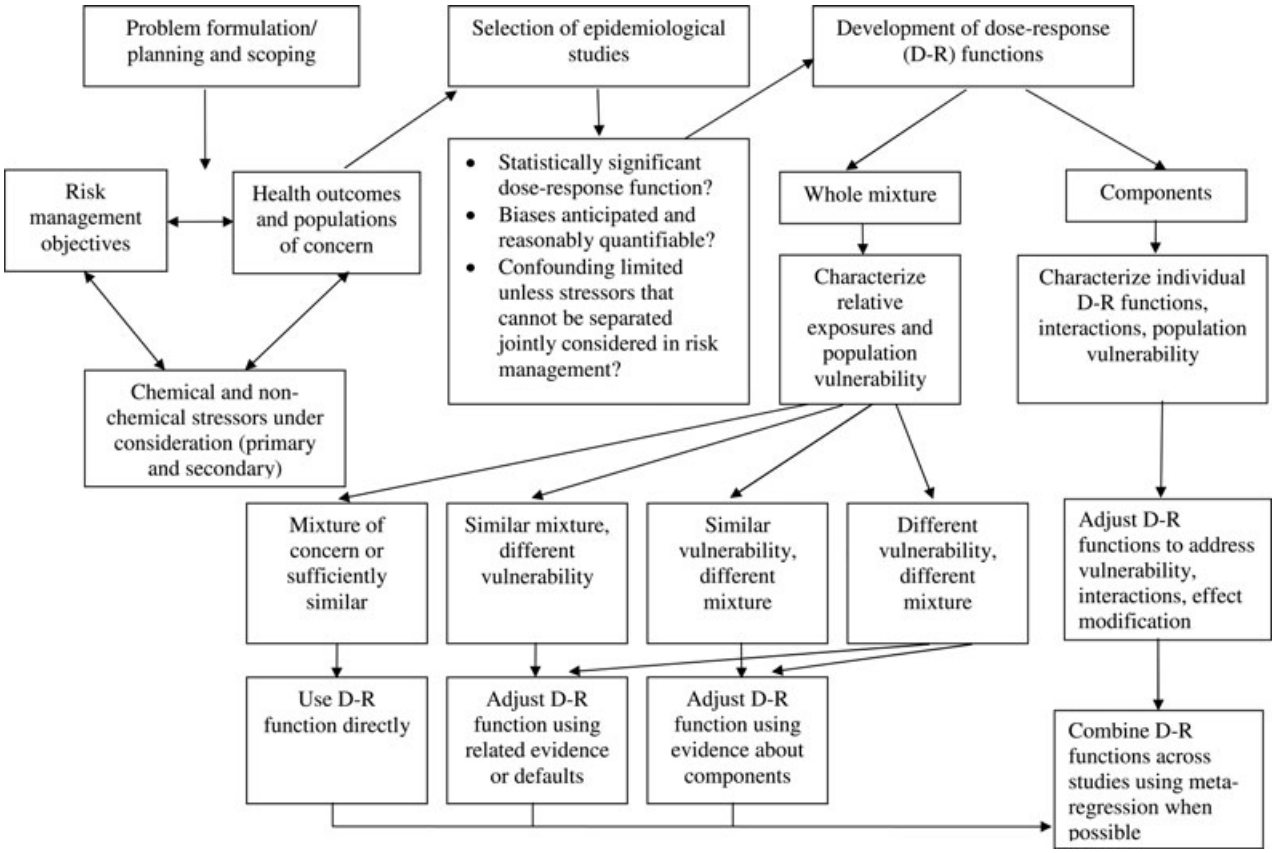

Fig. 1. A conceptual framework for the evaluation of epidemiological evidence for cumulative risk assessment.

EPA framework for chemical mixtures[15] and previously proposed criteria to determine the suitability of epidemiological studies for development of dose-response relationships,[16] but modifies these to account for the structure of cumulative risk assessment and the likelihood that evidence will need to be extracted from multiple studies. It also makes use of the multiphase approach proposed for evaluation of multiple stressors in cumulative risk assessment, derived in part from ecological risk assessment methods.[17]

Prior to discussing the details of the framework, it is important to consider more generally the characteristics of an ideal epidemiological study in this context, as this influences whether a study can be used directly, with modification, or not at all. An epidemiological study maximally informative for cumulative risk assessment would have the following attributes.

(1) It provides quantitative dose-response relationships within the exposure range of interest for all key stressors, with consideration of interactions or other joint effects. The stressors considered are related to risk management concerns and hypothesized to contribute to a specified disease process and health outcome.
(2) It explicitly and quantitatively addresses all relevant dimensions of vulnerability,[1] potentially including differential exposure, susceptibility/sensitivity, preparedness to withstand the insult of the stressor, and ability to recover from the effects of the stressor.
(3) It is based on a population similar in vulnerability and exposure characteristics as the population of interest, or at least includes all relevant subpopulations across these dimensions with adequate stratified analyses.

In most cases epidemiological evidence will not be available that fulfills all of these criteria, but presentation of these "gold standard" criteria allows for the development of a framework that makes best use of the evidence available.

As indicated in Fig. 1, the conceptual framework follows the Framework for Cumulative Risk

Assessment and begins with a problem formulation/planning and scoping step,[1] which involves determination of the health outcomes and stressors of interest given the overarching problem context. This helps to orient the assessment around a manageable subset of stressors and outcomes meaningful for risk management decisions. This would be an iterative process, where a more general health outcome may be of interest to risk managers (e.g., cardiovascular disease) but a more specific endpoint may be selected given the epidemiological evidence (e.g., cardiovascular hospital admissions), and where the stressors may dictate the outcomes or the outcomes may dictate the stressors, depending on the risk management context.

This step would also differentiate between those stressors affected by risk management efforts (defined herein as "primary stressors" and generally corresponding with epidemiological main effects) and those stressors that are not affected by risk management efforts but that may influence risk estimates (defined herein as "secondary stressors" and generally corresponding with epidemiological effect modifiers). For example, SES may not be a primary concern for risk management but could influence the effects of primary stressors, and could therefore be deemed a secondary stressor. Stressors that would influence the health outcome of interest but would neither be influenced by risk management nor modify the benefits of the stressors influenced by risk management would not need to be included unless risk managers were explicitly concerned with background risk patterns.

An epidemiological study would then be evaluated through a two-stage process. The first consideration is whether the study is suitable for the development of dose-response relationships for some or all primary stressors. Previously proposed criteria[16] for using epidemiological studies for quantitative dose-response assessment include having a moderate-to-strong positive association, strong biases ruled out or unlikely, confounding controlled or likely to be limited, and exposures quantified and linked to individuals.

A few minor modifications to these criteria are proposed. First, cumulative risk assessments will be most interpretable when using continuous dose-response functions. Any studies with such functions would by definition have quantitative exposure data, and the strength of the association would be driven by statistical significance of the slope across the exposure range of interest. Second, given the likely need to extrapolate across populations with different vulnerability characteristics (e.g., from occupational populations to the general public, from a random population sample to a low-income population), biases may be anticipated, and would therefore need to be reasonably quantifiable rather than ruled out. Finally, confounding would clearly need to be limited except in the special case when the epidemiological study cannot distinguish among stressors, all of which are included in the cumulative risk assessment, in which case there would only need to be sufficient information about the risks of joint exposure to allow for all necessary risk calculations.

If an epidemiological study is suitable for the development of dose-response functions, the next step is to determine what information can be extracted from the study. The initial question in this step is to determine whether the whole mixture of primary and secondary stressors within the cumulative risk assessment has been evaluated directly in an epidemiological study. This is analogous to having evidence on a specific Aroclor mixture of polychlorinated biphenyls (PCBs) as opposed to a collection of studies on specific PCB congeners.[15] The mixture in this case may include multiple chemicals, psychosocial stressors, socioeconomic factors, and other nonchemical stressors, and may not be a mixture as has been conventionally defined. However, the general concepts regarding characterization of the effects of joint exposure still apply, especially since the subset of stressors under consideration would have similar modes of action by definition.

If the whole mixture of stressors has been epidemiologically evaluated (Fig. 1), the proposed process parallels the chemical mixtures framework, with a determination of whether the mixture is the mixture of concern or sufficiently similar to that mixture. The determination of similarity is across two dimensions—relative exposures to the various stressors and vulnerability of the exposed population. In cases where the population attributes are sufficiently similar to the population of interest across key dimensions of vulnerability, and where the mixture is sufficiently similar and evaluated in such a way as to be applicable given the risk management context, the dose-response functions from the epidemiological study can be applied directly. The latter of these criteria can be met if the mixture is evaluated as a mixture or if the stressors are evaluated individually in a multivariate model accounting for interactions (in which case the mixture must only be similar in the range of exposures for each stressor).

If these criteria are not met, there are three possibilities—(1) the mixture is sufficiently similar but vulnerability attributes are not; (2) the mixture is not sufficiently similar but vulnerability attributes are; or (3) neither criterion is met. There may be some overlap between the mixture and vulnerability characterization (e.g., if SES is a secondary stressor and would influence the ability to recover from a stressor), but it is helpful to consider them separately.

In case #1, which could arise given an occupational epidemiology study for a general population cumulative risk assessment, the slope of the dose-response function may need to be adjusted to account for differences in vulnerability, either for subpopulations or for the whole. Studies of individual stressors in different subpopulations or with consideration of effect modification could be used to develop these adjustment factors, and default values or distributions could be established for cases where no direct evidence is available. Especially when evidence arises from occupational epidemiology, age and health status dependence would need to be formally addressed. When multiple studies are available, meta-regressions could be used to formally determine the influence of key vulnerability dimensions on the dose-response functions.[18–21] Such studies would formally evaluate factors that explain between-study variability in findings, both helping to pool epidemiological studies and determine the degree to which differences are due to characteristics of the populations or underlying study methods.

In case #2, the stressors may exist at different relative levels in the epidemiological study than in the study of interest. If the epidemiological output includes individual dose-response functions with appropriate consideration of interactions, and either the exposure levels are comparable or there is no evidence of deviation from linearity across the exposure levels, then the outputs can be applied directly. If the mixture of stressors has been evaluated together but the relative levels differ, adjustments to the dose-response function can be made based on evidence available elsewhere on individual relative risks and effect modifiers. If the mixture differs in both exposure and vulnerability characteristics (case #3), then both of the above adjustments may be needed.

If whole mixture information is not available, the general approach of considering stressors without interactions then addressing potential interactions[17] can be followed. More specifically, the dose-response functions for the individual primary stressors should be constructed, with explicit attention paid to vulnerability adjustments as described previously and effect modification by any primary or secondary stressors. In this case, epidemiological evidence would definitely need to be integrated across multiple studies, which may differ in population attributes and co-exposures in ways that may not be quantitatively addressed. For example, IQ decrements have been evaluated separately for mercury[22] and lead,[23] but the mercury studies were based on populations in the Faroe Islands, Seychelles, and New Zealand, whereas the lead studies were based on populations in the United States, Mexico, and Australia, and these populations may differ in multiple ways (including exposure to the other toxicant as well as nonchemical stressors and vulnerability factors). Once the individual dose-response functions are constructed (with or without adjustment), evaluation of possible interactions is needed. The literature will likely be inadequate to quantify interactions in all but a limited number of cases, in which case a determination of whether dose addition or response addition would be more appropriate would be the next logical step. Of note, if linear dose-response functions were present for all stressors, there would be no functional differences between estimates based on dose addition versus response addition.

4. CONCLUSIONS AND FUTURE DIRECTIONS

In this article, I have presented a general framework that would allow epidemiological evidence to be evaluated and incorporated into cumulative risk assessment. Such an approach is clearly necessary given the intended scope of cumulative risk assessment, and in spite of its limitations and assumptions, it is preferable to rely on analyses with significant uncertainties than to rely on analyses that are fundamentally incapable of answering the relevant questions. Although epidemiological studies may characterize social-environmental interactions with significant uncertainty, toxicological studies are not well equipped to characterize the effects of simultaneous exposure to an array of environmental, psychosocial, nutritional, and economic factors. This gap may be most substantial for factors like SES, which proxy for numerous stressors that cannot be simultaneously toxicologically evaluated.

Some limitations need to be acknowledged. First, there are many cumulative risk assessments where a critical mass of epidemiological information is not

available and would not be anticipated to become available in a decision-relevant period of time. The intent of this framework is not to imply that toxicological evidence could not be the basis of a meaningful cumulative risk assessment, but rather to provide a path for increased utilization of epidemiological evidence when available.

A related limitation is the fact that there may be epidemiological evidence for a subset of stressors but toxicological evidence for many more stressors for a defined health outcome. The framework is not meant to exclude toxicological evidence in this context, and analysts should pursue hybrid approaches rather than focusing solely on epidemiologically based estimates. This could involve developing quantitative dose-response measures in both cases and utilizing epidemiological evidence to draw inferences about different dimensions of vulnerability even in the absence of direct empirical evidence for the compounds of interest.

More generally, the proposed framework may be reasonable in principle but difficult to apply in practice given data limitations. This is not meant to be a precise roadmap or guidance document, but rather a starting point for discussion and a general illustration of a process by which epidemiology could be evaluated and incorporated, and there will need to be more specific methodological development to make this a systematic and reproducible process. It should also be recognized that epidemiology could play many roles beyond establishment of dose-response functions—for example, identification of the chemical and nonchemical stressors to include in the analysis, even if the quantitative analysis would be driven by toxicological evidence.

In the long term, enhancing the role of epidemiology in cumulative risk assessment will only be possible if there is substantive two-way communication between epidemiologists and risk assessors. Risk assessors must not simply be end users but must be willing and able to provide insight about how epidemiological studies should be designed and conducted to address key information gaps. Environmental epidemiologists concerned with the difficulties of parsing out the contributions of individual risk factors[7] may be amenable to a cumulative risk framework. Even if this modified focus is impractical in many settings, epidemiologists should minimally be aware of the informational needs within cumulative risk assessment and should strive to present information that can be used in these assessments.[6] Interactions between cumulative risk assessment and social epidemiology would be helpful as well, given a common "place-based" orientation.[24] Beyond direct evidence of interactions between the social and physical environment, social epidemiology can also provide conceptual frameworks within which the impacts of joint exposure to multiple stressors can be considered.[25]

In conclusion, cumulative risk assessment is unlikely to meet its ambitious and important mandate without more extensive application of epidemiological findings and insights. The framework proposed in this article is one path forward that can allow for the application of epidemiological evidence within cumulative risk assessment, and mechanisms for enhanced communication between epidemiologists and risk assessors should be explored to allow for the refinement of both fields.

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