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Cumulative Risk Assessment for Combined Health Effects From Chemical and Nonchemical Stressors

Ken Sexton, ScD, and Stephen H. Linder, PhD

Cumulative risk assessment is a science policy tool for organizing and analyzing information to examine, characterize, and possibly quantify combined threats from multiple environmental stressors.

We briefly survey the state of the art regarding cumulative risk assessment, emphasizing challenges and complexities of moving beyond the current focus on chemical mixtures to incorporate nonchemical stressors, such as poverty and discrimination, into the assessment paradigm. Theoretical frameworks for integrating nonchemical stressors into cumulative risk assessments are discussed, the impact of geospatial issues on interpreting results of statistical analyses is described, and four assessment methods are used to illustrate the diversity of current approaches.

Prospects for future progress depend on adequate research support as well as development and verification of appropriate analytic frameworks. (*Am J Public Health.* 2011;101:S81–S88. doi:10.2105/AJPH.2011.300118)

EXPOSURE TO MULTIPLE environmental agents, including biologic, chemical, physical, radiologic, and psychosocial stressors, can, under the right circumstances, modify the toxic effects of these same agents acting alone so that combined outcomes are either antagonistic (less than additive) or synergistic (more than additive).[1–4] There is empirical evidence that interactive effects from exposure to a mixture of environmental stressors can contribute to three categories of adverse health effects: (1) those where exogenous agents interfere with normal development and distort physiologic function, such as neurobehavioral abnormalities and sex steroid hormonal disruption; (2) those where exogenous agents cause direct cellular damage, such as neurodegenerative diseases and cancer; and (3) those that contribute to illness through a combination of both physiologic disruption and cell damage, for example, in cardiovascular disease.[1] Because traditional risk assessment has not routinely taken account of the potential for combined effects from exposure to diverse environmental factors, like those found in the real world, there is growing urgency about the need to develop effective and practical tools for assessing cumulative health risks.[5–9]

Cumulative risk assessment is a procedure for organizing and analyzing relevant information to examine, characterize, and possibly quantify the combined harmful effects from exposure to a mixture of environmental stressors.[7,8] The National Research Council[9] recently noted that although the need to evaluate combined risks from environmental stressors is becoming more acute, current practices do not adequately incorporate nonchemical stressors and important aspects of vulnerability into the assessment process. In the following, we provide a brief overview of the diversity of methods used to estimate cumulative health risks, distinguishing between traditional chemical-specific tools and the more recent approaches used to incorporate nonchemical stressors. Prominence is given to techniques that integrate psychological and social stressors, along with concepts of vulnerability, into the risk estimation procedure. The importance of spatial scale for analysis and interpretation of results is discussed, and practical applications of cumulative risk assessment are reviewed.

TECHNIQUES FOR CHEMICAL MIXTURES

In 1986, the Environmental Protection Agency (EPA)[10] issued guidelines for evaluating health risks from chemical mixtures, which were updated in 2000[11] and expanded in 2006.[12] The guidelines specified that when evaluating health effects, the first priority was to use evidence for the mixture of concern when it existed. If that was unavailable, the next highest priority was to use information about a similar mixture and, if no such information existed, the subsequent highest priority was to evaluate pairwise interactions between mixture constituents. Finally, if none of the preceding data were available, the default option was to assume that constituent interactions were additive. The 1986 guidelines made a distinction between dose additivity, where the mixture constituents had the same mechanism of action and the same health effects, and response additivity, where mixture constituents had the same health effects but different

TABLE 1—Comparison of Quantitative Methods for Assessment of Cumulative Health Risks from Chemical Mixtures[4]

Approach	Methodology
HI_{INT} approach using evidence or mathematical theory on pairwise interactions; $HI_{INT} = \sum_i f(HQ)_{pair}$ (extensive data requirements)	Assumes sum of interactions between pairs of chemicals represent the whole mixture. Requires pairwise effect data for major constituents of the mixture.
Toxicity equivalency factor (TEF) approach; $Dose_{TEQ} = \sum(dose_i \text{ for } TEF_i)$ (moderate data requirements)	Assumes the action of each chemical in the mixture is fully represented by an index chemical. Doses of all mixture constituents are treated as equivalent to the weighted sum of the activity of the mixture components.
Margin of exposure (MOE) approach using TEF; MOE = NOAEL ÷ $Dose_{TEQ}$ (moderate data requirements)	Assumes additivity of effects for mixture constituents. Appears to avoid the extrapolations inherent in uncertainty factors, but introduces the added responsibility to make explicit and account for the scientific concerns that gave rise to uncertainty factors in the first place. Single number summary for exposure obscures distributional nature of exposures.
HI approach using NOAEL or BMD; $HI = (HQ^2)_i = (\text{Exposure Metric}_i \div NOAEL_i \text{ or } BMD_i)$ (minimal data requirements)	Assumes additivity of effects for mixture constituents. NOAELs and BMDs used for comparison instead of RfDs or RfCs, but single comparison value still makes it difficult to discern scientific judgments about uncertain factors and hides distributional nature of exposures.
HI approach using RfD or RfC; $HI = (HQ^2)_i = \sum(\text{Exposure Metric}_i \div RfD_i \text{ or } RfC_i)$ (minimal data requirements)	Assumes additivity of effects for mixture constituents. Simplest approach with least resource requirements, but depends on scientific judgment to translate NOAELs or LOAELs into RfDs or RfCs. Not a true quantitative risk assessment, just a single comparison value that obscures scientific judgments about uncertainty factors and masks distributional nature of exposures.

Note. BMD=benchmark dose; HI=hazard index; HI_{INT}=interaction-based hazard index; HQ=hazard quotient; LOAEL=lowest observed adverse effect level; NOAEL=no observed adverse effect level; RfC=reference concentration; RfD=reference dose; TEQ=toxicity equivalency.

mechanisms of action. Most cumulative risk assessments since 1986 have focused on chemicals that have similar structure or similar mechanisms of action, such as evaluations of drinking water disinfectants, organophosphate pesticides, polycyclic aromatic hydrocarbons, polychlorinated biphenyls, and dioxins and furans.[9]

In the absence of biologically based physiologic, toxicokinetic, and toxicodynamic models for the chemical mixture of interest, assessors are forced to rely on science policy decisions that create methodological shortcuts, such as those summarized in Table 1, to estimate cumulative risk.[4] When appropriate data are available, the interactive hazard index (HI) approach, which modifies the HI based on a specified function to describe empirical data for the combined effects of mixture constituent pairs, is preferable. The next most preferable method is the toxicity equivalency factor approach, which sums the toxicity of individual mixture components relative to the potency of an index compound. Next in preference is the margin of exposure approach, which uses toxicity equivalency factors to calculate the margin between the estimated exposure and either the reference dose or the reference concentration, as appropriate. If adequate data are not available to support any of these methods, then it is necessary to sum HIs for each mixture constituent, where the HI is calculated by dividing the estimated exposure by either the no observed adverse effect level or the benchmark dose. As a last resort, if no observed adverse effect levels and benchmark doses are not available, assessors can sum HIs for mixture components, where the HI is calculated by dividing the estimated exposure by the reference dose or the reference concentration. The National Research Council[13] recently recommended that more emphasis be placed on evaluating cumulative risks from chemicals that contribute to common health effects but which may have different mechanisms of action, such as phthalates.

INCORPORATING NONCHEMICAL STRESSORS

As complicated as it is to evaluate interactive effects of chemical mixtures, even simple ones, the degree of difficulty increases dramatically when we attempt to include nonchemical stressors in the analysis. Particular attention has been focused lately on potentially important interactive effects of psychological and social stressors when they occur as part of exposures to complex environmental mixtures.[8,14–18] The terms "allostasis" and "allostatic load" have been coined to help conceptualize the cumulative biological toll taken on the human body through physiologic responses to life's everyday stress-provoking demands. Allostasis refers to the adaptive processes that maintain homeostasis by producing mediators such as adrenalin, cortisol, and other chemical messengers that promote adaptation following acute stress. Allostatic load refers to the cumulative cost over time of allostasis, where allostatic overload can lead to serious pathophysiology through wear and tear on the body and brain from being chronically "stressed out." The allostatic load model has been proposed as a framework for conceptualizing the cumulative biological burden exacted on an individual by allostasis, which is triggered by responses to the exigencies of day-to-day existence, including social conflict and other types of social dysfunction.[15,17,18]

Although the contribution of psychosocial stressors to cumulative risk and related health disparities is ill defined, there is clear and convincing evidence that health is not evenly distributed across levels of socioeconomic status (SES), and that people who have lower incomes, education, and occupational status, many of whom are people of color, are more likely to be unhealthy and to experience higher rates of morbidity and mortality.[19,20] In

addition, it is apparent that the burden of pollution all too often falls disproportionately on the disadvantaged and vulnerable,[6,21] who also tend to have higher allostatic loads.[14,22] The concept of allostatic load may provide a mechanism to link stress-induced biological responses to observed health disparities, and could be a valuable method for incorporating psychosocial stressors into cumulative risk assessments.[8,20,22,23]

There is empirical evidence that individuals in lower SES strata experience greater chronic stress, have lower perceived control at work, have lower levels of social support, and go through more events considered by them to be stressful.[22] Moreover, they are more likely to have a substandard diet, reside in dilapidated housing and less safe neighborhoods, lack access to health care, smoke cigarettes and drink alcohol to excess, and, in general, to live more stressful and less healthful lives.[20,21,23] Although these and associated factors undoubtedly contribute to allostatic load, discerning the mechanism by which psychosocial stressors influence cumulative risk and play a role in related health disparities depends, to a significant degree, on the posited analytic framework.[24]

Two recent conceptual frameworks for analyzing combined health effects of chemical and nonchemical stressors conceive a key role for community- and individual-level variables. The first approach, shown in Figure 1, is a multiple effects model that focuses on the role of race and ethnicity in the creation of health disparities.[25] The model emphasizes psychosocial stressors and associated chronic stress as mediating factors, and organizes them into categories contributing to community vulnerability or individual vulnerability. Juxtaposed alongside and interconnected is the conventional cascade of events leading from exposure to environmental pollutants, to internal dose, and ultimately to adverse health effects. The interactions among chemical and nonchemical stressors are postulated to account, at least in part, for observed health disparities. The second approach, shown in Figure 2, relies on an exposure–stress–effect framework in which both chemical and nonchemical factors contribute to chronic individual stress and allostatic load, which, in turn, increases individual vulnerability and thereby contributes to subsequent health disparities.[23] As part of its causal logic, the model distinguishes between community- and individual-level stressors, buffers, and related health outcomes.

These two theoretical constructs each incorporate multiple levels of analysis and link the combined effects of chemical exposures and psychosocial stressors to explain, at least partially, existing health disparities. In doing so, they extend conventional ideas about exposure assessment beyond the individual to incorporate the broader concept of community sources for both chemical and nonchemical stressors, which are assumed to interact in ways that create unequal stress burdens. This focuses attention on questions about why and how differential cumulative exposures occur in the first place, the conditions under which they give rise to divergent health risks, and the mechanisms by which they ultimately translate into health disparities. Most attempts to

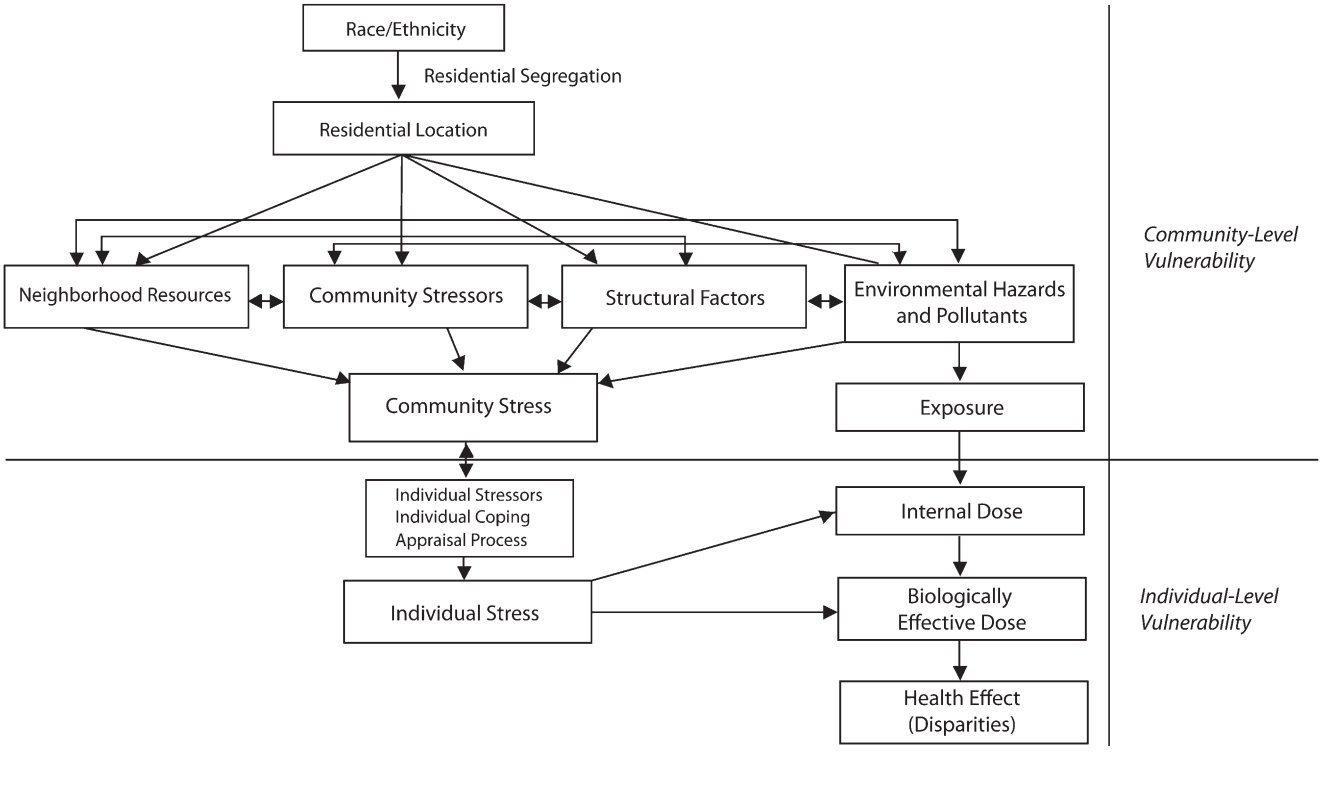
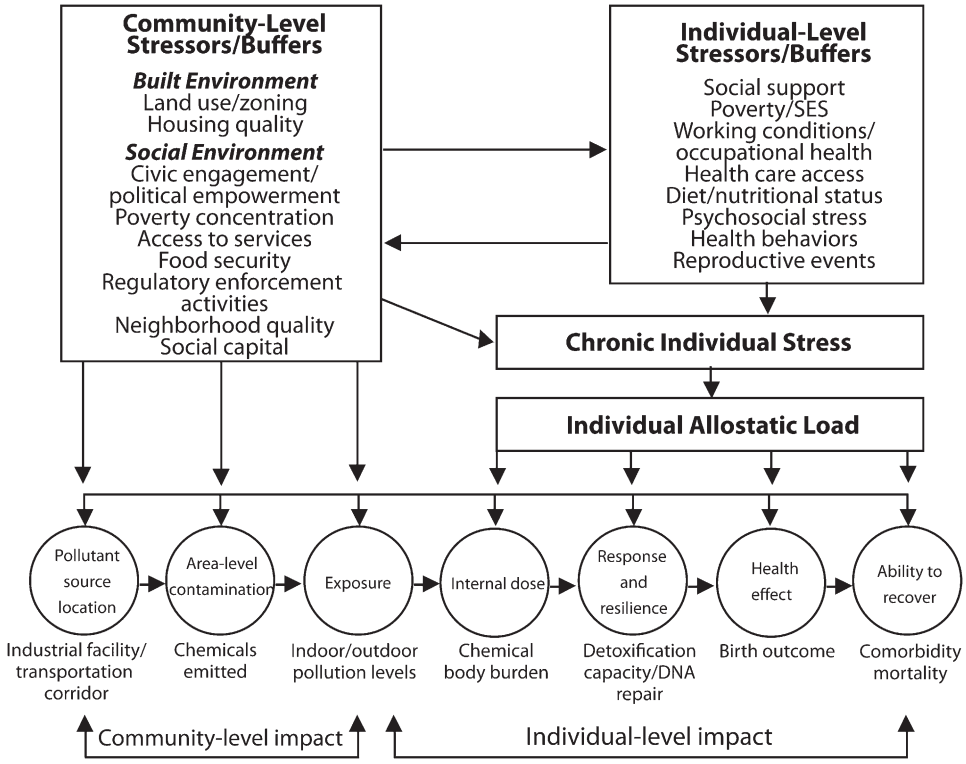


FIGURE 1—Conceptual model for the combined effects of multiple stressors on health.[25]



Note. SES = socioeconomic status.

FIGURE 2—Conceptual model incorporating allostatic load with the combined effects of chemical and nonchemical stressors on health.[23]

explore these and related questions have started with the premise that the uneven geospatial distribution of chemical and nonchemical stressors leads to unequal cumulative exposure and related effects.

GEOSPATIAL DISTRIBUTION OF STRESSORS AND RISKS

A fundamental goal of environmental health sciences is to understand the complicated process by which exposures to environmental agents either cause or contribute to adverse health outcomes, and to intervene where appropriate to prevent or reduce environmentally induced illness and injury. The focus, therefore, of most environmental health research studies and intervention strategies is on three key variables: (1) the magnitude, duration, frequency, and timing of human exposure to environmental stressors, (2) the prevalence or incidence of adverse health effects caused or exacerbated by exposure to environmental agents, and (3) the link between exposure and effect, with particular emphasis on variability in susceptibility and sensitivity for both individuals and communities. All three factors exhibit significant geospatial variability, which means that exposure, effect, and the exposure–effect link are conditioned by geographic location and neighborhood boundaries, the spatial scale of analysis, and the spatial resolution of the aggregated data.[26]

Geographers have long recognized that results from statistical analyses of these kinds of variables depend on geospatial realities; a situation that they have termed the modifiable areal unit problem (MAUP).[27] The implications of the MAUP for environmental health and cumulative risk assessment are noteworthy. For example, the true effect of exposure on disease occurrence is not a biological constant, but is modified by spatial scale. Disease patterns that appear random at one geospatial scale may appear clustered at another, and a regression analysis that is statistically significant at one spatial scale may be insignificant at a different scale. Thus, results of statistical analyses to compare exposure profiles among groups, infer causality, elucidate disease clusters, and characterize health disparities can change substantially depending on spatial boundaries, scale, and resolution. Consequently, a positive statistical finding linking environmental exposure with location of new disease cases suggests a possible association only at that particular spatial resolution of the data—which is to say, the resolution of exposure and health effects data circumscribes the spatial scale of detectable statistical association, thereby setting the context within which results must necessarily be interpreted.[26]

Studying health disparities and assessing cumulative environmental health risks from chemical and nonchemical stressors must unavoidably span multiple levels of analysis and different-sized geographic units. One way of visualizing the causal pathway from combined exposures through to adverse health outcomes assumes that causation flows from the macro level (e.g., government policies and regulations, market forces, institutional racism) to the meso level (e.g., neighborhood pollution levels, locally built and social environments, community resources) to the micro level (e.g., personal exposure concentrations, body burden measurements, health status, psychological factors, activities and behaviors, physical and demographic characteristics, economic realities).[28,29] Choosing which levels and geospatial units to analyze depends on several factors, including the research objective, the causal model selected, the exposures and health outcomes of interest, and the extent to which data are available.[29]

The availability of data are often the determining factor in decisions about geospatial issues. For example, sociodemographic variables (e.g., age, race/ethnicity, income, education, occupation) as well as indicators of social

disadvantage (e.g., uninsured, unemployed, poverty, single mother) and biologic vulnerability (e.g., pregnant women, infants and young children, elderly, infirm) are typically drawn mainly from the US Census[30] based on information obtained in the short form (completed by all participants) or the more thorough long form (completed by about 1 in 6 households). This means that these data are only available at certain geographic scales used by the census, such as: block groups; census tracts; Minor Civil Divisions (MCDs); Micropolitan Statistical Areas (μSAs); and Metropolitan Statistical Areas (MSAs). By contrast, to estimate environmental health variables, it is usually necessary to use either public or private databases that summarize information on: (1) human exposures,[31] including databases like the National-scale Air Toxics Survey[32] or the Toxics Release Inventory;[33] (2) body burdens using, for example, the National Report on Human Exposure to Environmental Chemicals[34] or the National Health and Nutrition Examination Survey[35] (NHANES); and (3) health status, relying on resources such as NHANES, the National Health Interview Survey,[36] or the Surveillance Epidemiology and End Results[37] program. Examples of the levels of geospatial scale for which data are available from selected sources are provided in Table 2.

CUMULATIVE RISK ASSESSMENT IN PRACTICE

Numerous applications of various forms of cumulative risk assessment for chemical mixtures have been reported over the past decade,[3,32,38,39] and summaries of available methods and tools have been published by the EPA[12,40–42] and others.[29,43] However, assessment of cumulative health effects from a combination of both chemical and psychosocial stressors is still in its infancy,[8,9] and substantial efforts are devoted to proposing and testing theoretical paradigms, causal orderings, and analytic frameworks.[7,20,23–25,44,45] Without a scientific consensus regarding conceptual approaches and causal pathways to structure empirical inquiry, an assortment of methodologies has been used. Four recent examples serve to illustrate the diversity of techniques currently available: the Cumulative Environmental Hazard Inequality Index[46] (CEHII) developed at the University of California–Berkeley; the World Health Organization's (WHO's) Urban Health Equity Assessment and Response Tool[47] (Urban HEART); the EPA's Community-Focused Exposure and Risk Screening Tool[42] (C-FERST); and the Environmental Justice Strategic Enforcement Screening Tool[48] (EJSEAT) from EPA's Office of Enforcement and Compliance Assistance.

The CEHII is a method proposed by scientists at the University of California–Berkeley for creating an index summarizing racial, ethnic, and socioeconomic inequalities from the cumulative effects of multiple environmental hazards.[46] Individual environmental inequity indexes are calculated based on unequal burdens of selected environmental hazards for groups defined by race/ethnicity and socioeconomic status. The CEHII combines putative effects of individual environmental hazards using either an additive or multiplicative model, and is calculated using the cumulative proportion of the study population, ranked by area-based racial/ethnic and socioeconomic composition—starting from the most disadvantaged—in combination with the cumulative environmental hazard aggregated based on specific weighting factors. The index can be used to characterize disparities in cumulative impact for relatively large geographic regions and is suitable for application at the regional level, such as counties or metropolitan areas. The CEHII method reduces the dimensionality of the targeted variables by collecting them in functional combinations, which are based on pragmatic considerations and require assumptions about appropriate combination rules and the scale of resulting composite indicators.

The assessment component of WHO's Urban HEART is a method for identifying and analyzing health disparities between people living in different sections of a city or between people belonging to different socioeconomic groups within or across cities.[47] Data are collected and analyzed for two categories of "core" indicators: (1) health outcome indicators, including (a) summary indicators, such as infant mortality rate and (b) disease-specific mortality/morbidity indicators, such as age-standardized diabetes death rate per 100 000 persons; and (2) indicators of social determinants of health, including (a) indicators of environmental and physical hazards associated with living conditions, such as access to safe drinking water and sanitation services, (b) indicators of social and human development, such as

TABLE 2—Examples of Data Sources and Geospatial Levels Available for Analysis of Cumulative Health Risks[29]

Data Source	Geospatial Levels Available
Demographic, economic, and social variables	
US Census	Block group, census tract, MCD, μSA, MSA
Environmental exposure	
AIRS (Aerometric Information Retrieval System)	County, MSA, state
NATA (National-scale Air Toxics Assessment)	Census tract, county, MSA, state
TRI (Toxic Release Inventory)	Individual facilities, county, state
SDWIS (Safe Drinking Water Info System)	Water system, county, MSA, state
SNAP (Superfund NPL Assessment Program)	Site locations, county, MSA, sate
Body burden	
NHANES (National Health & Nutrition Examination Survey)	Block group, census tract, county, MSA, state
National Report on Human Exposure	National reference ranges by pollutant
Health status	
NHANES	Block group, census tract, county, MSA, state
NHIS (National Health Interview Survey)	Block group, census tract, county, MSA, state
SEER (Surveillance Epidemiology & End Results)	Block group, census tract (CA only), MSA, state

Note: MCD=minor civil division; μSA=micropolitan statistical area; MSA=metropolitan statistical area.

access to education and health services, (c) indicators of economic status, such as job opportunities and potential for generating income, and (d) indicators of good governance, such as public participation in decision-making and government spending on health. Data for each indicator can, as appropriate, be disaggregated by population group (e.g., sex or age), location (e.g., neighborhood or district), or socioeconomic group (e.g., education or income). The indicators are arrayed in an urban health equity matrix to evaluate the comparative conditions of cities or neighborhoods within cities. Results for each geographic area are presented as color-coded profiles highlighting the highest comparative risks. The findings can be used to identify which geospatial areas or population groups are at highest cumulative risk, and tracking the indicators over time can provide information about trends. Because the dimensionality of the targeted variables is not reduced by forming functional combinations, there are few added measurement assumptions and no scaling beyond rank orders of relative size.

The EPA's C-FERST is a web-based tool—with links to existing EPA information and techniques—that is being developed for use by communities in identifying and prioritizing combined risks from chemical and nonchemical stressors.[42] It will incorporate relevant data, maps, model results, and local data collection methods, and will contain exposure-based cumulative risk characterizations. Although the current version focuses primarily on chemical stressors, future versions will include information on interactions and effects of nonchemical agents, such as noise and psychological stress, and exposures and risk will be calculated so that they can be summed across chemical and nonchemical stressors. Where a quantitative assessment spanning multiple environmental stressors is not possible, C-FERST will provide aggregate exposure or risk estimates so that users can examine the data collectively as part of a semiquantitative cumulative risk assessment. This is a mixed measurement approach that combines the two previously described methodologies to form a more complex picture of cumulative risk. It necessarily requires abundant assumptions to sustain it, and its conceptual underpinnings remain a work in progress. Nevertheless, C-FERST offers legitimate promise as an accessible, transparent, and practical assessment tool for use by members of affected communities.

The EJSEAT is intended to provide consistent identification of geographic areas with disproportionately higher burdens of harmful environmental features.[48] It is composed of 18 indicator variables divided into four categories: environmental—six indicators; compliance—four indicators; human health—two indicators; and sociodemographic—six indicators. Normalization procedures and a simple algorithm are used to identify areas with elevated EJSEAT scores, which indicate a high burden of dangerous or undesirable conditions. Values for all 18 EJSEAT indicator variables, which are derived from publicly available databases, have been obtained by the EPA for each of the approximately 65 000 census tracts in the United States.

CONCLUSIONS AND RECOMMENDATIONS

Development of appropriate procedures for evaluating combined threats from multiple environmental stressors is vital for understanding and resolving issues like health disparities and environmental injustices.[6,8,9,49,50] Although techniques for assessment of combined effects from chemical mixtures have been around for more than 20 years, they are still confined largely to relatively simple combinations. The formal inclusion of nonchemical stressors in cumulative risk assessments, specifically factors like residential crowding, neighborhood crime, and levels of social support, is a comparatively recent development that is hindered by unavailability of appropriate data, a deficiency of mechanistic understanding, and lack of consensual or verified analytic frameworks to direct research activity. We believe development of workable processes and practices for assessing cumulative health risk depends on implementation of a coordinated, overarching strategy that methodically works through a series of logical steps.

- Identify high-priority communities and populations likely to be at increased cumulative risk from exposure to a mixture of chemical and nonchemical stressors. This step could be accomplished at a national scale using an expert panel to prioritize generic at-risk populations (e.g., children who live in disadvantaged circumstances near major sources of pollution) and locations (e.g., poor, inner city neighborhoods), or it could be done at a local scale using available information on pollution sources, ambient concentrations, and socioeconomic characteristics to distinguish high-risk situations (e.g., immigrant families who are migrant farm workers) and settings (e.g., an economically depressed community adjacent to major freeways, industrial facilities, and abandoned waste sites) (for example, WHO's HEART[47] and EPA's EJSEAT[48]).
- Specify a prescribed analytic framework that formalizes postulated causal factors and pathways that will serve as a guide for collection and interpretation of empirical data. This step requires explicit commitment to a particular conceptual model that provides a simplified inventory of critical assumptions, concepts, indicators, and propositions, including a schematic representation depicting postulated connections among independent variables and between independent and dependent variables (for example, Linder and Sexton[24]).
- Undertake a coordinated research effort centered on the targeted population or community, including laboratory and field research aimed at (1) elucidating the magnitude, duration, frequency, and timing of relevant exposures, (2) determining whether mixture-related health effects are additive, antagonistic, or synergistic, and (3) explicating important interactive mechanisms of toxicity among mixture components. The emphasis must be on the complex, day-to-day exposures of real people that are the focal point of the cumulative risk assessment. Studies should answer the important (but difficult) questions, even if only imprecisely, rather than trying to answer the less important (but easier) questions definitively (for example, Callahan and Sexton[8] or the National Research Council's 2009 Report[9]).
- Conduct a thorough assessment of cumulative health risks in the target population or community using the chosen

analytic framework as a guide and relying on the best available data and most up-to-date scientific methods. Bridging the gap between the needs of risk assessors and existing scientific knowledge and understanding will likely require numerous science policy decisions to resolve critical uncertainties, which means that results may necessarily be semiquantitative or qualitative. Nevertheless, it is imperative to gain the experience and learn the lessons needed to eventually construct a workable system for assessing the severity of cumulative health risks in complicated, real-world situations (for example, EPA's C-FERST[47]).

- Use empirical and conceptual results to modify, revise, or discard the analytic framework as a practical guide to assess cumulative health risks. The goal is to appraise the framework rigorously and refine or reject it based on a thorough evaluation of relevant research findings and knowledge gained from conducting cumulative risk assessments in the field (for example, Linder and Sexton[24]).

Future progress is contingent not only on adequate funding to carry out the necessary studies, but also on advances in conceptual approaches, theoretical paradigms, and diagnostic frameworks that structure the research enterprise appropriately—helping us to ask the right questions, design the right studies, and draw the right conclusions. ■

About the Authors

Ken Sexton is in the division of Epidemiology, Human Genetics & Environmental Sciences, The University of Texas School of Public Health, Brownsville Regional Campus, Brownsville. Stephen H. Linder is in the division of Management, Policy and Community Health, The University of Texas School of Public Health, Houston.

Correspondence should be sent to Ken Sexton, The University of Texas School of Public Health, Brownsville Regional Campus, Brownsville, TX 78520. (e-mail: ken.sexton@uth.tmc.edu). Reprints can be ordered at http://www.ajph.org by clicking the "Reprints/Eprints" link.

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Expanding the Scope of Environmental Risk Assessment to Better Include Differential Vulnerability and Susceptibility

Joel Schwartz, PhD, David Bellinger, PhD, and Thomas Glass, PhD

The central paradigm of the Environmental Protection Agency is risk assessment. We examined how differential responses across population groups could be better integrated into the environmental risk assessment process, providing tools to achieve greater equity in health status in addition to risk reduction.

Such integration was difficult with paradigms like reference dose and was easier with consideration of dose–response curves, which incorporated nontrivial effects observed at low doses for common exposures.

We identified 6 assumptions implicit in standard chemical risk assessments that should changed: (1) risk independence, (2) risk averaging, (3) risk nontransferability, (4) risk synchrony, (5) risk accumulation and chaining, and (6) quantification of numbers of persons above certain thresholds or limit values sufficient to characterize risk. (*Am J Public Health.* 2011;101:S88–S93. doi:10.2105/AJPH.2011.300268)

THE CENTRAL PARADIGM FOR the US Environmental Protection Agency (EPA) standard setting is risk assessment. Based on scientific data, the EPA prepares quantitative estimates of changes in health status that will result in different potential levels of a standard, and uses that quantification as input into decision-making for situations in which risk management depends on other data as well. Specific regulatory actions are targeted to particular environmental agents, whose marginal impacts, sources, and control strategies often differ. A cruder approach is often taken. An acceptable dose of a chemical is defined (e.g., reference dose [RfD]), and risk assessment merely quantifies the number of people above versus below this dose or number for different regulatory choices. Implicit in the latter approach is that this quantity is meaningful and that risk is zero below the RfD and the same above the RfD, irrespective of the extent to which actual exposure exceeds the RfD. These simplifying assumptions can lead to both inaccuracy in risk estimation and inattention to distributional aspects.

A recent US National Academy of Sciences report declared that "..risk assessment is at a crossroads."[1(p.ix)] Its key recommendation was to abandon the RfD approach whenever possible and move to a quantitative estimate of changes in health. We support the National Academy of Science's conclusions, arguing that only with actual quantification of risk can differential patterns of susceptibility be examined, and point out that this makes understanding the shape of the dose–response relation central to risk assessment. In this article, the conceptual issues are addressed, and in 2 related articles,[2,3] examples are provided of where these concepts are important. Methodology is also discussed.

SUSCEPTIBILITY AND VULNERABILITY IN THE CONTEXT OF HEALTH

The standard definition of a person who is susceptible is one who is more responsive to exposure. Recently, the word vulnerability was used either to describe situations where the susceptibility arises from psychosocial, cultural, or economic differences, or as encompassing these plus biological vulnerability, but with the understanding that these components of overall vulnerability were different.[4] This distinction is not a good one, because recent research into how socioeconomic factors and stress exert influence on health identified clear biological pathways. Stress is associated with differential baseline levels and the differential response of the hypothalamic–pituitary–adrenal system. That is, these social factors describe people with different biological states. They are merely the "causes of the causes."[5(p1153)] Further, there are complex feedback loops between outside conditions and biological stress that make separating these phenomena even more difficult. A more useful distinction is one versus many. Just as in physics, collections of particles are capable of behavior quite