

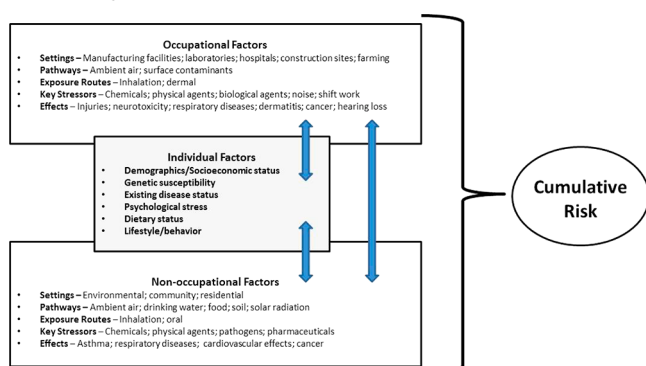
Cumulative Risk Assessment (CRA): Transforming the Way We Assess Health Risks

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Human health risk assessments continue to evolve and now focus on the need for cumulative risk assessment (CRA). CRA involves assessing the combined risk from coexposure to multiple chemical and nonchemical stressors for varying health effects. CRAs are broader in scope than traditional chemical risk assessments because they allow for a more comprehensive evaluation of the interaction between different stressors and their combined impact on human health. Future directions of CRA include greater emphasis on local-level community-based assessments; integrating environmental, occupational, community, and individual risk factors; and identifying and implementing common frameworks and risk metrics for incorporating multiple stressors.

■ INTRODUCTION

The methodology, practice, and breadth of human health risk assessments have evolved over the last several decades and are expected to continue to advance in the future. In particular, an awareness of children's dietary and nondietary exposures to multiple pesticides in food that have a common toxic effect¹ led to the 1996 *Food Quality Protection Act* (FQPA), which directed the U.S. Environmental Protection Agency (EPA) to move beyond single chemical assessments and focus on the aggregate and cumulative effects of simultaneous chemical exposures. Increasingly, risk assessments must also address subtle exposures and chronic effects, requiring a more in-depth evaluation of the combined effects of multiple low-level exposures than simpler approaches that have been used historically. CRA holds promise for transforming traditional health risk assessments beyond single chemicals/stressors, exposure routes/pathways, and health end points/effects.² Cumulative risk is defined as the combined risks from aggregate exposures to multiple chemicals and other stressors, while CRA is the analysis, characterization, and potential quantification of these combined risks.^{1,3} CRAs are broader in scope than the

traditional health risk assessment paradigm and consist of several key components (see Table 1).

Although CRAs have been conducted for certain chemical groupings, such as pesticides,⁴ dioxins,⁵ and phthalates,⁶ these assessments have not accounted for all of the factors envisioned for a complete and comprehensive CRA and much work remains to be done. The purpose of this article is to (1) provide an overview of the CRA framework developed by the EPA, (2) describe existing methods that have been used to evaluate cumulative exposures and risks in the United States and Europe, and (3) highlight efforts to extend CRA beyond traditional contexts, frameworks, and risk metrics. Along with other evolving methods and advanced risk initiatives, CRA offers potential novel opportunities for improving the risk assessment process and its application to various settings.⁷

■ CUMULATIVE RISK ASSESSMENT FRAMEWORK

The EPA^{8–10} framework and supporting guidance for conducting CRAs parallels the general framework for health risk assessment in the United States.^{3,11,12} EPA's CRA framework consists of three main phases: (1) planning, scoping, and problem formulation; (2) analysis; and (3) interpretation and risk characterization (see Table 2). The first phase establishes the purpose, goals, and scope of the

Table 1. Key Components of CRA

- Focus on multiple stressors
- Inclusion of both chemical and nonchemical (e.g., biological, radiological, physical, psychological, work life, lifestyle) stressors
- Assessment of aggregate exposures and risks (i.e., exposure to a single stressor by multiple routes)
- Assessment of combined risks for common effects (e.g., chemicals or stressors that have a common mechanism of toxicity)
- Population-based focus (i.e., assessment starts with the receptors or populations of interest and then determines which chemicals, stressors, or other risk factors are affecting them)

assessment and completes the conceptual model and analysis plan. The second phase integrates the hazard, exposure, and dose–response information in order to characterize the combined effects of multiple stressors, in addition to developing exposure profiles and cumulative exposure estimates. Difficult technical issues (e.g., stressor interactions, relevant analytical approaches, common metrics), vulnerable populations, and time-related aspects of exposure are addressed during the analysis phase. The final phase describes important

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Table 2. CRA Framework^{3,9}

phase	steps	tasks
planning, scoping, and problem formulation	planning and scoping problem formulation	define purpose, scope, participants, approach, resources, experience
analysis	possible outcomes integration of exposure, hazard, and dose-response information	develop conceptual model (i.e., define sources, stressors, pathways/routes, receptors, end points), develop analysis plan (i.e., describe methods, models, data gaps, uncertainties), and define appropriate risk metrics (i.e., define outcomes or benchmarks related to adversity and consequences, countervailing risks, risks and benefits) discuss possible outcomes to ensure scope and methods align with needs of the assessment consider time-related aspects (i.e., time sequence or life-stage), vulnerability (i.e., susceptibility to harm), and subpopulations with special exposure
interpretation and risk characterization	risk description uncertainty analysis	In order of increasing complexity: (1) Evaluate single stressor information (i.e., evaluate toxicologic independence and toxicologic similarity) (2) Evaluate multiple stressor information (i.e., evaluate stressor interactions and joint chemical toxicity) (3) Develop measures and metrics (i.e., develop decision indices, probabilistic approaches, qualitative approaches, common metrics, biomarkers) describe risk (i.e., describe probability of harm based on central tendency or high-end risk, individual vs population risk, risk to important subpopulations) be explicit about uncertainty (i.e., describe uncertainty vs variability, uncertainty and risk addition, sensitive parameters)

assumptions, limitations, and uncertainties associated with the assessment and interprets the estimates of cumulative risk in the context of their significance, reliability, and overall confidence. The CRA framework is intended to support broader risk-based decision-making efforts by considering risk-management options or interventions early on in the process.³

METHODS FOR EVALUATING CUMULATIVE RISKS

Aggregate/Cumulative Exposure Models. Numerous exposure assessment models have been developed and used by the EPA for regulatory, voluntary, and research purposes.¹³ These include aggregate and cumulative exposure models used by the Office of Pesticide Programs in response to FQPA to predict dietary and residential exposures to pesticides for the general population or specific subgroups in support of registration and reregistration activities (see Table 3). Important and necessary features of these models include the

Table 3. EPA Aggregate/Cumulative Exposure Models

model	web site link
dietary exposure evaluation model (DEEM)	http://www.epa.gov/pesticides/science/deem/
calendex	http://epa.gov/pesticides/science/calendex/
cumulative and aggregate risk evaluation system (CARES)	http://www.epa.gov/scipoly/sap/tools/atozindex/cares.htm
lifeline	http://cfpub.epa.gov/crem/knowledge_base/crem_report.cfm?deid=152263
stochastic human exposure and dose simulation model (SHEDS)-multimedia	http://www.epa.gov/head/products/sheds_multimedia/sheds_mm.html

ability to (1) assess the co-occurrence of different pesticide residues; (2) integrate exposure through food, water, and residential pathways to reflect both the probability of exposure by any given pathway and the timing of exposures through different pathways; and (3) preserve linkages between spatial, temporal, and demographic aspects of exposure for defined individuals or population members.^{4,14} Because modeled estimates account for the variability in human exposures they are considered more representative of population-level risks, rather than individual risks, and are considered health protective at the upper percentiles of exposure.

These models also share many commonalities with respect to exposure routes and pathways, model inputs and outputs, model steps and capabilities, and model evaluation efforts. For example, these models can include multiple chemicals with a common mechanism of toxicity, multiple routes of exposure (i.e., oral, dermal, inhalation), and multiple pathways of exposure (e.g., food, drinking water, air, indoor surfaces), resulting in multichemical/multiroute/multipathway assessments. Additionally, these models follow the same general steps: (1) simulate an individual and their activity patterns throughout the day; (2) combine activity information, consumption patterns, residue concentrations, and exposure factors in exposure algorithms; and (3) simulate population estimates using probabilistic sampling (i.e., the variability in population exposures is accounted for by running simulations for many individuals and then aggregating across all individuals). However, specific features of these models may differ, including the reliance on different data sources, assumptions, or algorithms (e.g., the SHEDS model is capable

of simulating longitudinal activity patterns). Modeled exposures are typically expressed as absorbed or potential doses (in units of mg/kg-day) for daily and chronic scenarios, and are represented by distributions that account for regional and temporal variations among populations. Cumulative risks are estimated by comparing predicted exposures across multiple pathways to toxicity benchmarks, such as EPA's reference doses. Because these particular models are designed to support higher-tiered (vs screening-level) assessments, they have undergone extensive peer review, including external reviews by EPA's Federal Insecticide, Fungicide, and Rodenticide Act Science Advisory Panel. Several approaches have also been used to evaluate these models or their components including comparing modeling results to environmental monitoring or market survey data, biomonitoring data, or each other (i.e., model-to-model comparisons).

Although health-based and regulatory drivers in the United States have been a strong impetus for CRA, the concept is recognized and maturing in a global context, and the International Program for Chemical Safety (IPCS) has published guidance on cumulative risk assessment.¹⁵ In Europe, a 5-year research project called NoMiracle (NOvel Methods for Integrated Risk Assessment of CumuLative stressors in Europe) has also resulted in the development of novel exposure assessment models and tools, including methods related to evaluating the degradation, fate, sampling, pollutant pathways, and spatial variability of exposure concentrations of chemicals and mixtures in the environment.¹⁶

Cumulative Toxicity/Risk Methods. Although characterizing health risks from multiple stressors is one of the most challenging aspects of the CRA approach, advanced dose-response and risk characterization methods and tools are being developed to address cumulative health risks. However, the complexity of CRAs should follow a tiered approach, in which more refined data and sophisticated techniques are invoked only when simpler health-protective methods and assumptions indicate a concern or impact decision-making.^{3,15} Current risk assessment guidance on chemical mixtures utilizes a decision-tree approach where whole mixture testing data are preferred, and in the absence of such data, a component-based approach is recommended.¹⁷ For noncarcinogens, the simplest form of this approach entails calculating the ratio of the level of exposure to the safe dose for each chemical (i.e., hazard quotient, HQ) and then summing all HQs to estimate the combined risk for the entire mixture (i.e., hazard index, HI) or only the components that have the same toxic effect or affect the same target organ.¹⁸ The greater the HQ/HI is above the value of one, the greater the concern for adverse health effects. For carcinogens, rather than summing the HQs, the estimated population lifetime cancer risk for the various mixture components is added regardless of the tumor type or its origin.

For higher-tiered assessments, the EPA recommends modifications to these approaches that incorporate mathematical interaction terms to account for additional toxicology understanding.¹⁷ This addresses a fundamental limitation of screening-level risk assessments that rely on the default assumption of additivity of dose or risk for mixed stressor exposure, because in reality, interactions that increase the risk (i.e., synergism) or decrease the risk (i.e., antagonism) are possible. For example, it is well-documented that the interaction between occupational exposure to asbestos and smoking significantly increases the lung cancer risk. Interaction profiles have recently been developed for common stressors of

concern at contaminated sites in the United States, such as arsenic, cadmium, chromium, and lead.¹⁹ Methods to analyze and incorporate data on possible stressor interactions under environmentally relevant exposure scenarios continue to evolve.^{20,21} Because many chemical interactions are driven by interactions in toxicokinetic behavior, advances in physiologically based pharmacokinetic modeling are being used to enhance such assessments.²² Along these lines, novel approaches for evaluating the cumulative effects of chemical and nonchemical stressors have been developed under the European NoMiracle research project, including methods that assess the joint effects of chemical mixtures (including integrating all end points and combining toxicokinetics and toxicodynamics) and interactions between chemical and natural stressors.¹⁶ Major findings from this research include the importance of understanding time-dependent toxicity and mechanistic processes, and the need to focus on receptors rather than chemicals or predefined stressors.

Advances in biology are allowing for further refinements to the mixture-based approach by combining the effects of chemicals in the same toxicological class based on the potency of an index chemical or centered on a similar toxicological effect.^{8,9,17} These refinements require an assessment of a chemical's toxic mode of action (MOA)—that is, the key steps in the biological process that lead from exposure to the onset of clinically relevant health effects.^{23,24} Chemicals that act via the same MOA are evaluated together in a CRA. One technique is to evaluate a chemical in terms of its potency relative to an index chemical. Specifically, a toxic equivalency factor (TEF) for each chemical is multiplied by the actual concentration of that chemical to derive a dose equivalent to the index chemical. Current risk assessments for certain dioxins and related chemicals use this approach.⁵ However, the TEF method assumes that the most sensitive adverse effects for all chemicals included in the assessment are driven by the same underlying MOA as the index chemical (e.g., arylhydrocarbon receptor activation for dioxins). Another technique is to identify a common toxic effect and estimate the relative potency inducing this effect for all chemicals that have the same MOA. This approach, which requires the calculation of a relative potency factor (RPF), has been used for organophosphate pesticides that act via inhibition of acetylcholine esterase.⁴ However, since the RPF method is centered on a sentinel toxic effect, chemicals included in the CRA may have other toxic effects that are more sensitive and which are not fully addressed in the cumulative risk estimate. The TEF and RPF methods are conceptually similar, but the latter is centered on the adverse effect and requires less detailed information on the underlying biological mechanisms involved. A key challenge for both methods is identifying the most appropriate end points for inclusion in a CRA, and it has been recommended that CRAs focus on chemicals or substances with a common adverse outcome regardless of mechanism or MOA.⁶

■ MOVING BEYOND TRADITIONAL CONTEXTS

Community-Based Assessments. Concerns about environmental justice issues and health inequities have led to greater interest in conducting CRAs at the local-scale community level. The intended focus of these efforts is on quantitatively assessing and prioritizing risks within individual communities using site-specific information and data on stressors most relevant for that community. For example, the EPA has initiated the Cumulative Communities Research

Program in order to develop, evaluate, and apply exposure models and tools for use in community-based CRAs.^{25,26} In particular, the Community-Focused Exposure and Risk Screening Tool (C-FERST) is a web-based “flagship tool” under development by EPA for supporting community-level multimedia assessments. C-FERST is intended to be a one-stop shopping tool for communities that provides (1) access to relevant exposure and risk-related information and resources, (2) maps of local demographic data and environmental pollutant concentrations, (3) the ability to generate community issue profiles, and (4) links to guidance documents and best practices in other communities.²⁷ The ultimate goal of this tool includes characterizing cumulative risks within communities and at the individual-level, identifying “hot spots” and vulnerable communities, and prioritizing community risk issues. Current priority environmental issues include diesel exhaust from traffic, selected toxic substances (e.g., benzene, lead, mercury), childhood asthma, lung cancer from radon and second-hand smoke, and early neurotoxicity effects. Although the test version of C-FERST is limited to chemical stressors, anticipated future enhancements include incorporating other risk-modifying factors. Prior to its public release, C-FERST is being pilot tested in several communities nationwide, which is expected to further refine the tool and expand its applicability and transferability.²⁶

State environmental agencies are in the process of developing and evaluating similar types of methods for assessing cumulative impacts in communities. For example, New Jersey has developed a preliminary screening tool designed to integrate various environmental measures or indicators with demographic and socioeconomic factors in order to identify communities of concern.²⁸ California has proposed a new screening methodology for assessing the combined effects of various pollutants in communities, particularly in situations where multiple pollution sources may be disproportionately concentrated or there is the potential for increased sensitivity to pollution in a population.²⁹ Both tools are screening approaches intended to rank order and identify communities with the greatest cumulative impacts for priority setting purposes, but do not provide quantitative estimates of community-health risk.

Accounting for Occupational Risk Factors. Occupational risk factors, such as workplace conditions and chemical and nonchemical stressor exposures, have long been known to compromise the health of workers.³⁰ Although chemical risk assessments have traditionally focused on inhalation exposures, greater attention is being paid to integrating dose across exposure routes (e.g., inhalation and dermal) as part of aggregate risk assessments in the workplace. Further consideration of aggregate risks from multiple sources and pathways are addressed through the use of measured internal doses with comparison to exposure guides, such as biological exposure indices (BEIs).³¹

Despite the recognition that human health risks are often driven by occupational risk factors, CRAs conducted to date have focused solely on community or environmental exposures to chemical stressors, and have not attempted to integrate these contexts with occupational settings. While many models exist for evaluating either occupational or nonoccupational exposures, there are currently no well-vetted CRA models that are capable of integrating total exposure across these two domains. Depending on the scenario, the failure to include occupational risk factors in a CRA could substantially affect the utility of such

an assessment. For example, hearing loss is associated with an array of factors, including genetics, age, exposure to noise, and exposure to certain ototoxicants, such as lead and toluene.^{32,33} Because many of these risk factors are not unique to a single setting and are encountered in the general environment, workplace, and/or community, multiple sources of exposure can contribute to the cumulative risk for hearing loss. Accounting for occupational risk factors may not be necessary for all CRAs, but these should at least be considered early on in the assessment to ensure that dominant risk factors are not overlooked or resources are not expended on noncritical risk factors. Additional considerations will be needed to address regulatory and other structures that have traditionally separated the assessment of occupational and nonoccupational health risk factors.

In an effort to more thoroughly address the role of the work environment on the overall health of individuals, the National Institute for Occupational Safety and Health has initiated the Total Worker Health program.³⁴ This strategic initiative promotes an integrated approach to occupational safety and health that focuses on understanding the impact of the interactions between the workplace and individual lifestyle risk factors, such as age, educational level, or preexisting medical conditions. This program, which is comprised of multiple research efforts in the fields of medicine, social sciences, economics, and health sciences, complements existing approaches used to evaluate cumulative risks because it emphasizes the consideration and integration of different risk factors that have traditionally been considered separately. An example of research being conducted under this program relates to the impact of inadequate sleep on work safety and maintaining optimal health.³⁵ Although this initiative is currently qualitative in nature, it is important because it sets the philosophical stage for linking chemical risk and lifestyle risk for workers. Another initiative currently being explored by NIOSH and others has been coined the “exposome,” which is defined as a measure of all internal and external exposures an individual receives over a lifetime, and is also intended to improve our understanding about how exposures from the environment, workplace, lifestyle, and other factors interact with individuals’ unique characteristics (e.g., genetics, physiology, epigenetic makeup, existing disease state) to cause disease.^{36,37}

Going forward, refinements are needed to the CRA framework to allow for the identification and inclusion of the full range of relevant risk factors (including occupational risk factors) in assessments of cumulative risk (see Figure 1). Preferably, common metrics and algorithms will be developed and used to quantify cumulative risks so that different types of risks or individual risk factors can be compared and prioritized. There are many possible options for how this can be done (e.g., presentation of individual risk scores that can be rank-ordered or normalization of risk scores that can be aggregated to determine relative risk), but a hierarchy or suite of potential alternatives remains to be developed.

■ MOVING BEYOND TRADITIONAL FRAMEWORKS AND RISK METRICS

Integrating Chemical and Non-Chemical Stressors. Despite being a key feature of the CRA approach, nonchemical stressors have not been routinely incorporated in quantitative CRAs. One important challenge is identifying which non-chemical stressors are most relevant for the populations and

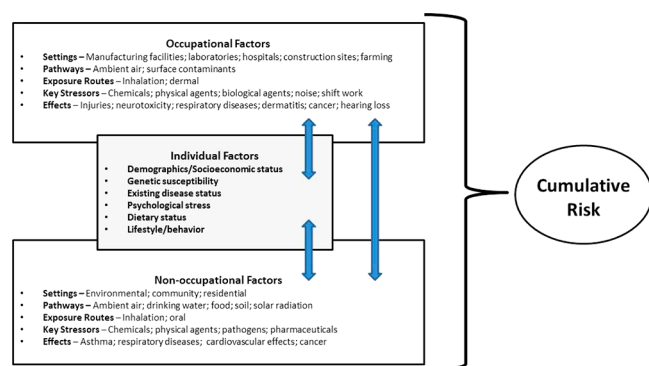


Figure 1. Accounting for Occupational and Non-Occupational Risk Factors in CRAs.

effects of interest and obtaining sufficient data on these stressors. For example, there are many different types of nonchemical stressors that can potentially enhance or attenuate the toxic effects of chemical or other nonchemical stressors including psychological stress, noise, sociodemographic factors and socioeconomic status, residential crowding, violence and crime, behavior and lifestyle characteristics, and occupational exposures and risk factors. There is currently no generally accepted list of nonchemical stressors or associated health outcomes that should be included in CRAs, and various stressors have been mentioned inconsistently in the literature.³⁸

A major reason for this lack of consensus is the difficulties associated with quantifying dose and response metrics for this class of hazards. Simplified risk-assessment tools are needed to address the complexity of considering multiple factors simultaneously.³ For diverse stressors, an approach that integrates adverse health response across all stressors at a common end point or risk measure is needed. Such metrics might be at the community level (e.g., number of hospital visits) or at the individual or biological level (e.g., total level of serum inflammatory markers). Whatever approach is used, efforts to validate the quantitative relationship between stressors and health metrics will require significant research and several research efforts are underway that explore these issues. For example, a community-scale CRA of radon in the presence of smoking was conducted in order to establish a screening-level approach for well-known stressor interactions that could be generalized to other multiple stressor scenarios.³⁹ Theoretical frameworks or “families” of conceptual models that have an established theoretical basis or have been empirically verified have also been proposed to support more realistic and reliable CRAs in the future.^{40,41} These include (1) social determinant models (i.e., health is regarded as a product of social factors), (2) health disparity models (i.e., health is regarded as a product of biological and contextual interactions), and (3) multiple stressor models (i.e., health is regarded as a product of exposure to environmental stressors).

Regardless of which stressors are identified or what type of framework is used to evaluate cumulative risks, common metrics will be needed to integrate exposure and effects data for chemical and nonchemical stressors. Resolution of such issues will require ongoing dialogue among stakeholders, development of cases studies, and guidance for application of novel techniques. Recognition of this need has led to various research alliances and collaborations that may serve as a useful model for how to solve the complexities associated with the CRA approach.⁴²

Biomarker-Based Risk Assessment. One way to gain a better understanding of the cumulative impacts of disparate stressors is to identify common exposure and effect metrics as an integration point for the analysis, such as using biomarkers. Developments are well underway to address all three basic prongs of the biomarker spectrum: exposure, susceptibility, and effect.⁴³ Perhaps most advanced is our progress related to integrating multiple sources and exposure pathways through increased access to measures of chemicals in biological tissues. Specifically, biological monitoring (or biomonitoring) is a method for assessing human exposure to chemicals by measuring the chemicals or their metabolites in human biological media (e.g., blood, urine, expelled air, hair, nails). Biomonitoring is therefore considered a “biomarker of exposure” in that chemicals that have entered the human body leave biologic indicators (markers) reflecting this exposure.⁴⁴ Biomonitoring data provide a direct measure of how much of a chemical has been absorbed into the body from all potential sources, and many population-based biomonitoring efforts are underway.^{44,45} Biomonitoring data can be compared to toxicity benchmarks on the basis of internal doses (biological equivalents) derived from traditional safe doses for general population risk assessments.⁴⁶ This type of approach is needed to put measured concentrations of chemicals in biological media in the general population into a risk context.

There has also been an increased interest in understanding the basis for human variability, including efforts to evaluate biomarkers of human susceptibility. For example, that National Institutes of Health is leading a program focused on developing innovative tools and technologies to determine how environmental exposures (including diet, physical activity, stress, drug use) contribute to human disease. While many individual factors contribute to human variability in susceptibility, in the context of biomarkers, significant attention has been paid to genetic determinants of variable response. For example, differences in drug metabolism due to polymorphism of xenobiotic metabolizing enzymes have a robust history of study (i.e., pharmacogenetics). The same enzyme systems are active in metabolizing environmental pollutants, and quantitative methods to address such polymorphisms in environmental settings have been demonstrated.⁴⁷ Future advancements related to biomarkers of susceptibility will elucidate epigenetic effects (i.e., heritable changes in gene expression that are not due to changes in the underlying DNA sequence).

Although CRAs have been limited to common MOA categories from mixed chemical exposures or empirical effect measurements for binary chemical/nonchemical stressor interactions, this limitation may be partially addressed through the use of biomarkers of effect in the risk assessment process. The maturation of computational and systems biology approaches that use biomarkers of effect centered on common disease pathways has been touted as the future direction of risk assessments.⁴⁸ Biomarkers of effect focus on early events in the sequence of biological events that lead from exposure to adverse health effects. Examples of such measures include activation of cellular receptors or the initial changes in gene expression patterns that arise from such interactions. Efforts to validate markers for early perturbations of normal cell or tissue homeostasis are the focus of many research efforts.⁴⁹ The reliance on biomarkers to determine cumulative exposures and risks from community and occupational settings has many ethical considerations, and may prove controversial for employers and the public. For example, there will likely be

concerns about maintaining the privacy of study participants and preventing the improper use of personal data, such as using biological specimens as a means of pre-employment screening (e.g., to identify or discriminate against individuals with pre-existing health conditions or genetic susceptibilities to work-related diseases).⁵⁰

CONCLUSIONS

Human health may be negatively affected by an array of stressors arising from environmental, occupational, and community settings, in addition to lifestyle or behavioral risk factors and those unique to each individual. Assessing the risk associated with the combinations of and interactions between these stressors has not been possible using traditional health risk assessment approaches. Where beneficial, CRA has the potential to overcome these shortcomings, but the successful application of this innovative approach will likely require significant research and multidisciplinary expertise in public and occupational health, toxicology, epidemiology, environmental science, mathematics, and the social sciences. Many scientific and technical challenges must also be overcome to advance the principals and practice of CRA. These include (1) identifying relevant risk modifying factors and common effects, (2) integrating nonoccupational and occupational exposures, and (3) developing and implementing a cohesive common metric or framework for combining chemical and nonchemical stressors. Although much work is still needed, future enhancements to CRA may enable risk assessors and risk managers to identify the primary contributors to public health risk, thereby leading to better informed decisions and more effective risk reduction strategies. Moving forward on this initiative is timely given the significant emphasis on harmonization of risk assessment methods.⁵¹

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