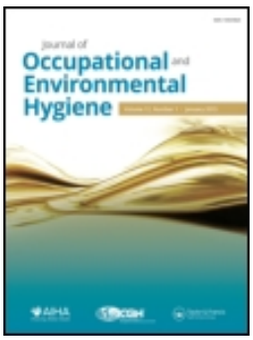

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Aggregate Exposure and Cumulative Risk Assessment—Integrating Occupational and Non-occupational Risk Factors

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Occupational exposure limits have traditionally focused on preventing morbidity and mortality arising from inhalation exposures to individual chemical stressors in the workplace. While central to occupational risk assessment, occupational exposure limits have limited application as a refined disease prevention tool because they do not account for all of the complexities of the work and non-occupational environments and are based on varying health endpoints. To be of greater utility, occupational exposure limits and other risk management tools could integrate broader consideration of risks from multiple exposure pathways and routes (aggregate risk) as well as the combined risk from exposure to both chemical and non-chemical stressors, within and beyond the workplace, including the possibility that such exposures may cause interactions or modify the toxic effects observed (cumulative risk). Although still at a rudimentary stage in many cases, a variety of methods and tools have been developed or are being used in allied risk assessment fields to incorporate such considerations in the risk assessment process. These approaches, which are collectively referred to as cumulative risk assessment, have potential to be adapted or modified for occupational scenarios and provide a tangible path forward for occupational risk assessment. Accounting for complex exposures in the workplace and the broader risks faced by the individual also requires a more complete consideration of the composite effects of occupational and non-occupational risk factors to fully assess and manage worker health problems. Barriers to integrating these different factors remain, but new and ongoing community-based and worker health-related initiatives may provide mechanisms for identifying and integrating risk from aggregate exposures and cumulative risks from all relevant sources, be they occupational or non-occupational.

Keywords aggregate exposure, cumulative risk, occupational

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INTRODUCTION

Occupational exposure limits (OELs) have traditionally focused on preventing morbidity and mortality arising from inhalation exposures to individual chemical stressors in the workplace. While there are other strategies for pursuing or promoting risk prevention and avoidance of occupational hazards, many of which enhance effectiveness when used in conjunction with OELs, the theme of this manuscript and its accompanying manuscripts pertains specifically to the establishment of OELs and the potential for incorporating new science into this practice. The basis and impetus for OELs

stem from early industrial hygiene practice, in which elevated airborne concentrations of certain chemicals in occupational settings presented acute toxicity hazards such as irritation beyond tolerability (as with sulfur dioxide), peripheral nervous system effects (as with many organic solvents), or poisoning leading to unconsciousness or death (e.g., carbon monoxide or hydrogen sulfide). Methods for measuring such occupational exposures and related effects were derived or could be developed.[1–3] That is, to the extent that airborne contaminants in the workplace could be identified qualitatively and measured quantitatively, it was believed that occupational health risk could be characterized or controlled by establishing thresholds and applying safety factors below which adverse health effects would not be expected to occur among workers (i.e., OELs). The establishment of OELs has also been extended to address more subtle associations between exposures and chronic health effects using epidemiology data. While OELs are useful, they are limited as a refined disease prevention tool because they do not account for all of the complexities of the work and non-occupational environments and are based on varying health endpoints. Additionally, regulatory OELs may be set by taking into account considerations other than just adverse health effects. To enhance occupational risk assessment and to help address increasingly challenging risk related questions, OELs and other risk management tools could incorporate considerations for more complex exposure and risk scenarios. For example, modern occupational risk assessments should integrate consideration of risks from multiple exposure pathways and routes (risk assessment of aggregate exposures leading to an evaluation of aggregate risk) as well as the combined risk from exposure to chemical and non-chemical stressors, including the possibility that such exposures may modify the toxic effects observed or their severity through interactive processes (cumulative risk). A more complete consideration of the composite effects of occupational and non-occupational risk factors is also needed to fully assess and manage worker-health issues. In this article, we highlight the key regulatory, scientific, and social drivers for more complex occupational risk assessments and present current and novel techniques for evaluating aggregate and cumulative risks. Table I summarizes key terms used in this manuscript.

TABLE I. Glossary of Key Terms

Key Term	Definition
Aggregate risk	The sum of risks associated with exposures from multiple pathways and routes
Biomarkers	Internal measures or markers of exposures or effects for a chemical or agent in the body
Cumulative risk	The combined risk from exposure to chemical and no-nchemical stressors, including the possibility that such exposures may modify the toxic effects observed or their severity through interactive processes
Exposome	The measure of all the exposures of an individual in a lifetime and how those exposures relate to health
Exposomics	The study of the exposome, which relies on the application of internal and external exposure assessment methods
Occupational exposure limit	A threshold below which adverse health effects would not be expected to occur among workers; used as a risk management tool for minimizing occupational health risk through characterization and control of exposure to workplace hazards
Total Worker Health	The NIOSH strategy to integrate occupational safety and health protection with general health promotion to prevent worker injury and illness and to advance overall worker health and well-being
Toxicodynamics	The effects of a chemical or agent in the body induced at the level of the affected tissue
Toxicokinetics	The disposition of a chemical or agent in the body

Although the science and practice of risk characterization and assessment continue to evolve, risk assessment of aggregate exposures and cumulative risk assessment have not yet reached the stage of widespread utility and implementation in occupational health. Methods and tools developed and used in the broader environmental and public health arenas have contributed to the advancement of these approaches, but they generally do not account for the unique characteristics and risk factors germane to occupational settings. Ongoing and future efforts to assess risk due to aggregate exposures and cumulative risks may lead to more inclusive and better defined representations of conditions that affect the health of workers. By extension, comprehensive approaches to worker health awareness and well-being can potentially be developed based on this information, which may better inform risk management decisions.

Key points of emphasis covered in this article include:

- There is a growing emphasis on ensuring that occupational risk assessment and characterization account for more complex exposures in the workplace. This emphasis includes risk assessment of aggregate, or multiple, exposure pathways and routes to determine aggregate risk, as well as the assessment of cumulative risk from combined exposure to chemical and non-chemical stressors.
- Aggregate and cumulative exposure and risk assessment techniques are consistent with and build on traditional exposure and risk assessment approaches that have been used

in industrial hygiene for many years. Methods and tools for evaluating aggregate and cumulative risk, that potentially may be adapted or modified for occupational health scenarios, are being developed and used in other disciplines. Technology transfer of methods and tools across allied fields will facilitate the consideration of both occupational and non-occupational risk factors. Such a strategy is currently being developed in the context of programs and initiatives aimed at achieving Total Worker Health.

DRIVERS FOR AGGREGATE AND CUMULATIVE RISK ASSESSMENT

A confluence of many factors has led to increased consideration of complex exposures and attendant health outcomes in occupational risk assessments. Occupational health and safety professionals have a fairly mature history of successfully controlling exposures to airborne contaminants, thereby minimizing opportunities for acute reactions or more immediate and severe adverse health effects.[1–3] Many other factors have also resulted in reductions in airborne exposures to hazardous chemicals including dramatic shifts away from manufacturing to service sector industries, the mechanization or enclosure of processes to reduce the number of workers exposed, increased sampling of airborne concentrations and medical monitoring in the workplace, greater awareness of hazardous conditions and educational outreach efforts, and new or updated regulatory standards prescribing safe exposure levels. While hazardous situations involving inhalation exposures to individual contaminants still exist, particularly in developing countries where regulations or enforcement may be less restrictive, the need to consider the impact of multiple exposures and combined risks for affected worker populations is growing. Highlighted below are some of the key regulatory, scientific, and social drivers behind the push for more complex occupational exposure and risk assessments.

REGULATORY AND PUBLIC POLICY DRIVERS AFFECTING RISK ASSESSMENT

The concept of aggregate exposures and cumulative risk assessment in the regulatory and public policy arena is traceable to work performed by the Environmental Protection Agency (EPA) in 1993 and referenced in a National Academy of Sciences report "Pesticides in the Diets of Infants & Children,"[4] which characterized the exposures of infants and children to multiple pesticides in food and other non-dietary sources that have a common toxic effect. The NAS concluded that estimates of exposure and risk for this subpopulation could be improved by accounting for simultaneous exposures and similar effects. Certain changes to then-current regulatory practice and scientific methods were recommended that would allow for estimates of total pesticide residue exposures, taking into account the unique characteristics of the diets of infants and children and all non-dietary intake of pesticides. [5–8] The Food Quality Protection Act of 1996 directed the EPA to focus on the cumulative effects of aggregate chemical exposures occurring simultaneously instead of the traditional approach of single chemical assessments, whether for aggregate or single pathways/routes of exposure. Cumulative effects were defined under the Food Quality Protection Act as pesticide residues and other substances that have a "common mechanism of toxicity," and this term was further defined by the EPA as chemicals or substances that "cause a common toxic effect(s) by the same, or essentially the same, sequence of major biochemical events" (i.e., mode of action). Subsequent EPA documents, such as the "General Principles for Performing Aggregate Exposure and Risk Assessments,"[5] "Framework for Cumulative Risk Assessment,"[7] and others, developed guidance for evaluating aggregate exposures and structuring cumulative risk assessments that provide a framework, general principles, and methods for estimating aggregate and cumulative risks.[5–8] Since then, the EPA has determined that the following five groups of pesticides require cumulative risk assessments because they each have a common toxicity: organophosphates, N-methyl carbamates, triazines, chloroacetanilides, and pyrethrins/pyrethroids. The EPA has noted that the use of the term aggregate risk may be redundant when discussing cumulative risk assessment for some risk assessors; however, for the purposes of discussing the assessment of aggregate exposures, such terminology is used.[7] This convention is utilized for the purposes of the issues discussed in this article.

ADVANCES IN SCIENCE AND TECHNOLOGY PROPELLING RISK ASSESSMENT

Advances in science and technology have increasingly enabled the ability to characterize the contribution of and interactions among multiple exposures and their effect on human health, including in occupational settings. Perhaps most critical is the capability to measure or estimate exposures and effects at the level of the affected individual or worker. For example, at the physiological level, exposures and effects are influenced or determined by toxicokinetics, the disposition of the chemical or agent in the body and by toxicodynamics, the effects induced at the level of the affected tissue. These concepts, in turn, relate to the identification and application of biomarkers (i.e., internal measures or markers of exposures or effects) during the risk assessment process. With respect to biomarkers of exposure, occupational safety and health professionals have traditionally used biological monitoring as the primary integration tool for assessing chemical exposures via multiple pathways or routes of exposure. Although alternatives to invasive direct measurement techniques such as individualized monitoring via medical biotechnology are needed, applications of biological monitoring still provide value in worker health evaluations. Other types of exposure or dose estimation tools and computational models such as stochastic analysis and Bayesian statistics are being applied with utility in the occupational safety and health community. For example, dosimetry and toxicokinetic modeling tools have been developed to address internal target tissue dose estima-

tion across different exposure scenarios, and such models are increasingly being used to assess the toxicokinetic impacts of mixed exposures from multiple routes and chemicals.[8–10]

However, biological monitoring and other exposure estimation tools have typically focused on internal dose, whereas markers of biological effects are ultimately needed to inform control strategies to minimize disease. From a practical standpoint, the earliest point of integration for assessing aggregate and cumulative risks is at the boundary of dose and effect. Access to data at this interface has improved through a better understanding of molecular toxicology and the development of assays to measure immediate and subtle perturbations in physiologic function. A vision for how to use emerging scientific and technological advances in risk assessment has been laid out through expert group discussions, for example, as articulated by the National Academy of Sciences[11] and through implementation programs, such as the EPA Next Generation Risk Assessment (NexGen) Program.[12, 13] As such techniques continue to develop, the challenge for the occupational safety and health community will be how to integrate and incorporate such early effect biomarker data into the risk assessment process.

Although the concepts of risk assessment of aggregate exposure and cumulative risk assessment originated in the environmental health arena for a specific subpopulation, the science and practice of these concepts may be relevant to other populations or contexts, including occupational and community-based settings. As a means of utilizing the knowledge gained from cumulative risk approaches, coupled with prudent risk management practices, the National Institute for Occupational Safety and Health (NIOSH) has promoted an approach focusing on Total Worker Health™. Total Worker Health™ begins to integrate occupational safety and health protection with general health promotion to prevent worker injury and illness and to advance overall worker health and well-being. This more holistic approach recognizes that the work environment and the broader health, safety, and well-being of individuals are strongly connected and must be considered together.[14, 15] For example, ill health and injury, whether caused by work or resulting from non-work activities, can reduce quality of life, opportunity, and income for workers and those dependent upon them.[16–18] In contrast, workplaces with a low risk of injury and enhanced opportunities for the total health of workers can lead to a vibrant, engaged, and highly performing workforce.[19, 20] For example, recent work has suggested that knowledge of the work and non-work factors that can affect health may enhance intervention and prevention activities such as raised awareness of occupational factors improving smoking reduction/cessation among unionized building trade workers.[21–23] The concept of Total Worker Health can be explored in greater detail at http://www.cdc.gov/niosh/TWH/totalhealth.html.

Just as the Total Worker Health approach advances efforts to address aggregate and cumulative risk, so too does an improved understanding of the interaction of individual characteristics and environmental conditions. Specifically, the health impact of environmental or occupational exposures can vary among individuals because of differences in physiologic status, socioeconomic realities, cultural perspectives on risk, and other personal factors. In an attempt to address this issue, the concept of the "exposome," which is defined as the measure of all the exposures of an individual in a lifetime and how those exposures relate to health, has recently emerged in environmental and occupational contexts.[24] Advances in this approach may help determine why some people will develop a disease while others with the same or greater exposure will not. A key factor in describing the exposome is the ability to quantify exposures and their effects. Mapping an entire exposome for an individual will be difficult if not impossible because of the complexity of a lifetime of exposure. Some of the potential practical and ethical considerations impacting exposomics are described in the companion manuscripts by DeBord et al.[13] with respect to systems biology and Schulte et al.[64] regarding integration of genetic and epigenetic information. However, the evolution and maturity of this concept as well as the science of exposomics (i.e., the study of the exposome, which relies on the application of internal and external exposure assessment methods) can be viewed as a practical extension of aggregate and cumulative risk assessment that ultimately seeks to inform risk management strategies. Additional details about the exposome and exposomics can be found at http://www.cdc.gov/niosh/topics/exposome/.

SOCIETAL PRESSURES INFLUENCING RISK ASSESSMENT

During the past several decades, the role of growing social consciousness, manifested as efforts to promote corporate social responsibility, community right-to-know campaigns, and environmental justice or product stewardship programs, has also influenced efforts to improve the risk assessment process. One example is the increased emphasis on sustainability and "green" practices that protect, or at least minimize, negative impacts to environmental resources. Dedicated efforts are also underway to ensure that occupational safety and health and the human element are incorporated into broader sustainability initiatives.[25, 26] Although traditionally targeted separately, opportunities exist at the intersection of environmental protection and occupational health to broaden approaches to assessing more complex exposures and their associated risks.

One consequence of increased public expectation regarding chemical safety is the development of new community-based initiatives and tools by regulatory agencies. The EPA has been at the forefront of such efforts aimed at assessing cumulative risks at the community level. Led by the EPA Office of Research and Development, the Cumulative Communities Research Program "focuses on exposure tools for advancing the science and understanding of cumulative risk to communities and individuals."[27] Ultimately, these tools will assist in characterizing community risks according to a calculus that allows combining of risks across chemical and

nonchemical stressors, for example, taking into consideration chemical mixtures and interactions as well as risk modifying factors such as noise and stress. The focus on community (i.e., non-occupational) exposures is driven by many factors, but can likely be attributed to people's desire to know about the multiple stressors (e.g., pollutants) to which they are exposed, what the associated health risks are, and how these exposures and related risks can be prevented or reduced. Similar efforts to assess the cumulative impacts faced by communities are underway in various states, such as California[28] and New Jersey.[29]

Community-based initiatives for the cumulative assessment of chemical and nonchemical stressors in the environmental context may represent a class of approaches with the potential to extend to the evaluation of risk in the workplace. The concept of integrating the health impact of all stressors from occupational and non-occupational sources is consistent with the NIOSH Total Worker Health™ Program and EPA initiatives relating to environmental justice.

RISK ASSESSMENT OF AGGREGATE EXPOSURE: ADDRESSING ONE STRESSOR VIA MULTIPLE ROUTES/PATHWAYS

Aggregate risk assessment focuses on evaluating the health risks of a single, specific, stressor from multiple exposure pathways or routes. Exposure pathways refer to the variety of sources and routes and fate and transport mechanisms with which the exposure is associated. As part of an aggregate risk assessment, the relevant toxicological endpoints for each potential exposure and duration are identified along with exposure estimates for each route of exposure. These datasets are merged to characterize potential routes and durations of exposure that might lead to one or more adverse health effects. The outcomes of an aggregate risk assessment include the identification and characterization of possible exposure scenarios and quantitative estimates of route-specific, health-effect specific, and aggregate risks. This approach to the risk assessment of aggregate exposures may have application to the determination of risk assessment-based OELs, but several issues require further methods development.

Calculating risk for aggregate exposures is a complex process consisting of multiple factors that must be addressed to accurately characterize relevant exposure and health effect scenarios for a given stressor. The development of exposure scenarios includes a critical examination of all possible (known) exposure sources, routes, pathways, and settings. For example, aggregate risk from exposure to organic solvents may arise from the inhalation of vapors from direct emissions in the breathing zone, inhalation of vapors from indirect sources in the background air, and dermal contact with the liquid. Such exposures may occur in occupational settings where solvents are applied during specific tasks or processes as well as in non-occupational settings where solvents are used in home maintenance activities, such as personal auto repairs and gardening/lawn maintenance. The graphical representation of the typical exposure pathways of relevance to aggregate risk assessment presented in Figure 1 indicates where exposures may occur via multiple exposure pathways and routes in occupational and non-occupational settings. Consideration of these types of exposure scenarios is needed to adequately characterize aggregate risk. The potential for both chemical and non-chemical factors to be of equal importance in the workplace[23] may also require the extension of approaches to aggregate chemical exposures to address non-chemical variables.

Despite the difficulties in assessing aggregate exposures to a chemical, practical approaches and tools are available to occupational health practitioners to assist in characterizing aggregate exposures, determining the risk of health effects, and informing risk management decisions. One approach is biomonitoring, which involves the collection and analysis of biological media to assess exposure, metabolic processing, and effects for a chemical. As mentioned above, occupational health practitioners have historically used biomonitoring to complement the findings of environmental monitoring by providing supplemental information that can be used to estimate the internal dose of a chemical or its metabolites via all exposure routes and pathways. The collected data are used to characterize exposure patterns and potential health risks, in addition to identifying susceptible subpopulations and serving as tools for screening and surveillance.[30, 31] Interpretation of biomonitoring data occurs via its comparison against established workplace biological reference values, such as the Biological Exposure Index developed by the American Conference of Governmental Industrial Hygienists (ACGIH).[32] Such an approach with biomonitoring allows additional characterization of risk by combining considerations for exposure data, internal dose, metabolic processes, and qualitative or quantitative measures of biological impacts. Biomonitoring of non-chemical exposures in the workplace may be another area of importance, with further work needed to develop exposure markers, identify relevant metabolic processes, and measure health effects. For example, ACGIH has developed guidance regarding hand-arm vibration in certain work tasks.[32] An approach analagous to the risk assessment of aggregate chemical exposure may provide improved understanding of the range of pathways in which vibration may impact health, not only via musculoskeletal/vascular routes, but through others, such as psychological routes. Accordingly, the phrase "route of exposure" would need to expand to apply to a non-chemical factor, in this case a physical exposure in the workplace. The collection and use of personal biomonitoring data need to be carefully considered so as not to violate the Health Insurance Portability and Accountability Act of 1996 rules which address the use and disclosure of individuals' health information.

A key strength of risk assessment of aggregate exposures is the ability to identify the relative contribution of different exposure routes to total exposure and risk. In setting regulatory standards for contaminants in water, the EPA develops relative source contribution (RSC) factors to apportion the chemical's allowable dose (i.e., reference dose, or RfD) for various en-

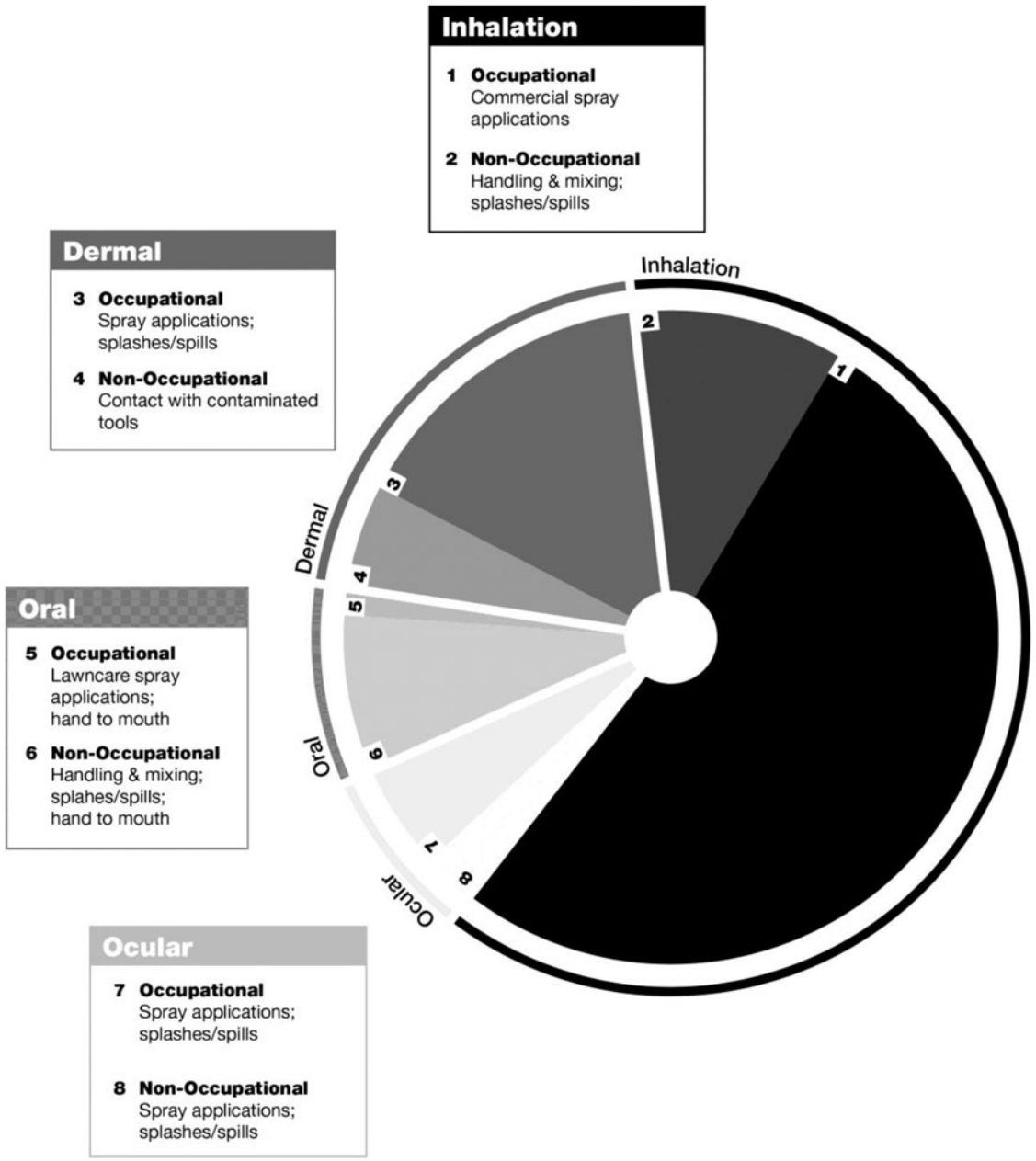

FIGURE 1. Illustration of relative contribution to exposure. This figure illustrates a theoretical case study of aggregate exposure to organic solvents. In this scenario, exposures may occur via multiple exposure pathways and routes. The relative contribution to total exposure to organic solvents is proportionally represented for each of the primary exposure routes and further delineated by setting, (i.e., occupational vs. non-occupational).

vironmental media. The RSC factor is used to ensure that the concentration of a chemical allowed by a regulatory criterion or multiple criteria, when combined with other identified sources of exposure common to the population of concern, will not result in total exposures that exceed the permitted dose or RfD. An exposure model is used to identify relevant potential sources for receptors, and an RSC factor for a chemical is developed by application of the Exposure Decision Tree approach developed by the EPA[33] to the existing potential exposure data. RSC factors are used in the development of ambient surface water standards under the Clean Water Act and drinking water standards under the Safe Drinking Water Act.[34]

Use of this approach involves consideration of the adequacy of available exposure data, including relevant sources and media of exposure. Depending on chemical-specific circumstances, either a subtraction or percentage method can be used. When other sources of exposure (i.e., other than drinking water and fish exposure) can be considered "background," the subtraction method is used, where the background is sub-

tracted from the RfD, thus reducing the amount of the RfD "available" for water-related sources of intake. The percentage method is used if adequate data exist to quantify exposure from sources other than the source of concern. In this instance, the percentage of total exposure typically accounted for by drinking water (RSC) is applied to the RfD to determine the maximum amount of the RfD "apportioned" to drinking water. Typically, a maximum contribution or "ceiling" level of 80% and a minimum contribution or "floor" level of 20% of the RfD apportioned to drinking water are applied regardless of method, implying that the criterion, standard, or guidance cannot correspond to estimated human doses more than 80% of the RfD, nor less than 20% of the RfD. For example, the EPA Drinking Water program applies a default RSC factor of 20% in the absence of adequate data to characterize exposure. The default assumes that the major portion (80%) of the total exposure comes from other sources, such as diet, and therefore the amount of the chemical permissible in drinking water should be minimized. Use of these upper and lower boundaries ensures that the total exposure is maintained at or less than the RfD, while generally avoiding an extremely low criterion in a single medium that represents just a relatively minor fraction of the total exposure.

The RSC concept as developed by the EPA may have application in the development of OELs when the consideration of multiple occupational and non-occupational sources for a chemical exposure is important for adequately protecting human health. Further, the delineation of the relative contribution of different exposure routes to total exposure and risk may likely be important for both chemical and non-chemical stressors. Methods for the risk assessment of aggregate exposures would ideally provide estimates of the likelihood of the occurrence of an adverse health effect resulting from multiple routes of exposure to a single stressor.

CUMULATIVE RISK ASSESSMENT: ADDRESSING MULTIPLE STRESSORS VIA MULTIPLE ROUTES/PATHWAYS

In reality, workers and the general public are typically simultaneously exposed to a variety of chemicals and other stressors from various sources. Although any given exposure may by itself be insignificant to human health, the impact of multiple exposures may result in increased health risk due to the additivity of the dose or response or other types of mechanistic interactions. To address this concern, public health groups and regulatory agencies have developed frameworks and guidelines for assessing the combined risk from exposures to multiple stressors, including vulnerability factors and chemical, physical, and biological exposures from all contributing sources.[7, 33, 35]

By definition, cumulative risk assessment involves assessing the combined effects of multiple stressors rather than focusing on single compounds. This approach also extends beyond chemicals to include psychosocial, physical, and other factors, and provides population-based assessments rather than source-based assessments.[7, 8] Cumulative risk assessments are broader in scope than risk assessments of individual chemicals, whether from one or multiple pathways/routes of exposure. Cumulative risk assessments consist of the following key components: (1) multiple stressors, (2) chemical and non-chemical stressors, (3) aggregate exposures and risks, and (4) combined risks for common effects by chemical or stressor groupings.[36, 37] A current approach to cumulative risk assessment for chemicals, as developed by the EPA, is to focus on the grouping of chemicals that are structurally similar such as dioxins and phthalates or are known to have a common mechanism of toxicity (i.e., chemicals that affect the body through the same biological pathway). A complete cumulative risk assessment in this paradigm would, therefore, include aggregate exposure assessments for all of the common mechanism chemicals as well as estimating cumulative hazard, dose-response assessment, and risk characterization. Figure 2 illustrates key risk factors associated with occupational and non-occupational settings in addition to individual factors included in the considerations that govern cumulative risk assessment.

METHODS AND TOOLS

Although the principles of aggregate and cumulative risk assessment increasingly are being applied for the general population in environmental and community-based settings, greater adoption, and implementation of these approaches are needed for workers in occupational settings. This is of particular importance because, for many individuals, occupational scenarios are assumed to account for the greatest magnitude of exposure, and the combined effects of multiple sources of exposure are likely to have the greatest health risk impact in occupational settings.

STRATEGIC APPROACHES AND MODEL FRAMEWORKS

The EPA[6–8] has developed a framework and supporting guidance for conducting cumulative risk assessments that consists of a planning, scoping, and problem formulation phase, an analysis phase, and an interpretation and risk characterization phase. In the first phase, the purpose, goals, and scope of the assessment are established, and a conceptual model and analysis plan are completed. In the second phase, the hazard (and associated health effect), exposure, and dose-response information are integrated to characterize the combined effects of multiple stressors. One commonly used method for cumulative risk assessment of chemicals is to determine groupings that are toxicologically similar and then develop relative potency factors to normalize the toxic response of each chemical to the toxicity of an index chemical. This phase also includes developing exposure profiles and cumulative exposure estimates, which can be accomplished through numerous quantitative and qualitative techniques. In the third phase the important assumptions, limitations, and

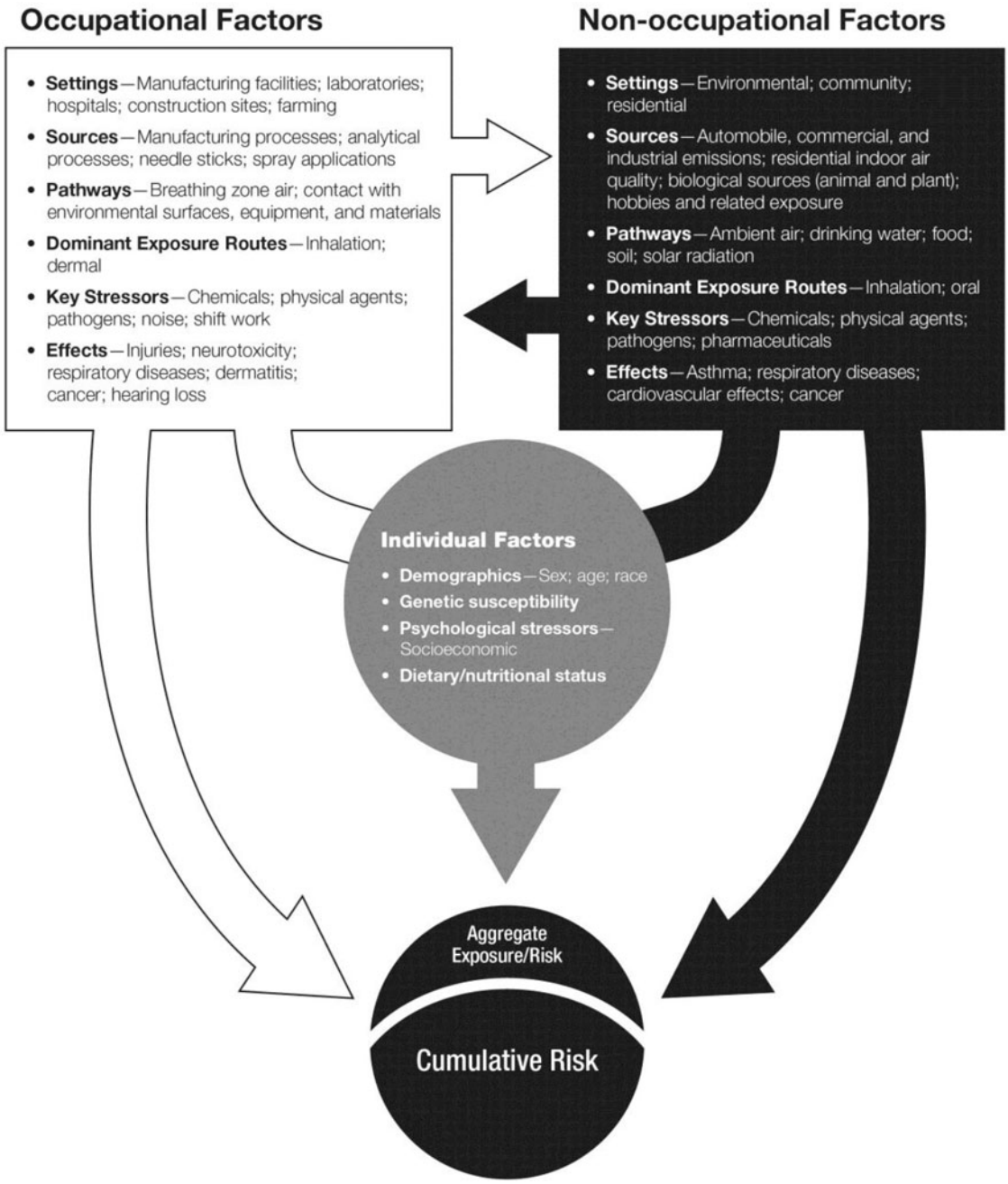

FIGURE 2. Illustration of the relationship between key factors considered in cumulative risk assessment. This figure illustrates key risk factors that may contribute to aggregate and cumulative risk. The primary factors are organized into three categories: (1) occupational factors, (2) non-occupational factors, and (3) individual factors. For each category, examples of the primary settings, sources of risk, exposure routes, key stressors, and effects are included to aid in illustrating considerations that should be included in assessing aggregate and cumulative risk to various hazards.

uncertainties associated with the assessment are described, and estimates of cumulative risk are interpreted in the context of their significance, reliability, and overall confidence. Various approaches are available for addressing the variability and uncertainty in risk estimates including sensitivity analyses and one-dimensional and two-dimensional stochastic analyses such as with Monte Carlo simulation.

With respect to the second phase of cumulative risk assessment, several techniques have been developed to examine environmental and occupational exposures. Three of the more common techniques are (1) exposure monitoring, (2) exposure modeling, and (3) biomonitoring. These methods are intended to provide estimates of the external exposure concentration to which the target population has been exposed or to provide

measures of internal dose to assess whether such exposures exceed health benchmarks.

In the EPA cumulative risk assessment paradigm, exposure monitoring measures the environmental concentrations of each chemical of interest. Such measurements are quantitative in nature and are intended to represent chemical concentrations that the target population has been exposed to during a defined period. Various techniques have been developed that are capable of measuring chemical concentrations within different media (e.g., air, water, soil) and via different routes (e.g., inhalation, dermal contact). In occupational settings, air samples are collected to estimate workers' inhalation exposures, and surface wipe samples are collected to estimate workers' dermal exposures.

Although a thorough review of these techniques is beyond the scope of this article, numerous resources are available that provide in-depth discussions on methods used for chemical exposures in occupational settings.[38, 39] A number of exposure models have also been developed or used to assess aggregate and cumulative risks in environmental settings, particularly related to pesticide exposures. These include the Dietary Exposure Evaluation Model, Calendex, the Cumulative and Aggregate Risk Evaluation System, Lifeline, and the Stochastic Human Exposure and Dose Simulation Model. The LifeLine Community Based Assessment Software™(C-BAS) is part of a software suite that allows users to evaluate potential exposures and risks across a community or population. The community information is collected and entered into the C-BAS™is intended to enable investigation of potential exposures and risks to the population of interest from substances of concern in the living environment and diet. More information is available at http://www.thelifelinegroup.org/cbas/index.php. Such models are capable of assessing co-exposures via multiple sources and exposure routes, while preserving spatial, temporal, and demographic linkages among different population groups.[37] As mentioned above, the collection of biological specimens (i.e., biomonitoring) has increasingly been used to provide a measure of total exposure from all sources and routes of exposure. In addition, difficult technical issues must be addressed during the second phase of cumulative risk assessment, including (1) evaluating the toxicity of mixtures and interactions among stressors, (2) defining relevant approaches and common metrics, and (3) considering vulnerable populations and time-related aspects (e.g., time sequence or life-stage of exposure).

Some programs have incorporated occupational chemical exposures into their cumulative risk assessment evaluations, including the EPA Office of Pesticide Program and Office of Pollution Prevention and Toxics (OPPT), the World Health Organization/International Programme on Chemical Safety,[35] and the European Commission's Registration, Evaluation, Authorization, and Restriction of Chemical (REACh) Substances. The occupational setting, however, necessitates the evaluation of chemical and non-chemical exposures, often as equally important variables. This is a dimension of cumulative risk assessment that requires moving beyond current methodologies with respect to exposure assessment, risk assessment of aggregate exposures, cumulative exposure-response modeling, and risk characterization and management. Furthermore, exposure to chemical mixtures or non-chemical factors in the workplace each present challenges for risk assessment.

DETAILS ON CHEMICAL MIXTURES

Components of a chemical mixture can elicit similar action, independent/dissimilar action, or interaction.[33, 40] Similarly acting and independently acting components in a mixture are assumed not to influence mechanisms/modes of action for each other's toxicity.

EVALUATION OF INTERACTIONS (SYNERGISM AND ANTAGONISM)

Exposures to environmental mixtures are usually composed of multiple chemicals from diverse sources with dissimilar chemical structures and mechanisms/modes of action. Some components in a mixture may have similar or dissimilar mechanisms/modes of action, while other components may interact directly with each other when present simultaneously or with other chemicals in biological systems. These interactions can alter tissue disposition (kinetics) and/or response at the organ or cellular level (dynamics), thus raising concerns about the potential adverse effects of such interactions.

Three major mechanisms for toxicant interactions have been identified: direct chemical-chemical, toxicokinetic, and toxicodynamic mechanisms.[41, 42] Each interaction mechanism can affect the toxicological response, resulting in a response being less than additive (e.g., antagonistic or reduced toxicity) or greater than additive (e.g., synergistic or enhanced toxicity). While interactions usually occur at medium or high dose levels (relative to the lowest effect levels), they are not likely to occur or are toxicologically insignificant at low exposure levels. Such interactions, when likely to occur, need to be considered in a cumulative risk assessment.

Advances in Mixtures Risk Assessment

Regulatory bodies and others[32–33, 41–43] have recommended approaches for estimating human health risk of chemical mixtures with respect to occupational and environmental exposures, depending on whether or not the chemicals in the mixture act toxicologically similarly or independently of each other or whether the potential to interact with each other in a biological system exists. A whole-mixtures approach in which exposure data and toxicological information on the mixture of concern or a sufficiently similar mixture is used to assess the health risks associated with the exposure to a mixture. A component-based approach is used in the absence of data on the whole mixture. This approach focuses on mixture components that are present at toxicologically significant exposure levels and considers the potential toxicological interaction of certain chemical components in the mixture to estimate the toxicity of the mixture. The main component-based methodologies for estimating risk to chemical mixtures range from

those that ignore interactions among the mixture components (dose addition and independent action) to more sophisticated tools that model biological fate of the components taking into account the biochemical interactions affecting both internal exposure and the toxic potency of the mixture.

DOSE AND RESPONSE ADDITION TOOLS

A general occupational risk assessment approach to chemical mixtures is based on the dose additivity principle.[44] Four commonly used forms of component methods that are based on dose addition include the hazard index (HI), the relative potency factor (RPF) method, the toxicity equivalence factor (TEF) method, and reciprocal calculation procedure (RCP).

The HI approach is one of the most straight-forward ways to assess mixtures. The method commonly involves calculation of an HI by summing individual hazard quotients for each known chemical in a mixture. The HI is used as a total estimate of the non-cancer risk of exposure to a simple mixture, the components of which are not likely to be carcinogenic. It does not require knowledge of similar mode of action nor does it consider interactions between components in the mixture, but requires only similarity in the target organ. A separate HI is determined for each target organ of concern. As the value of HI reaches or exceeds 1, concern for health risk from the mixture increases.

Chemicals that have similar endpoints and a common toxic effect, including dose descriptors for critical effects such as benchmark doses, lowest observed adverse effect levels (LOAELs) or no observed adverse effect levels (NOAELs), can be grouped together, and a scaling factor or RPF is calculated. RPFs may be derived when the mechanism/mode of action is less certain or is known for only a subset of all health endpoints. In this approach, the toxicity of the related components in a mixture is predicted from an index chemical with respect to health information—an index chemical is usually the best studied chemical in the mixture—by scaling the exposure level of each component by its toxicity relative to the index chemical. The component exposure levels are then converted into an equivalent index chemical exposure. The mixture risk is then quantified by comparing the mixture's equivalent dose in terms of the index chemical to the dose-response assessment of the index chemical. The EPA considers the RPF approach appropriate for polycyclic aromatic hydrocarbons, using benzo[a]pyrene as the index chemical.

TEF is a special type of RPF that is derived when abundant data support a specific mode of action that is pertinent to all health endpoints. This approach is applied to all health endpoints, exposure routes, and exposure durations. The EPA considers this approach to be appropriate for the dioxins and dioxin-like compounds. For mixtures containing such components, the EPA expresses the consequence of exposure to each compound in terms of an equivalent exposure of 2,3,7,8-tetrachlorodibenzodioxin by multiplying the concentrations of the individual congeners by their assigned TEF. Estimation of the risk associated with the mixture of these congeners involves summation of the resulting 2,3,7,8-tetrachlorodibenzodioxin toxicity equivalents.

The RCP is specifically developed for calculating OELs for mixtures of certain refined hydrocarbon solvents derived from petroleum containing saturated aliphatic (alkanes), cycloaliphatic (cycloalkanes) and aromatic hydrocarbons.[32] The approach is applicable when chemical constituents of the petroleum-based refined hydrocarbon solvent have similar toxicity and the toxicological effects act in an additive manner.

INTERACTION TOOLS

Dose addition or response addition tools do not take into consideration interactions occurring between components in a mixture. Given that toxicokinetic and toxicodynamic interactions do occur, resulting in lower toxicity (antagonism) or greater toxicity (synergism) of mixtures, tools (e.g., interaction-based hazard index), and physiologically-based pharmacokinetic (PBPK) modeling are being developed that take into consideration interaction among components in a mixture.[33, 43, 45]

An interaction-based hazard index approach is a modification of the hazard index approach that accounts for interactions among components of the mixture, using the weight of evidence for interactions among pairs of mixture components.[33, 43] The EPA uses this approach as default for mixtures of chemicals that produce toxicity not adequately described by dose addition. In this approach, the HI developed for additive effects is used as a basis, and interactions are accounted for by multiplying the HI with a factor reflecting both the uncertainty and the strength of evidence that interactions take place.

PBPK models are increasingly employed in cumulative risk assessment to predict the potential for the pharmacokinetic interactions among components following exposure to chemical mixtures.[33, 43, 45] The models are useful in predicting internal dose of components in the mixture at target organs for risk assessment applications or possibly for non-cancer or cancer health effects from the mixture. PBPK models have been employed to evaluate the potential toxicity from chemical mixtures in occupational exposure settings.[45] PBPK/pharmacodynamics models and others are being developed that allow for integration of concurrent exposure to multiple chemicals through integrating cellular and molecular biology information of the component chemicals and available mechanistic data. The predictive capability of PBPK/pharmacodynamic models is expected to be enhanced by integrating them with other approaches such as Monte Carlo simulation, response surface methodology, and quantitative structure-activity relationship (QSAR) models.[43] Other models that combine the concepts of concentration addition, response addition, and toxicokinetic chemical interaction to assess toxicity of chemical mixtures are under development and validation.[46, 47]

EXPOSURES TO NON-CHEMICAL STRESSORS

Non-chemical stressors have increasingly been the focus of attention in occupational safety and health. This class of stressors includes personal risk factors and occupational hazards. Non-chemical hazards such as work stress, heat stress, noise exposures, and vibrational exposures have been investigated for their relationship to occupational illness and injury.[48–51] Traditional quantitative and qualitative risk assessment has been used predominantly for assessing risks of exposure to individual chemicals. Quantitative risk assessment of exposure to non-chemical stressors requires modification or development of new methods of study design, hazard identification, exposure assessment, outcome definition, dose-response modeling, and risk characterization methodologies.

Early occupational safety and health work in the United States focused on chemicals as the dominant hazards of concern with respect to occupational illness. Establishment of workplace regulations and exposure controls, coupled with monitoring for and intervening in occupational illness related to chemical exposures, has resulted in decreasing incidence of classic occupational illnesses.[52, 53] More complex safety and health situations, including exposure to simultaneous chemical and non-chemical hazards, requires a combined approach to understanding the impact on health.[23, 54]

Risk assessment for aggregate exposures requires appropriate assessment metrics, aggregation methods, and approaches based on multiple sources, pathways, and routes.[55] This is likely true of non-chemical exposures as much as it is for chemical exposures, for example workplace vs. non-occupational noise. To carry out aggregate risk assessment, appropriate metrics for health effects and definitions for background rates of effects related to the exposure, adverse effects in occupational populations, and dose-response modeling approaches must be developed.[56] For non-chemical stressors, significant methods development is required regarding exposure and health effect metrics, exposure-response modeling, and risk characterization. Recent work, for example, focused on modeling muscle force output in response to weight-bearing loads in a rodent model, highlighted the complexity of examining exposure-response associations for non-chemical exposures, and reinforced the need to consider various characteristics of the variable, particularly the impact of time, on models.[57] The role of nonchemical stressors as mediating or moderating variables in the development of occupational illness or injury can have differing implications for safety and health research, risk assessment, and all stages of prevention/intervention activities.[58]

When considering the need for greater attention to these types of hazards, several changes in the workplace are germane. Changes in the worker (e.g., aging, chronic disease, or obesity status), in the matrix of chemical and/or non-chemical exposures, and in the organization of work (e.g., irregular work hours or shift work) point to the greater complexity of the modern U.S. workplace.[23] While research has evaluated the impact of some nonchemical factors on workers, quantitative risk assessment-based approaches are currently less developed. However, the complexity of the work environment demands that new approaches to study design, hazard identification, exposure assessment, health effect definition, dose-response modeling, and risk characterization be developed in order that nonchemical stressors may be appropriately considered within the context of mixed exposures and total worker health.

TABLE II. Critical Factors and Key Questions to Inform and Guide Aggregate and Cumulative Risk Assessments

Critical factors	Key questions
• Advances in exposure science	• Which mixtures are most important from a public or occupational health perspective?
• Increased technical capabilities associated with exposure monitoring and analytical techniques	• What is the nature (i.e., duration, frequency, and timing) and magnitude (e.g., exposure concentration and dose) of relevant cumulative exposures for the population of interest?
• Application of toxicokinetics and toxicodynamics data to characterize the consequences and variability of mixed exposures to environmental stressors	• What is the mechanism (e.g., toxicokinetic or toxicodynamic) and consequence (e.g., additive, less than additive, more than additive) of the mixture's interactive effects on exposed populations?[63]
	• What does one do with such exposure information (i.e., understanding variables that define contact with environmental stressors and the factors that influence the contact)?[60]
	• What roles does exposure science play in situations beyond observational analyses and interpretation?[60]

DISCUSSION AND SUGGESTED STEPS FORWARD

Recent advances in the scientific theory and applications for aggregate and cumulative risk assessment methods provide opportunities to enhance the utility of and approaches for occupational risk assessments. Expanding research and advances in this area include EPA's resource toolboxes, cumulative risk framework and conceptual models, exposure factor handbooks, toxicity databases,[8] specific fate models, community involvement processes, and new visualization tools.[59] Development of such approaches will allow for assessments to

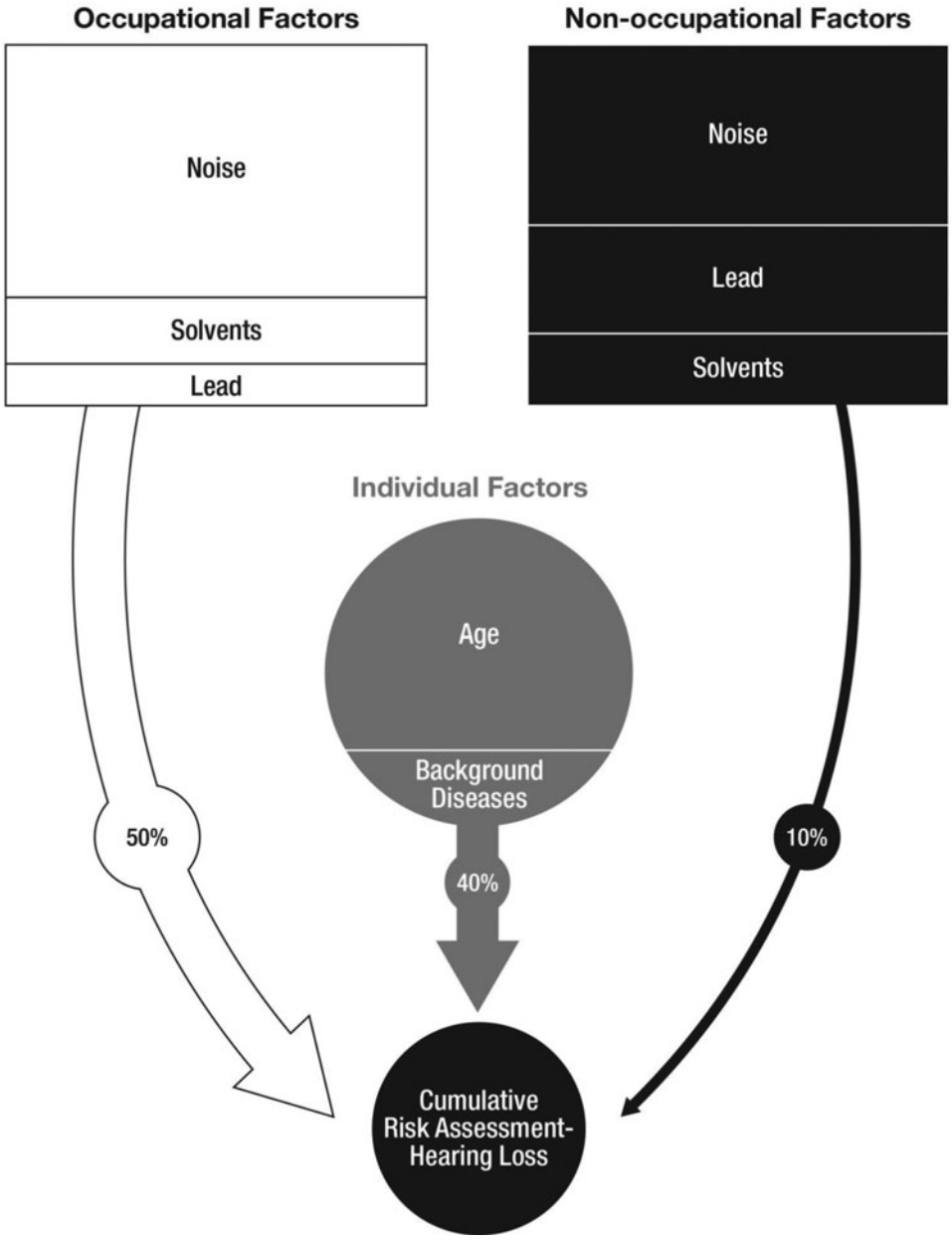

FIGURE 3. Case study of potential risk factors included in the assessment of cumulative risk for hearing loss. Note: The percentages indicated represent hypothetical values of the occupational, individual, and non-occupational contributions that might be determined for comparison of the sources and opportunities where interventions and controls might best be provided.

better reflect and characterize real-world situations. Emphasis in this area has gradually increased in the occupational safety and health community on the basis of recent frequency of symposia and information sessions on this topic; a case-in-point is the "Risk Assessment Symposium – Converging Risk Analysis, Management, and Perception" convened at the 2011 Professional Conference on Industrial Hygiene (PCIH 2011, Baltimore, MD, November 3–9). A proactive approach for accomplishing this goal is to incorporate such concepts in new chemical registration and use processes, where such techniques play an important role in preventing exposures before chemical use and introduction. With this goal in mind several steps to enhance current processes could be taken. Some of these include the following.

(a) Developing a concise review, building on descriptions above, of the degree to which:

- current risk assessment processes incorporate occupational scenarios; and
- occupational assessments incorporate considerations of risk assessment of aggregate exposures and cumulative risk assessment.

This article would include easy-to-use tabular summaries that highlight potential leveraging opportunities for incorporation of approaches used by other organizations.

(b) Focusing on chemical registration purposes to develop a qualitative list of considerations or checklist of issues for use in new assessment review and development. This list would provide a resource for requesting additional detailed assessments of aggregate or cumulative risks (consistent with the World Health Organization tiered assessment approach and the Office of Pesticide Program approach of screening vs. full assessment).

(c) Developing detailed case studies. Such an effort would:

- identify methods development needs;
- serve as a resource for future implementation guides; and
- provide an outreach and training tool.

This type of resource is consistent with the approach used in the OPPT Sustainable Futures Program—where case study examples highlight OPPT expectations for future submissions by external parties.

(d) Future efforts based on these initial steps could include development of a methods guidance document and training modules.

CASE STUDY EXAMPLE AND CONCLUSIONS

The factors and questions summarized in Table II represent opportunities for improving the practice of determining appropriate OELs given consideration for aggregate exposure and cumulative risk assessment in occupational and environmental settings. These factors also indicate the complexity associated with aggregate exposure and cumulative risk assessment and the development of appropriate and effective risk management strategies.

Exposure science is the discipline that studies and elucidates the conditions for contact with toxicants, characterizing the quality and quantity of the toxicant following a continuum from its sources to its transport and receipt by or interaction with the human body.[60–62] Addressing these questions given advances in exposure science and risk assessment methods will seemingly provide a foundation for improved tools for aggregate exposure and cumulative risk assessment and risk management.

As a practical means to illustrate key considerations and issues that would arise with the integration of occupational risk factors into cumulative risk assessments, a case study example is provided in Figure 3. It is not intended to capture all of the technical details, but to identify the scope of potential issues that will need to be addressed. Specifically, this graphic is intended to show elements to be considered for the cumulative risk assessment of hearing loss. Accordingly, this scenario shows a hypothetical individual for which exposures to noise (from occupational and non-occupational sources) represent the greatest contribution to the hazard, followed by exposures to solvents and lead in varying proportions depending upon the occupational and non-occupational setting. Other factors such as age and background diseases or general health that contribute to the assessment of cumulative risk of hearing loss are indicated in the center of the graphic. Again, the details are purposely vague and represent a hypothetical worker, yet the clear message presented is the thought process and considerations required for performing a more holistic and cumulative assessment of the risk.

As the details become more evident and better characterized through application of the toxicological and risk assessment approaches and tools described here, occupational safety and health practitioners and industrial hygienists may be able to develop assessments of cumulative risk that will then serve to inform better risk management strategies.

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