Cumulative Risk: Environmental & Occupational Perspectives

Pamela R.D. Williams, MS, ScD
Presentation Outline

• Traditional risk assessment process and limitations
• Definition and drivers of cumulative risk assessment
• Existing guidance, framework, methods and tools
• Future directions
  – Moving beyond traditional contexts
  – Moving beyond traditional frameworks and risk metrics
Cumulative Risk Assessment (CRA): Transforming the Way We Assess Health Risks

Pamela R. Williams,§ G. Scott Dotson,§ and Andrew Malo§

Environmental Science & Technology

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 components of multiple chemical and nonchemical stressors for various health effects. CRA is 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.

II. INTRODUCTION

The methodology, practice, and benefit of human health risk assessments have evolved over the last several decades and are expected to continue to advance in the future. In particular, awareness of children's dietary and mandatory exposure to multiple pollutants in food that can cause chronic toxic effects led to the development of the Environmental Protection Agency (EPA) to move beyond single chemical assessments and focus on the aggregate and cumulative effects of multiple chemical exposure. Environmental risk assessment must also address health outcomes and chronic effects requiring a more in-depth evaluation of the combined effects of different chemical stressors. CRA holds promise for transforming traditional health risk assessments beyond single chemical exposure assessment frameworks and risk metrics for incorporating multiple stressors.

CRA framework and supporting guidelines for conducting CRAs parallel the general framework for health risk assessment in the United States. The EPA's CRA framework consists of three main phases (Table 1). The first phase establishes the purpose, goals, and scope of the CRA. The second phase integrates the hazard assessment and dose–response information in order to characterize the combined effects of multiple stressors in addition to developing exposure profiles and cumulative exposure estimates. The third phase translates relevant technical data into action, relevant health metrics, vulnerable populations, and time-related aspects of exposure are addressed during the analysis phase. The final phase describes important health risk assessment paradigms and consist of several key components (see Table 1).

Although CRAs have been conducted for certain chemical groups, such as pesticides, monitoring and pesticide levels, these assessments have not accounted for all of the factors involved 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 existing methods and advanced risk analyses, CRA offers potential novel opportunities for improving the risk assessment process and its application to various settings.
Risk Assessment Process (Environmental)
Evolution of Risk Assessment (Environmental)
## Risk Assessment Process (Occupational)

<table>
<thead>
<tr>
<th>Industrial Hygiene</th>
<th>Environmental</th>
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<tr>
<td>Anticipation and Recognition</td>
<td>Hazard identification</td>
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<td>Evaluation</td>
<td>Exposure and toxicity assessment and Risk characterization</td>
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<td>Control</td>
<td>Risk management</td>
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<td>Hazard communication</td>
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Evolution of Risk Assessment (Occupational)
Limitations of Traditional Risk Assessment Process

• Does not adequately address multiple chemicals or stressors, sources, pathways, and effects in varied populations
• Does not always rely on best or most current science to support or revise default assumptions
• Does not adequately characterize or communicate uncertainty and variability in all steps
• Does not adequately utilize advances in science and technology and new tools to assess interactions and cumulative risks
Key Drivers of Cumulative Risk Assessment (CRA)

- 1993 NAS report highlighted children’s exposures to multiple pesticide residues from food and other non-dietary sources
- 1996 Food Quality Protection Act (FQPA) directed the U.S. EPA to assess the cumulative effects of chemical exposures occurring simultaneously
- Cumulative effects were defined as pesticide residues or other substances that have a common mechanism of toxicity
Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework

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Introduction

This paper describes a framework for the risk assessment of combined exposure to multiple chemicals. It was developed subsequent to the World Health Organization/International Program on Chemical Safety Workshop on Aggregate Cumulative Risk Assessment (Combined Exposure) in Multiple Chemicals in 2007. The framework is designed to address the need to develop a standardised procedure for the risk assessment of combined exposure to multiple chemicals. It is based on a shared risk approach with expertise from health and safety considerations of risk and harm, and health effects of chemicals. The framework includes a number of components, including a threshold of toxicological concern, exposure assessment, and risk assessment.

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Definition of CRA

- The analysis, characterization, and potential quantification of the combined risks posed by aggregate exposure to multiple chemicals and other stressors that cause varied health effects.
Differs from “Cumulative Risk” in Occupational Settings

• A cumulative dose metric is often used to characterize total exposure over a working lifetime.
• Estimated as exposure concentration multiplied by duration of exposure (e.g., ppm-years, f/cc-year).
• Usually involves a single chemical and exposure route (inhalation) and not account for timing of exposure.
Key Components of CRA

• Shift from focus on single to multiple chemicals or stressors
• Includes both chemical and non-chemical (e.g., biological, radiological, physical, psychological) stressors
• Considers all relevant sources, pathways, and routes of exposures for each chemical or stressor (i.e., aggregate exposures)
• Requires groupings of chemicals or other stressors by common endpoint or effect
• Accounts for combined risk (not necessarily added) including potential for interactions and timing or sequence of exposures
CRA Conceptual Model

A Generalized Conceptual Model
with Examples of Possible Elements and Linkages

Sources
- Activities that generate or release stressors
  - Manufacturing
  - Fossil fuel combustion (e.g., for transportation, heating, electricity)
  - Waste processing
  - Mining
  - Agricultural activities
  - Natural processes

Stressors
- Chemical, physical, or biological agents that cause an effect
  - Chemical
    - Organic
    - Inorganic
  - Biological
    - Pathogens
    - Exotic spp.
  - Physical
    - Thermal
    - Erosion
    - Sedimentation
    - Habitat alteration

Pathways / Exposure Routes
- For individuals, ingestion, inhalation, or absorption are the routes of exposure.
- For ecological entities, biotic and abiotic interactions are keys to how stressors are presented to receptors.
- Surface water, air, indoor air, groundwater, or soil are pathways.

Receptors
- Ecological
  - Populations, ecological communities, and ecosystems may be receptors for some stressors.
- Human Health
  - Individuals and groups of people are also receptors
    - Infants
    - Sensitive pop
    - Occupational
    - Minorities
    - Env. Justice Communities

Endpoints
- Ecological Endpoints
  - Habitat structure, species distribution, diversity
  - Ecosystem conditions
    - Population levels
    - Environmental process rates
  - Status of critical species or species of special concern.
- Human Health Endpoints
  - Mortality and illness, such as: Cancers
  - Leukemia, lung, etc.
  - Other adverse health effects
    - Asthma, respiratory impacts
    - Kidney disease
    - CNS effects
    - Etc.

A variety of other factors (e.g., health status, access to health) may impact individual or population susceptibility to above stressors.

Aggregate and Cumulative Exposure Models

- Models developed in response to FQPA (e.g., DEEM, Calendex, CARES, Lifeline, SHEDS)
- Necessary model features:
  - Assess co-occurrence of pesticide residues
  - Integrate exposures through food, water, and residential pathways (probability and timing)
  - Preserve linkages between spatial, temporal, and demographic aspects of exposure
- Modeled estimates account for variability in human exposures (population-level risks)
Model Examples


Differs from Exposure Models Used in Occupational Settings

• Inhalation models typically used to estimate individual worker exposures (air concentration)
  – Zero ventilation (saturation)
  – General ventilation (box or mixed space)
  – Two-zone (near field/far field)
  – Dispersion (diffusion)
• Separate models or methods used to assess dermal exposures
  – Qualitative consideration of aggregate exposure (skin notations)
Cumulative Toxicity and Risk Methods

• Hazard Index (HI) approach used to assess risk of whole mixture or components if little or no mechanistic data are available
  – Assumes additivity of dose or response
• Interaction-based HI approach used to account for chemical interactions (synergism or antagonism)
• Relative Potency Factors (RPF) or Toxic Equivalency Factors (TEFs) used when mechanism or mode of action are well characterized
Whole Mixture Vs. Components

Hazard Index (HI)

- Hazard quotient (HQ) is calculated for each chemical
  - Ratio of exposure to acceptable level (e.g., RfD)
- HQs for all chemicals are added together to yield a hazard index (HI)
  - Total (combined) non-cancer risk for mixture
- The greater these values are above 1, the greater the concern for health risk

\[ HI = \sum_{i=1}^{n} \frac{E_i}{RfD_i} \]
Interaction-Based HI

\[ HI_{INT} = \sum_{i=1}^{n} (HQ_i \times \sum_{j \neq i}^{n} f_{ij} M_{ij}^{B_{ij} \theta_{ij}}) \]  

where:

- \( HI_{INT} \) = HI modified by binary interactions data,
- \( HQ_i \) = hazard quotient for chemical i (unitless, e.g., daily intake/RfD),
- \( f_{ij} \) = toxic hazard of the j\(^{th}\) chemical relative to the total hazard from all chemicals potentially interacting with chemical i (thus j cannot equal i),
- \( M_{ij} \) = interaction magnitude, the influence of chemical j on the toxicity of chemical i,
- \( B_{ij} \) = score for the strength of evidence that chemical j will influence the toxicity of chemical i, and
- \( \theta_{ij} \) = degree to which chemicals i and j are present in equitoxic amounts.

Relative Potency Factor (RPF)

- Determine toxic endpoint or effect(s)
- Determine chemical groupings that are toxicologically similar
- Calculate RPF for each chemical
  - \( RPF_n = \frac{\text{Toxic potency (index)}}{\text{toxic potency (chemical n)}} \)
- Convert each chemical exposure to index equivalent exposure
- Aggregate all index equivalent exposures to estimate total exposure
- Estimate joint toxicity or risk from the combined exposure using the dose-response information for the index chemical

Margin of Exposure (MOE) Approach

\[
\text{MOE} = \frac{\text{POD}_{\text{Index}}}{\sum_{\text{Route}} \text{Exposure}}
\]

- Determine point of departure (POD) for the index chemical
  - Point in the dose-response curve at which a change in response can be reliably said to be due to dosing with the chemical (e.g., NOAEL, LOAEL, BMD\textsubscript{10})

\[
\text{MOE}_{\text{total}} = \frac{1}{\text{MOE}_{\text{oral}} + \text{MOE}_{\text{dermal}} + \text{MOE}_{\text{inhalation}}}
\]

*Oral is the total oral exposure from food and drinking water plus oral, nondietary contacts such as hand-to-mouth exposure from residential pesticide uses.*

- Compare route-specific toxicity benchmarks to exposure estimates
- Calculate MOE for each exposure route
- Combine route-specific MOEs to generate total MOE

CRA Example: OP Pesticides

- U.S. EPA conducted CRA of 31 OP pesticides considered to have a common toxicity (acetylcholinesterase inhibition)
- DEEM/Calendex models used to estimate combined risk from food, water, and residential exposures (5 scenarios)
- RPF approach used to estimate cumulative exposures (i.e., account for each chemical’s relative potency)
- Route-specific and total MOE estimated
CRA Example: OP Pesticides

- Cumulative risk did not exceed level of concern (i.e., MOE >100)
- Greatest contribution to cumulative risk from food sources (low contribution from drinking water)
- Residential uses (due to inhalation) also a major source of risk at the upper percentiles of population exposure

### Table I.C-2 Exposure and MOE Values for the 21-Day OP Cumulative Food Assessment

<table>
<thead>
<tr>
<th>Category</th>
<th>95th Percentile</th>
<th>99th Percentile</th>
<th>99.9th Percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Exposure (mg/kg)</td>
<td>MOE</td>
<td>Exposure (mg/kg)</td>
</tr>
<tr>
<td>All infants</td>
<td>0.000097</td>
<td>820</td>
<td>0.000017</td>
</tr>
<tr>
<td>Children 1-2 yrs</td>
<td>0.000015</td>
<td>550</td>
<td>0.000032</td>
</tr>
<tr>
<td>Children 3-5 yrs</td>
<td>0.000012</td>
<td>670</td>
<td>0.000027</td>
</tr>
<tr>
<td>Children 6-12 yrs</td>
<td>0.000099</td>
<td>810</td>
<td>0.000018</td>
</tr>
<tr>
<td>Youth 13-19 yrs</td>
<td>0.000097</td>
<td>820</td>
<td>0.000011</td>
</tr>
<tr>
<td>Adults 20-49 yrs</td>
<td>0.000098</td>
<td>820</td>
<td>0.000013</td>
</tr>
<tr>
<td>Adults 50+ yrs</td>
<td>0.000099</td>
<td>810</td>
<td>0.000016</td>
</tr>
<tr>
<td>Females 13-49 yrs</td>
<td>0.000098</td>
<td>820</td>
<td>0.000013</td>
</tr>
</tbody>
</table>
Similar to Mixtures Approach Used in Occupational Settings

- ACGIH TLV guidelines incorporate mixture formula
- Consider combined (additive) effect when two or more hazardous substances act on the same organ system
- Dose addition incorporated into OSHA Rules
  - Hazard Communication rule (whole mixture or components)
- NORA research agenda includes complex mixtures
Future Directions

• Moving beyond traditional contexts
  – Community-based assessments
  – Accounting for occupational risk factors
• Moving beyond traditional frameworks and risk metrics
  – Integrating chemical and non-chemical stressors
  – Biomarker-based risk assessment
Community-Based Assessments

• Driven by concerns about environmental justice and health inequities

• Goal is to identify “hot spots” and prioritize risks within individual communities

• Risks are evaluated using local or regional data for most relevant stressors

The EPA's human exposure research program for assessing cumulative risk in communities

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Communities are faced with challenges in identifying and prioritizing environmental issues, taking actions to reduce their exposure, and determining their efficiencies for reducing human health risks. Additional challenges include determining what scientific tools are available and most useful, and understanding how to use those tools, given these barriers, community groups tend to rely more on risk perception than science. The U.S. Environmental Protection Agency's Office of Research and Development, National Exposure Research Laboratory (NERL), and collaborators are developing and applying tools (models, data, methods) for informing cumulative risk assessments. The NERL's “Cumulative Communities Research Program” focuses on key issues: (1) How to systematically identify and prioritize key environmental stresses within a given community; (2) How to develop estimates of exposure to multiple stressors for individuals in epidemiological studies; and (3) What tools can be used to assess community-level distributions of exposure for the development and evaluation of the effectiveness of risk reduction strategies. This paper provides community partners and scientific remit with an understanding of the NERL's research program and other efforts to address cumulative community risks, and key research needs and opportunities. Some initial challenges include the following: (1) Many useful tools exist for component risk assessments, but need to be developed collaboratively with and used more comprehensively and user-friendly for practical application; (2) Tools for quantifying cumulative risks and impacts of community risk reduction activities are also needed; (3) More data are needed to assess community and individual-level exposures, and to risk exposure-related information with health effects; and (4) Additional research is needed to incorporate risk-modifying factors ("covariate exposures") into cumulative risk assessments. The purpose of this research program will advance the science for cumulative risk assessments and empower communities with information so that they can make informed, cost-effective decisions to improve public health.


Keywords: EPA, cumulative, exposure, community, risk, community-based

Background

People want to know what their health risks are from the multiple stressors they are exposed to every day, including environmental pollutants, and how to prevent or mitigate these risks. Communities and individuals within them are faced with the challenges of identifying and prioritizing environmental issues, determining what tools are available to assist them, understanding how to use those tools to make more informed science-based decisions, and implementing risk reduction actions. Tools as defined here include information, strategies, exposure models, datasets, sampling/analytical methods, and geographic information systems (GIS) maps. Addressing these needs and protecting the health of Americans from environmental pollutants is a key goal of the U.S. Environmental Protection Agency (EPA) policies and programs. As indicated in the EPA's Report on the Environment (USEPA, 2008a), the Agency has taken a number of actions to fulfill this goal, including establishing the standards for pollutants in the environment, requiring sources to limit their pollution, and educating members of the public about actions they can take to protect their health. The EPA has also responded to recommendations from the National Academy of Sciences, the National Academy of Public Administration, the EPA Science Advisory Board, and other peer reviews and requests from the EPA region and local communities to develop guidance documents and other tools for supporting community-based cumulative risk assessments (NAPA, 2004; NAC, 2004, http://dodc.ohsu.edu/dodc/pt_brief/ERA_brief_final.pdf). The EPA's long-term strategic planning documents (USEPA, 2008a, b) articulate specific plans and programs for measurement-driven databases, methods, and models to better understand how people are exposed to multiple pollutants for enhanced cumulative risk assessments, and to conduct community-based risk assessments. The Agency has developed a number of guidance documents in these areas (USEPA, 2003, 2007a). In addition, research efforts and applications have been conducted by other organizations, including the Centers for
Tools available to communities for conducting cumulative exposure and risk assessments

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This paper summarizes and assesses over 70 tools that could aid with gathering information and taking action on environmental issues related to community-based cumulative risk assessments (CBCRA). Information on tool use, development and research needs, was gathered from websites, documents, and CBCRA program participants and researchers, including 21 project officers who work directly with community groups. The tools were assessed on the basis of information provided by project officers, community members, CBCRA researchers, and by case study applications. Tables summarize key environmental issues and tool features: (1) a listing of CBCRA-related environmental issues of concern to communities; (2) web-based tools that map environmental information; (3) step-by-step guidance documents; (4) databases of environmental information; and (5) computer models that simulate human exposure to chemical stressors. All tools described here are publicly available, with the focus being on tools developed by the US Environmental Protection Agency. These tables provide sources of information to promote risk identification and prioritization beyond risk perception approaches, and could be used by CBCRA participants and researchers. The purpose of this overview is twofold: (1) To present a comprehensive, though not exhaustive, summary of numerous tools that could aid with performing CBCRA; and (2) To use this toolset as a sample of the current state of CBCRA toolkits to critically examine their utility and guide research for the development of new and improved tools.


Keywords: cumulative exposure, cumulative risk, community-based, exposure assessments, exposure tools.

Introduction

Regulatory agencies involved with environmental hazard identification, classification and health effects have begun to expand beyond the single-chemical, single-pathway research paradigm to include human exposures to mixtures of chemicals that occur through multiple media (e.g., air, water, soil, diet) and routes (e.g., inhalation, ingestion, dermal) (NRC, 1995, 1994; NAPA, 1995; PCAR, 1997; USEPA, 2000, 2003). These cumulative exposure and risk assessments attempt to quantify the health risks associated with exposure to multiple chemicals in multiple media through multiple pathways (Menet et al., 2007; Ryan et al., 2007; Sexton and Harris, 2007; deFur et al., 2007; NAS, 2008; USEPA, 2008a) as opposed to a single-chemical and pathway. Chemical mixtures may reflect real-world exposure scenarios encountered by individual communities, which are generally represented by a geographic area on the order of several square miles, and may include a host of pollutant types and sources.

Community-based risk assessments have been gaining momentum as community groups become involved in identifying, prioritizing, and mitigating their environmental concerns (Kinney et al., 2000; Arquette et al., 2002; O’Fallon and Dunyard, 2002; Perera et al., 2002; Corburn, 2002a; NIEJAC, 2004; Schell et al., 2005), many of which are pollutant-based. In these types of programs, communities play a central role in defining problems and required data, supplying local knowledge, and interpreting results in the context of local understanding and decision-making. Researchers and agencies may conduct exposure and risk assessments through community case studies, addressing the community pollutants, and working directly with community members (Clinton, 1994; O’Fallon and Dunyard, 2002; USEPA, 2005, 2007; Denholm and Martin, 2008).

Community-based cumulative risk assessments (CBCRA) combine principles of cumulative exposure assessments with community-based profiles and/or participation. “Profiles” in this sense refer to the pollutant types, sources, and exposure patterns for individuals within a given community. Challenges

Statewide CRA Initiatives

• Similar types of methods have been developed by state agencies to assess cumulative impacts in communities (e.g., CA)

• These are screening tools intended to rank order and identify communities with the greatest cumulative impacts

• Tools do not provide quantitative estimates of community-health risk

Accounting for Occupational Risk Factors

- Longstanding recognition of significant role of workplace exposures on health
- However, occupational risk factors are not typically considered in environmental or community-based CRAs
- Refinements are needed in CRA framework to allow for identification and inclusion of full range of relevant factors
Consideration of Relevant Risk Factors

**Occupational Factors**
- **Settings** – Manufacturing facilities; laboratories; hospitals; construction sites; farming
- **Pathways** – Ambient air; surface contaminants
- **Exposure Routes** – Inhalation; dermal
- **Key Stressors** – Chemicals; physical agents; biological agents; noise; shift work
- **Effects** – Injuries; neurotoxicity; respiratory diseases; dermatitis; cancer; hearing loss

**Non-occupational Factors**
- **Settings** – Environmental; community; residential
- **Pathways** – Ambient air; drinking water; food; soil; solar radiation
- **Exposure Routes** – Inhalation; oral
- **Key Stressors** – Chemicals; physical agents; pathogens; pharmaceuticals
- **Effects** – Asthma; respiratory diseases; cardiovascular effects; cancer

**Individual Factors**
- Demographics/Socioeconomic status
- Genetic susceptibility
- Existing disease status
- Psychological stress
- Dietary status
- Lifestyle/behavior

NIOSH Total Worker Health™ Program

- Strategic initiative that integrates occupational safety and health with health promotion
- Represents an evolution of prior programs and initiatives
  - Steps to a Healthier US Workforce
  - NIOSH WorkLife
- Focus is on understanding interactions between workplace and individual lifestyle risk factors
  - Age, educational level, preexisting medical conditions

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WorkLife

A National Institute for Occupational Safety and Health Initiative

October 2008

Essential Elements of Effective Workplace Programs and Policies for Improving Worker Health and Wellbeing

Introduction

The Essential Elements of Effective Workplace Programs and Policies for Improving Worker Health and Wellbeing is a resource document developed by the National Institute for Occupational Safety and Health (NIOSH) with substantial input from experts and interested individuals.

This document, a key part of the NIOSH WorkLife Initiative, is intended as a guide for employers and employee-employer partnerships working to establish effective workplace programs that sustain and improve worker health. The Essential Elements document identifies twenty components of a comprehensive work-based health protection and health promotion program and includes both guiding principles and practical direction for organizations seeking to develop effective workplace programs.

The WorkLife Initiative is intended to identify and support comprehensive approaches to reduce workplace hazards and promote worker health and well-being. The purpose of this Initiative, based on scientific research and practical experience in the field, is that comprehensive practices and policies that take into account the work environment—both physical and organizational—while also addressing the personal health risks of individuals, are more effective in preventing disease and promoting health and safety than each approach taken separately.

The twenty components of the Essential Elements, presented below, are divided into four areas: Organizational Culture and Leadership, Program Design, Program Implementation and Resources, and Program Evaluation. The document is a framework that will be enhanced by links to resource materials intended to assist in the design and implementation of workplace programs and offer specific examples of best and promising practices.

Organizational Culture and Leadership

1. Develop a “Human Centered Culture.” Effective programs thrive in organizations with policies and programs that promote respect throughout the organization and encourage active worker participation, input, and involvement. A Human Centered Culture is built on trust, not fear.

2. Demonstrate leadership. Commitment to worker health and safety, reflected in words and actions, is critical. The connection of worker health and safety to the core products, services and value of the company should be acknowledged by leaders and communicated widely. In some notable examples, corporate Boards of Directors have recognized the value of workplace health and well-being by incorporating it into an organization’s business plan and making it a key operating principle for which organization leaders are held accountable.

3. Engage mid-level management. Supervisors and managers at all levels should be involved in promoting health-supportive programs. They are the direct links between the workers and upper management and will determine if the program succeeds or fails.
Examples of Promoting Worker Health

• Impact of inadequate sleep on work safety and optimal health
• Impact of the work environment on obesity among low income workers
• Impact of noise, ototoxicants (e.g., toluene, lead), and personal factors (e.g., age, genetics) on hearing loss
Exposome

- Concept that is complementary to mapping the human genome
- Measure of total exposure (internal and external) of an individual in a lifetime
- Focus is on understanding how exposures from environment, workplace, diet, and lifestyle interact with individual characteristics (e.g., genetics, physiology) to cause disease

Integrating Chemical and Non-Chemical Stressors

- Non-chemical stressors have not been routinely incorporated in quantitative CRAs to date
- Many challenges:
  - identifying relevant non-chemical stressors
  - obtaining sufficient data on all stressors
  - quantifying exposure and effects data using common metrics
Identifying Families of Conceptual Models

Biomarker-Based Risk Assessment

• One way to better understand the cumulative impacts of disparate stressors is to identify common exposure and effect metrics as an integration point for analysis
  – Biomarkers of exposure
  – Biomarkers of susceptibility
  – Biomarkers of effect

• The maturation of computational and systems biology approaches is expected to change the future direction of risk assessment
Biomarkers of Exposure

- Chemicals that have entered the human body leave “markers” reflecting this exposure
- Biomonitoring is a method for assessing human exposure by measuring chemicals or metabolites in human tissues or fluids
  - blood, urine, breast milk, expelled air, hair, nails, fat, bone
- Data provide a direct measure of how much of a chemical has been absorbed into the body from all potential sources
Biomarkers of Susceptability

• Many individual factors contribute to human variability in susceptibility

• Recent attention focused on genetic determinants of variable response

• NIH’s Genes, Environment and Health Initiative (GEI) is supporting research to improve understanding of genetic contributions and gene-environment interactions in common disease

Improved Measures of Diet and Physical Activity for the Genes, Environment, and Health Initiative (GEI)

**Description**
The Genes, Environment, and Health Initiative (GEI) is a NIH-wide project led by the National Institute of Environmental Health Sciences (NIEHS) and the National Human Genome Research Institute (NHGRI). The overarching goal of the GEI is to determine the etiology of common diseases by focusing on the interaction of genetic and environmental factors to better understand how these interactions contribute to health and disease. The GEI is an investment in genetic studies and environmental monitoring technologies. The genetic component is focused on genome-wide association studies and data analytic methods. As genes alone do not tell us much about our health, the GEI component examines exposure biology.

**Exposure Biology**
Recent increases in the incidence of chronic disease such as diabetes, childhood asthma, obesity, or autism are not fully due to major changes in the human genome. The increases in chronic disease are influenced by interactions among genetic, environmental, dietary, and activity levels, which may lead to disease in genetically predisposed persons.

The Exposure Biology Program, one component of the GEI, solicited five RFAs to catalyze the development of innovative wearable sensors to accurately measure diet, physical activity, environmental exposures, psychological stress, and addictive substances. The program also focuses on improved measures of diet and physical activity. The goal is to create innovative, accurate technologies to use in large population studies that have both genetic and environmental components. The RFA is led by the National Cancer Institute (NCI) and the National Heart, Lung, and Blood Institute (NHLBI), with $16 million in funding over 4 years for seven grants, beginning in August 2007.

Diet and physical activity are lifestyle and behavioral factors that play an important role in the etiology, prevention, and treatment of many chronic diseases, including heart disease, vascular disease, chronic lung disease, metabolic disorders, cancer, and psychiatric conditions. The focus of this RFA is on assessments of these two behaviors, and not on the determinants.

Accurate data on diet and physical activity are critical in understanding how these factors may impact health and functional status over the human lifespan. On an individual basis, diet and physical activity may influence disease risk. An improved understanding of these genetic and environmental interactions affect disease risk may lead to better prevention or treatment approaches.

The measurement of usual dietary intake (considered the long-term average intake over the past year) or physical activity over varying time periods or in the past has, by necessity, relied on self-report instruments. A variety of such instruments exist, but they can be cognitively difficult for respondents and prone to varying degrees of measurement error depending on the time period considered, the instrument’s ease of use, and the ethnic and demographic characteristics of the study population. To address these issues, the GEI supports the development of improved measures and more objective methods to assess dietary intake and physical activity.
Biomarkers of Effect

- Proposed toxicity testing system relies on understanding “toxicity pathways”
- New rapid assays and high-throughput techniques used to evaluate biologically significant alterations
- Shift from high-dose whole-animal testing (targeted testing would continue)
- Toxicity testing quicker, less expensive, and more directly relevant to humans
Considerations and Challenges

- Science and technology
- Regulatory and public policy
- Social and ethical
• Identifying relevant risk factors and common effects
• Obtaining data on relative toxicities, interactions, and vulnerabilities
• Developing and implementing a common metric or framework for combining chemical and non-chemical stressors

- Non-Chemical Stressors and Cumulative Risk Assessment: An Overview of Current Issues and Initiatives (8/12)
- Characterizing Cumulative Air Pollution Risks (9/12)
- Cumulative Environmental Vulnerability Analysis: Opportunities for Innovation (10/12)
- Assessing the Health Impact of Multiple Environmental Chemicals (11/12)
- Cumulative Levels and Effects: Implementing A Unique Environmental Justice Statute in Permitting in Minnesota (12/12)

Regulatory and Public Policy

- Integrating risk factors that have traditionally been considered separately
  - Environmental
  - Community
  - Occupational
  - Individual
- Focus on identifying and controlling risks that matter (i.e., priority setting)
Social and Ethical

- Invasive data collection (e.g., biological specimens)
- Maintaining privacy and preventing improper use of personal data (e.g., pre-employment screening)
- Communicating risks to public and employees

"But this is the simplified version for the general public."
Conclusions

• Human health may be negatively affected by an array of risk factors (may not be dominated by one domain)

• Assessing the risk associated with the combinations of an interactions between various chemical and non-chemical stressors has not been possible using traditional methods

• CRA has the potential to overcome these shortcomings, but will require significant research and multi-disciplinary expertise
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