Cumulative Risk: Environmental & Occupational Perspectives

Pamela R.D. Williams, MS, ScD

Presentation at the 38th Annual Meeting of the Yuma Pacific Southwest (YPSW) Section of the American Industrial Hygiene Association
January 24, 2013; San Diego, CA

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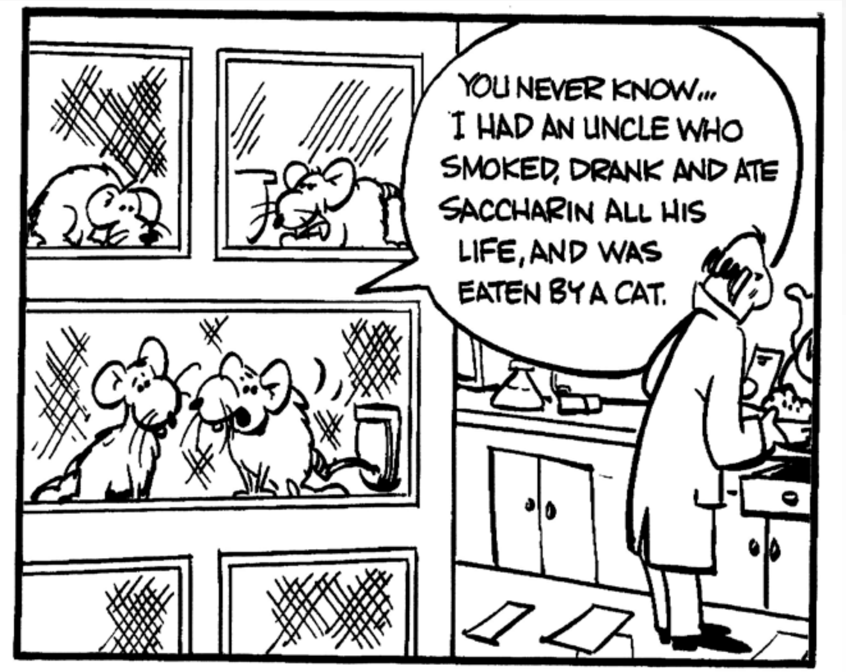
Presentation Outline

- 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



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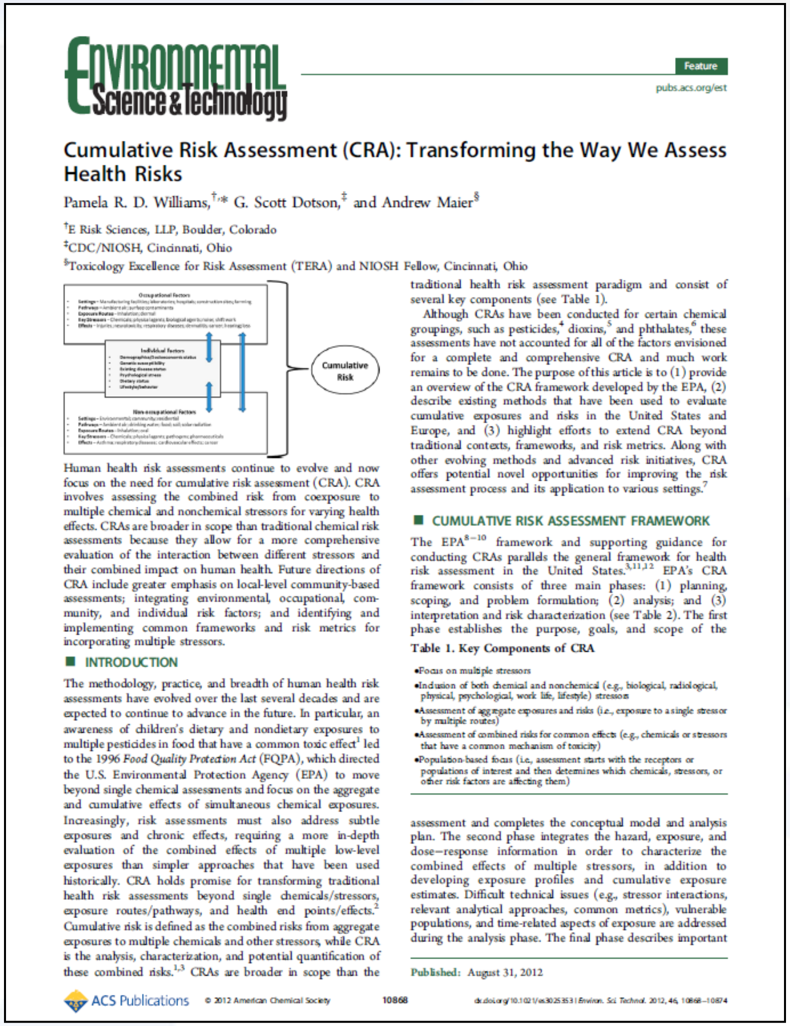
Williams et al. 2012



Environmental Science & Technology
Feature
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Cumulative Risk Assessment (CRA): Transforming the Way We Assess Health Risks

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

INTRODUCTION

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

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

CUMULATIVE RISK ASSESSMENT FRAMEWORK

The EPA[8−10] framework and supporting guidance for conducting CRAs parallels the general framework for health risk assessment in the United States.[3,11,12] EPA's CRA framework consists of three main phases: (1) planning, scoping, and problem formulation; (2) analysis; and (3) interpretation and risk characterization (see Table 2). The first phase establishes the purpose, goals, and scope of the assessment and completes the conceptual model and analysis plan. The second phase integrates the hazard, exposure, and dose−response information in order to characterize the combined effects of multiple stressors, in addition to developing exposure profiles and cumulative exposure estimates. Difficult technical issues (e.g., stressor interactions, relevant analytical approaches, common metrics), vulnerable populations, and time-related aspects of exposure are addressed during the analysis phase. The final phase describes important

Table 1. Key Components of CRA

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

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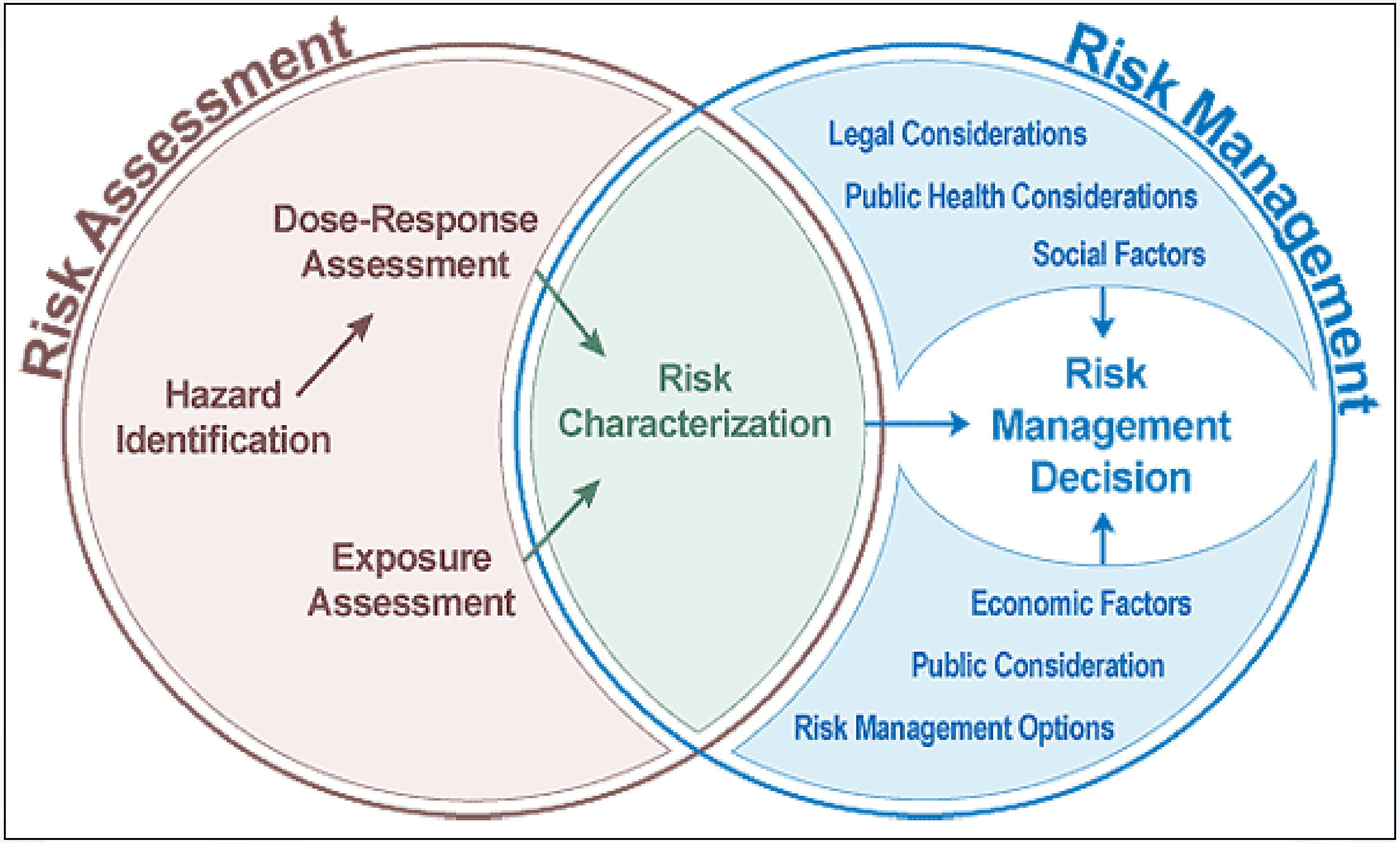
   dx.doi.org/10.1021/es3025353 | Environ. Sci. Technol. 2012, 46, 10868−10874

Risk Assessment Process (Environmental)



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Evolution of Risk Assessment (Environmental)

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Risk Assessment Process (Occupational)

Industrial Hygiene	Environmental
Anticipation and Recognition	Hazard identification
Evaluation	Exposure and toxicity assessment and Risk characterization
Control	Risk management
Hazard communication	Risk communication

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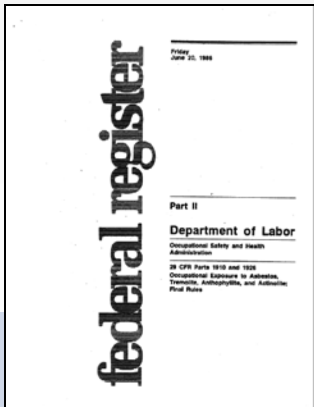
Evolution of Risk Assessment (Occupational)

1980


federal register

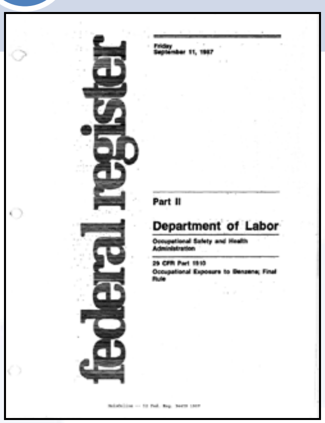
Friday
June 20, 1986

Part II

Department of Labor

Occupational Safety and Health Administration

29 CFR Parts 1910 and 1926
Occupational Exposure to Asbestos, Tremolite, Anthophyllite, and Actinolite; Final Rules


federal register

Friday
September 11, 1987

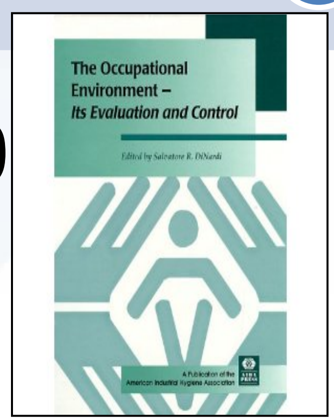
Part II

Department of Labor

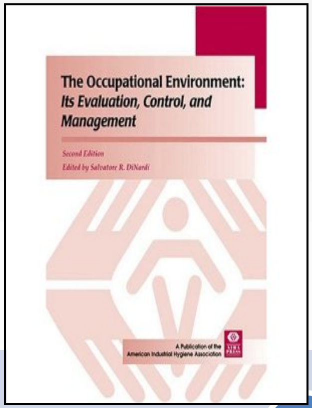
Occupational Safety and Health Administration

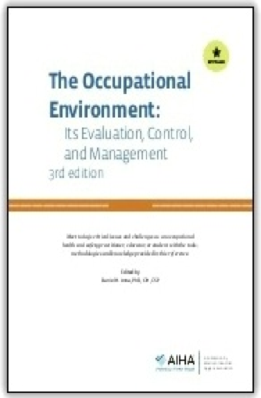
29 CFR Part 1910
Occupational Exposure to Benzene; Final Rule

1990

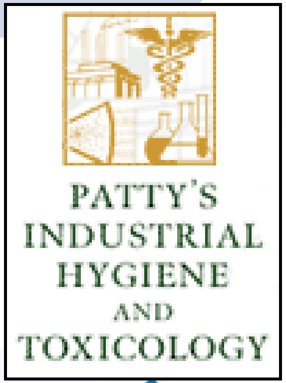


2000





2010



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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

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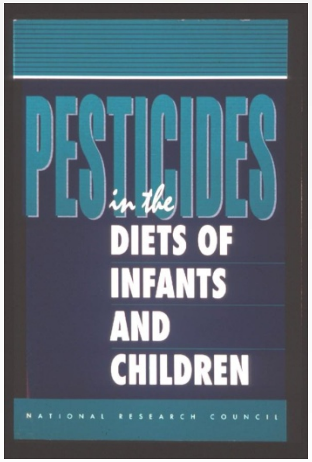
Key Drivers of Cumulative Risk Assessment (CRA)

- 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



PUBLIC LAW 104–170—AUG. 3, 1996 110 STAT. 1489

Public Law 104–170
104th Congress

An Act

To amend the Federal Insecticide, Fungicide, and Rodenticide Act and the Federal Food, Drug, and Cosmetic Act, and for other purposes.

Aug. 3, 1996
[H.R. 1627]

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

Food Quality Protection Act of 1996.
7 USC 136 note.

SECTION 1. SHORT TITLE.

This Act may be cited as the "Food Quality Protection Act of 1996".

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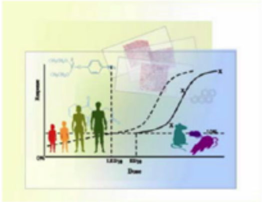
U.S. EPA Guidance and Resource Documents

Fax-On-Demand
Fax Number: (202) 401-0527
Item: 6043

General Principles For Performing Aggregate Exposure And Risk Assessments



Environmental Protection Agency
Office of Pesticide Programs

November 28, 2001

Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity

Office of Pesticide Programs
U.S. Environmental Protection Agency
Washington, D.C. 20460

January 14, 2002

EPA/630/P-02/001F
May 2003

Framework for Cumulative Risk Assessment

Risk Assessment Forum
U.S. Environmental Protection Agency
Washington, DC 20460

EPA/600/R-06/013F
August 2007

Concepts, Methods and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document

National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

in collaboration with

U.S. Department of Energy Argonne National Laboratory
Environmental Assessment Division
Argonne, IL 60439

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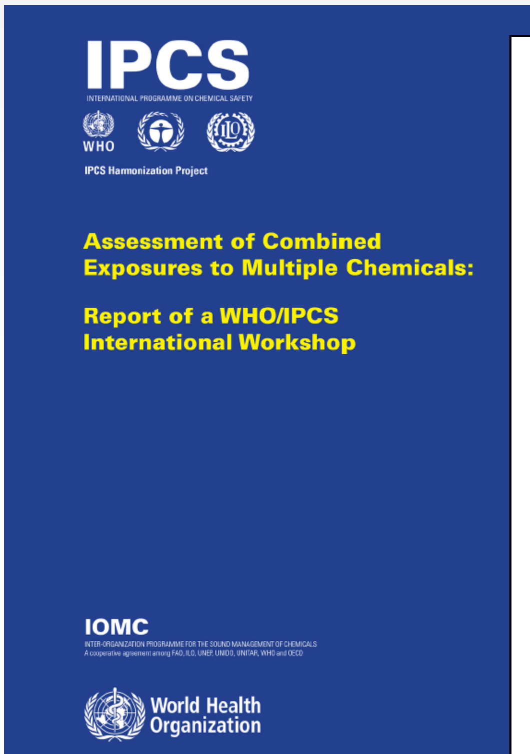
International Guidance and Research Projects


IPCS

INTERNATIONAL PROGRAMME ON CHEMICAL SAFETY

WHO

IPCS Harmonization Project

Assessment of Combined Exposures to Multiple Chemicals:

Report of a WHO/IPCS International Workshop

IOMC

INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS

A cooperative agreement among FAO, ILO, UNEP, UNIDO, UNITAR, WHO and OECD

World Health Organization


Regulatory Toxicology and Pharmacology 60 (2011) S1–S14

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Risk assessment of combined exposure to multiple chemicals: A WHO/IPCS framework

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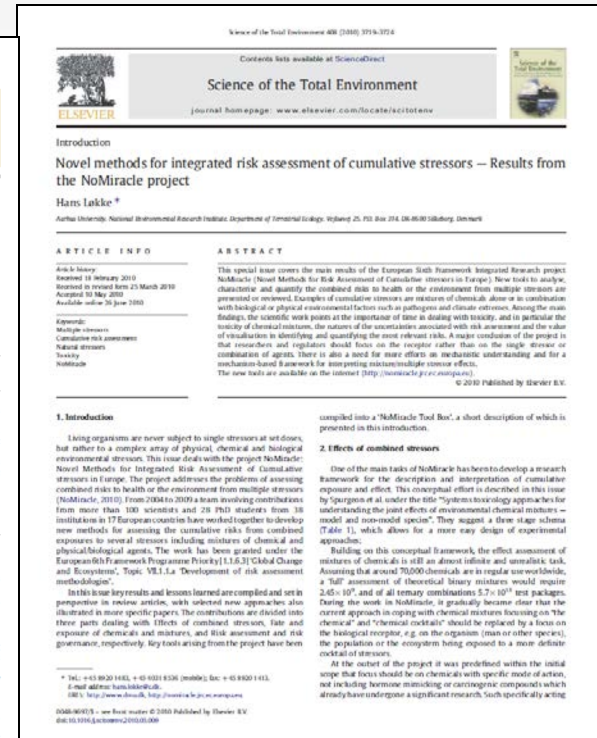
Screening-level assessment
Tiered approach
Threshold of toxicological concern

ABSTRACT

This paper describes a framework for the risk assessment of combined exposure to multiple chemicals based on and developed subsequent to the World Health Organization/International Programme on Chemical Safety Workshop on Aggregate/Cumulative Risk Assessment (Combined Exposures to Multiple Chemicals) held in 2007. The framework is designed to aid risk assessors in identifying priorities for risk management for a wide range of applications where co-exposures to multiple chemicals are expected. It is based on a hierarchical (phased) approach that involves integrated and iterative consideration of exposure and hazard at all phases, with each tier being more refined (i.e., less cautious and more certain) than the previous one, but more labor and data intensive. It includes reference to predictive and probabilistic methodology in various tiers in addition to tiered consideration of uncertainty. The paper also annexes two case studies that have been developed to test and refine the framework.

1. Introduction


Science of the Total Environment 408 (2010) 3719–3724

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Introduction

Novel methods for integrated risk assessment of cumulative stressors — Results from the NoMiracle project

Hans Løkke *

ARTICLE INFO

ABSTRACT

1. Introduction

2. Effects of combined stressors

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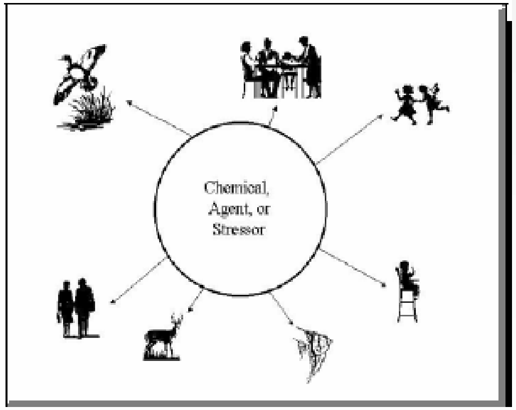
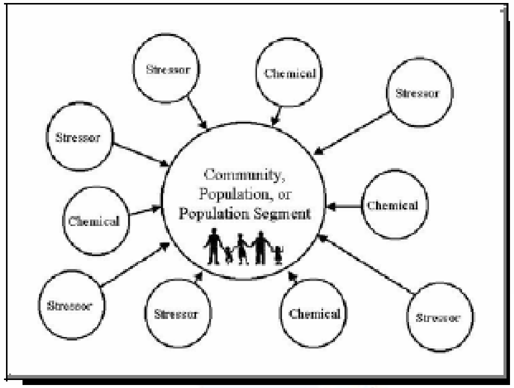
Definition of CRA

- 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



Chemical-Focused

Population-Based Focus



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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

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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

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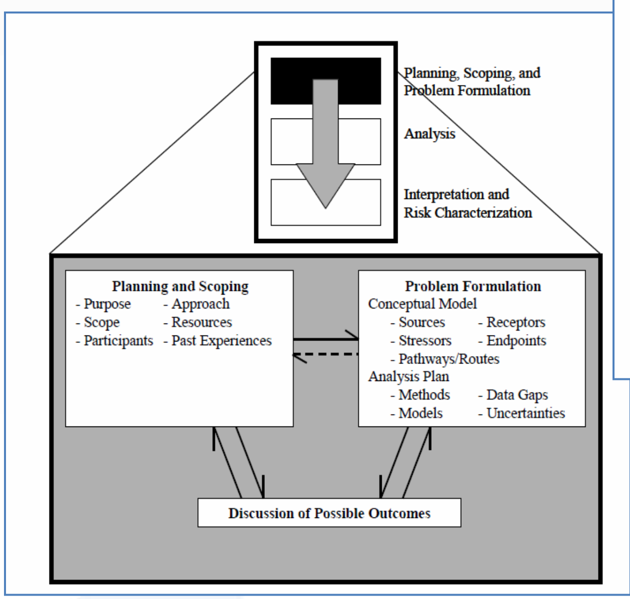
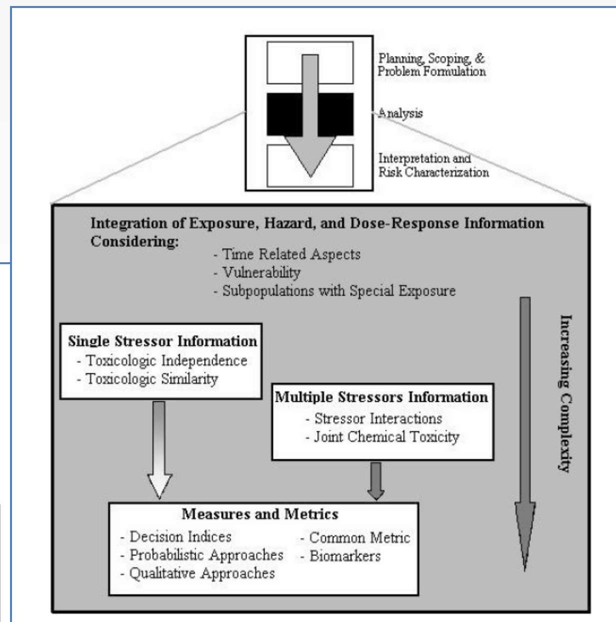
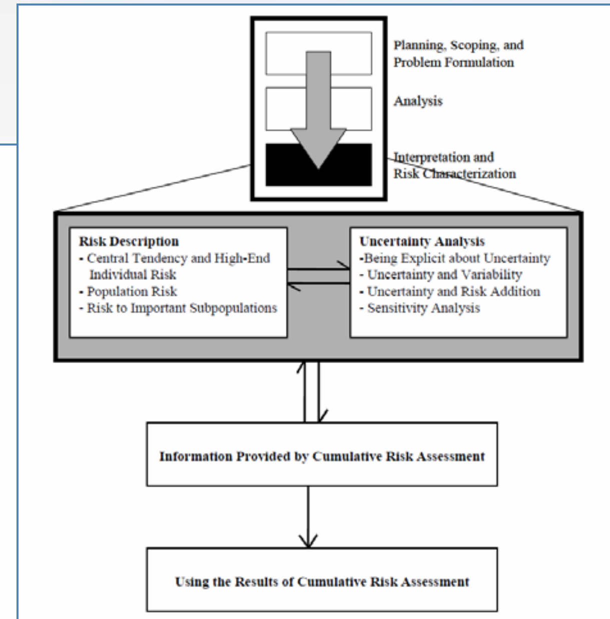
CRA Framework (U.S. EPA)







Source: *Framework for Cumulative Risk Assessment*; EPA/630/P-02/001F; United States Environmental Protection Agency: Washington, DC, 2003.

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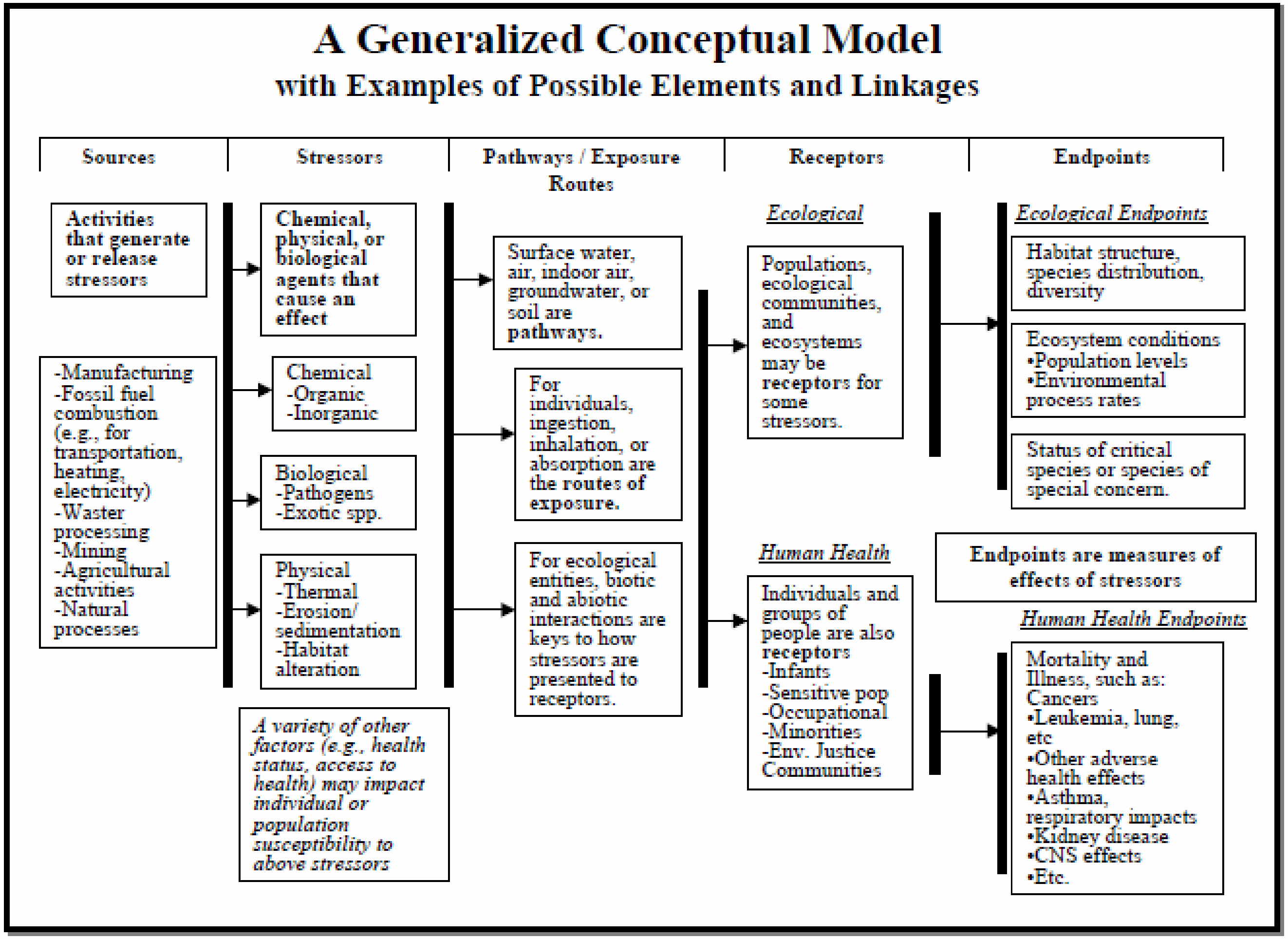
CRA Conceptual Model



Source: EPA (2003). *Framework for Cumulative Risk Assessment*.

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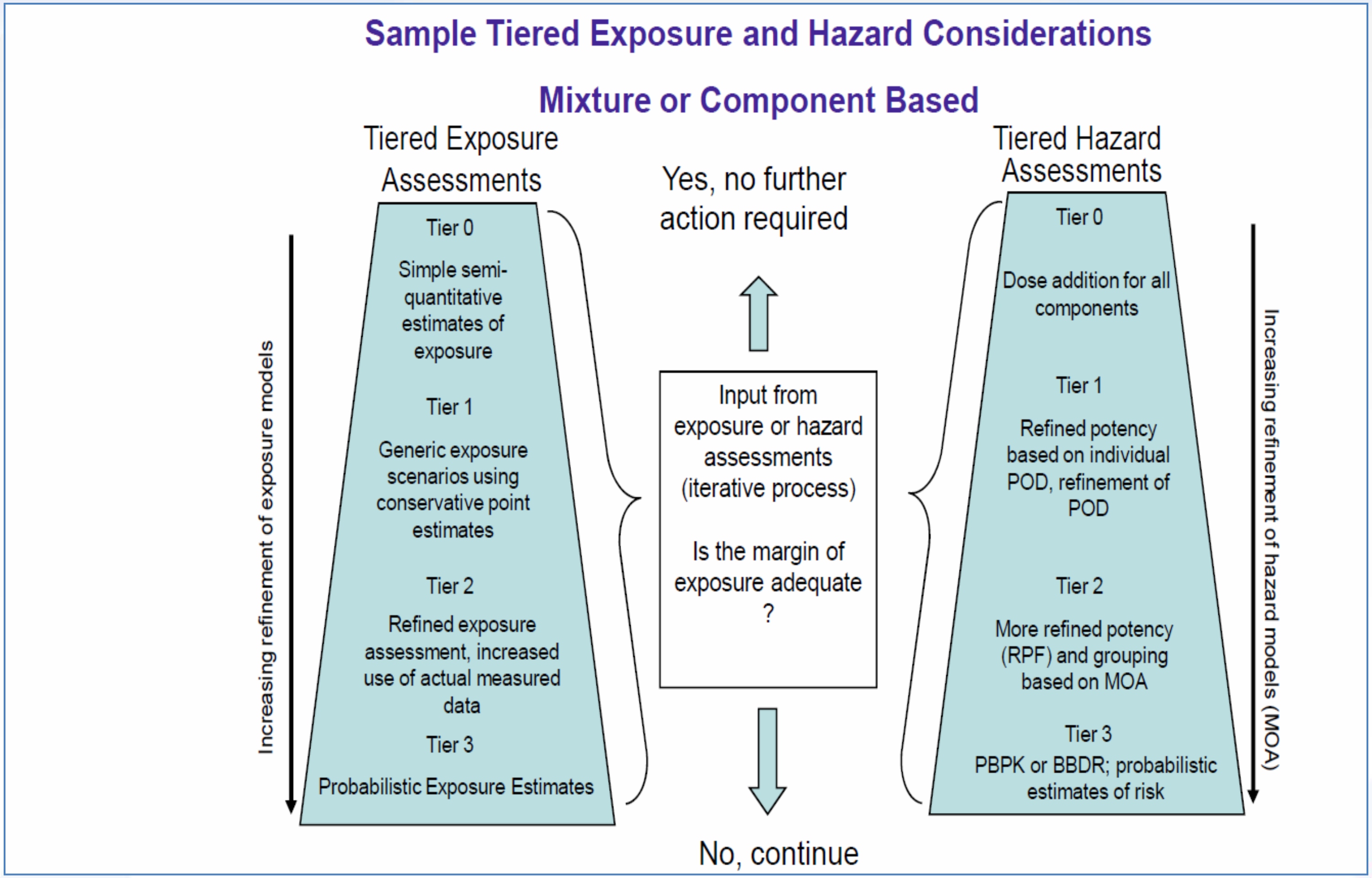
WHO/IPCS Tiered Approach



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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)

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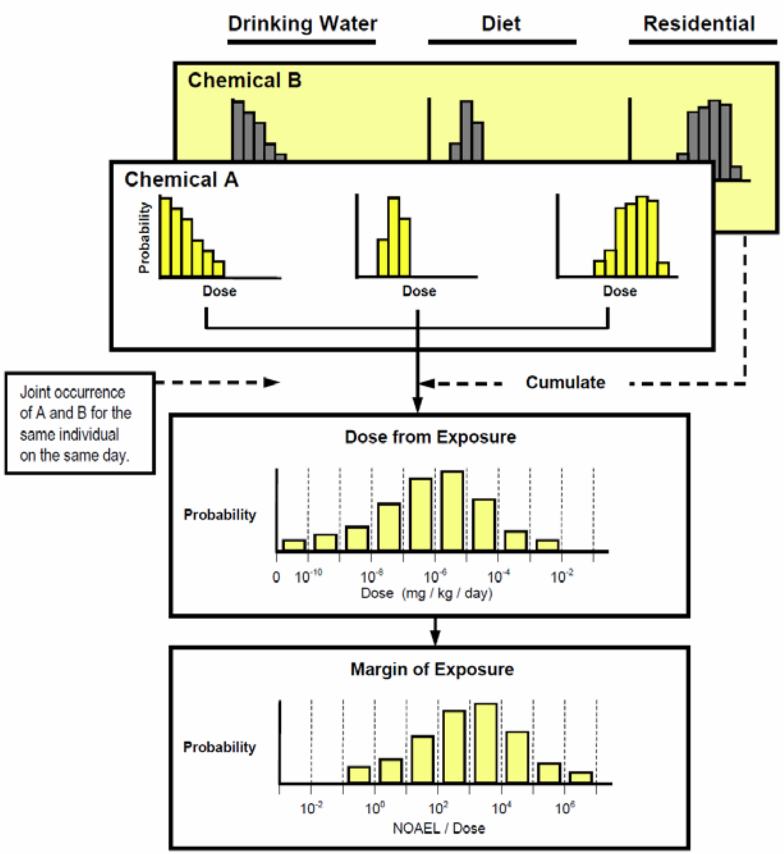
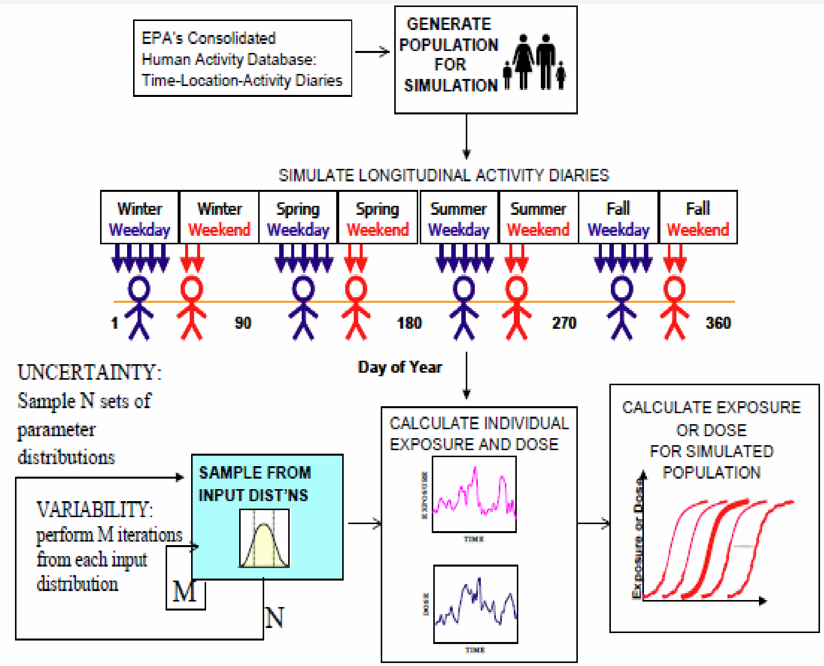
Model Examples



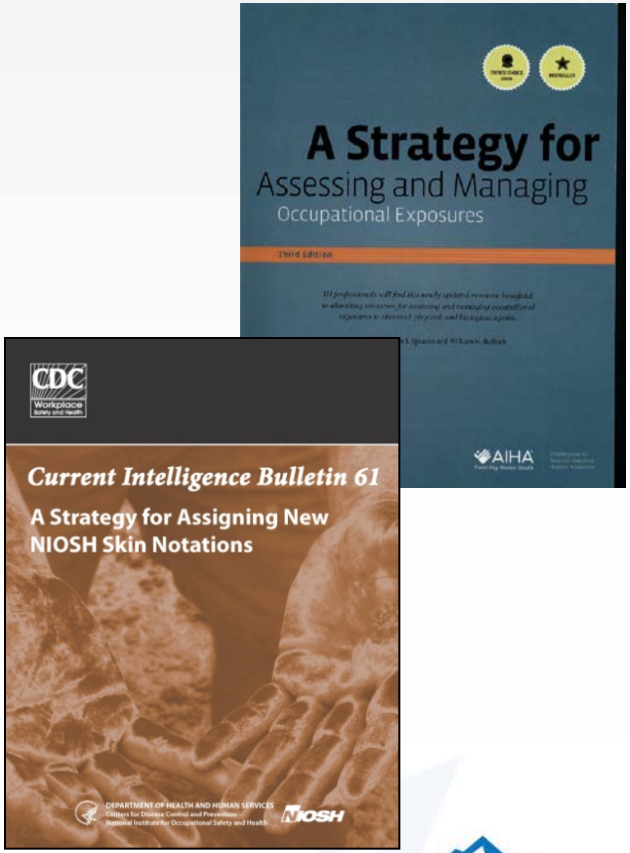
Source: CARES 1.0, Technical Manual, CropLife America, 2002.



Source: SHEDS-Multimedia Model version 3, Technical Manual, U.S. EPA, 2007.

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)



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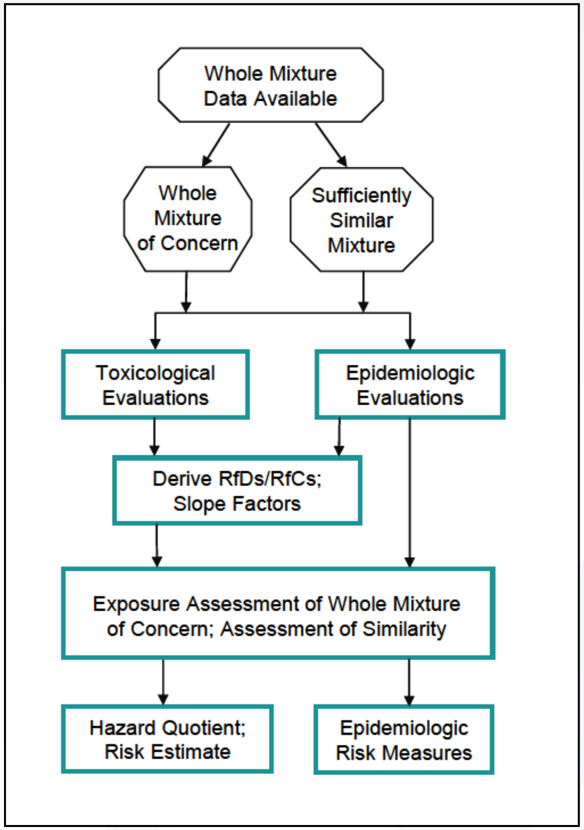
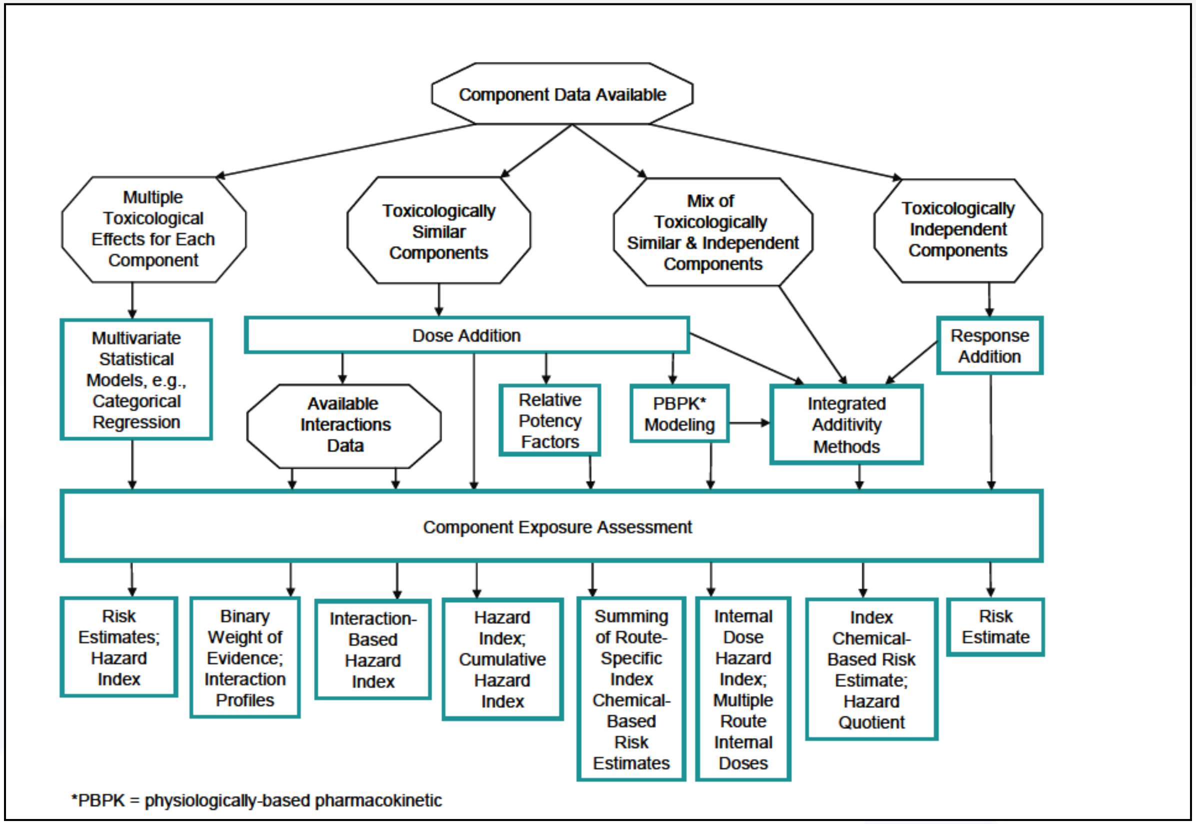
Cumulative Toxicity and Risk Methods

- 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





Source: *Concepts, Methods and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document*; EPA/600/R-06/013F; United States Environmental Protection Agency: Washington, DC, 2007.

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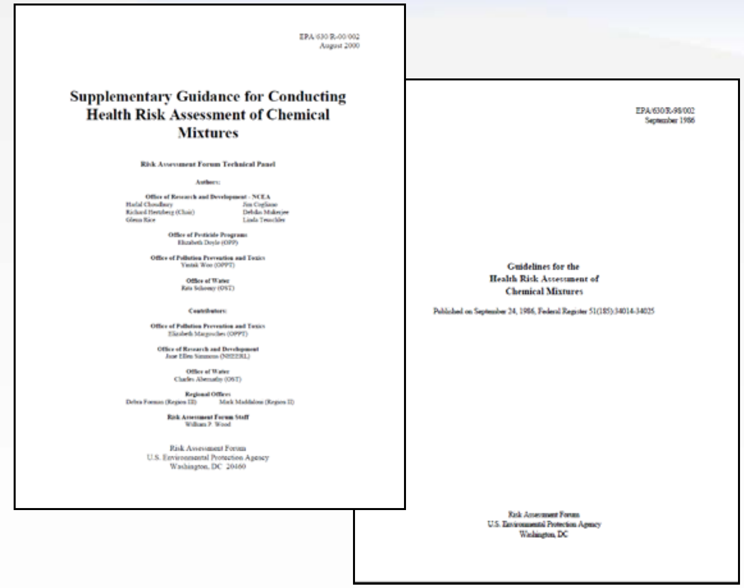
Hazard Index (HI)

- 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


EPA/630/R-00/002
August 2000

Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures

Risk Assessment Forum Technical Panel

Authors:

Office of Research and Development - NCEA

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Office of Pollution Prevention and Toxics

Office of Water

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Regional Offices

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EPA/630/R-98/002
September 1986

Guidelines for the Health Risk Assessment of Chemical Mixtures

Published on September 24, 1986, Federal Register 51(185):34014-34025

Risk Assessment Forum
U.S. Environmental Protection Agency
Washington, DC

$$HI = \sum_{i=1}^{n} \frac{E_i}{RfD_i}$$

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Interaction-Based HI

$$HI_{INT} = \sum_{i=1}^{n} \left(HQ_i * \sum_{j \neq i}^{n} f_{ij} \; M_{ij}^{B_{ij}\theta_{ij}} \right) \qquad (4\text{-}15)$$

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

θ_{ij} = degree to which chemicals i and j are present in equitoxic amounts.

Source: *Supplementary Guidance for Conducting Health Risk Assessment of Chemical Mixtures;* EPA/630/R-00/002; United States Environmental Protection Agency: Washington, DC, 2000.

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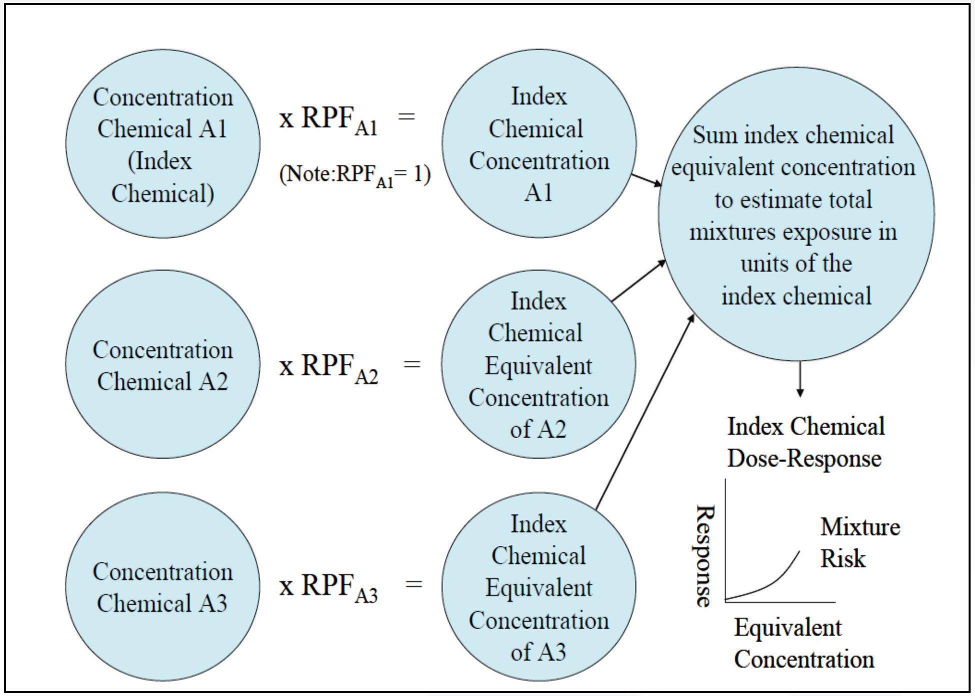
Relative Potency Factor (RPF)



Source: *Concepts, Methods and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document*; EPA/600/R-06/013F; United States Environmental Protection Agency: Washington, DC, 2007.

- Determine toxic endpoint or effect(s)
- Determine chemical groupings that are toxicologically similar
- Calculate RPF for each chemical
  - RPF_n = Toxic potency (index) / 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

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Margin of Exposure (MOE) Approach

$$MOE = POD_{Index} \div \sum_{Route} Exposure$$

$$MOE_{total} = \frac{1}{\frac{1}{MOE_{oral}}^{*} + \frac{1}{MOE_{dermal}} + \frac{1}{MOE_{inhalation}}}$$

**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.*

Source: EPA (2002). *Guidance on Cumulative Risk Assessment of Pesticide Chemicals That Have a Common Mechanism of Toxicity*.

- 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_{10})
- Compare route-specific toxicity benchmarks to exposure estimates
- Calculate MOE for each exposure route
- Combine route-specific MOEs to generate total MOE

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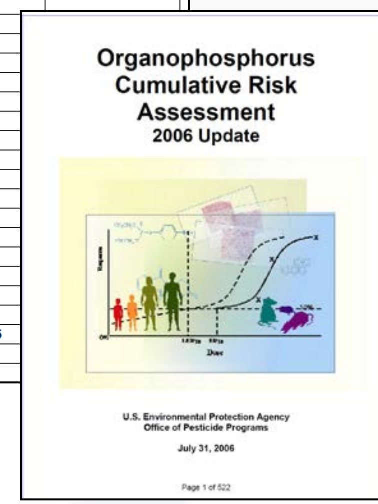
CRA Example: OP Pesticides

- 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

Relative Potency Factors for Female Brain Cholinesterase Activity

Chemicals	Oral	Dermal	Inhalation
Acephate	0.08	0.0025	0.208
Azinphos-methyl	0.10		
Bensulide	0.003	0.0015	
Chlorethoxyfos	0.13		
Chlorpyrifos	0.06		
Chlorpyrifos-methyl	0.005		
Diazinon	0.01		
DDVP	0.03		0.677
Dicrotophos	1.91		
Dimethoate	0.32		
Disulfoton	1.26	0.47	6.596
Ethoprop	0.06		
Fenamiphos	0.04	1.5	0.315
Fenthion	0.33	0.015	
Fosthiazate	0.07		
Malathion	0.0003	0.015	
Methamidophos	1.00	1.00	
Methidathion	0.32		
Methyl-parathion	0.12		
Mevinphos	0.76		
Naled	0.08	0.075	
Omethoate	0.93		
Oxydemeton-methyl	0.86		
Phorate	0.39		
Phosalone	0.01		
Phosmet	0.02		
Phostebupirim	0.22		
Pirimiphos-methyl	0.04		
Profenofos	0.004		
Terbufos	0.85		
Tetrachlorvinphos	0.001	0.00075	
Tribufos	0.02		
Trichlorfon	0.003	0.0075	



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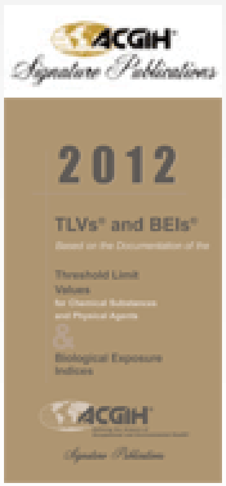
CRA Example: OP Pesticides

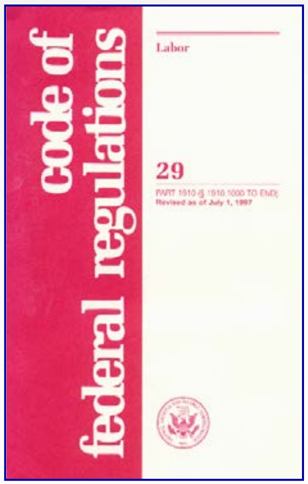
- Cumulative risk did not exceed level of concern (i.e., MOE >100)
- Greatest contribution to cumulative risk from food sources (low contribution from drinking water)
- Residential uses (due to inhalation) also a major source of risk at the upper percentiles of population exposure

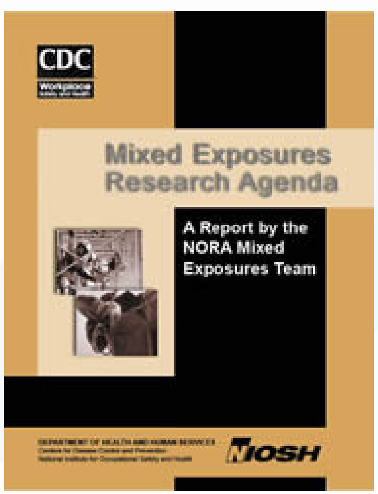
Table I.C-2 Exposure and MOE Values for the 21-Day OP Cumulative Food Assessment.

	95th Percentile		99th Percentile		99.9th Percentile	
	Exposure (mg/kg)	MOE	Exposure (mg/kg)	MOE	Exposure (mg/kg)	MOE
All infants	0.000097	820	0.00017	480	0.00048	170
Children 1-2 yrs	0.00015	550	0.00032	250	0.00076	110
Children 3-5 yrs	0.00012	670	0.00027	300	0.00081	99
Children 6-12 yrs	0.000099	810	0.00018	460	0.00049	170
Youth 13-19 yrs	0.000097	820	0.00011	740	0.00027	300
Adults 20-49 yrs	0.000098	820	0.00013	610	0.00028	280
Adults 50+ yrs	0.000099	810	0.00016	510	0.00033	240
Females 13-49 yrs	0.000098	820	0.00013	620	0.00028	290

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

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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

"YOU CAN'T SAY THE GOVERNMENT ISN'T TRYING."

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Community-Based Assessments

Open

Journal of Exposure Science and Environmental Epidemiology (2010) 20, 351–358

www.nature.com/jes

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 exposures, and determining their effectiveness for reducing human health risks. Additional challenges include determining what scientific tools are available and most relevant, 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 enhancing cumulative risk assessments. The NERL's "Cumulative Communities Research Program" focuses on key science questions: (1) How to systematically identify and prioritize key chemical stressors within a given community?; (2) How to develop estimates of exposure to multiple stressors for individuals in epidemiologic studies?; and (3) What tools can be used to assess community-level distributions of exposures for the development and evaluation of the effectiveness of risk reduction strategies? This paper provides community partners and scientific researchers with an understanding of the NERL research program and other efforts to address cumulative community risks; and key research needs and opportunities. Some initial findings include the following: (1) Many useful tools exist for components of risk assessment, but need to be developed collaboratively with end users and made more comprehensive and user-friendly for practical application; (2) Tools for quantifying cumulative risks and impact of community risk reduction activities are also needed; (3) More data are needed to assess community- and individual-level exposures, and to link exposure-related information with health effects; and (4) Additional research is needed to incorporate risk-modifying factors ("non-chemical stressors") into cumulative risk assessments. The products 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.
Journal of Exposure Science and Environmental Epidemiology (2010) **20,** 351–358; doi:10.1038/jes.2009.20; published online 15 April 2009

Keywords: *EPA, cumulative, exposure, communities, 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 those 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, databases, sampling/analytical methods, and geographic information system (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's Science Advisory Board, and other peer reviews and requests from the EPA regions and local communities to develop guidance documents and other tools for supporting community-based cumulative risk assessments (NAPA, 2008; NAS, 2008, http://dels.nas.edu/dels/rpt_briefs/IRA_brief_final.pdf). The EPA long-term strategic planning documents (USEPA, 2006a, b) articulate specific plans and programs for measurement-derived 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

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Received 23 October 2008; revised 30 January 2009; accepted 2 February 2009; published online 15 April 2009

- 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

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CRA Screening Tools: U.S. EPA

Journal of Exposure Science and Environmental Epidemiology (2010) 20, 371–384

www.nature.com/jes

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 25 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 CBCRAs; and (2) To use this toolset as a sample of the current state of CBCRA tools to critically examine their utility and guide research for the development of new and improved tools.
Journal of Exposure Science and Environmental Epidemiology (2010) **20,** 371–384; doi:10.1038/jes.2009.25; published online 29 April 2009

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, 1993, 1994; NAPA, 1995; PCCRARM, 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 (Menzie et al., 2007; Ryan et al., 2007; Sexton and Hattis, 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 Dearry, 2002; Perera et al., 2002; Corburn, 2002a; NEJAC, 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 Dearry, 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

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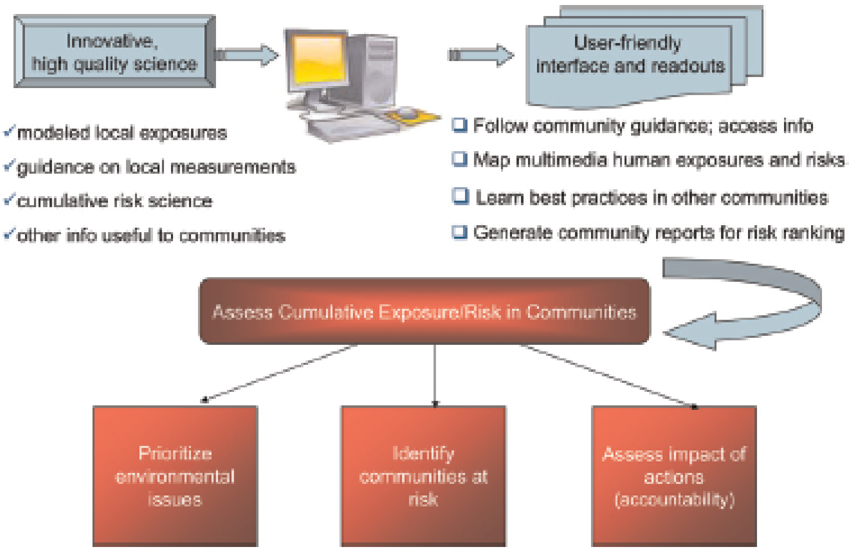

FIGURE 2—Community-Focused Exposure and Risk Screening Tool conceptual framework.

Source: Zartarian, et al. The Environmental Protection Agency's community-focused exposure and risk screening tool (C-FERST) and its potential use for environmental justice efforts. *Am. J. Public Health*. **2011**, *101* (S1), S286-S294.

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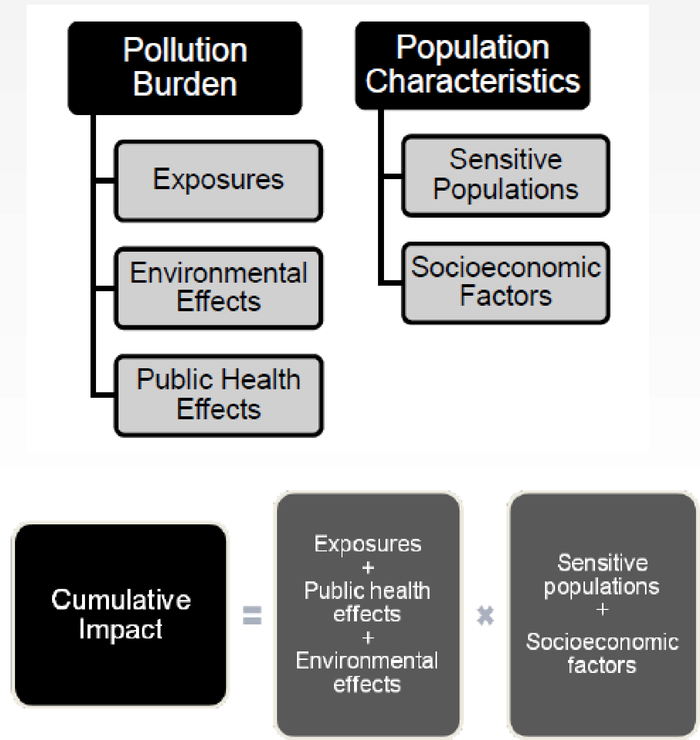
Statewide CRA Initiatives

- 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



Source: *Cumulative Impacts: Building a Scientific Foundation;* OEHAA, California Environmental Protection Agency: Sacramento, CA, 2010.

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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

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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

Individual Factors

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

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

Cumulative Risk

Source: Williams, et al. Cumulative risk assessment (CRA): transforming the way we assess health risks. *ES&T.* **2012**, *46*, 10868-10974.

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

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 employer-employee partnerships wishing 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 premise 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 workforce health and safety to the core products, services and values of the company should be acknowledged by leaders and communicated widely. In some notable examples, corporate Boards of Directors have recognized the value of workforce health and wellbeing 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.

Department of Health and Human Services
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National Institute for Occupational Safety and Health
CDC NIOSH
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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

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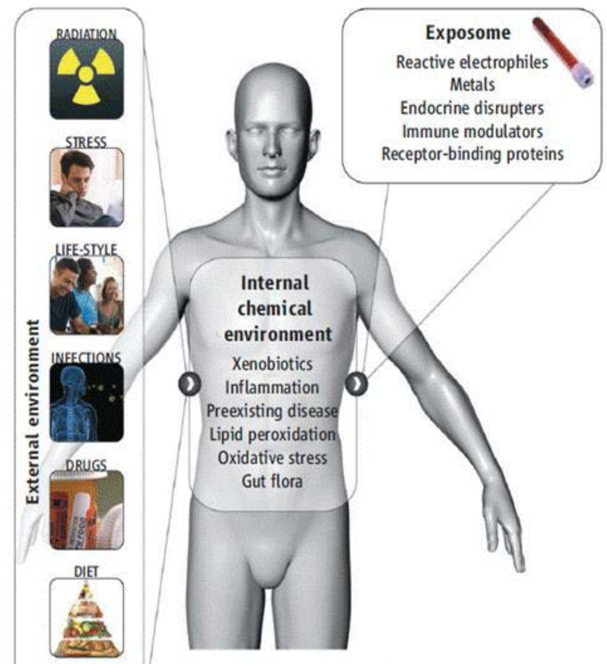
Exposome

- 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



Characterizing the exposome. The exposome represents the combined exposures from all sources that reach the internal chemical environment. Toxicologically important classes of exposome chemicals are shown. Signatures and biomarkers can detect these agents in blood or serum.

Source: Rappaport, S.M. and Smith, M. T. (2010). Environment and Disease Risks. Science, 330:.460-461.

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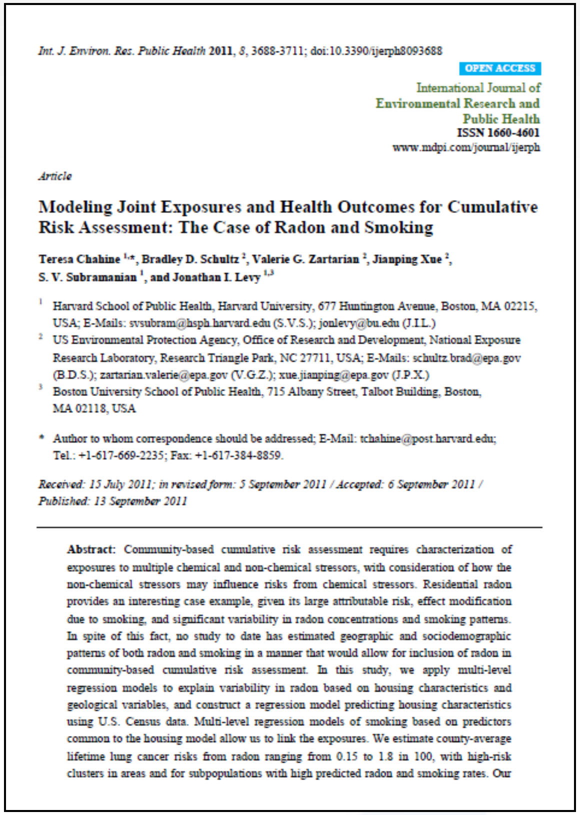
Integrating Chemical and Non-Chemical Stressors

- 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


Int. J. Environ. Res. Public Health **2011**, *8*, 3688-3711; doi:10.3390/ijerph8093688

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Article

Modeling Joint Exposures and Health Outcomes for Cumulative Risk Assessment: The Case of Radon and Smoking

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Abstract: Community-based cumulative risk assessment requires characterization of exposures to multiple chemical and non-chemical stressors, with consideration of how the non-chemical stressors may influence risks from chemical stressors. Residential radon provides an interesting case example, given its large attributable risk, effect modification due to smoking, and significant variability in radon concentrations and smoking patterns. In spite of this fact, no study to date has estimated geographic and sociodemographic patterns of both radon and smoking in a manner that would allow for inclusion of radon in community-based cumulative risk assessment. In this study, we apply multi-level regression models to explain variability in radon based on housing characteristics and geological variables, and construct a regression model predicting housing characteristics using U.S. Census data. Multi-level regression models of smoking based on predictors common to the housing model allow us to link the exposures. We estimate county-average lifetime lung cancer risks from radon ranging from 0.15 to 1.8 in 100, with high-risk clusters in areas and for subpopulations with high predicted radon and smoking rates. Our

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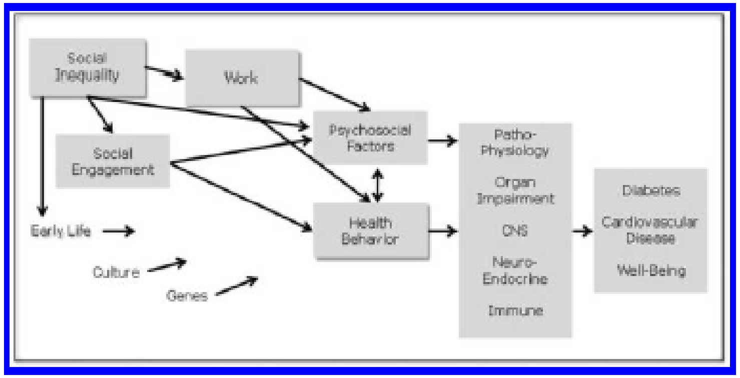
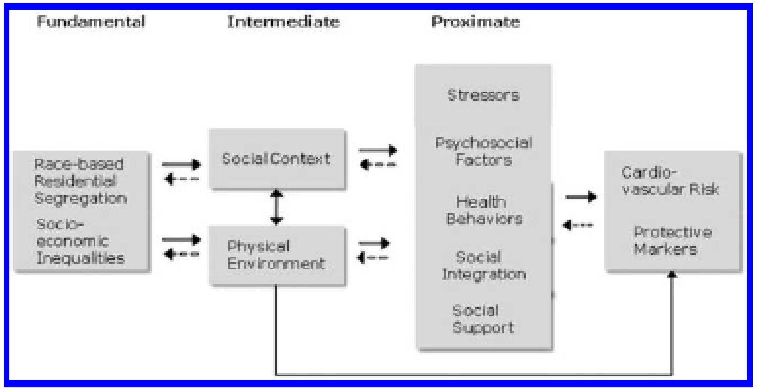
Identifying Families of Conceptual Models



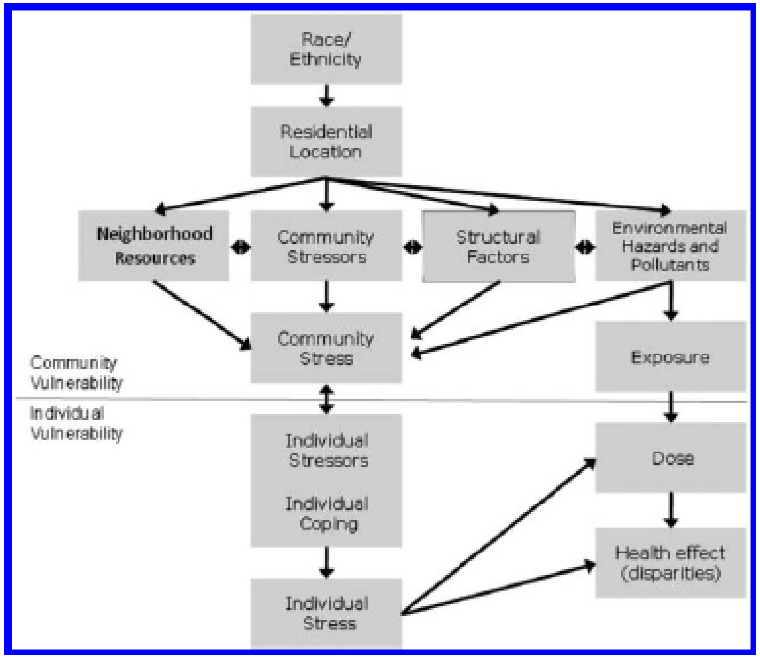
Source. Goldman[9] and Bruner and Marmot.[10]

FIGURE 1—A social determinant conceptual model.



Source. Schultz et al.[22]

FIGURE 4—A health disparity conceptual model.



Source. Gee and Payne-Sturges.[29]

FIGURE 5—The multiple stressor conceptual model.

Source: Linder, S. H.; Sexton, K. Conceptual models for cumulative risk assessment. *Amer. J. Public Health.* **2011**, *101* (S1), S74-S81.

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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

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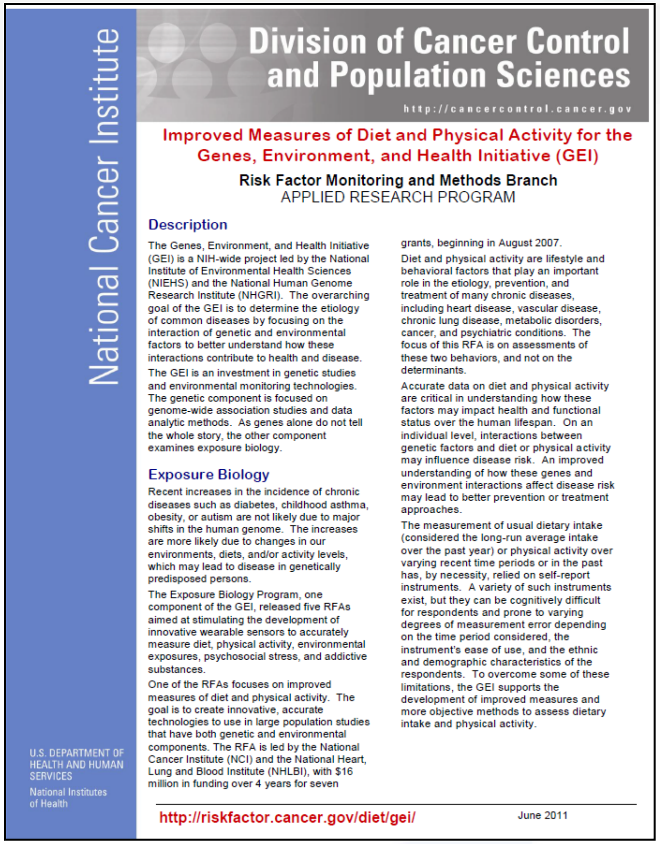
Biomarkers of Susceptability

- Many individual factors contribute to human variability in susceptability
- 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



National Cancer Institute

Division of Cancer Control and Population Sciences

http://cancercontrol.cancer.gov

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

Risk Factor Monitoring and Methods Branch
APPLIED RESEARCH PROGRAM

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 the whole story, the other component examines exposure biology.

Exposure Biology

Recent increases in the incidence of chronic diseases such as diabetes, childhood asthma, obesity, or autism are not likely due to major shifts in the human genome. The increases are more likely due to changes in our environments, diets, and/or activity levels, which may lead to disease in genetically predisposed persons.

The Exposure Biology Program, one component of the GEI, released five RFAs aimed at stimulating the development of innovative wearable sensors to accurately measure diet, physical activity, environmental exposures, psychosocial stress, and addictive substances.

One of the RFAs 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 level, interactions between genetic factors and diet or physical activity may influence disease risk. An improved understanding of how these genes and environment interactions affect disease risk may lead to better prevention or treatment approaches.

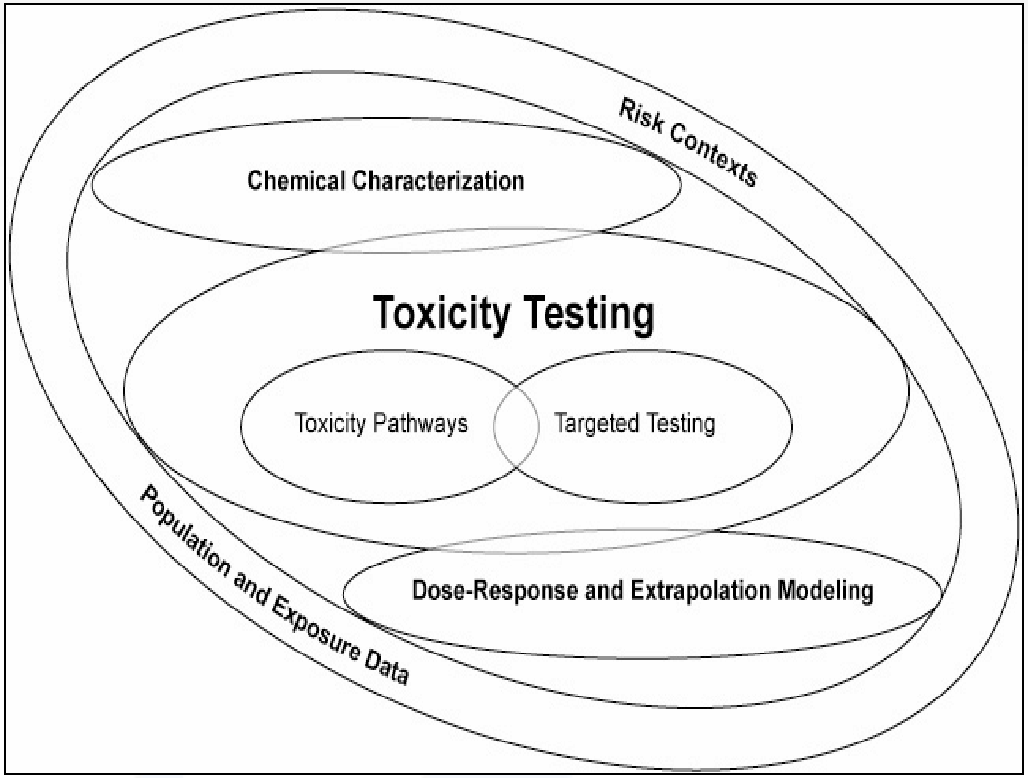
The measurement of usual dietary intake (considered the long-run average intake over the past year) or physical activity over varying recent time periods or in the past has, by necessity, relied on self-report instruments. A variety of such instruments exist, but they can be cognitively difficult for 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 respondents. To overcome some of these limitations, the GEI supports the development of improved measures and more objective methods to assess dietary intake and physical activity.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
National Institutes of Health

http://riskfactor.cancer.gov/diet/gei/

June 2011

Biomarkers of Effect



Source: *Toxicity Testing in the 21st Century: A Vision and a Strategy*; National Research Council; The National Academies Press: Washington, DC, 2007.

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- 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

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Considerations and Challenges

- Science and technology
- Regulatory and public policy
- Social and ethical

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Science and Technology

- 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

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ANALYSIS & TOOLS FOR DECISION-MAKING

U.S. EPA Monthly Webinar Series (2012)

- 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)

http://epa.gov/ncer/multimedia/videos/cumulative-risk/webinar/2012/index.html

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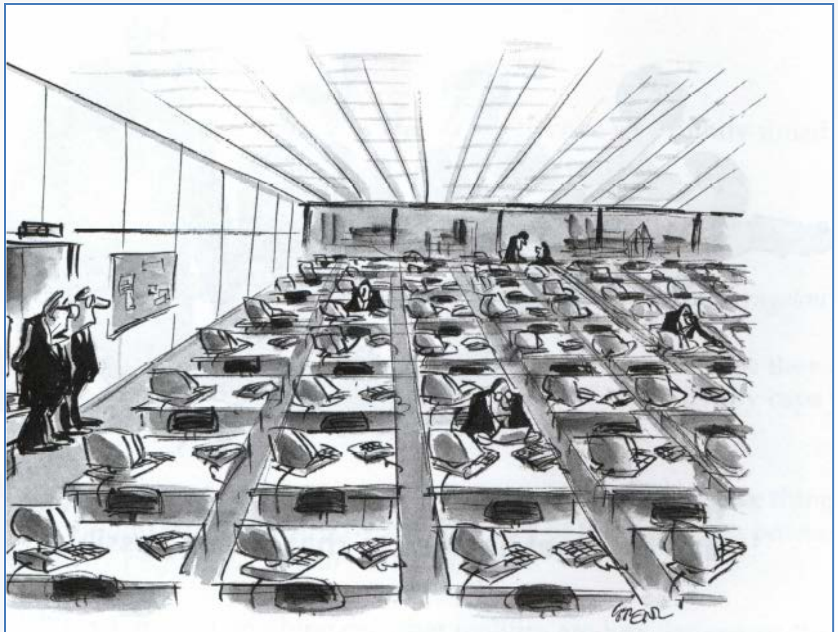
Regulatory and Public Policy

- 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)



"Maybe zero tolerance is setting the bar too high."

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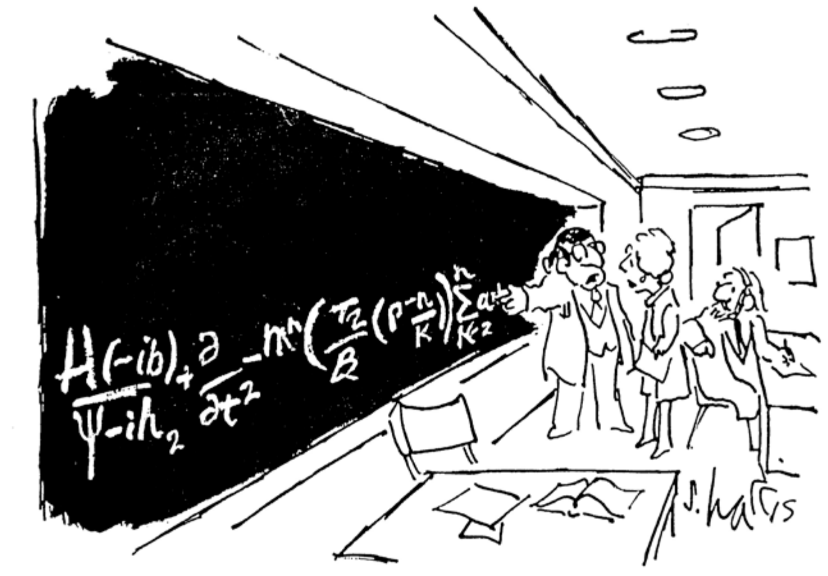
Social and Ethical

- 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."

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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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