EPA
United States
Environmental Protection
Agency

PROCEEDINGS FROM THE PROGRESS REVIEW MEETING ON CUMULATIVE RISK GRANTS

May 14, 2012

EPA Headquarters, East Building | Map Room 1153
1201 Constitution Avenue, NW | Washington, D.C. 20004

Office of Research and Development
Science To Achieve Results (STAR) Research Program

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Progress Review Meeting on Cumulative Risk Grants

May 14, 2012

EPA Headquarters, East Building, Map Room 1153
1201 Constitution Avenue, N.W.
Washington, DC 20004

Monday, May 14, 2012

Session Title	Speakers	Time
PART 1 – Open to EPA Staff and Webinar Access to EPA MAP Room EPA EAST 1153		
Welcome	*Devon Payne-Sturges, Assistant Center Director for Human Health, NCER*	8:30 – 8:40 a.m.
Theme I: Applying Cumulative Assessments to Inform Environmental Decision Making		
Topic: Characterizing Cumulative Risk in EPA Criteria Pollutant Benefits Assessments: Moving Toward a More Comprehensive Accounting of Population Risk	*Neal Fann, Office of Air Quality Planning and Standards, EPA*	8:40 – 9:00 a.m.
Topic: The U.S. EPA Cumulative Risk Assessment Guidelines	*Lawrence Martin, Risk Assessment Forum, Office of Science Advisor, EPA*	9:00 – 9:10 a.m.
Topic: Integrating Chemical and Non-Chemical Stressors in Cumulative Risk Assessment (with copy of white paper)	*Jonathan Levy, Professor, Boston University School of Public Health and STAR Grantee*	9:10 – 9:20 a.m.
Topic: Intramural CRA Research at EPA and a View on How It Relates to CRA Grants	*Bradley D. Schultz, National Exposure Research Laboratory, EPA*	9:20 – 9:30 a.m.
Discussion	*All*	9:30 – 10:00 a.m.
BREAK		10:00 – 10:15 a.m.
Theme II: Data Analysis Methods for Combining Stressors		
Topic: Issues Related to Backward and Forward Translation of Toxicological and Epidemiological Studies of Cumulative Risk Assessment	*Deborah A. Cory-Slechta, Professor, Department of Environmental Medicine, University of Rochester School of Medicine*	10:15 – 10:30 a.m.
Topic: Innovative Approaches to Qualitative Data Analysis	*Madeleine Kangsen Scammell, Assistant Professor, Boston University School of Public Health*	10:30 – 10:45 a.m.
Discussion	*All*	10:45 – 11:05 a.m.
Adjourn - End of Part 1		11:05 a.m.

Part 2 – Grantees Only
EPA East Room 1117A

Theme III: CBPR; Community Partnerships		
Community Engagement in Research Spectrum Exercise. What Are the Challenges? What Are the Opportunities?	*Moderator: Tina Yuen, Association of Schools of Public Health (ASPH) Fellow, NCER*	11:10 – 11:20 a.m.
Reflections from the Exercise	*Grantees and Their Community Partners*	11:20 – 11:30 a.m.
Theme IV: Grants Management		
Topic: Q & A with EPA Office of Grants and Debarment	*Jill Young, OGD, and La Shaun Phillips, OGD*	11:30 – 12:00 p.m.
Working Lunch	*Grantees ONLY*	12:00 – 1:00 p.m.
Topic: Open Discussion	*All*	
Adjourn for Social Stressors Workshop		1:00 p.m.

Cumulative Risk Grants
Grantee Progress Review Meeting

EPA Headquarters, East Building
Room 1153 (Map Room)
1201 Constitution Avenue, NW
Washington, D.C. 20004

May 14, 2012

MEETING SUMMARY

Welcome and Opening Remarks
Devon Payne-Sturges, National Center for Environmental Research (NCER), Office of Research and Development (ORD), U.S. Environmental Protection Agency (EPA)

Dr. Payne-Sturges welcomed the meeting participants and said that the purpose of the meeting was to share and discuss the progress of the grantees of the Science To Achieve Results (STAR) cumulative risk grants. Assessing the reality of environmental impacts on human health is imperative. Over the years, the EPA has tended to focus on the average person, one medium, one agent and/or one source of pollution; however, to better reflect reality, steps need to be taken to understand the impacts of multiple sources, multiple agents, multiple media and whole-community characteristics.

In 2009, the STAR program released a request for applications (RFA) for research that moves toward better reflecting reality. Seven grants were awarded initially. In addition, during the past several years there have been a number of efforts at the EPA to develop tools for cumulative risk assessment (CRA) and to apply those tools.

Dr. Payne-Sturges expressed the need for expertise and knowledge across multiple disciplines. She also commented that the terminology that is used makes a difference. She encouraged meeting participants to question what the word "cumulative" means. Participants were asked to provide their responses by writing them on the large pieces of paper supplied at the meeting.

THEME I: Applying Cumulative Assessments to Inform Environmental Decision-making

Characterizing Cumulative Risk in EPA Criteria Pollutant Benefits Assessments
Neal Fann, Office of Air and Radiation, EPA

Mr. Fann said that he would discuss the EPA's approach to estimating health impacts for Regulatory Impact Assessments, and opportunities for improving that approach and characterizing cumulative criteria pollutant risk.

There is a pyramid of effects that are related to air pollution. In the array of impacts associated with exposure to air pollution, death is at the top of the pyramid and more transient effects, such as inflammation, cardiac effects and so forth, populate the base of the pyramid. Although mortality is at the top of the pyramid, accounting for a small portion of the air pollution impacts, it is associated with the largest monetary cost.

To estimate the health impacts of air pollution, epidemiology data are inputted into health impact mathematical functions. Software then maps environmental benefits and assigns a value to health impacts. Mr. Fann adheres to this approach for each scenario and each pollutant. Multiple pollutants are not handled with this approach. Estimates for the health impacts of air pollution use a baseline of no environmental policy. The software then is used to examine the effect of various regulations and policies. Frequently, particulate matter (PM) and ozone are examined. Other air pollutants are studied rarely because they are more data intensive. When reporting PM and ozone impacts, the preference is to use epidemiology studies that control for covariates.

Mr. Fann explained that there is a reduction in the risk of mortality with educational attainment. This is relevant because PM mortality coefficients were stratified by educational attainment. Populations with less than a grade 12 education level are at higher risk of mortality due to PM; however, their risk has been dropping precipitously.

Mr. Fann and colleagues characterized the overall percentage of deaths attributable to PM and ozone in 2005 as 6.1 percent. They now are moving their focus to a nonregulatory characterization of cumulative risk. This will help inform decision-makers because they will be able to ascertain overall risk and magnitude, as well as spatial distribution. For example, a study that identified populations that were vulnerable to PM air pollution in Detroit, MI, found that focusing on a local area can generate superior information concerning demographics and exposure. These data can better target changes that are necessary to alter air pollution. Data types that can be used to determine populations that are susceptible and vulnerable to air pollution include hospitalization, poverty, education and so forth.

There are many ways that the EPA could better account for cumulative risk, including informing air-quality management strategies, as well as demographic, baseline health and baseline risk estimates; broadly applying education-modified PM mortality risk coefficients; and assessing risk across a more comprehensive array of pollutants (nitric oxide [NO], sulfur monoxide [SO], mercury [Hg], lead [Pb]). For future risk assessments, temperature-pollutant and multipollutant interactions should be accounted for, as well as the effects that are modified by other variables.

The U.S. EPA Cumulative Risk Assessment Guidelines
Lawrence Martin, Risk Assessment Forum, Office of the Science Advisor (OSA),EPA

The definition of CRA according to the CRA framework (2003), is "an analysis, characterization and possible quantification of the combined risks to health or the environment from multiple agents or stressors." The CRA panel and the EPA have been working for more than a decade on the complications of CRA. A technical panel was formed following an Executive Order, and the panel was charged with developing guidance for CRA. They developed a framework for CRA in 2003, and in 2010, the panel was re-formed to further hone guidelines.

The re-formed CRA technical panel has four assignments: (1) prepare responses to the National Research Council (NRC) recommendations in *Science and Decisions*, and in *Phthalates and CRA for the Human Health Colloquium* (October 2010); (2) design and oversee the conduct of an environmental justice (EJ) CRA project; (3) complete work on a compendium of lessons learned and best practices; and (4) prepare guidelines for the conduct of CRA.

The preparation of guidelines will be the panel's most challenging task. The CRA panel has worked with various researchers and EPA staff to identify case studies and white papers for use in developing the guidelines. Key concepts for the guidelines include planning and scoping the assessment to constrain focus, analysis and cost; combining chemical and nonchemical stressors; integrating human and ecological risk; and informing decisions about sustainability initiating factors. The guidelines for CRA will focus on integrated characterization of items such as public health data, mixtures toxicity, population vulnerabilities, population illness, chemical concentrations and so forth. The guidelines were thus far five chapters in length and were expected to be completed in 2013. The CRA lessons learned and current practices were expected to be available within a month or two following this meeting.

The panel believes that CRA is not too complicated to handle quantitatively because available data may support that approach, and new science is perpetually expanding what is possible.

Integrating Chemical and Nonchemical Stressors in Cumulative Risk Assessment
Jonathan Levy, Boston University

Dr. Levy said that he would focus on the white paper, "Integrating Chemical and Non-Chemical Stressors in Cumulative Risk Assessment," prepared to support the development of CRA guidelines. This white paper, which was distributed to meeting participants, focused on areas that were under discussion,

including the incorporation of nonchemical stressors, explicit consideration of the exposure assessment step, more direct recognition of the role of epidemiology, and the use of the *Science and Decisions* dose-response approach.

The working definition of nonchemical stressors includes all stressors that have not been examined in CRAs to date. The white paper was structured by examining each step of risk assessment (the conventional four steps from the "EPA Red Book"), scoping to build a conceptual model, restricting the number of stressors, and using a framework that is more risk management-based.

Hazard identification should be similar to the standard risk assessment process, with a few refinements. These refinements include considering stressors that only act as modifiers, even in the absence of direct effects for the outcome of interest, and using the effects- versus stressor-based orientation to narrow the hazard identification process.

Four key dimensions of exposure assessment are discussed in the white paper. These four dimensions are: (1) using mode of action/common adverse outcomes to determine the appropriate form of exposure assessment; (2) using proxy variables for nonchemical stressors that cannot be ascertained directly; (3) considering correlations among exposures for appropriate joint characterization; and (4) establishing default assumptions in the absence of population-specific data.

For dose-response modeling, the white paper examines guidance for chemical mixtures. Chemical mixture guidance is applicable to dose-response modeling in theory; however, the lack of quantitative data for nonchemical stressors in some settings can be challenging. Additionally, chemical mixtures guidance can be extended to nonchemical stressors if relevant dose metrics are available.

Toxicology can be used for risk assessments; however, there are limits because it is not possible to incorporate many nonchemical stressors toxicologically. For example, there is no toxicological equivalent for lacking access to health care. Using nonchemical stressors, however, can help researchers understand the threshold versus non-threshold phenomenon. Diet, obesity and other factors can be captured in physiologically based pharmacokinetic (PBPK) models to examine delivered doses or pharmacodynamic outcomes.

Epidemiology is an important way forward for cumulative risk; it is rare, however, to have sufficient epidemiologic data for a multistressor assessment. Combining epidemiology and toxicology can produce a hybrid approach that could be viable to build a conceptual model.

Risk characterization was not covered extensively in the white paper. The white paper did reinforce, however, that CRA is not equivalent to comparative risk assessment. Additionally, descriptions should emphasize which stressors the EPA does and does not have authority over, and whether or not a risk-management construct is used.

Some of the core recommendations of the white paper already are occurring with the research being carried out from STAR grants. These recommendations include the formalization of planning and scoping with expanded conceptual model development, the incorporation of common adverse outcome orientation, elucidation of the mechanisms of action for nonchemical stressors via more primary research, production of a nonchemical stressors exposure factors handbook, and development of case examples.

Intramural CRA Research at the EPA and a View on How it Relates to CRA Grants
Brad Schultz, National Exposure Laboratory, EPA

Mr. Schultz summarized intramural EPA research, sustainable and healthy communities research, and the potential coordination of research. One challenge is that decision-makers need information, but CRAs have gaps. Some communities have limited resources and access to information. EPA-funded research is intended to fill in these informational gaps.

The following EPA research programs were reorganized in fiscal year 2011: Air, Climate and Energy (ACE); Safe and Sustainable Waters (SSWR); Chemical Safety for Sustainability (CSS); and Sustainable and Healthy Communities (SHC). The human health risk assessment and homeland security research programs did not undergo reorganization.

SHC research programs use stressor- and effects-based approaches. Community public-health research includes asthma health effects research, CRA science, community public-health tools (i.e., screening tools), health impact assessments (HIAs) and community case studies.

Needs and external drivers are related to tools and other research. According to *Science and Decisions: Advancing Risk Assessment* (NRC 2009), "EPA should focus on development of guidelines and methods for simplified analytic tools that could allow screening-level CRA and could provide tools for communities and other stakeholders to use in conducting assessments."

One community public health tool is the Community-Focused Exposure and Risk Screening Tool (C-FERST). This tool is a web-based community assessment tool that is geographic information system (GIS) supported. It supports CRA and decision-making, and is user-driven. Community guidance involves a community-cumulative assessment tool, a HIA roadmap, an EJ toolkit, Protocol for Assessing Community Excellence in Environmental Health (PACE-EH) and a community action for a renewed environment (CARE) roadmap. For self-directed use of C-FERST there is an alphabetical listing of issues as well as stressor and health effects options. Another feature is the community data table. Issues are broken into environmental community estimates, human exposure estimates (by zip code, county, state or nation-wide) and human risk estimations for data. These categories have been consistent across many issues.

The community assessment map in C-FERST can be broken down by census tract estimates and used to separately consider categories of data. One example of how this has been implemented is in estimates of the lifetime risk of lung cancer from radon exposure and smoking.

Discussion

A participant said that the presenters commented on issues related to partnerships for sustainable communities (indicators, performance measures and so forth). She questioned whether partnerships should explore the concept of education as a surrogate. Mr. Fann responded that in analyses, education was found to modify the relationships among qualifier media, long-term exposures and risk of premature death. He noted that education was a surrogate for an indicator that characterized access to health care, proximity to roadways and so forth. To the extent that that information exists, it can be helpful in risk assessments to characterize risk in subgroups differentially.

Jane Clougherty (University of Pittsburgh) asked about the distinction between the terms "susceptibility" and "vulnerability" in the EPA framework. Mr. Fann responded that within the literature and the EPA, there is no clear distinction between those two terms. "Susceptibility" often refers to individual population characteristics, primarily health-based, that suggest that exposure to pollutants would result in

an increased risk of an adverse health effect. "Vulnerability" is related more to a population exposure to elevated pollutant levels and is less health-based. Dr. Levy agreed that there is not a clear distinction. Mr. Martin commented that the panel will work to achieve clarity on this matter in the CRA guidelines.

THEME II: Data Analysis Methods for Combining Stressors

Issues Related to Backward and Forward Translation of Toxicological and Epidemiological Studies of Cumulative Risk Assessment
Deborah A. Cory-Slechta, University of Rochester School of Medicine

Dr. Cory-Slechta said that most complex diseases and disorders arise from interactions of multiple risk factors. These factors, some of which are protective, are unique to each individual and include stress, smoking, exercise, deleterious genes and chemical exposures, among others. Most neurotoxicology models, however, study toxicants in isolation and in healthy, young organisms. Chemical studies should be improved so that they include all types of people and combine toxicants.

EPA guidance and CRA began in 1994, and STAR grants have begun to support this. The risk assessment paradigm relies heavily on animal models and uses uncertainty factors to accommodate the differences between animals and humans. This methodology is best used when corresponding human data exists. STAR grants may be able to assist in overcoming these challenges.

The word "translation" has been used to suggest the importance of findings moving from the research bench to the bedside. Human studies can benefit from animal models, but animal models also can be refined further by incorporating human study data.

Stress is a component of cumulative risk. Stress can complicate epidemiological and toxicological studies because there are different consequences of stress, depending upon the particular stress that is being applied. Stress can cause resilience or psychopathology. The degree to which animal stress simulates human stress is not entirely understood. In addition, gender differences are involved in the human stress response. These gender differences can yield results that are exactly opposite for males versus females. Averaging these stress responses yields null results, even though males and females each had a strong but polarized response. There are statistical limitations for evaluating interactions; a better methodology is required for examining interactions with limited sample sizes.

Dr. Cory-Slechta emphasized that not all stress is detrimental. The stress response of resilience versus vulnerability is dependent upon the conditions of the stressor. Less pronounced types of stressors can lead to resilience later in individual's lifetime; however, more severe stressors can lead to pathophysiological problems later in an individual's life. Additionally, stressors that are uncontrollable and unpredictable lead to psychopathology, but those that are controllable and predictable can lead to a more resilient phenotype.

Stress protocols for animal models most commonly utilize immobilization (restraint) stress, maternal separation and intruder stress. Additional stressors that are utilized include chronic homotypical stress and chronic variable stress. Dr. Cory-Slechta explained that restraint and maternal separation stresses yield inconsistent results. Intruder stress better represents human responses to stress; however, it matches the response better for males than females.

As biomarkers for stress, corticosterone and noradrenaline can be examined and compared in animals exposed to unpredictable and uncontrollable stress versus predictable and controllable stress. Results indicate that corticosterone normalization and increased noradrenaline define "stress."

There are limitations to evaluating statistical interactions, and it is important to understand how these limitations apply to risk factor interactions. One limitation is sample size; however, achieving the required large sample size for statistical validation is not always feasible. A biostatistical approach is needed to evaluate smaller sample sizes in human and animal studies. Such an approach should assess potential interactions based on factors such as the co-occurrence of environmental chemical exposures and the extent to which they share biological targets.

An example of why interaction effects are critical comes from a brain study that examined Pb exposure in males versus females. In males, there was more of an effect of Pb exposure and stress history, and less of a change in females. This is a striking gender difference, and if interaction effects are not separated by gender, large differential factors can be overlooked.

Innovative Approaches to Qualitative Data Analysis
Madeleine Kangsen Scammell, Boston University School of Public Health

Dr. Scammell explained that there are two types of innovation for qualitative data analysis: (1) erasing the distinction between quantitative and qualitative data analysis; and (2) suggesting analytical methods for handling qualitative data. Dr. Scammell said that her presentation would introduce the study location and methodology used in her work, convince attendees that working within a framework that distinguishes two types of data is not helpful, provide a brief analysis of handling data using standard methods, and introduce innovative analytic methods.

Dr. Scammell's work occurred in the Sea of Chelsea near Boston, MA. There are oil tank storage areas along the Chelsea Creek near locations where data were gathered. These areas are EJ regions based on demographic information, not on environmental exposures. In addition to oil tanks, a liquid natural gas tanker regularly enters the area. A census tract that was used for the study included four designated port areas and one commercialized district.
Five hundred interviews were conducted with residents in the designated areas. There were 180 questions, of both open and closed types. Interviewees provided a wide range of responses to the open-ended questions. These responses were turned into data via a coding methodology. The code was applied to certain aspects of these comments, such as a reference to being in an oil tank area or near to the natural gas tanker. These codes then were entered into software, and the qualitative data analysis proceeded hierarchically.

Themes were identified, followed by larger concepts. One theme indicated that three out of five respondents had fears of disaster. This theme was uncovered by aggregating several codes. Instead of determining the frequency of special answers, the actual reasons for people feeling the way that they did were examined. At a higher level than theme, concepts, which show how themes are related, are used. Concepts are better representations of environmental burdens and stress. Assigning codes to data, followed by the identification of themes and concepts, is an appropriate way to characterize environmental burden and is not unlike handling quantitative data.

Quantitative research usually is defined by numeric data, with measurements that are standard and generalizable. Qualitative research, however, generally refers to non-numeric data that "increases depth of understanding" and provides insight into thoughts, feelings, opinions and motives.

All research requires measurement, and when representing data with numbers, this measurement is quantitative. In risk assessments, non-numeric representations are relied upon, and this can be achieved by utilizing diagrams that exhibit spatial relationships and logic. It is incorrect to think that numbers are a privileged representation of reality.

As an example, Dr. Scammell discussed smoking. Smoking intensity and duration are measured by two different measures: the number of cigarette packs that smokers consume per day (intensity) and years that smokers have smoked (duration); both measures supply numeric data. Dr. Scammell analyzes these data structurally and visually. The concepts of smoking intensity and duration are kept separate. By doing this, the data can indicate the reasons for peoples' smoking style. Reliance on quantitative data would lose some of this vital information.

Dr. Scammell concluded by saying that lattice mathematical structures can be used to delve into data and interpret it. Data gathered by open- and close-ended questions can be used quantitatively to study cumulative risk and make assessments.

Discussion

Mr. Fann requested that Dr. Scammell further explain the lattice mathematical diagram. Dr. Scammell explained that the lattice structure compares smoking intensity to years. Smoking intensity has more to do with health risk and duration; however, reducing data to just smoking intensity creates the loss of other important data.

A participant questioned how Dr. Scammell proposed to distinguish between the two measures of smoking intensity and duration. Dr. Scammell responded that a bigger question is how researchers can decide what factors to examine in relation to others. The smoking data that she presented is driven by what is already known; without that previous knowledge, however, it would be difficult to know where to tease apart differences in data.

A participant asked about the resilience factor, how it can be expressed and what its mechanisms are. Dr. Cory-Slechta gave an analogy. If children never experience disappointments in life, then they never have any experience with that type of stress. This means that they will not do well in later life. If they have severe stress, however, there can be a lifetime of negative consequences. It is difficult to look at the human world via research because it is not ethical to formulate certain kinds of experiments. Resilience (the ability to respond to stressors and stress challenges later in life) is addressed in a confusing manner in the scientific literature. Many papers on the biomarkers of stress do not differentiate appropriately and predictable, controlled stress (resiliency) versus uncontrollable, unpredictable stress. Until these complications are resolved, it is difficult to identify reliable stress biomarkers. Cortisol is the best example of a stress biomarker. The levels of cortisol depend entirely upon a person's history. There is a feedback loop regarding cortisol levels, and that loop can be delayed depending on the types of stressors to which a person has been exposed.

A participant commented that stress response is a learned phenomenon. People learn how to deal with stress; for uncontrollable, unpredictable stress, however, there is not much to be done. Another participant said that the capacity to overcome stress is a factor that speaks to EJ circumstances. She questioned if EJ can become a component in risk assessment analysis. Dr. Cory-Slechta responded that she currently had a grant to examine this. She said that this would be an animal study initially and would involve the examination of historical data sets.

Dr. Payne-Sturges requested a comment on how stress can be examined from a community-wide perspective. Dr. Scammell responded that currently the community level is considered an aggregate of individuals that reflects the community experience of stress. Dr. Cory-Slechta said that she conducted a cohort study in Rochester, NY, in which mothers came in every 6 months to have their childrens' blood drawn. She said that mothers consistently commented that chemical risks and stressors were not a high priority because they were more concerned with paying their health insurance or rent. Dr. Cory-Slechta felt that this was indicative of the state of many communities.

A participant commented that there is an analytical problem when community responses are mined. When handling one community at a time, data can be skewed; it is important to examine several communities at once. That is another possibility for analyses and requires analytical methodology to be broadened. Dr. Scammell agreed that scale is a very important component of analyses. For her studies, she commented that each census tract represents a different type of community.

A participant commented that to examine community stress, questionnaires are designed to ask about community meetings that include EJ questions, racial questions and so forth. These questions could indicate some shared community stresses.

Adjournment
Dr. Payne-Sturges, NCER, ORD, EPA

Dr. Payne-Sturges thanked the participants for attending and the speakers for their presentations. Grantees continued the meeting in a closed session, followed by a social stressors workshop in the afternoon. Dr. Payne-Sturges adjourned the meeting.

Abstracts and Presentations

Devon Payne-Sturges

Welcome

Devon Payne-Sturges
Assistant Center Director for Human Health, NCER, EPA

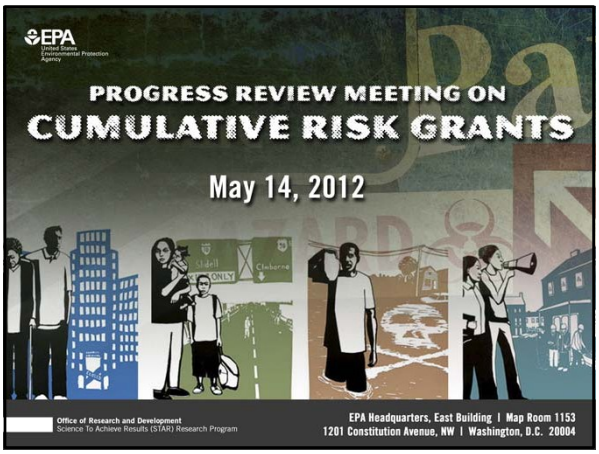
Multiple aspects of the environment in which we live, learn, work and play impact our health. However, it is the general practice of governmental agencies/policy makers responsible for protecting public health and the environment to focus on one factor at a time, more specifically one environmental contaminant at a time. For example, EPA traditionally has used the risk assessment paradigm to assess exposures and risks to single chemicals. For many years, the environmental justice movement and local communities have advocated for the consideration of multiple exposure and cumulative impacts in environmental policy and decisions. Further, the social context/real word context in which exposures to environmental contaminants occur also needs to be reflected in the science that supports EPA's decision-making, as emerging evidence demonstrates that social and contextual factors may enhance the toxic effects of both single and multiple environmental contaminant exposures. Such considerations require new models for assessing the toxicity of environmental hazards, advanced methods for analyzing complex interactions between multiple stressors, and enhanced access to community-level knowledge and resources. Under a 2009 RFA, the EPA STAR program awarded 7 grants to fund cumulative human health risk assessment research on how the combination of harmful factors affect human health, including poor and underserved communities with extensive pollution problems.

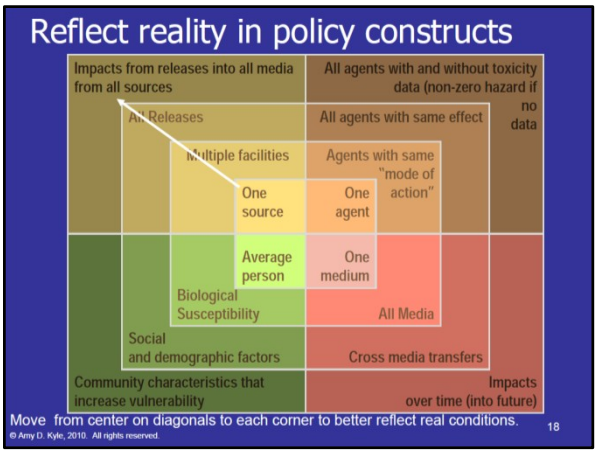
Goal:

The goal of the meeting was to share and discuss progress of this ground-breaking research on cumulative risks and methods for assessing the combined health impacts of multiple stressors.

Outcomes:

1. Shared knowledge about innovative approaches for data analysis methods for combining stressors.
2. Understanding the opportunities and barriers for applying cumulative assessments in environmental decision-making.
3. Enhancing community engagement in research on cumulative risk.





What does cumulative mean to you?

This Morning's Agenda

Part 1 8:30AM – 11:05AM

Theme I: Applying Cumulative Assessments to Inform Environmental Decision-making

Theme II: Data Analysis Methods for Combining Stressors

Adjourn 11:05AM

1:00PM Workshop on Interactions between Social Stressors and Environmental Hazards

Theme 1

Applying Cumulative Assessments to Inform Environmental Decision Making

Neal Fann

Characterizing Cumulative Risk in EPA Criteria Pollutant Benefits Assessments: Moving Toward a More Comprehensive Accounting of Population Risk

Neal Fann
U.S. Environmental Protection Agency,
Office of Air and Radiation

In this presentation, I will describe the U.S. Environmental Protection Agency's (USEPA) methods for assessing the cumulative effect of population exposure to multiple criteria pollutants. The first portion of my discussion will focus on the way in which USEPA assesses these impacts in a regulatory context, with an emphasis on the recently promulgated Cross-State Air Pollution Rule. In particular, I will detail the human health benefits assessment, the evaluation of welfare benefits and the Environmental Justice assessment. Next, I will describe an Environmental Justice Assessment performed as part of a multi-pollutant pilot project for Detroit (Fann et al., 2011). In that project, USEPA used a combination of demographic, baseline health and exposure data to identify susceptible and vulnerable populations and then evaluated the ability of alternate air quality management strategies to deliver air quality improvements among these population sub-groups.

Characterizing Cumulative Risk in EPA Criteria Pollutant Benefits Assessments

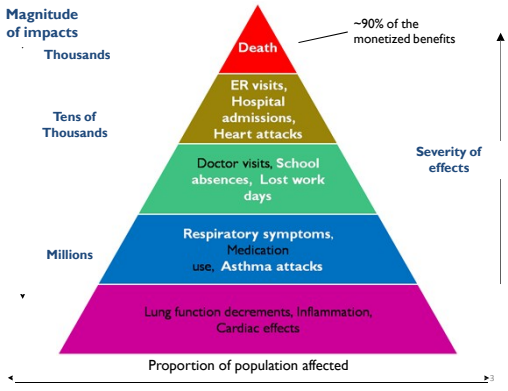
Moving toward a more comprehensive accounting of population risk

Presentation to cumulative risk grantee progress review meeting
May 14th, 2012

Overview

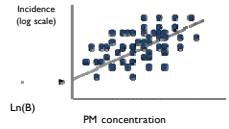
- EPA's approach to estimating health impacts for Regulatory Impact Assessments
- Characterizing cumulative criteria pollutant risk
- Opportunities for improving our approach

A "Pyramid of Effects" from Air Pollution



Step One: Derive Health Impact Functions from Epidemiology Literature

Epidemiology Study



$Ln(y) = Ln(B) + \beta(PM)$

Health impact function

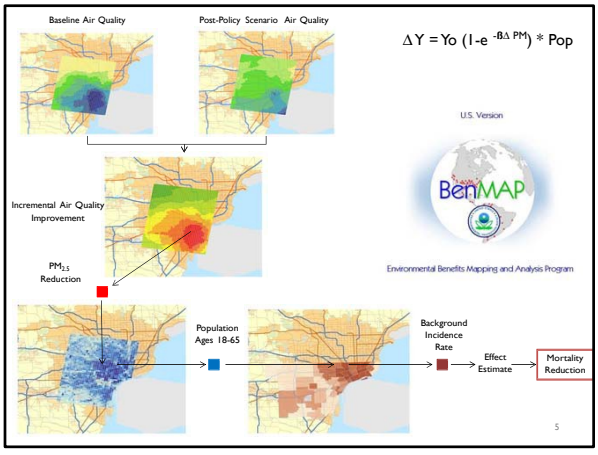
$\Delta Y = Yo\ (1 - e^{-\beta \Delta PM}) * Pop$

Yo – Baseline Incidence

β - Effect estimate

ΔPM – Air quality change

Pop – Exposed population



EPA Regulatory Analyses: Health Benefits of 2014 Cross-State Air Pollution Rule

Summary of health impacts avoided

Health endpoint	Value
$PM_{2.5}$-related mortality (Pope et al. 2002)	13,000 (5,200—21,000)
$PM_{2.5}$-related mortality (Laden et al. 2006)	34,000 (18,000—49,000)
O_3-related mortality (Bell et al. 2004)	27 (11—42)
O_3-related mortality (Levy et al. 2005)	120 (90—160)
$PM_{2.5}$-related chronic bronchitis	8,700 (1,600—16,000)
$PM_{2.5}$-related non-fatal heart attacks	15,000 (5,600—24,000)
$PM_{2.5}$ and O_3-related respiratory hospitalizations	2,900 (1,300—4,300)
$PM_{2.5}$ and O_3-related emergency department visits	9,900 (5,800—14,000)

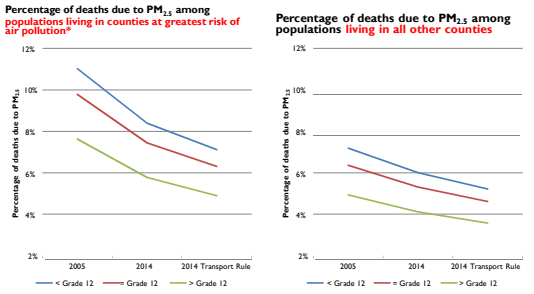
Monetized health and welfare benefits[A]

Endpoint	Value (billions of 2006$)
Human health[B]	
Pope et al. 2002 $PM_{2.5}$ and Bell et al. 2004 O_3 mortality estimates	$120 ($14—$350)
Laden et al. 2006 $PM_{2.5}$ and Levy et al. 2005 O_3 mortality estimates	$280 ($29—$810)
Visibility	$3.6
Total	
Pope et al. 2002 $PM_{2.5}$ and Bell et al. 2004 O_3 mortality estimates	**$120 ($10—$360)**
Laden et al. 2006 $PM_{2.5}$ and Levy et al. 2005 O_3 mortality estimates	**$290 ($26—$850)**

[A] All values rounded to two significant figures
[B] Discounted at 3%

Source: http://www.epa.gov/airtransport/pdfs/FinalRIA.pdf

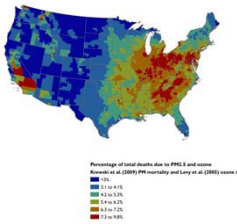
Assessing Education-Modified $PM_{2.5}$ Mortality Risk in the 2014 Cross-State Rule



*Analysis uses PM risk estimates that account for the increased level of baseline risk experienced by those populations with lower levels of educational attainment.

Burden Assessments: Estimating the Risk Attributable to Recent $PM_{2.5}$ and Ozone Levels

Percentage of O_3 and $PM_{2.5}$ related deaths due to 2005 air quality levels by county



Summary of National $PM_{2.5}$ & O_3 impacts due to 2005 air quality	
Excess mortalities (adults)[A]	130,000 to 340,000
Percentage of all deaths due to $PM_{2.5}$ and O_3[B]	6.1%
Impacts among Children	
ER visits for asthma (age <18)	110,000
Acute bronchitis (age 8-12)	200,000
Exacerbation of asthma (age 6-18)	2,500,000

Source: Fann N, Lamson A, Wesson K, Risley D, Anenberg SC, Hubbell BJ. Estimating the National Public Health Burden Associated with Exposure to Ambient $PM_{2.5}$ and Ozone. Risk Analysis; 2012a

[A] Range reflects use of alternate PM and ozone mortality estimates
[B] Population-weighted value using Krewski et al. (2009) PM mortality and Levy et al. Ozone mortality estimates

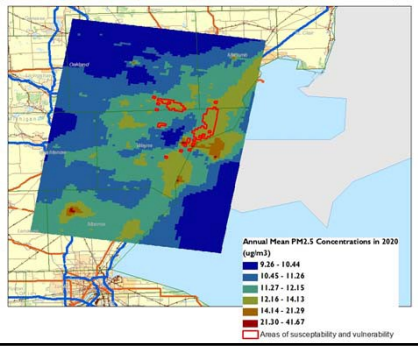
8

Identifying Populations Susceptible and Vulnerable to $PM_{2.5}$ Air Pollution in Detroit

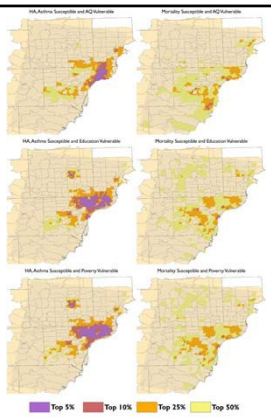
Populations susceptible to $PM_{2.5}$ impacts
Asthma hospital visits

Populations vulnerable to $PM_{2.5}$ impacts
Annual mean $PM_{2.5}$ air quality levels

Populations susceptible and vulnerable to $PM_{2.5}$ impacts



- Analysts can consider alternate variables to identify susceptible and vulnerability populations
  - Susceptibility:
    - Hospital Admissions
    - Mortality
  - Vulnerability
    - Annual mean $PM_{2.5}$ levels
    - Educational attainment
    - Poverty
- Irrespective of variables used, the multi-pollutant risk-based approach provides greatest reductions in $PM_{2.5}$ exposure



Source: Fann N, Roman HR, Fulcher C, Gentile M,Wesson K, Hubbell BJ, Levy JI. Maximizing Health Benefits and Minimizing Inequality: Incorporating Local Scale Data in the Design and Evaluation of Air Quality Policies, *Risk Analysis*, 2011; in press.

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Table II: Reduction in annual mean $PM_{2.5}$ exposure per-person, according to air quality scenario and approach to identifying vulnerable & susceptible populations ($\mu g/m^3$/person)[A]

	PM changes among vulnerable & susceptible populations		PM changes among rest of population		Ratio of PM changes among vulnerable & susceptible populations to PM changes among rest of population	
Approach to identifying vulnerable & susceptible populations	*Status-Quo*	*Multi-pollutant, risk-based*	*Status-Quo*	*Multi-pollutant, risk-based*	*Status-Quo*	*Multi-pollutant, risk-based*
Rate of asthma hospitalizations and level of baseline $PM_{2.5}$ exposure	0.3	1.04	0.28	0.48	1.1	2.2
Rate of asthma hospitalizations and educational attainment < grade 12	0.29	0.79	0.28	0.45	1	1.8
Rate of asthma hospitalizations and poverty rate	0.28	0.77	0.28	0.44	1	1.8
Mortality rate and level of baseline $PM_{2.5}$ exposure	0.29	0.96	0.28	0.53	1	1.8
Mortality rate and educational attainment < grade 12	0.26	0.85	0.28	0.53	0.9	1.6
Mortality rate and poverty rate	0.24	0.87	0.28	0.53	0.8	1.7

[A] Estimates rounded to two significant figures

Source: Fann N, Roman HR, Fulcher C, Gentile M,Wesson K, Hubbell BJ, Levy JI. Maximizing Health Benefits and Minimizing Inequality: Incorporating Local Scale Data in the Design and Evaluation of Air Quality Policies, *Risk Analysis*, 2012b.

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How Might we Better Account for Cumulative Risk?

- Using available data and tools:
  - Inform air quality management strategies with demographic, baseline health and baseline risk estimates
  - More broadly apply education-modified $PM_{2.5}$ mortality risk coefficients
  - Assess risk across a more comprehensive array of pollutants (NO_2, SO_2, Hg, Pb)
- Future assessments:
  - Account for temperature-pollutant and multi-pollutant interactions
  - Account for effect modification by other variables

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Prepared for U.S. Environmental Protection Agency Office of Air Quality Planning and Standards. Research Triangle Park, NC. Available on the Internet at <http://www.epa.gov/air/benmap>

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Levy JI, Greco SL, Spengler JD, The Importance of Population Susceptibility for Air Pollution Risk Assessment: A Case Study of Power Plants Near Washington, DC. Environmental Health Perspectives, 2002 110(12): 1253—1260.

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Lawrence Martin

The U.S. EPA Cumulative Risk Assessment Guidelines

Lawrence Martin, Risk Assessment Forum, Office of Science Advisor, EPA

The EPA Framework for Cumulative Risk Assessment (CRA) was published in 2003. In the intervening years, the EPA CRA Technical Panel has sponsored three workshops, a dozen white papers, and prepared an interim "lessons learned" document. Concurrently, the EPA's Office of Research and Development and the program offices have developed methods to advance discrete dimensions of CRA. The CRA Technical Panel expects to complete a draft of the CRA Guidelines for review in 2013. Writing teams are being assembled and are integrating the knowledge from across the agency and from the expert authored topical papers. This presentation will provide an overview of the draft outline for the CRA Guidelines, and highlight key issues defining the project. Topics include addressing vulnerable and susceptible populations, integrating chemical and non-chemical stressors, how to organize the boundaries of a CRA, integrating human health and ecological information, and how CRA can be used to inform sustainability analysis.

The US EPA Cumulative Risk Assessment Guidelines

Cumulative Risk Assessment An analysis, characterization, and possible quantification of the combined risks to health or the environment from multiple agents or stressors. (CRA Framework, 2003)

Lawrence Martin
EPA Office of Science Advisor
Risk Assessment Forum Staff

United States Environmental Protection Agency

Technical Panel on Cumulative Risk Assessment

CRA Panel Re-formed July 2010

Co-Chairs

- Gino Scarano OCSPP/OPPT
- Linda Teuschler ORD/NCEA

Sub-panels

Environmental Justice

Integrating Chemical and Non-Chemical Stressors

Current Practices and Lessons Learned

2

United States Environmental Protection Agency

Cumulative Risk Assessment Technical Panel

Assignments

- Prepare responses to the NRC recommendations in Science and Decisions, and in Phthalates and CRA for the Human Health Colloquium (October, 2010);
- Design and oversee the conduct of an environmental justice CRA project (CCAT);
- Complete work on a compendium of lessons learned and best practices; &
- Prepare guidelines for the conduct of CRA.

3

United States Environmental Protection Agency

CRA EPA Foundation Documents

- Framework for Cumulative Risk Assessment (2003)
- Concepts, Methods and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document (ORD/NCEA, 2007)
- CRA Lessons Learned – narrative built upon 7 White Papers and 12 case studies. (Est. July, 2012)
- White Papers (2012)
  - How much information is enough?
  - Use of CRA by Program Offices & Regions
  - Integrating Chemical and Non-Chemical Stressors
  - CRA Current Practices
  - Plannning, Scoping and Problem Formulation
  - Sustainability
  - Communication

4

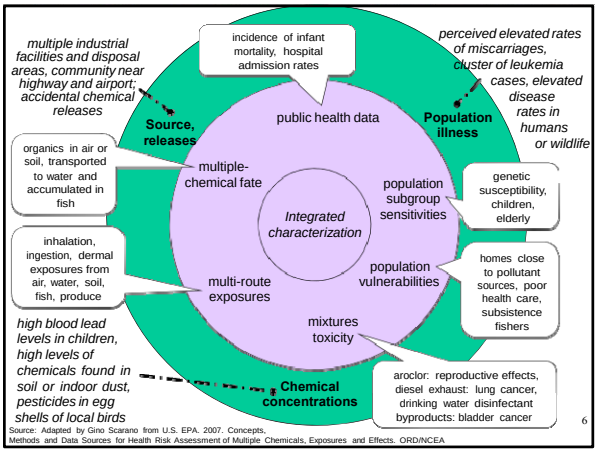
United States Environmental Protection Agency

Some Key CRA Concepts for the Guidelines

- Planning and scoping the assessment to constrain focus, analysis, and cost
- Combining Chemical and Non-Chemical stressors
- Integrating Human + Ecological Risk
- Informing Decisions about Sustainability
- Initiating Factors

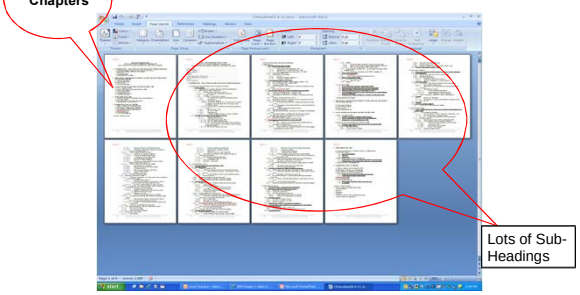
5

United States Environmental Protection Agency



6

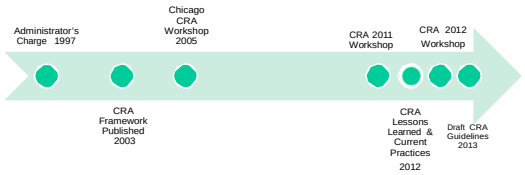
The Outline



The Five Chapters

- Ch. 1– Intro and Approach to Develop Guidelines
- Ch. 2 – Conceptual Principles of CRA Phases (2003 Framework)
  - Planning & Scoping, Problem Formulation, Risk Analysis, Risk Characterization
- Ch. 3 – Using the 2003 Framework and Moving Forward
- Ch. 4 – Risk Communication
- Ch. 5 – Resources/Data for CRA

CRA Technical Panel Timeline



Jonathan Levy

Intramural CRA Research at EPA and a View on How It Relates to CRA Grants

***Jonathan Levy*[1] *and Jane E. Clougherty*[2]**
[1]Professor, Boston University School of Public Health and STAR Grantee;
[2]Assistant Professor, University of Pittsburgh

In a white paper titled "Integrating Chemical and Non-Chemical Stressors in Cumulative Risk Assessment," we focused on strategies for inclusion of non-chemical stressors in human health cumulative risk assessment. We began by discussing the planning and scoping phase of the analysis, building on previously proposed frameworks to delineate the contexts in which non-chemical stressors should and should not be included in cumulative risk assessments, as well as strategies for their inclusion. We then considered the hazard identification step, as an initial qualitative determination of the stressors under consideration in the analysis. We discussed available databases and metrics that could allow for characterization of exposure to non-chemical stressors, considering theoretical ideal parameters as well as proxy measures or default assumptions that could be used in the absence of detailed population-specific data. For dose-response modeling, we presented strategies that could be used for either epidemiological or toxicological evidence, with a broad-based discussion regarding similarities and differences from the chemical mixtures problem. We briefly addressed risk characterization as a step that synthesizes evidence across outcomes from a stressor-based cumulative risk assessment, or appropriately contextualizes the findings from an effects-based cumulative risk assessment. We concluded by identifying significant data and methodological gaps that could be addressed by targeted research.

Integrating chemical and non-chemical stressors in cumulative risk assessment

JONATHAN LEVY, SC.D.
PROFESSOR OF ENVIRONMENTAL HEALTH
BOSTON UNIVERSITY SCHOOL OF PUBLIC HEALTH

PROGRESS REVIEW MEETING ON CUMULATIVE RISK GRANTS
MAY 14, 2012

Overview

- White paper prepared to support development of cumulative risk assessment guidelines
- Co-authors: Jane Clougherty, Peter deFur
- Coordinated by Scientific Consulting Group (Steve Gibb)
- Presented at Workshop on Integrating Non-Chemical and Chemical Stressors in Cumulative Risk Assessments (November 2011)

Background/framing

- Focus of white paper on dimensions that had not been extensively addressed previously
  - Incorporation of non-chemical stressors
  - Explicit consideration of exposure assessment step (for both chemical and non-chemical stressors)
  - More direct recognition of the role of epidemiology
  - Use of the Science and Decisions "Chapter 5" dose-response approach

Working definition

- Non-chemical stressor:
  - Any exposure in the physical or social environment that can impact human health through pathways other than those chemical media and pathways traditionally included in health risk assessment
  - Examples: Lack of health care, personal activities, natural phenomena, biological pathogens, psychosocial stress, noise, heat, income, ecosystem services, etc., etc., etc.

Planning and scoping

- White paper builds on foundation in 2003 EPA Framework, Menzie 2007, Science and Decisions
- Key steps
  - Build a conceptual model (effects-based vs. stressor-based vs. receptor-based/community-based)
  - Restrict the number of stressors under study using risk management framework (if relevant), formal hazard identification process, insight from screening assessment

Hazard identification

- Similar to standard risk assessment process with a few proposed refinements
  - Consider stressors that only act as exposure/dose/effect modifiers even in the absence of direct effects for the outcome of interest
    - Example: Piperonyl butoxide and pyrethroids
    - Example: Calcium and lead
  - Use effects-based vs. stressor-based orientation to narrow the hazard id process

Exposure assessment

- Four key dimensions discussed
  1. Using mode of action/common adverse outcomes to determine appropriate form of exposure assessment
  2. Using proxy variables for non-chemical stressors that cannot be directly ascertained
  3. Considering correlations among exposures for appropriate joint characterization
  4. Establishing default assumptions in the absence of population-specific data

Dose-response modeling

- Can chemical mixtures guidance be used?
  - Applicable in theory, though the lack of quantitative data for non-chemical stressors in some settings could be challenging
  - Phthalates report approach for chemical mixtures can be extended to non-chemical stressors if relevant dose metrics are available
    - "Sufficient similarity" might need a broad-based redefinition, potentially using common adverse outcomes rather than mode of action as an organizing principle

Using toxicology

- Many non-chemical stressors cannot be feasibly incorporated toxicologically, although animal models of stress are being utilized regularly
- Non-chemical stressors can inform the choice among Science and Decisions conceptual models, or can be captured in PBPK models to examine delivered doses or pharmacodynamic outcomes

Using epidemiology

- Sufficient epidemiology for a multi-stressor assessment will be rare
- When it exists, diagnostic questions include:
  - Are dose-response functions based on multivariate models, or can significant confounding be ruled out?
  - Has effect modification been examined?
  - Do the vulnerability attributes of the study population align with those of the cumulative risk assessment?
  - Is there a clear conceptual model that would inform the interpretation of sociodemographic variables as non-chemical stressors?

Combining toxicology and epidemiology

- Hybrid approach could be viable
  - Use limited epidemiology to determine appropriate conceptual model for toxicological data
  - Use toxicological studies to establish dose equivalence between a chemical and non-chemical stressor, to re-interpret epidemiology
    - Example: Toluene and alcohol
  - Combine evidence from both in special circumstances where adverse outcomes were comparable and vulnerability characteristics can be aligned

Risk characterization

- Cumulative risk assessment should not be equated with comparative risk assessment
- Descriptions should emphasize which stressors EPA does and does not have authority over, whether or not a risk management construct is used
- QALYs/DALYs/other weights can be used to integrate across health outcomes in a stressor-based assessment, but should be used with caution
- Qualitative information should be presented on comparable footing as quantitative findings

Recommendations

- Planning and scoping should be formalized with an expanded conceptual model development
- Common adverse outcome orientation would be appropriate to incorporate
- Need more primary research to elucidate mechanisms of action for non-chemical stressors
- Non-chemical stressor Exposure Factors Handbook would be warranted
- Case examples should be developed

Bradley D. Schultz

Intramural CRA Research at EPA and a View on How It Relates to CRA Grants

Bradley D. Schultz
National Exposure Research Laboratory, EPA

The EPA is working to advance cumulative risk assessment (CRA) through intramural and extramural research programs, ongoing development of CRA Guidelines, and other activities. The objectives are to improve health and well-being in the United States and reduce health disparities, using high-quality science and fostering economically informed decisions. The goal of this presentation is to describe intramural EPA research efforts and how they complement activities inside and outside EPA as well as the EPA CRA Guidelines under development. CRA in the new EPA research structure will be summarized, as well as a November 2011 workshop on integrating chemical and non-chemical stressors in CRA and plans for a follow-up autumn 2012 workshop. The presentation will assess some accomplishments to date as well as remaining scientific and implementation challenges.

Intramural CRA research at EPA and a view on how it relates to CRA grants

Brad Schultz

with contributions from Valerie Zartarian, Andrew Geller, & Shannon O'Shea
Office of Research and Development, National Exposure Research Laboratory

Progress Review Meeting on Cumulative Risk Grants | May 14, 2012 | Washington, DC

1

Outline

Summary of intramural EPA research

Sustainable & Healthy Communities research

- **Community Public Health tools & CRA**

Potential coordination of research

2

Common Challenge:

Decision-makers need information, but...

- CRA science has many gaps
- CRA implementation is difficult
- Some communities have limited resources
  - o limited access to info. as well as disproportionate impacts

EPA-funded research is intended to...

- Fill information gaps
- Improve communities' access to CRA science
- Be coordinated

3

EPA Research Programs

Program Office → / Research program ↓	Air & Radiation	Water	Solid Waste and Emergency Response	Pesticides/ Pollution Prevention & Toxics	Other offices (OEJ, OCHP, etc.)
Air, Climate & Energy	*				*
Safe & Sustainable Waters		*			*
Chemical Safety for Sustainability				*	*
Sustainable & Healthy Communities	*	*	*	*	*
Human Health Risk Assessment	*	*	*	*	*
Homeland Security			*		*

Some primary linkages are shown above, although there are considerable cross-linkages

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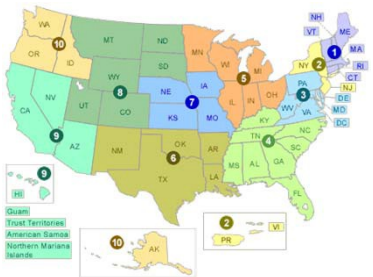
EPA Regional offices also support community work



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Sustainable & Healthy Communities (SHC) research

CRA stressor-based approaches

- Housing and infrastructure
- Transportation
- Land use
- Waste and materials
- Ecosystem services, etc.

CRA effects-based approaches

- Community Public Health component of SHC
- Many linkages

6

Community Public Health

- **Asthma health effect research**
  - environmental factors
  - clinical, epi, exposure, etc.
- **CRA science**
  - exposure, effects, combining non-chemical stressors
  - animal studies, clinical, epi
- **Community Public Health Tools**
  - Community-FERST, Tribal-FERST
- **Health Impact Assessments** (EPA-related part)
- **Community case studies**

7

Needs & External Drivers

- **Science & Decisions: Advancing Risk Assessment (2009)**

  "EPA should focus on development of guidelines and methods for simplified analytic tools that could allow screening-level cumulative risk assessment and could provide tools for communities and other stakeholders to use in conducting assessments." *(pp. 10, 236)*

- **NAPA, NEJAC reports**
- **EPA Administrator priorities**
- **EPA Sustainable & Healthy Communities research program**

8

Community Public Health Tools

Community-**F**ocused **E**xposure and **R**isk **S**creening **T**ool (C-FERST)/Tribal-FERST

- GIS and Web-based community assessment support tool
- Support CRA and decision-making
- User-driven or following community guidance

For more information visit: http://www.epa.gov/heasd/c-ferst

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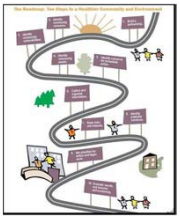
Community Guidance

- **CARE Roadmap →**
- **PACE-EH**
- **EJ Toolkit**
- **HIA roadmap**



- **Community-Cumulative Assessment Tool**

10

Self-directed use of C-FERST

- **Alphabetical listing of issues**
  - o including individual chemicals
  - o to meet current user needs
- **Stressor option**
- **Health effects option**

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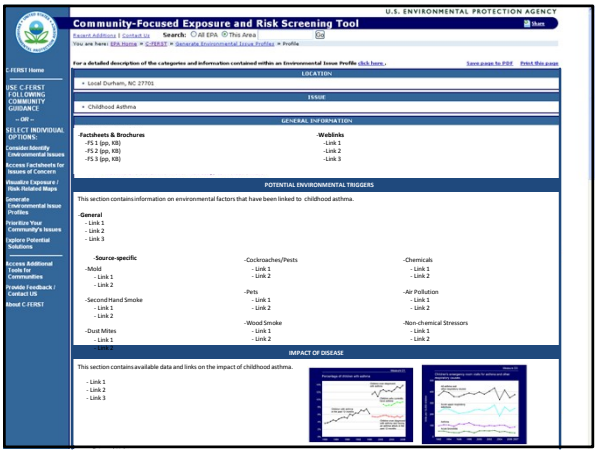

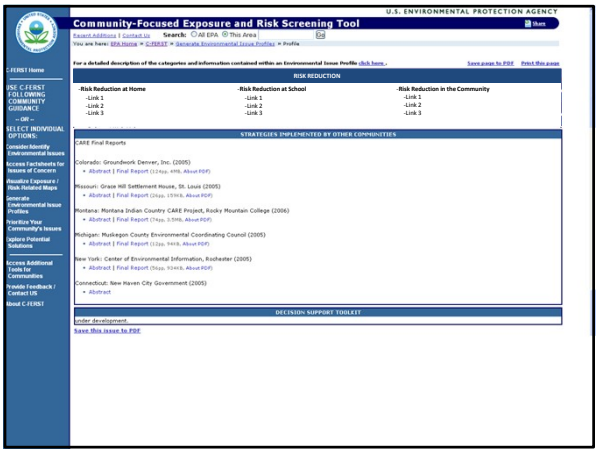

Community Data Table (Summary)

Data Metrics	Your Community: ZIP Code 27704	Durham County, NC	North Carolina	National Average	Data Info/Notes*
Environmental Concentration Estimates (µg/m³)					
Outdoor Air - Acetaldehyde	2.3	2.3	2.2	1.9	NATA 2005
...others collapsed as a default...					
Human Exposure Estimates (mg/day or µg/m³ avg)					
Outdoor Air - Acetaldehyde (µg/m³ annual avg)	1.8	1.8	1.7	1.5	NATA 2005
Aggregate Childhood Lead (GM µg/dL in blood)	TBD	TBD	TBD	Available	
...others collapsed as a default...					
Health Risk Estimates (in One Million)					
Cumulative Air Toxics Cancer Risk	40.4	42.9	39.4	49.8	NATA 2005
Cumulative Air Toxics Non-Cancer Respiratory Risk†	1.2	1.4	1.2	2.3	NATA 2005
Cumulative Air Toxics Non-Cancer Neurological Risk†	0.03	0.04	0.04	0.06	NATA 2005
Outdoor Air - Acetaldehyde **	3.9	4	3.7	3.3	NATA 2005
Outdoor Air - Arsenic	0.8	0.9	0.8	1.3	NATA 2005
Outdoor Air - Benzene	3.9	4.8	4.6	7.4	NATA 2005
Outdoor Air - Butadiene **	1.1	1.3	1	1.9	NATA 2005
Outdoor Air - Chromium **	0.6	0.7	0.7	1.4	NATA 2005
Outdoor Air – Formaldehyde **	22.9	23.7	21.5	22.5	NATA 2005
Outdoor Air - Naphthalene **	0.6	0.7	0.6	2.3	NATA 2005
Outdoor Air - PAH **	0.6	0.7	0.8	1.5	NATA 2005
Indoor radon excess lung cancer mortality	N/A	N/A	N/A	Avail (PI)	NRRRA
Excess hospitalizations due to PM2.5	N/A	Available	Available	Available	BenMAP
Excess mortality due to PM2.5	N/A	Available	Available	available	BenMAP
Excess mortality due to ozone	N/A	Available	Available	available	BenMAP

† These values are expressed as a Hazard Quotient.
***see clarifying metadata for approach description*

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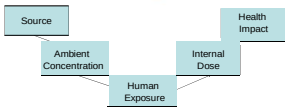
Source-outcome Paradigm & Implied Indicators



- **Ambient concentrations**
- **Human exposure estimates**
- **Biomarker estimates**
- **Risks/Health outcomes**
  - **Cancer, asthma, early neurotoxicity effects, etc.**

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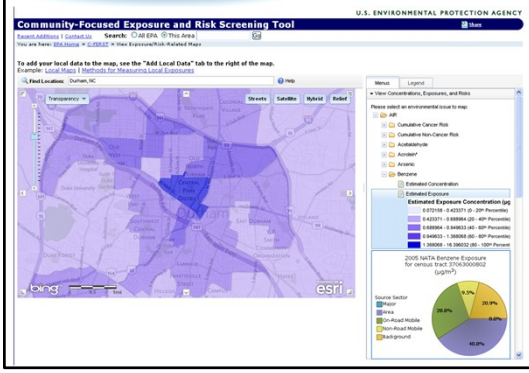

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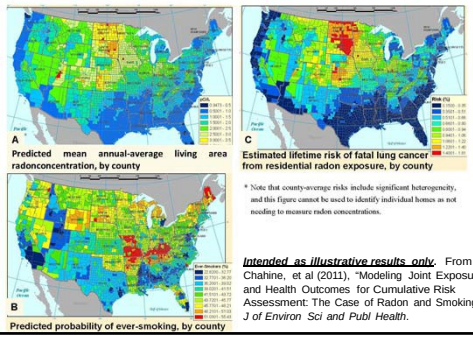
Radon and Smoking CRA Example



* Note that county-average risks include significant heterogeneity, and this figure cannot be used to identify individual homes as not needing to measure radon concentrations.

Intended as illustrative results only. From Chahine, et al (2011), "Modeling Joint Exposures and Health Outcomes for Cumulative Risk Assessment: The Case of Radon and Smoking" *Int J of Environ Sci and Publ Health*.

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C-FERST provides

Web-based means for using roadmaps

Structure for stressor & effects-based RA

- Geographically-specific screening-level estimates (a default)
- Can peer review components in advance
- Gives credibility to risk assessment when risk management options are discussed
- Facilitates stakeholder involvement
- Web-based tool allows linkage to risk management options

Much work remains

- But structure for consistency in research

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Conclusions

- ***Need for CRA science & implementation***
- ***EPA addressing guidelines & screening-level approaches recommendations in S&D***
- ***CPH tools (C-FERST) provide a structure and platform to implement these goals***
- ***CRA grants results eagerly awaited***
- ***Great potential for coordination & collaboration*** (in multiple areas)

Thank you!

Questions?

Theme 2

Data Analysis Methods for Combining Stressors

Deborah A. Cory-Slechta

Issues Related to Backward and Forward Translation of Toxicological and Epidemiological Studies of Cumulative Risk Assessment

Deborah A. Cory-Slechta
Professor, Department of Environmental Medicine, University of Rochester School of Medicine

Toxicological studies have the potential to assist in hypotheses and experimental designs of related epidemiological studies, and epidemiological study outcomes can provide information critical to further refinement of animal models. However, several issues currently attenuate the extent to which toxicological and epidemiological studies can inform and advance each other. In the case of "stress" as a component of cumulative risk, there is the acute need to recognize in both toxicological and epidemiological studies that stress can have both positive and negative consequences, leading, for example, to either resilience or further behavioral pathology. Although grounded in the scientific literature that includes underlying mechanisms and pathways, it would be extremely useful for toxicological studies to develop stress protocols that better simulate human and environmental conditions. Both toxicological and epidemiological studies can benefit from better methods for evaluating interaction effects, a particular problem when human sample sizes are limited. Finally, based on toxicological study outcomes, separation of effects by gender in human studies is critical.

Issues Related to Backward and Forward Translation of Toxicological and Epidemiological Studies of Cumulative Risk Assessment

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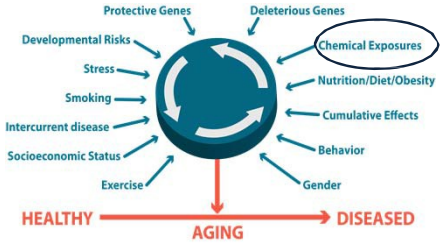
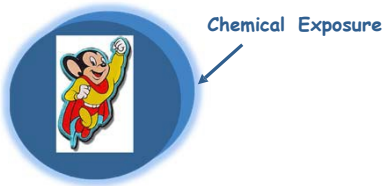
Most Complex Diseases and Disorders Arise from Interactions of Multiple Risk Factors



Risk Factors that are Unique to Each Individual

In Contrast, Most Neurotoxicology Models Study Toxicants as Risk Factors in Isolation



Study of one chemical in isolation in a healthy young organism, maybe examining e.g., gender

There is a critical need to develop animal models and design epidemiological studies that better simulate human conditions and to include interactions of risk factors

EPA and Cumulative Risk Assessment

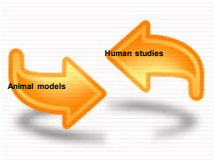
- EPA guidance on cumulative risk assessment began as early as 1994
- As we all know, the STAR program has begun to support such initiatives:
  - EPA-G2009-STAR-E1: Developing Statistical and Other Analytical Techniques for Cumulative Risk Assessments
  - EPA-G2009-STAR-E2: Evaluating the Interaction of Nonchemical and Chemical Stressors

The Risk Assessment Paradigm

- Relies heavily on data from animal models where human data is not available
  - Establishment of LOAELs or NOAELs and setting benchmark doses
  - Use of 'uncertainty (safety) factors' to accommodate differences between humans and animal models.
- Is best served when corresponding data are available from human studies and animal models
  - This possibility can be significantly enhanced by the scientific translation of findings from toxicological studies into human studies, and from human studies to the further refinement of animal models.

Research Translation: It Works Both Ways

- The word translation has been narrowly used to suggest the import of findings from animal models to humans (bench to bedside).
  - However, human study designs can benefit from findings in animal models including mechanistic insights
  - Similarly, animal models can be further refined by incorporating outcomes from human studies



Stress as a Component of Cumulative Risk

- Issues that complicate integration of epidemiological and toxicological studies
  - Different consequences of different stress
    - Resilience vs. psychopathology
  - How well do animal stress protocols simulate human stress?
  - The critical role of gender differences
  - Statistical limitations of evaluating interactions
    - The constant limitation of sample sizes

Not All Stress is Detrimental: Resilience vs. Vulnerability

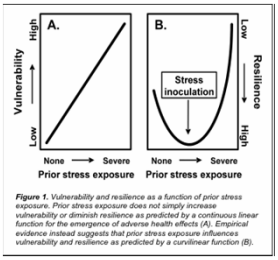
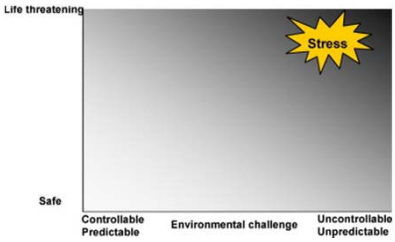


Figure 1. Vulnerability and resilience as a function of prior stress exposure. Prior stress exposure does not simply increase vulnerability or diminish resilience as predicted by a continuous linear function for the emergence of adverse health effects (A). Empirical evidence instead suggests that prior stress exposure influences vulnerability and resilience as predicted by a curvilinear function (B).

Stress has always been difficult to define. It has also become increasingly clear that the consequences of stress exposure are dependent upon the conditions of the stressor and can have either beneficial or adverse consequences.

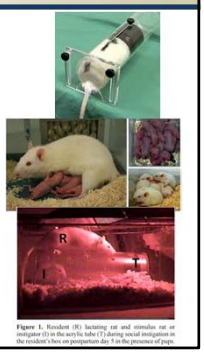
Not All Stress is Detrimental: Resilience vs. Vulnerability



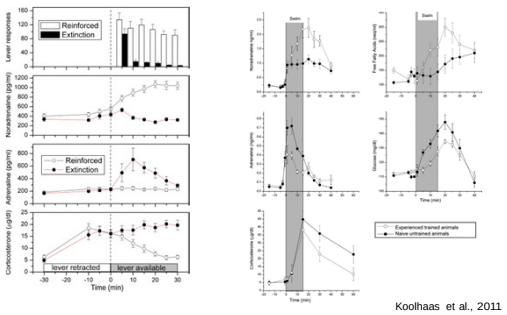
Schematic illustrating the proposed restriction of the term 'stress' to stimuli that are perceived as uncontrollable, unpredictable and life threatening, whereas those events that are 'controllable and predictable' tend to lead to resiliency phenotypes

Stress Protocols for Animal Models: How Well do they Simulate Human Stress?

- Most Common:
  - Immobilization (restraint) stress
  - Maternal separation
  - Intruder stress
- Other Approaches:
  - Chronic homotypical stress
  - Chronic variable stress



Corticosterone Normalization and Increased Noradrenaline Define 'Stress'

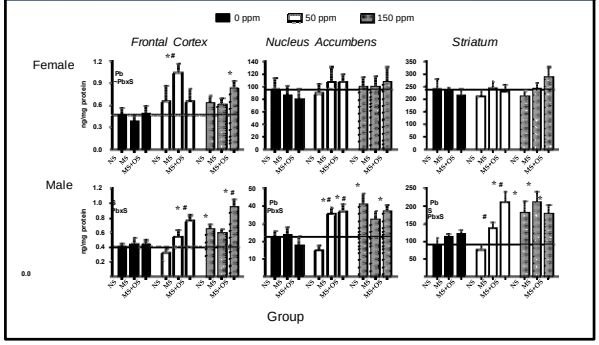


Koolhaas et al., 2011

Limitations of Evaluating Statistical Interactions

- An important source of our understanding of which non-chemical stressors may influence the toxicity of an environmental chemical comes through assessment of interactions
  - Since assessment of interactions in human studies typically requires large sample sizes that are not feasible, new biostatistical approaches for evaluating interactions that do no depend upon very large sample sizes are critically needed.
  - Both human and animal studies can employ an approach of assessing potential interactions based on factors such as co-occurrence of the factor with the environmental chemical exposure and the extent to which they share biological targets.

Gender: An Example of Why Interaction Effects are Critical



Innovative Approaches to Qualitative Data Analysis

Madeleine Kangsen Scammell
Assistant Professor, Boston University School of Public Health

No abstract provided.

ChelseaSTAR
SCIENCE TO ACHIEVE RESULTS

Innovative Approaches to
Qualitative Data Analysis

Madeleine Kangsen Scammell, D.Sc.
David Ozonoff, MD, MPH

BU
Boston University School of Public Health
Department of Environmental Health

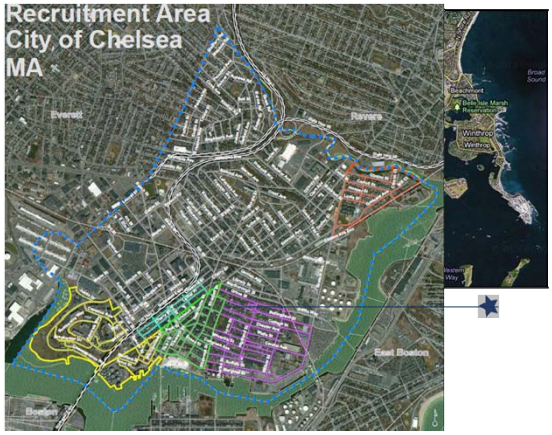
Chelsea Collaborative
Empowering people, building our community.

Objectives

1) introduce study location and data collection methods, with a brief example of the type of data we want to understand
2) convince you that working within a framework that introduces a distinction between qualitative and quantitative data is not helpful
3) provide an even briefer example of the analysis of our data using "standard" methods
4) introduce our "innovative" analytic methods

And probably…

5) conclude with many questions left unanswered



77. I have asked about the environment, odors, noises and access to the water. Do you have any environmental concerns, problems, or things you have thought about that you would like to mention before we move to the next set of questions?

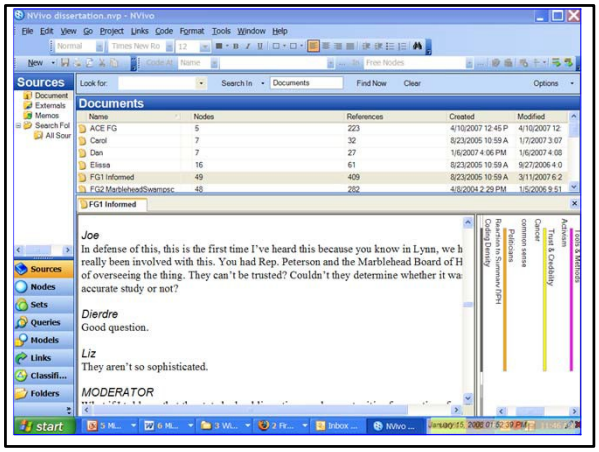
Natural gas boats that come in. LNG tanker. If you listen to all the experts, they tell you nothing bad will happen, but that's all lies. Some people say if one of those goes, there won't be Admirals Hill. Also the airport and airplanes contribute to pollution. New windows from MassPort let in draft. (ID 100)

I think it's not great that the LNG tankers are this close to the city. I think it's crazy. It doesn't seem to be a safe thing. (ID 101)

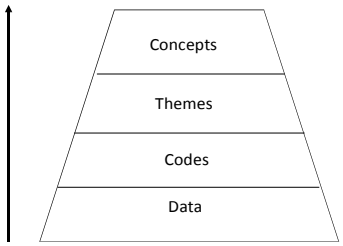
I think about the salt pile and the poor people who live close to it. I think about the oil tanks and the possibility of explosion. I think about an airplane losing power and crashing into my house. (ID 132)

No big concerns but I'm grateful that the FBI will be in Chelsea. (ID 163) No comment. (ID 501)

Here there are too many people in Chelsea who smoke, and this smoke does more damage to those who don't smoke than to those who do. (ID 505)



Qualitative Data Analysis: codes ⟶ concepts

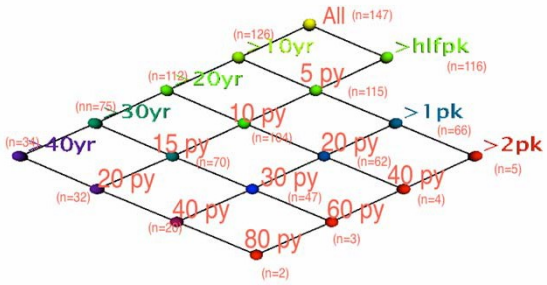


quantitative v. qualitative research

- Quantitative: numeric data, usually measurements that are standard and generalizable
- Qualitative: non-numeric data that "increases depth of understanding" and provides insight into thoughts, feelings, opinions, motives

Michael Quinn Patton (2002) Qualitative Research & Evaluation Methods 3rd edition Sage.

Lattice



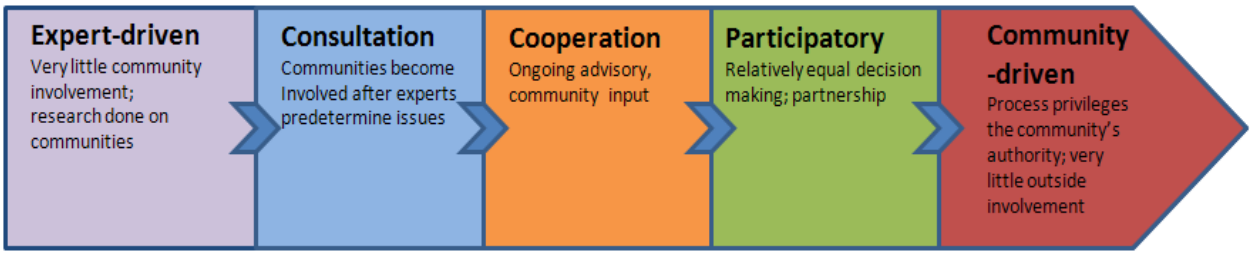
Theme 3

CPBR; Community Partnerships

All of the cumulative risk grantee projects were required to provide a community-based participatory research (CBPR) plan, which outlined the level of community involvement in the development of and the execution of the projects. Community participation enables the identification of variables that might otherwise be missed, and their involvement is critical to obtaining community knowledge and understanding complex cumulative exposures. The research projects also had to be cognizant of how engaging in the research project would be able to enhance the capacity of the community and to provide resources for their participation. Community participation is a crucial component of the cumulative risk research program.

During the progress review meeting, a separate session was held to allow the grantees time to reflect and discuss community involvement as it pertains to their project. A community engagement exercise was developed and presented. A community engagement spectrum was shared as depicted below. At the far left, "Expert-Driven" research projects incorporate community as participants primarily with very little control or influence over the project. "Consultation" involves the community after the research issues have been determined. "Cooperation" is where communities are engaged in an advisory role, but they have no authority to make decisions. "Participatory" describes equally shared decision-making power over the project. This is seen as the ideal CBPR partnership. "Community-Driven" is the complete opposite of "Expert-Driven" in that "Community-Driven" privileges the community's authority over that of academic partners with very little outside involvement. Grantees, both academic and community partners if both were present, were asked to decide amongst themselves where they fell along this continuum. Signs were posted along a wall of the different boxes. Each grantee team was asked to stand along the wall next to or between signs that best defined where their project fell within this continuum.

Figure 1: Spectrum of Community Engagement in Research



Most of the grantee teams were clumped together around "Cooperation" and "Participatory." Very few groups were standing along "Consultation" or at either ends of the spectrum. In the discussion, most everyone voiced agreement that future RFAs and review processes should allow for flexibility in the community involvement requirements. Definitions and attributes of community partnerships should be less prescriptive and allow for variations in the manifestations of partnerships, acknowledging that not all productive partnerships may fall within a rigid conceptualization. Additionally, the grantees commented that not all communities and academic partners are at the same level for establishing partnerships at the beginning of a grant. They urged NCER to support and adopt funding models that would allow for partnerships to develop and communities to organize around topics of interest either through an elongated grant cycle or multiple grant phases.

Theme 4

Grants Management

No abstracts or presentations were provided for this theme session.

U.S. EPA Progress Review Meeting on Cumulative Risk Grants

May 14, 2012

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