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MULTIDISCIPLINARY RESEARCH: STRATEGIES FOR ASSESSING CHEMICAL MIXTURES TO REDUCE RISK OF EXPOSURE AND DISEASE

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Abstract. The Precautionary Principle is founded on the use of comprehensive, coordinated research to protect human health in the face of uncertain risks. Research directed at key data gaps may significantly reduce the uncertainty underlying the complexities of assessing risk to mixtures. The National Institute of Environmental Health Sciences (NIEHS) has taken a leadership role in building the scientific infrastructure to address these uncertainties. The challenge is to incorporate the objectives as defined by the Precautionary Principle with the knowledge gained in understanding the multifactorial nature of gene-environment interactions. Through efforts such as the National Center for Toxicogenomics, the National Toxicology Program, and the Superfund Basic Research Program, NIEHS is translating research findings into public health prevention strategies using a 3-pronged approach: 1) identify/evaluate key deviations from additivity for mixtures; 2) develop/apply/link advanced technologies and bioinformatics to quantitative tools for an integrated science-based approach to chemical mixtures; 3) translate/disseminate these technologies into useable, practical means to reduce exposure and the risk of disease. Preventing adverse health effects from environmental exposures requires translation of research findings to affected communities and must include a high level of public involvement. Integrating these approaches are necessary to advance understanding of the health relevance of exposure to mixtures.

Key words:
Multidisciplinary, Chemical mixtures, Precautionary Principle

INTRODUCTION

The key to protection is prevention. This concept lies at the heart of both the Precautionary Principle and public health primary prevention strategy. Scientists, public health officials, and policy makers face an enormous challenge as they work to minimize the impacts of human exposure to mixtures of environmental contaminants. Our ability to prevent disease resulting from exposure to chemical mixtures is constrained by both our limited ability to study and quantify how chemicals in a mixture interact with one another and with biological systems, and by our incomplete understanding of the complexities of human physiology. In the face of such uncertainty, the Precautionary Principle dictates that we take steps to reduce further environmental contamination and to prevent human exposure to chemical contaminant mixtures already in our environment. The Precautionary Principle can serve as a valuable tool in decision-making processes, particularly in situations where there is incomplete information, as it supports the concept that implementation of appropriate primary prevention strategies should not be delayed by uncertainty.

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Development of strategies to reduce environmental degradation and human exposure to environmental contaminants must rely on new technologies and a much broader foundation than the traditional community of environmental scientists. It is critical that communication be improved not only among researchers, but scientists must also reach beyond academic audiences to new sectors including community members, public health and environmental policy makers, industry representatives, engineers, urban and rural planners, architects, and others who create our built environments and who establish the policies that govern them.

A BROADER APPROACH

Our approach to reduction of human health impacts of environmental contamination containing chemical mixtures must be both multidisciplinary and multiorganizational [1]. Research provides the key framework, but it is critical that the knowledge is appropriately communicated to the many sectors that can apply these findings to create healthier environments and promote healthier lives. Comprehensive, synchronized research should be designed with the ultimate goals of generating new scientific knowledge and of translating that knowledge into clinical applications and intervention strategies that will reduce the incidence of environmentally related diseases. Researchers must devise strategies to create multi-directional pathways of communication between the research community and end-users [2]. As shown in Fig. 1, impacted communities and the public at large should be involved in the design and implementation of prevention-oriented research strategies. Not only will researchers need to change their approaches to the design and implementation of their work, but also funding agencies must provide the infrastructure to support researchers in their efforts to transfer and communicate research findings.

As research tools advance, it is increasingly important that community-based research expand and evolve at the same rate [3]. Community-based research, by definition, implies that communities participate in the process of shaping research agendas and approaches. Communities bring to the table a wealth of practical knowledge and expertise. They recognize important community, cultural, and social issues that impact how research advances are accepted. In return, through their participation, they gain a better understanding of health effects of risks of exposure, the complexity and limitations of the science and the research process. These factors improve the relevance of the research and increase the acceptance of research outcomes.

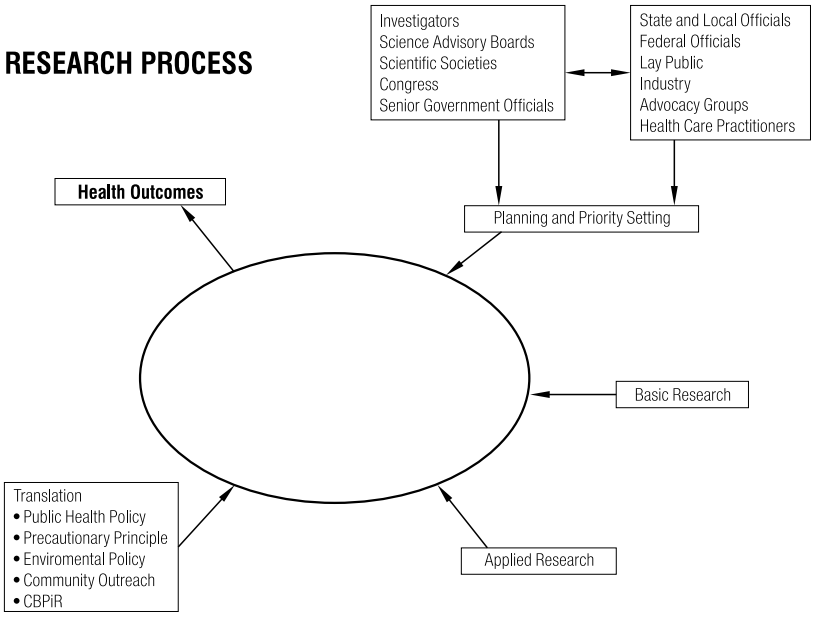

Fig. 1. Model for the design and implementation of prevention-oriented research strategies.

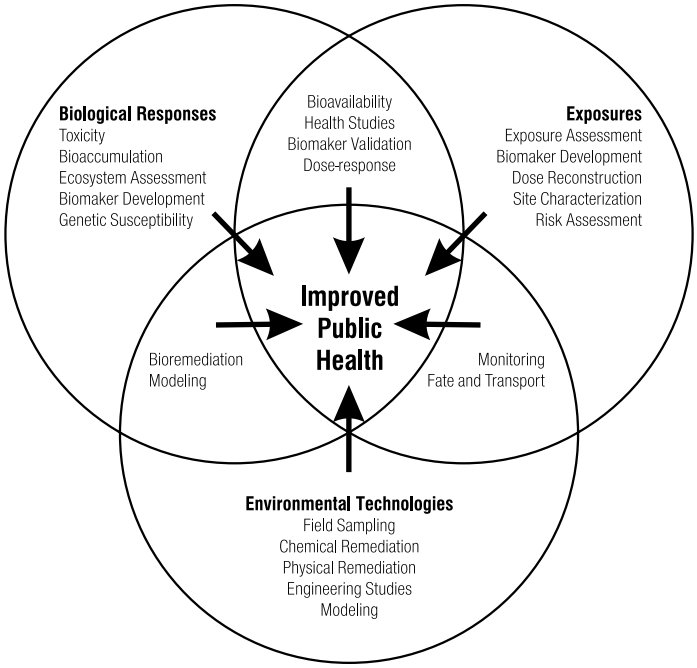

Fig. 2. Spectrum of disciplines needed to participate in research for improving public health.

For research on chemical mixtures to be truly successful, we must interpret the findings and then transfer the knowledge to the appropriate end users:

- to enable environmental policy makers and public health officials develop and implement policies to protect human health;
- to stimulate the development and application of new technologies to prevent or reduce further environmental contamination, to prevent or reduce human exposure to environmental contaminants, and to advance the study of human exposures and disease;
- to assist health care practitioners to incorporate the findings into practice; and to educate the public so individuals can take appropriate action to protect the health of their families and their communities.

Researchers should provide all stakeholders the information they need in a form they can use and actively engage stakeholders to apply the information and to help generate the next set of research questions. Innovative, cutting-edge research must serve as a foundation to foster creative solutions that result in the development and implementation of regulatory, public health, and community education strategies to protect vulnerable populations.

The research required to provide a foundation for the development of public health and environmental policies to limit or prevent human exposure to chemical mixtures will require a broad, multidisciplinary approach that goes beyond the traditional boundaries between academic disciplines [4]. As shown in Fig. 2, in order to gain a more comprehensive understanding of the complex scientific and policy issues, as well as to develop and apply to broadest possible range of research tools, it will be critical to synthesize information and approaches from wide ranging disciplines [5]. Collaboration among a diverse community of peers will bring to light questions, factors, and perspectives that might not be considered by researchers focused on a single discipline. Scientific developments are increasingly dependent on cross fertilization from different disciplines which enable researchers to work at the edge of their field and to be exposed to different perspectives and approaches for conducting research. Interaction among scientists from different disciplines creates opportunities and challenges scientists to think differently about the way they conduct studies and communicate results.

Multidisciplinary research strategies are not easy to implement as many government, industry, and academic pro-

grams tend to foster and reward narrower approaches to problem solving. The National Institute of Environmental Health Sciences (NIEHS) Superfund Basic Research Program (SBRP) serves as a model of a successful program where biomedical researchers cooperate and collaborate with ecologists, engineers, mathematicians, etc., resulting in creative synergisms and novel approaches to address the complex problems at Superfund sites in the United States. For example, the SBRP currently funds approximately 40 different research projects addressing the issue of arsenic contamination of drinking water. Since the early 1990s SBRP researchers have participated in multidisciplinary investigations incorporating basic molecular studies, epidemiology, fate and transport, and methods for remediation of arsenic in soils and groundwater. SBRP researchers are contributing seminal data necessary for improved risk assessments and environmental and public health policy. They have focused not only on the research, but have shown commitment to the critical component of translation of research findings to stakeholders. SBRP researchers are deeply involved in the development and support of the New Hampshire Consortium on Arsenic. This Consortium brings together university scientists and the New Hampshire Departments of Environmental Services and Health and Human Services and the US Geological Survey. Formation of this group has led to increased communication among the agencies and has resulted in the design and undertaking of inter-agency projects to collect data to support risk assessments. The New Hampshire Consortium on Arsenic has successfully raised the level of awareness of the issue of arsenic in drinking water, resulting in greater testing of private wells by the public and enhanced awareness of potential health impact.

Multidisciplinary research also played an important role in precautionary strategies regarding polychlorinated biphenyl (PCB) contamination in the Hudson River region. Between the mid 1940s and mid 1970s, approximately 1.3 million pounds of PCBs were released into the Hudson River. In 1995, based on numerous studies that linked PCBs with skin irritation, chloracne, injury to cellular tissue, and serious liver injury, the New York State Department of Health issued advisories that most Hudson River fish were unsafe for human consumption because of PCB contamination [6]. Two years later, the US Environmental Protection Agency (EPA) banned PCB production under the Toxic Substances Control Act and made it illegal to discharge any PCBs into navigable waters under the Clean Water Act [7]. Continuing primary prevention strategies, public health agencies issued additional fish advisories with particular emphasis on women of childbearing age, before the weight of scientific evidence mandated that such actions were critical to prevent exposure to children *in utero* and from breast milk. Advisories against eating any fish from specific areas of the Hudson River are currently in effect for infants, children under the age of fifteen and women of childbearing age [8].

THE PRECAUTIONARY PRINCIPLE, CHEMICAL MIXTURES, AND THE DATA GAPS

Potential for environmental or occupational exposure to chemical mixtures presents a major public health threat. More than 80 000 chemicals are registered for use in commerce in the United States, and an estimated 2000 new ones are introduced annually for use in everyday items such as foods, personal care products, prescription drugs, household cleaners, and lawn care products [9]. Ten percent of these chemicals are recognized as carcinogens and most have not been adequately tested for toxicity [10]. Mixtures of chemical contaminants are ubiquitous in ground and surface water, in our air, food, and drinking water, as well as in soil surrounding leaking toxic waste disposal sites. Examples of environmentally prevalent chemical mixtures are cigarette smoke, diesel and automobile exhaust, disinfection by-products from chlorination, and dioxin and dioxin-like compounds formed as by-products of incomplete combustion of municipal and medical waste [11]. Most human organ systems are vulnerable to exposure to one or more substances commonly found in our environment – and there are extensive interactions among many of the various organ systems, such that alteration of one may influence the function of others. Some of the major broad categories of human diseases suspected to result from exposure

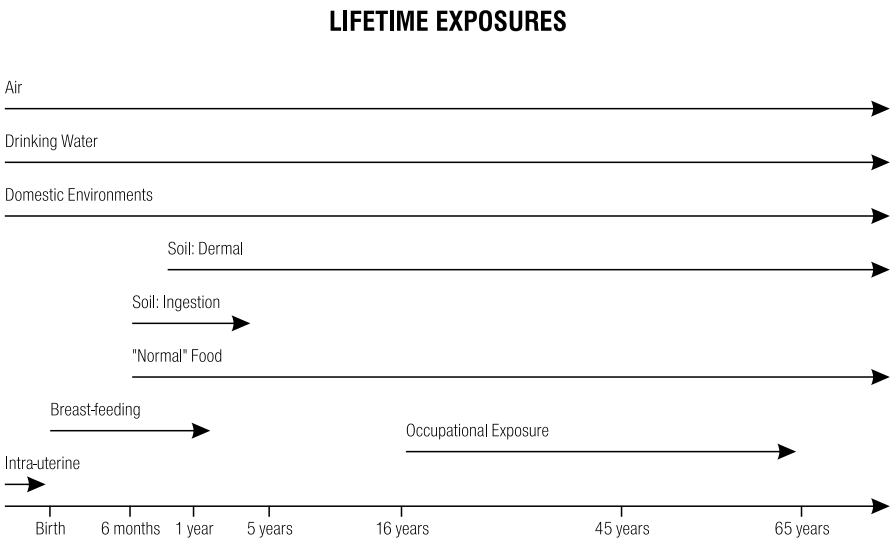

Fig. 3. Illustration of potential human exposures to environmental contaminants.

to environmental contaminants include cancer, birth defects, immune system defects, reduced intelligence quotient (IQ), behavioral abnormalities, decreased fertility, altered sex hormone balance, altered metabolism, and specific organ dysfunctions [12].

Historically, research on the effects of chemicals on human health has been conducted one chemical at a time – often limited to consideration of the impact of a single exposure at a specific point in development. As shown in Fig. 3, the reality of the public health threat arising from potential exposures to chemical contaminants in the environment is that individuals may be exposed, either concurrently or sequentially, to a large number of chemical agents throughout their lifetime.

In a biologic system, chemicals can interact in a number of different levels, through absorption, metabolism, distribution, and at the site of action [11]. Components of a mixture can also interact in several ways, complicating the toxicologic evaluation of mixtures [13].

Two or more compounds may have:

- no interactions;
- additive effects as a result of acting at the same site, altering the same process by different mechanisms, or as a result of one compound altering the metabolism of the second in such a way as to generate a toxic metabolite;
- antagonistic effects reducing the toxicity of one or more components of the mixture;
- this may occur if one component activates a receptor or enzyme and another binds without activating or binds with a slow dissociation constant;
- synergistic effects in which exposure to a mixture results in much greater response than the sum of results of exposure to the individual components; this positive interaction may be the result of multiple agents enhancing the toxicity of each other (cosynergism), one agent with no toxicity itself acting to increase the toxicity of another component of the mixture (potentiation); or multiple agents with no known toxic effects interacting to cause a toxic effect (coalitive) [14].

Many chemicals have multiple sites of action and their toxic effects may be mediated by totally different mechanisms at different sites. Interactions among the components of a mixture may occur at some but not all sites. From a public health perspective, our inability to predict whether agents act in additive, synergistic, or antagonistic ways at concentrations encountered in the environment creates real problems for health risk assessment and management.

Several factors contribute additional uncertainty into our understanding of the toxic effects of environmental or occupational exposure to chemical mixtures [13]. First, many of the effects of exposure are subtle and difficult to quantify. Second, many environmental contaminants are changed to metabolites or conjugates in the body, and these new products may also have biologic activity

that may or may not be similar to the parent compound. Thus, even a single compound may become a functional mixture. Third, a single environmental contaminant may lead to different effects when exposure occurs at different ages. Researchers need to design studies that will evaluate long-term, delayed and potential transgenerational health effects resulting from environmental or occupational exposures. Fourth, as Carpenter et al. [15] points out in his recent review, humans may be exposed to a nearly infinite number of combinations of contaminants, and we do not know what dose ranges or which biologic endpoints should be studied.

The majority of diseases are the consequence of both environmental exposures and genetic factors [16]. Individual susceptibility to environmentally-induced disease is another source of uncertainty in research and public health efforts to address environmental and occupational exposure to chemical mixtures. A better understanding of genetic influences on environmental response could lead to more accurate estimates of disease risks and provide a basis for disease prevention and early intervention programs directed at individuals and populations at increased risk [17]. Identifying functionally significant polymorphisms also could shed light on disease pathways and suggest targets for therapeutic intervention [18]. To understand the relationship between exposure and adverse health effects, scientists are working to develop biomarkers – key molecular or cellular events that link a specific environmental exposure to a health outcome [19]. Molecular biomarkers may play a central role in addressing the relationships between exposure to toxic environmental chemicals and development of chronic human diseases and in identifying those individuals at high risk for disease. The challenge is to use biomarkers to establish associations between exposure and human disease in epidemiological studies and then to use the knowledge to design and conduct appropriate preventative interventions in high-risk individuals or populations.

Researchers, environmental policy makers, and public health officials are faced with the challenge to design and implement strategies to reduce human disease and dysfunction resulting from exposure to chemical mixtures. Classical scientific approaches, though functioning well for assessments of the impact of single chemicals on the functioning of a biologic system, may be inadequate to address aggregate and cumulative exposures to multiple chemicals in living systems. Multidisciplinary programs that emphasize the critical nature of translation of research results, such as the SBRP, provide a valuable model for research frameworks that hold as their primary objective expansion of the base of scientific knowledge necessary to make informed decisions based on biological relevancy; reduce the amount and toxicity of hazardous substances; and, ultimately, prevent adverse human and ecological health effects.

Research is needed to reduce the uncertainties that exist with respect to interactions among the components of a chemical mixture and gene-environment interactions. Scientists must determine optimal research designs to address issues of dose ranges, age and duration of exposures, and biologic endpoints. In the meantime, the Precautionary Principle states that strategies and policies must be formulated on the basis of the best currently available scientific information, while erring on the side of caution.

THE PROMISE OF ADVANCED TECHNOLOGIES

The issues of interactions among the components in a mixture and gene-environment interactions may be difficult to study, but should be seen as a challenge to develop more complex and sensitive methods – not as a limit to scientific progress. To address the complexities and uncertainties surrounding human exposures to mixtures of chemical contaminants, it will be necessary to fully utilize and integrate cellular and molecular biology methodologies, mechanistically based short-term toxicology studies, computational technology, and mathematical and statistical modeling [20].

Considering there are more than 80 000 chemicals in commerce, the task of testing these chemicals on an individual basis, let alone as mixtures, is simply not feasible. The integration of short-term, focused, mechanistic toxicology with some or all of the recent advances of technology and biotechnology may provide high-through-put and scien-

tifically credible bioassays for carcinogenicity and other toxicities. Through the incorporation of technological advances in microarrays, laser capture "microdissection", imaging, high-through-put, technologies, it may be feasible to study the properties of mixtures in greater detail and begin to define those characteristics that confer sufficient similarity to allow extrapolation of data from one mixture to another. Bioinformatics and other computational approaches would also be integrated into this research scheme, not only for data analysis but to develop predictive models that could be used for risk assessment.

Integrated approaches to investigate chemical mixtures will be necessary to advance our understanding of the health relevance of exposure to mixtures. Rapid scientific advancements and implementation of public health intervention strategies will depend on the development of a rich knowledge base and its availability to all of the scientific community. Application of these new technologies may result in the generation of data on large numbers of chemicals and exposure conditions and to the development of an unprecedented knowledge base that can be used to guide future research, improve environmental health, and aid in regulatory decisions [21].

Through efforts such as those at the National Center for Toxicogenomics, the National Toxicology Program, and the Superfund Basic Research Program, NIEHS is providing a leadership role in efforts to improve and apply the methodologies and information of genomics science to significantly improve our understanding of basic biological responses to environmental stressors/toxicants. These programs represent a remarkable opportunity to have a dramatic impact on environmental health and chemical and drug safety, particularly in the areas of human risk assessment, human exposure assessment, and identification of individuals with increased susceptibility to environmental exposure. This information will dramatically change our understanding of human disease risk and will provide new opportunities to protect human health and prevent disease.

The implications of the "omic" sciences to environmental and public health researchers are many and direct. Genomics, toxicogenomics, proteomics, and metabonomics, along with other emerging technologies, have the potential to change the classic risk assessment paradigm and the way we approach mechanistic research conducted to support applications of the paradigm. We will not be limited to single-exposure assessments or predicting risks for populations. Instead, we will have the tools to assess total exposures and predict the risk to an individual. Such techniques may enable us to address the complexities introduced by the non-homogeneity of human populations and provide a stronger foundation for public health policy. Research will no longer be focused on the stepwise identification of single biomarkers to indicate exposure to a specific chemical. The "omic" technologies will enable scientists to begin research with the potential to develop suites of biomarkers that identify multiple environmental stressors. This knowledge will allow us to sort out the subtleties of multiple and cumulative exposures as well as investigate the effects of timing, duration, and sequence of exposures [3].

In addition to potentially leading to our improved understanding of human health impacts of exposure to chemical contaminants, advanced technologies may also serve as practical tools for use in basic research that must be conducted in support of public health initiatives to decrease or reduce human exposures. Emerging analytical and computational technologies may enhance our abilities to identify "hot spots" of environmental contamination; to monitor fate and transport of contaminants in the environment; and to monitor the progress of environmental remediation activities.

In addition, advanced technologies may serve as valuable tools for surveillance. The Precautionary Principle theme that those who propose change must prove that no reasonable environmental or human harm will result from the action applies to research efforts and public health initiatives, as well as to industry [22]. We must ensure that all risks and consequences are taken into account when a research program or public health strategy is designed and must monitor progress carefully to detect threats of adverse consequences as early as possible to maximize the value of the precautionary activity. Wider application of the Precautionary Principle in environmental health

research and public health policy may rely on additional research to address the scientific uncertainties surrounding gene-environment interactions and the impact of exposures to chemical mixtures, as well as the computational and statistical challenges of interpreting findings from small populations of exposed individuals.

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