National Conversation on Public Health and Chemical Exposures

Scientific Understanding Work Group Report
December 2010

I. Introduction

The *National Conversation on Public Health and Chemical Exposures* is a collaborative project, supported by the Centers for Disease Control and Prevention (CDC) and the Agency for Toxic Substances and Disease Registry (ATSDR). The *National Conversation* vision is that chemicals are used and managed in ways that are safe and healthy for all people. The project's goal is to develop an action agenda with clear, achievable recommendations that can help government agencies and other organizations strengthen their efforts to protect the public from harmful chemical exposures. The *National Conversation* Leadership Council will author the action agenda, utilizing input from six project work groups, and members of the public who choose to participate in web dialogues and community conversations.

National Conversation work groups were formed to research and make recommendations on the following six cross-cutting public health and chemical exposures issues: monitoring, scientific understanding, policies and practices, chemical emergencies, serving communities, and education and communication. This report is the product of the Scientific Understanding work group's deliberations. While issued to the *National Conversation* Leadership Council, the work group hopes that this report will be of value to others in a position to act on the recommendations contained herein.[1]

CDC and ATSDR worked with several groups to manage the *National Conversation*, including RESOLVE, a nonprofit organization dedicated to advancing the effective use of consensus building in public decision making, the American Public Health Association, the Association of State and Territorial Health Officials, and the National Association of County and City Health Officials. These organizations and others helped ensure that a broad range of groups and individuals were engaged throughout this collaborative process, including government agencies, professional organizations, tribal groups, community and non-profit organizations, health professionals, business and industry leaders, and members of the public.

For more information on the *National Conversation* project, please visit www.atsdr.cdc.gov/nationalconversation.

[1] This report was developed as part of the *National Conversation on Public Health and Chemical Exposures.* This is a voluntary, independent process involving multiple sectors, which was facilitated by RESOLVE, a neutral non-profit consensus building organization. This report represents the work of one of six *National Conversation* work groups and reflects the consensus of the work group members. Consensus is defined as each member being able to ~~"li~~live with" the report taken as a whole, rather than as agreement with each recommendation. Members were asked to participate as individuals, rather than on behalf of their organizations or constituencies. Recommendations for action are directed to a wide range of public and private actors, who have full latitude to consider them through the appropriate decision making procedures for implementing changes within their organization. While federal participants were involved with their agencies' knowledge and provided important insights into the role of the federal government in addressing chemical exposures, their membership on the work group does not constitute agency endorsement of the recommendations. In particular, the role of work group chairs was to ensure that diverse perspectives were considered and that common ground was found rather than to take a position, particularly on issues that might be considered by their agency or organization. The Centers for Disease Control and Prevention's National Center for Environmental Health and the Agency for Toxic Substances and Disease Registry provided funding for the facilitation, member travel, meetings, Web dialogues, community conversations, and other costs associated with the *National Conversation*. This report does not necessarily reflect the views of the Centers for Disease Control and Prevention, the Agency for Toxic Substances and Disease Registry, RESOLVE, or other organizations involved in the *National Conversation*.

Membership

Work groups were formed in 2009 following an open nomination process. Work group members were selected based on a three stage process designed to ensure that each work group would have the capacity to address and reflect different individual and organizational perspectives.[2]

In addition to seeking members representing a diverse range of sectors, the following additional skill sets were sought in selecting members of the Scientific Understanding work group: technical expertise, experience in various routes of chemical exposure, ability to engage in technical and scientific discussions with a group of individuals with diverse perspectives and expertise, and reputation in the individual's field and ability to reach out to others in the sector. Furthermore, to achieve overall balance, the team sought to compose a diverse work group in terms of discipline, perspective, gender, and geographic region.

The Scientific Understanding work group is chaired by Kevin Teichman, Deputy Assistant Administrator for Science in the Environmental Protection Agency's (EPA) Office of Research and Development. The work group is comprised of 24 members representing a broad range of experience and expertise. Members are affiliated with 23 organizations and groups including local, state and federal government agencies; professional organizations; tribes; community and nonprofit organizations; industry; and academia. Ed Murray, Director of ATSDR's Division of Toxicology and Environmental Medicine, serves as the Senior Liaison from the National Center for Environmental Health (NCEH)/ATSDR to the work group. Abby Dilley and Gail Bingham, from RESOLVE, have shared responsibility for facilitating the work group and Kim DeFeo from NCEH/ATSDR, staffs the work group. A list of the work group members can be found in Appendix A.[3]

This report is being submitted by the Scientific Understanding work group for consideration by the *National Conversation* Leadership Council as it develops its action agenda.

In this report, the Scientific Understanding work group recommends improvements in scientific understanding in order to:

A. Achieve a more complete understanding of chemicals and their health effects
B. Gain a better understanding of variations in individual susceptibility, factors that increase the vulnerability of certain communities, and the impacts of low-dose, multiple, and cumulative chemical exposures, including exposures to naturally occurring toxins
C. Improve the effectiveness of the scientific methods used by ATSDR and other public health agencies to investigate the public health impacts in communities and increase community participation in scientific research and decision making
D. Develop the scientific knowledge needed for decision making to improve public health protection

Work group charge, scope and objectives

The Scientific Understanding work group's charge is to (a) identify shortcomings in our current scientific understanding that limit, and (b) make recommendations to fill knowledge gaps that could enhance, our ability to assess health effects and to inform decisions at all levels to minimize the health risks of chemicals.

[2] For additional information on the work group member selection process, see http://www.atsdr.cdc.gov/nationalconversation/docs/membership_selection_process_report.pdf

[3] As noted in footnote 1, members were asked to participate as individuals, rather than on behalf of their organizations or constituencies. Consensus is defined as each member can ~~l~~ive with" the report taken as a whole, rather than as agreement with each recommendation.

Research related to many scientific disciplines is needed to fill the large gaps in knowledge about the causes and consequences of human exposure to toxic chemicals (including chemicals emitted by biological sources). Recent scientific advances provide the opportunity to address some of these gaps.

Caveats and limitations

While the Scientific Understanding work group drew upon the wide expertise and experience of its members, the group acknowledges the limitations of its expertise and experience and its impact on this report. A second limitation was the limit of twelve recommendations that each of the workgroups could put forward for the Leadership Council's consideration. There are certainly additional actions that could be taken to advance our scientific understanding than are included in Section IV.

Lastly, the work group found it difficult to separate "scientific understanding" from "policies and practices." The recommendations that follow are intended to provide the scientific basis for, but be neutral with respect to, various policy approaches. It is also anticipated that policy direction will be reflected in the report from the Policies and Practices work group.

II. Current status of issues under consideration

Chemicals are ubiquitous in our society; they are dispersed throughout our environment, in our water, air, soil, and food. Data show that chemical manufacturers in the United States reported producing or importing about 27 trillion pounds of 6,200 chemicals,[4] or about 74 billion pounds per day, in 2005 (Wilson & Schwarzman, 2009). In addition, global chemical production is projected to continue growing—about 3% per year, with a doubling rate of 24 years. While our society welcomes the benefits of chemical use, we also bear the burden of harm that exposures to some of these chemicals can bring.

Evaluating the Potential of Chemicals for Toxicity

The Toxic Substances Control Act (TSCA) serves as a statutory foundation for the science of chemical risk assessment. TSCA has created a standard of substantiation, which has led the EPA to collect large quantities of data—both through the general advance of toxicology and risk assessment as well as through voluntary programs with industry. At the same time, TSCA has many weaknesses. Of the approximately 62,000 chemicals existing at the time of passage of TSCA in 1976, EPA was able to review the risks of about 1,200 (2%) within the first 15 years (GAO, 1994). Based upon production volume and chemical properties, EPA estimated that approximately 16,000 (26%) were potentially of concern. However, the lack of requirement for toxicity data on these existing chemicals has fostered an environment hindering the development of newer and potentially less hazardous chemicals. For new chemicals, over 95% of the pre-manufacturing notices (PMNs) claimed some of the information as confidential (GAO, 2005a), 85% lacked data on health effects, and 67% lacked general environmental data (EPA, 2007). As of 2010, EPA's TSCA Chemical Substance Inventory shows there are over 84,000 chemicals substances in commerce (EPA, 2010a). In 1998, EPA reported that 2,863 of the substances in this inventory were high production volume (HPV) chemicals, chemicals that the U.S. either produces or imports in quantities of over 1 million pounds per year (EPA, 1998). EPA determined that only 7% (just 202 chemicals) of these HPV chemicals had publicly available results for all eight of the standard, basic screening tests. Almost half of these chemicals (43%) had no publicly available data in any test category. Companies have sponsored approximately 1,400 chemicals through the HPV Challenge Program and over 860 chemicals through international efforts (EPA, 2010b). Other chemicals, however, remained unsponsored in the voluntary program (EPA, 2006).

[4] Numbers of "chemicals" mentioned throughout this report may vary due to differing terminology, as defined by the supporting references. Refer to the supporting references for clarification.

Although basic hazard data for these unsponsored chemicals can be obtained through regulatory efforts such as TSCA Section 4 Test Rules and TSCA Section 8(a)/8(d) Rules (EPA, 2010c), TSCA's provisions place a high standard for proof of harm on EPA before regulatory action can be taken to limit use of, or ban, a chemical from commerce. Since TSCA was enacted in 1976, the EPA has used its formal rule-making authority to restrict only 5 chemicals or chemical classes (GAO, 2005a).

The successes in the regulation and substitution of chemicals are based on extensive and targeted research efforts examining the health effects of heavy metals, such as lead and methylmercury. While the human health effects of these chemicals were initially identified through cases of poisoning, data sufficient for regulatory guidelines were based upon extensive epidemiological studies on childhood exposure to lead and the establishment of experimental animal models of neurodevelopmental deficits. Over time, improved scientific understanding of lead's developmental toxicity resulted in acceptance that levels of lead exposure previously deemed to be safe posed significant health risks (Gilbert & Weiss, 2006). The subsequent removal of lead from paints and gasoline resulted in the reduction in air pollution and a decrease in blood lead levels by 70% in children (Browner, 1996). A similar protective effort has been successful for methylmercury as a result of epidemiological studies of childhood poisoning and experimental animal studies (EPA, 2010d).

The overwhelming number of chemicals used in manufacturing with the potential for environmental contamination and human exposure has driven the direction of toxicity testing. The procedures used for acute toxicity screening assays have been extended to chronic exposure assays. An individual's overall exposure to environmental factors begins before birth and continues throughout the full lifespan.[5] An individual's underlying physiological condition also can significantly influence the impact of exposure and the manifestation of an adverse health effect. The challenge lies in protecting our health and our environment, and identifying underlying physiological conditions such as age, disease state, and impact of prior exposure, that identify vulnerable populations, including children, the elderly and the health compromised. Steps to do so include coordinating observations within a community of exposures and health effects, identifying a chemical's potential for toxicity, understanding the impacts of multiple and cumulative chemical exposures, developing test methods that will detect more subtle adverse effects or populations that may be more susceptible, translating such effects back to the human, acting upon that information for assessing risk, communicating potential hazards to the community for action, and taking action to protect public health.

Evaluating and Communicating Public Health Impacts

Addressing the impact of the myriad of chemicals to which the public is exposed poses many challenges to government and private industry. These challenges include addressing the impact of chemicals, both individually and in combination, on vulnerable populations such as children and the elderly. The government's efforts to regulate potentially harmful chemicals have been constrained by TSCA which grandfathered over 60,000 chemicals in use and placed the burden of proof on EPA, a task that, as described earlier, has resulted in few chemicals being regulated. On September 29, 2009, EPA Administrator Lisa Jackson released a set of core principles to strengthen U.S. chemical management laws. In parallel with this announcement, EPA is initiating a comprehensive approach to enhance the Agency's current chemicals management program within the limits of existing authorities (EPA, 2010e).

One possible model that may be useful in updating TSCA comes from the European Union (EU). In 2006, the EU issued a sweeping new regulation, known as the Registration, Evaluation, Authorisation and

[5] EPA's Office of Children's Health Protection provides information about unique susceptibilities at different life stages. See http://yosemite.epa.gov/ochp/ochpweb.nsf/content/homepage.htm

Restriction of Chemicals (REACH), which requires producers to disclose some hazard and exposure information on an estimated 30,000 industrial chemicals. Chemical manufacturers must also gain government authorization to use certain "substances of very high concern" (REACH, 2007). These new requirements—both for providing data and for proving safe use—are expected to improve knowledge and promote the development and use of safer chemical substances, closing the technology gap by fueling new investment in green chemistry science, technology, and education (Wilson & Schwarzman, 2009).

The treaty that establishes the European Union calls for "community policy on the environment" to be "based on the precautionary principle" (European Union, 1992), a framework that people from multiple sectors and perspectives have argued our nation also needs to move toward. Support has grown for use of a decision making approach rooted in precaution – one in which risk assessment is seen as a useful tool in the appropriate context but is not the scientific paradigm for decision making. For example, in its recently released report entitled *Reducing Environmental Cancer Risk: What We Can Do Now*, the President's Cancer Panel calls for a shift away from our current risk management approach toward one based on the precautionary principle (Reuben, 2010).

Current methods for evaluating the impact of exposures to low levels of toxic chemicals rely on traditional quantitative risk assessment that has many limitations and uncertainties. Improvements to risk assessment methods, such as proposed by the National Research Council (NRC) in 2009 in their publication *Science and Decisions: Advancing Risk Assessment*, are clearly needed. The NRC report acknowledged that risk assessment is "at a crossroads," facing "a number of substantial challenges," that "its credibility is being challenged," and that the "regulatory risk assessment process is bogged down." If critical improvements can be made, then information collected as part of a quantitative risk assessment can be useful when considering exposure and adverse health information as part of a precautionary analysis. Mechanisms for assessing confidence in comparative risks among alternatives that incorporate life cycle understandings of chemical use will be important to achieving this goal.

The challenge to evaluting the impact of exposure to toxic chemicals is especially difficult in communities where large numbers of people are exposed to low levels of mixtures of toxic chemicals. Community groups across the country have criticized the lack of scientific rigor and effectiveness of Public Health Assessments (PHAs) and Health Consultations (HCs), epidemiological studies, and disease cluster investigations conducted by ATSDR and other public health agencies, in particular charging that these investigations and studies "…lack the ability to properly attribute illness to toxic exposures, and the methodologies used [by ATSDR] to identify suspected environmental exposures to hazardous chemicals are doomed from the start" (Majority Staff of the Subcommittee on Investigations and Oversight of the Committee on Science and Technology, 2009).

The coordination of comprehensive databases providing information on individual- and community-level exposures, underlying biological conditions, and health outcomes is necessary to identify and evaluate adverse health effects of chemical exposure. Without accurate health data, well-matched to exposure data by time and place, correlating exposures with health outcomes is difficult. An improved data collection system is necessary to identify and reduce unhealthy chemical exposures and improve public health. The access to such information by the community is critical.

Community involvement is critical in all phases of research and decisions that are made regarding chemical exposures. Early involvement helps ensure that research efforts address critical concerns raised by those most affected, that local knowledge is taken into account in such research, and that collaboration between stakeholders leads to improvements in research methods, study design, and interpretation of findings. Such preemptive interactions will serve to address concerns of the communities, identify resources to provide data and information to databases and affected populations, as well as aid in the translation and communication of risk back to the community for intervention to minimize health effects.

III. Vision of a Successful System

The Scientific Understanding work group recognizes every person's right to health and the obligation of our nation to provide its residents with a clean and healthy environment (―International Covenant," 1966; WHO, 2008). This ideal has been operationalized in statutes like the Occupational Safety and Health Administration (OSHA) General Duty Clause, which directs employers to furnish its employees with a workplace ―free from recognized hazards that are causing or are likely to cause death or serious physical harm" (Occupational Safety and Health Act, 1970); the Clean Air Act, which authorizes EPA to regulate hazardous air pollutants (1970); the Clean Water Act, which permits EPA to set water quality standards (1972); and the Safe Drinking Water Act, which gives EPA the authority to regulate contaminants found in drinking water (1974).

The Scientific Understanding work group understands that achieving this vision is predicated on expanding our knowledge and understanding of chemicals: their sources of exposure, toxicity, modes of action, and the adverse health impacts they can cause, along with differences in people's susceptibilities based on age, health, where they live, and other social and physiological factors. In addition, chemical information needs to be easily accessible to the public and to decision makers so that they can make informed decisions on how to best protect public health. Therefore, our vision of a successful system includes developing, where needed, greener chemicals and informing decision makers at all levels so that they understand the chemical life cycle, enabling them to safely and effectively manage the selection, use, and disposal of chemicals.

There is much important research that needs to be done to minimize the consequences of chemical exposures. We need further research into the connection between chemical exposures and multiple health outcomes (including neurobehavioral, developmental and reproductive endpoints). We also need to investigate the impacts of low-dose, multiple, and cumulative exposures to chemicals and to understand the role non-chemical stressors play in combination with chemical exposures. Understanding emerging concerns, including mold, nanotechnology, and chemical intolerance are other areas that merit research. Attention also needs to be focused on the interplay between genes and the environment, individual susceptibility, and disproportionate community risks. All of these research areas will draw upon recent technological advances in both the traditional sciences (e.g., biology, chemistry, and toxicology) and new cross-cutting technologies (e.g., computational toxicology, ―omics," and bioinformatics).

IV. Action Recommendations

The Scientific Understanding work group makes the following recommendations for consideration by the *National Conversation* Leadership Council. The work group particularly wishes to call attention to the overarching importance of considering children as a uniquely susceptible population. This permeates our recommendations. The work group also notes the relevance of ongoing studies being conducted to examine physiological differences associated with normal development and with normal behaviors that can cause special exposure concerns. As childhood does not represent all components of susceptibility, a similar level of attention should be given to the elderly and those with health conditions that affect their vulnerability to harmful chemical exposures.

A. Recommendations to achieve a more complete understanding of chemicals and their health effects

Recommendation 1. Fill data gaps in the scientific knowledge of the health risks of chemicals and prioritize all chemicals of concern for further assessment of hazard and risk.

Recommended Action: U.S. Environmental Protection Agency (EPA) should define a targeted set of toxicologic, epidemiologic, clinical, chemical use, chemical transport, and exposure data as appropriate for a robust assessment of chemical hazard and risk, and EPA should develop a prioritization method for further assessment. Specific suggested actions include:

In the near term, EPA should define a targeted set of toxicologic and exposure data, along with all available information necessary for a robust assessment of chemical hazard and risk. This effort should build upon previous efforts, such as the Screening Information Data Set for high production volume chemicals developed by the Organisation for Economic Co-operation and Development (OECD, n.d.). To protect human health and the environment, EPA needs to assess the safety and risk of new and existing chemicals. EPA and other regulatory agencies should identify a targeted data set for all chemicals in use. The targeted data set must be adequate to allow determinations that new and existing chemicals in commerce pose an acceptable level of risk and do not endanger the public or the environment. The targeted data set should be reviewed periodically and adjusted by EPA and other regulatory agencies to incorporate new scientific understanding of data necessary to assess critical health endpoints.

In the medium term, EPA should develop a prioritization method focused on chemical safety and health, with special emphasis on sensitive subpopulations, e.g., children, the aged, and the health compromised. Based on the prioritization method, EPA should identify those chemicals posing the greatest potential hazards and risks, as well as those contaminants requiring more toxicological information (including naturally occurring contaminants, such as mycotoxins). Results of the prioritization method should trigger additional appropriate analysis for chemicals posing a substantial hazard or risk, such as alternatives assessments; research to determine effective exposure-reduction strategies, including the adoption of inherently safer technology and "green chemistry;" and additional testing. EPA should reassess a chemical's prioritization when there is a change that may affect public health risk, such as increased production volume, new uses, or new information on potential hazards or exposures.

Current status of issues under consideration: While the Toxic Substances Control Act (TSCA) has enabled many successes, the legislation also limits our ability to protect human health and the environment. It has been observed that TSCA has produced three major barriers to action. The first is the "Data Gap," because concerns have been raised that the great majority of chemicals in commerce have been incompletely assessed for risk, and this information, where it exists, has been insufficiently communicated (Wilson & Schwarzman, 2009). A quality and scientific risk assessment must be based on a sound, comprehensive set of data. The second barrier, the "Safety Gap," contends that "[g]overnment lacks the legal tools it needs to efficiently identify, prioritize, and take action to mitigate the potential health and environmental effects of hazardous chemicals." The third barrier, the "Technology Gap," posits that incentives are lacking for industry to develop cleaner and safer chemical alternatives.

As a first priority, the federal government needs to close the "Data Gap." EPA and other key research agencies should have access to information about the potential risks of existing chemicals (as soon as possible) and new chemicals (before they enter commerce). Federal access should include chemical toxicity, use, storage and manufacture, transport, disposal, exposure, as well as the chemicals incorporated into consumer products. If this information is unavailable or incomplete, it should be provided to the federal government by manufacturers, downstream processors, and users. At a minimum, manufacturers should provide a targeted set of information on the acute and chronic effects of the

chemical necessary for a robust assessment of that chemical's risk, which could include profiles for persistence/bio-accumulation/toxicity (PBT), carcinogenic/mutagenic/reproductive (CMR) effects, developmental effects, and endocrine disruption, as necessary.

The availability of sufficient data, information, industry assessments, assessments done by other governments, and third-party assessments will enable EPA and others to identify, screen, and prioritize all contaminants for further scientific assessment and regulatory review. Improved scientific understanding will inform actions to protect human health and the environment (—States' Principles," 2009).

Desired outcomes and implementation

Outcomes of efforts to fill data gaps in the scientific understanding of health effects from chemicals used in commerce should be evaluated on an ongoing basis and reported periodically (annually at a minimum), by EPA and other federal agencies. Evaluation reports should be publicly available online and presented to Congress.

Finally, an online public database should be created and maintained that identifies each chemical used in commerce, identifies the chemical manufacturer(s), and indicates whether each element of the required targeted toxicological and exposure data set has been adequately provided by the manufacturer(s). EPA should disclose all data provided by manufacturers on chemical toxicity, storage and manufacture, use, transport, disposal, exposure, as well as the chemicals incorporated into products, as soon as possible after receipt of information from chemical manufacturers, taking steps to protect information that can legitimately be claimed to be confidential business information. In addition to review by EPA and other federal agencies, public comment opportunities should be created to allow citizens, researchers, and other stakeholders to provide input on the adequacy and quality of scientific data provided by chemical manufacturers.

Recommendation 2. Improve knowledge of existing databases and increase the accessibility of information across multiple databases.

Recommended actions: The federal government should lead the establishment of a National Data Management Advisory Committee, the creation of a National Registry of significant databases, and the development of a knowledge-based search engine to access data across multiple agencies' and organizations' databases.

In the short term, the U.S. federal government should establish a National Data Management Advisory Committee. This Committee would include knowledgeable representatives from major government agencies, industry, academia, non-governmental organizations, and the general public. The Committee would need to be appropriately funded and given access to the managers of all relevant sources of data within various agencies and organizations. This Committee would facilitate development of a strategy and process for the collection of information for a National Registry of significant databases. It would address issues of confidential or non-public information, working closely with the managers of the databases. The Committee would also identify relationships between independent databases and opportunities for synthesis. To ensure performance and accountability, the Committee would need to establish targets and publicly report its progress.

In the medium term, the federal government should create a National Registry of significant databases on chemicals and other contaminants. There is a significant amount of information available in various databases maintained by the Environmental Protection Agency, the Centers for Disease Control and Prevention, the Organisation for Economic Co-operation and Development, the National Library of Medicine, and many other federal and state agencies. There is a need to understand the information that currently exists in the various databases. There is also a need to determine how much of this data is

unique and how much is duplicated from another source. This effort should expand beyond the borders of the United States to include the European Union, Canada, and Asia-Pacific sources.

In the long term, the federal government should lead the development of a knowledge-based search engine to access data across multiple agencies‘ and organizations‘ databases. This search engine will build on the efforts already taken by several of the agencies to expand their capabilities. In order to navigate the databases contained in the National Registry, a search engine is needed that is capable of accessing multiple data sources across federal, state, and international sources. The intent would be to develop a knowledge-based system, rather than an information-based one, capable of fielding detailed questions that would allow a user to find relevant data and sources. This effort will require a focus on identifying interrelationships of data between chemical toxicity, exposure, and human health fields. This effort will require significant resources and should be directed by the Advisory Committee.

Current status of issues under consideration: Government agencies at all levels have made significant efforts to collect various data, and numerous databases exist both inside and outside of the government. In many cases, data has been collected to answer specific needs. Hence, accessibility and interoperability of data are all challenges. When data are not easily accessible to researchers and the public, our ability to understand chemicals and their impacts on public health is hampered. When data are not compiled in a consistent manner or entered into databases that have harmonized platforms, locating and integrating data from various databases is tedious and time consuming. Risk assessments could be expedited and enhanced if the breadth of existing information were more fully available and useful to researchers.

Therefore, there is a need for a comprehensive strategy to register existing data sources and to make the data represented in this registry accessible to all stakeholders.

Desired outcomes and implementation: It is expected that these actions will lead to incremental improvements that will range from being very visible to improvements that are procedural changes within agencies with limited visibility. Regardless, data and database management has the potential to significantly enhance our knowledge of contaminant risks and improve the quality and timeliness of risk assessments.

Recommendation 3. Evaluate the translational relevance of in vitro screening technologies utilized in toxicity testing to the impact on human health.

Recommended actions: Reevaluate and refine approaches for toxicity evaluation to develop targeted testing approaches in the whole organism (*in vivo*) and to determine the validity of cell culture (*in vitro*) and alternative model systems to predict *in vivo* toxicity.

In the near term, convene working groups of national and international scientific experts to generate a series of guidance documents for *in vitro* toxicity screening within the framework of predictive validity for *in vivo* toxicity. These documents would focus on specific organ systems and/or types of cellular toxicity. They would identify and focus efforts toward promising endpoints using the *in vitro* toxicity pathways approach. Concurrently, a reevaluation of *in vivo* toxicity testing approaches to screen for toxicity should be conducted to evaluate sensitivity, relevance, and translation to the potential for human health effects.

Utilization of new technologies and advances in systems biology are necessary to integrate a tiered and targeted approach for examining the potential toxicity of chemicals and human health impact. Over the medium to long term, efforts should be undertaken to foster collaborations between basic biomedical researchers and toxicologists to update *in vivo* methods for detecting exposure-related toxicities, identify biological processes associated with toxicity, develop methods of greater sensitivity for evaluating target

organ specific toxicities, develop approaches to examine interrelationships between biological systems in toxicity (e.g., immune and nervous, respiratory, or reproductive systems), and understand underlying mechanisms of toxicity to advance the identification of biomarkers of effect.

For the utilization of culture or alternative models, it is important to identify data sets and opportunities to evaluate the predictive validity of *in vitro* assays for determining toxicity relevant to human health and environmental effects (e.g., U.S. Environmental Protection Agency [EPA] Endocrine Disruptor Screening Program of drinking water contaminants). This effort would lead to the design of a series of coordinated interdisciplinary experiments to determine the predictive validity of a targeted group of *in vitro* assays with specific *in vivo* organ system toxicities and identification of subgroups of assays having a greater likelihood of detecting toxic effects of biological relevance. It would also serve to eliminate underperforming assays.

Eventually, assays and pathways relevant to toxicity in specific organ systems need to be identified and methods to identify chemicals or classes of chemicals based upon biomonitoring of exposure and internal tissue burden need to be developed. From these analyses, testing efforts can be focused on either target organs or translated to relevant human exposure levels. A coordinated program also is needed across multiple federal, state, and local health agencies and academic or private groups to utilize tissue to determine internal organ-specific human chemical exposures, consistent with ethical protocols for human studies research.

Current status of issues under consideration: The large number of chemicals in commerce today, along with problems posed by many environmental and biological contaminants, requires new technologies to assess potential human health hazards. One approach has been high-throughput screening of human cell lines to evaluate biologically significant perturbations in key toxicity pathways using computational biology. The expectation is that cell-specific pathways can characterize target organ toxicity in humans. However, the current cell culture (*in vitro)* testing approach raises important questions about the underlying biological processes being tested, the predictive validity of the *in vitro* cell based systems to whole animal (*in vivo)* toxicity, and ultimately the relevance of these findings to human health. Additionally, questions remain as to how data from *in vitro* assessment of toxicity pathways can be used in risk assessment given several uncertainties (e.g., defining ―adverse effect," extrapolation at the low end of the dose-response curve, susceptible subpopulations, e.g., children, the aged, and the health compromised, developmental status [critical windows of susceptibility], application of uncertainty factors).

Desired outcomes and implementation:

- Define, characterize, and confirm critical cellular pathways as causative of *in vivo* toxicity on a target organ basis.
- Identify specific high-throughput and high content assays validated for examination of each pathway.
- Enhance the ability to detect and characterize *in vivo* toxicity with the incorporation of new technologies.
- Incorporate biomonitoring of exposure and target organ concentrations into *in vivo* studies.
- Identify and validate tests systems (using comparative *in vitro* and *in vivo* models) sufficient to detect adverse effects of exposure on an organ or biological system basis, including effects that have no known cellular response pathway.
- Develop approaches that allow for the evaluation of susceptible subpopulations.

Important products of this initiative would be the identification of test systems with predictive validity for adverse human health effects. Initially this would focus on identification of human target organ/systems

for which the *in vitro* screening approach would be successful and those systems for which an *in vivo* approach is still required. Additionally, the evaluation of the signaling pathways and receptor activation, as they are relevant to specific *in vivo* organ systems, will contribute to the refinement and focus of subsequent *in vivo* assessments. The inclusion of new technologies in toxicity testing and chemical evaluation will increase the sensitivity to detect adverse effects and foster the identification of specific and critical pathways for inclusion into the *in vitro* high-content analysis effort. In the near term, this activity will help bolster our current datasets for future use. As an example, *in vivo* imaging of the heart may identify changes in cardiac function related to ion channel signaling. This observation could then be used to develop *in vitro* systems to detect the relevant ion channels and their function and to compare results back to the *in vivo* system, thus validating the *in vitro* endpoint approach for subsequent studies.

Inclusion of available data obtained from 1) biomonitoring of biological samples (blood, urine, hair), 2) chemical body burden as it refers to the total amount of chemicals that are present in the body at a given time as calculated across multiple biological samples (e.g., blood, urine, fat, hair, tissues samples), and 3) target organ concentration will identify relevant exposure levels for *in vitro* evaluation. The increased level of sensitivity and refinement in the *in vivo* models will translate into a decrease in the use of animals and the inclusion of more relevant *in vitro* test assays, which are likely to increase acceptance by the public, as well as the regulatory community.

The 2007 National Research Council report *Toxicity Testing in the Twenty-First Century: A Vision and a Strategy* recommended that research programs directed to this strategy would be assessed every 3-5 years by well-recognized scientific experts in both *in vivo* and *in vitro* testing models, independent of vested interests in the public and private sectors. Evaluation criteria shall include the identification of assays with predictive validity, the establishment of more sensitive *in vivo* test methods to detect for toxicity, and, more importantly, the integration of data from both *in vivo* and *in vitro* assays to provide a basis for inclusion into the risk assessment process.

Determining the predictive validity of *in vitro* systems falls under the auspices of various agencies including the National Institutes of Health (NIH), National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP), and the EPA (e.g., EPA Endocrine Disruptor Screening Program [EDSP], EPA‘s National Health and Environmental Effects Research Laboratory, EPA‘s National Center for Computational Toxicology). The effort would be facilitated by a coordinated effort across granting agencies of NIH, National Science Foundation, Department of Defense, and the Department of Energy.

Target organ/system exposure would fall under the auspices of the Centers for Disease Control and Prevention, and could be facilitated by the involvement of NIH/NIEHS and NTP (of which the National Institute for Occupational Safety and Health is an integral part) for either tissue collection or chemical analysis support. Access to tissue sample collection would be fostered by the assistance of local health departments, state coroners‘ offices, private physicians, hospitals, and patient advocacy groups, as relevant.

Recommendation 4. Identify and improve scientific knowledge of adverse health effects from indoor air pollutants, including mold and mycotoxins, with a focus on the linkage to neurologic, mental health, endocrine and immunologic diseases.

Recommended actions: Improve the scientific understanding of the effects of indoor air pollutants and their impact on identifying individual susceptibilities. Specific suggested actions include:

In the near term, exposure assessments for indoor air quality should incorporate multiple endpoints for assessing the overall contribution of mold and its products, volatile and semi-volatile compounds like

pesticides (VOCs and SVOCs), small particles including ultrafine particles (e.g., from combustion), and allergens. These particulates can be categorized by likely exposure routes. Air sampling can be subdivided by particle size and shape to identify those most likely to remain in air and, therefore, most likely to be respirable and penetrate deep into the lung. This can be accomplished by providing supplemental resources to existing studies for the expansion of air/dust analysis and by capturing results in databases allowing for cross comparison with health data.

Given growing concern over prenatal exposures and exposures to children, adults, pregnant women, the physically compromised, and the elderly, and the fact that Americans spend 90% of their day indoors (Woodcock & Custovic, 1998), an evaluation of the impact of indoor air quality and its various components during development should be conducted by an authoritative group (e.g., National Toxicology Program [NTP] Center for the Evaluation of Risks to Human Reproduction, National Academy of Sciences). Such evaluation should include physician case reports, clinical studies, exposure simulation studies, epidemiology studies, and animal studies. Because childhood exposure may not, in all instances, reflect the most sensitive population, the susceptibility of older populations or individuals with differing physiological conditions or underlying respiratory, cardiovascular, and neurological diseases should also be considered. Given an aging population combined with the predominance of indoor activities, an evaluation of exposure and impact of air quality components on the elderly could contribute to health promotion efforts across the life-stages.

To determine the extent of indoor exposures, biomarkers of exposure for each of the compounds of interest need to be developed and validated. In the case of mold, for example, potential biological markers of exposure such as urinary mycotoxin levels, cytokine and antibody changes, or other specific markers can be tested and validated through exposure simulation studies. The validation of a biomarker of exposure could advance the evaluation of exposure-related adverse effects in human epidemiological and case-control studies and in animal models. Validated biomarkers could then be included in appropriate databases for assessing adverse effects, disease associations, and therapeutic interventions.

Current status of issues under consideration: Efforts to identify subpopulations more susceptible to adverse effects from chemicals should include assessment of the history of indoor environmental exposures of the individual as well as genetic and physiological factors. Indoor air quality is a major contributor to respiratory compromise, in general, and asthma in particular (EPA, 1994; McGwin, Lienert, & Kennedy, 2010). These effects are potentially hazardous throughout the life-span, with possibly greater vulnerability to the developing organism, *in utero*, in childhood and among women and the elderly.

Indoor air quality is affected by building design and construction, materials and furnishings, operations and maintenance products and practices including selection of cleaning agents and the use of scented products, and activities and personal care products of building occupants (NIBS, 2006). In addition, the quality of indoor air is affected by dampness, moisture, and mold (IOM, 2004) with mold present in 1.5 to 20% of modern homes (Bornehag et al., 2004; 2005).

Mold exposure can have direct health effects and may also interact with other exposures. Potential health effects due to indoor exposures have contributed to the rising interest in sustainable building design and fostered green technology with the use of low-emitting building products and selection of finishing materials to minimize moisture retention and mold growth. While associations between indoor air quality and health have been demonstrated (Campbell, Thrasher, Gray, & Vojdani, 2004), the impact of indoor air pollution on individuals who are especially susceptible to chemical exposures has not been adequately addressed (Miller & Ashford, 2000). There is emerging data raising the issue of mold exposure and direct health effects (Thurman, Creasia, & Trotter, 1989; Campbell, Thrasher, Gray, & Vojdani., 2004; Kilburn, 2009) raising the concern of whether such exposure should be considered within the framework of assessing the health impact of environmental exposures.

Desired outcomes and implementation: The Scientific Understanding work group envisions several aspirational goals. First, a database of indoor air pollutants categorized to interface with health data will be created. Next, the impacts of individual components of indoor air on human health will be defined. Lastly, the influence of exposure to indoor air pollutants (including mold and mycotoxins) on the susceptibility of individuals to other chemicals will be better understood.

It is expected that these actions will lead to the identification of critical indoor air exposures that can adversely affect human health and productivity. It is also expected that the characteristics of susceptible populations that can inform additional studies on genetic-, gender-, and age-based susceptibilities will be identified and will enhance efforts for identifying green chemistry-based alternatives, thus improving indoor air quality. It is also expected that progress will be made on the development of indoor air quality standards for common indoor air pollutants.

Federal agencies (e.g., the National Institute of Environmental Health Sciences [NIEHS] and Institute of Medicine [IOM]) actively engaged in indoor air quality issues should form a consortium to review and report out on the progress and impacts of the ongoing activities listed above (see ―recommended actions") and research needs.

Actions can be taken by appropriate agencies, including NTP/NIEHS with a review conducted by the NTP Center for the Evaluation of Risks to Human Reproduction, EPA indoor air quality divisions for research and monitoring, and ATSDR for population exposure assessments. Specific nominations can be submitted to the National Toxicology Program for consideration of toxicity testing.

B. Recommendations to gain a better understanding of variations in individual susceptibility, factors that increase the vulnerability of certain communities, and the impacts of low-dose, multiple, and cumulative chemical exposures, including exposures to naturally occurring toxins (e.g., mold and mycotoxins)

Recommendation 5. Identify and define vulnerability characteristics of communities in terms of both structure and function, and their influence on increasing the susceptibility to environmental chemical exposures.

Recommended actions: To adequately assess and understand cumulative risks in communities, questions about community-specific situations and vulnerabilities should be incorporated into exposure assessments, risk assessments, and existing surveys. This would lead to developing a more holistic risk management approach that identifies and measures cultural impacts and integrates them with human health and ecological effects.

As an example, members of Native American, immigrant or ethnic communities often have greater exposures resulting from traditional cultural practices that have not been factored into standard risk assessments that could lead to adverse health effects. Additionally, some of these communities have been forced to change or abandon traditional cultural practices because of contamination of resources they depended on (Arquette et al., 2002).

Pilot research projects should be undertaken to identify and define ―vulnerability characteristics" in appropriate communities. These questions could also be incorporated into some existing surveys (e.g., National Health and Nutrition Examination Survey [NHANES], Agency for Toxic Substances and Disease Registry [ATSDR], census-derived follow-ups, and the U.S. Environmental Protection Agency's [EPA] Community Action for a Renewed Environment grants program). They should also be

incorporated into traditional risk assessment models, which need to be modified to take these cultural differences into account. Ultimately, based on what is learned in the pilot projects, guidance for including these questions should be developed for all relevant programs.

Communities need to be involved in describing their specific situations and vulnerabilities. A place to start might be some research initiated within the new National Institute of Environmental Health Sciences (NIEHS) Partnerships for Environmental Public Health. The establishment of this program demonstrates NIEHS' commitment to supporting initiatives for communities and scientists to work together on contemporary issues in environmental public health. This umbrella program is intended to support partnerships between researchers and communities.

As additional vulnerabilities are identified, toxic site remediation actions and local emergency response planning efforts (e.g., floods, man-made disasters) should be tailored to the specific, empirically derived, vulnerability characteristics of a community.

Current status of issues under consideration: Improving health in contaminated communities is difficult because little is known about how communities differ with regard to factors that may increase the risks posed by toxic chemicals. In addition, risk assessments completed by federal agencies use standardized templates for exposure scenarios in lieu of community-specific scenarios. Risk management decisions are determined independent of the communities' concerns leaving these populations at greater risk due to inadequate characterization of risk and remedial options. This in turn may leave the communities at a greater risk. Traditional risk assessment models need to be modified to take into account cultural differences of communities.

The recent National Research Council's document *Science and Decisions: Advancing Risk Assessment* (2009) recommended that EPA "develop guidelines and methods for simpler analytical tools to support cumulative risk assessment and to provide for greater involvement of stakeholders. In the short-term, EPA should develop databases and default approaches to allow for incorporation of key non-chemical stressors in cumulative risk assessments in the absence of population-specific data, considering exposure patterns, contributions to relevant background processes, and interactions with chemical stressors." Risk assessment and risk management agencies should also allow the flexibility to incorporate community-specific data in risk assessment and risk management decisions. Holistic models such as those developed by Arquette et al. (2002) should be considered to amend traditional risk assessment models to include cultural information when making risk management decisions. Arquette argues that even the definition of health used by Native people is significantly different than the definition used by risk assessors, which leads to the need to expand current definitions and incorporate traditional knowledge into decision making.

Research is needed to identify and define "vulnerability characteristics" of communities. Those assessing risks in communities need to understand how community characteristics in both structure (e.g., age, socio-economic factors, proximity to pollution sources, cultural and religious practices) and function (e.g., social organization, capacity to address impacts, language barriers) serve as both risk and protective factors for chemical exposures.

Recommendations made at a recent conference support the need to consider these many variables: "For Agency personnel charged with ameliorating toxic contamination, it is critically important to be aware that the problems confronting contaminated communities are related not only to technical clean-up and physical health, but also to social aspects of the community. In many contaminated communities, a destructive social process develops that exacerbates the psychological and physical health impacts on community residents. If this goes unrecognized, outside agency intervention may make the social process even more destructive. On the other hand, if an agency works in partnership with a community, it is

possible to decrease the development of social stresses and increase the social capital and collective efficacy available to a community to respond to contamination" (Tucker, Coles, Couch, & McEwen, 2010).

The major strengths of this recommendation are incorporating empirical data of "real world" community scenarios in cumulative risk assessment approaches and identifying specific cultural/ethnic and traditional practices that may affect risk. The major weaknesses of this recommendation are not being able to confirm any causal connections between all the variables identified, nor being able to extrapolate vulnerability characteristics across all communities. Impediments might be privacy concerns, liability concerning sensitive information being used for adverse insurance decisions or housing resale losses, and media coverage of the information collection effort jeopardizing its scientific integrity.

Desired outcomes and implementation: This research improves risk assessments of communities by helping to identify the influence of vulnerabilities on chemical exposures, identify the influence of neurological and behavioral impacts on chemical exposures, and develop methods to incorporate background exposures and thus identify the influence of background exposures on risk.

Communities will be better served and protected because cumulative risk assessments will incorporate key non-chemical stressor data based on the vulnerability characteristics of the community being studied, e.g., children, the aged, and the health compromised. Fewer default-based judgments and arbitrary factors are invoked, which translate into risk assessments reflecting real-world scenarios.

Communities receiving cumulative risk-based interventions designed to reduce community vulnerability should be randomized, and independent evaluations should be contracted to determine if the intervention worked and what lessons were learned to apply to other communities.

It is recommended that National Institute of Health/NIEHS, Centers for Disease Control and Prevention/ATSDR, EPA, state health departments, tribal nations, and the Indian Health Service consider implementing this recommendation.

Recommendation 6. Identify and define gene-environment interactions as they relate to chemical or environmental exposure and social and lifestyle factors.

Recommended actions: Develop a Gene-Environment Interaction Steering Committee to foster national and international collaborations, and develop a Prospective Cohort Study of Genes and the Environment, which will allow for the definition of gene-environment interactions in many common diseases. Specific suggested actions include:

A Gene-Environment Interaction Steering Committee should be formed in the near term to foster national and international collaborations to integrate existing and newly developed clinical databases, registries, specimen repositories and other resources to allow for the study of large numbers of people with well characterized phenotypes, with known exposures to environmental risk factors and known genetic risk factors, to assess gene-environment interactions for more conditions. This Committee would also make specific recommendations on adding genetic studies to DNA repositories of subjects in investigations of environmental risk factors for disease (e.g., the Sister Study[6]) and add environmental studies to genetic investigations.[7] The activities of the Gene-Environment Interaction Steering Committee would expand on the National Institutes of Health (NIH) Genes, Environment and Health Initiative (GEI)[8] to include

[6] See http://www.sisterstudy.org
[7] For example, see http://www.genome.gov/gwastudies
[8] See http://www.genome.gov/19518663

studies of international groups, those in military and civilian populations with unusually high toxic environmental exposures, rare diseases, and studies to understand genetic risk factors for adverse events to drugs and biologic agents (McKeown-Eyssen et al., 2004).

Over the longer term, development of a prospective cohort study of genes and the environment will allow for the definition of gene-environment interactions in many common diseases (Collins, 2004).

Current status of issues under consideration: Most common human diseases likely arise from a combination of genetic and environmental risk factors, which include lifestyle, occupation, exposure to environmental chemicals, the impact of social communities, and stress-related factors. The understanding of these interactions is critical to defining risk and focusing preventative measures at the individual level (Chakravarti & Little, 2003). The familial nature of many complex diseases suggests an underlying genetic susceptibility. At the same time, factors outside the genome, such as environmental exposures and epigenetic influences, can also be important.

The current scientific view is that virtually all health conditions will reveal evidence of interactions between genes and the environment (GxE) if studied in adequate detail. However, these data are often not available for adequate numbers of individuals for most diseases. Evidence of statistical interactions between genetic and environmental risk factors is often used as evidence for the existence of an underlying mechanistic interaction. GxE interactions may be additive or multiplicative or they may be negative (or antagonistic) when protective genes or protective environmental exposures interact (Clayton & McKeigue, 2001).

Desired outcomes and implementation: Define additional GxE interactions that lead to disease, as well as those that are protective for disease, to enhance understanding of molecular pathogenic mechanisms, increase the safety of drugs, and prevent illness by reducing environmental exposure in genetically susceptible individuals when possible, or if not, by developing gene therapies or other treatments which compensate for genetic inadequacies in xenobiotic metabolism (Breton et al., 2007; Wan & Diaz-Sanchez, 2007).

Important products of this initiative would be estimates of the specific risk of developing a number of diseases by individuals with different genotypes after exposure to a wide range of common environmental factors. Initially the focus would be on environmental risk factors with high associations with particular diseases that have known genetic risk factors. When possible, environmental and genetic protective factors would also be studied along with their interactions to allow for informed exposure decisions by many individuals with varying genotypes and the development of new therapies.

1. Lists of new GxE associations with diseases or phenotypes would be annually compiled and curated into an interactive and searchable website.

2. Studies would be undertaken that would seek to demonstrate how altering environmental exposures in genetically susceptible individuals would decrease disease incidence over time.

The Gene-Environment Interaction Steering Committee could include U.S. and international representatives from NIH, Centers for Disease Control and Prevention, U.S Food and Drug Administration, U.S. Environmental Protection Agency, Department of Defense, clinicians trained in environmental exposure and genomic interpretation, pharmaceutical companies and academic centers to coordinate and facilitate the proposed action items, develop needed resources and assess the outcomes of the initiatives.

Recommendation 7. Improve understanding of individual susceptibility to chemical exposures.

Recommended actions: Improve the understanding of individual susceptibility and chemical intolerance through improved data collection and research. Specific recommended actions include:

In the next year:

1) Investigate the feasibility of incorporating a scalable, validated and reportable statistical tool, such as the published Quick Environmental Exposure and Sensitivity Inventory (QEESI) instrument into Centers for Disease Control and Prevention (CDC)/Agency for Toxic Substances and Disease Registry (ATSDR) exposure and community investigations (Miller & Prihoda, 1999).[9]
2) Create an interdisciplinary group to develop and implement research on chemical intolerance. This could include CDC/ATSDR, U.S. Environmental Protection Agency (EPA), National Institutes of Health (NIH)/National Institute of Environmental Health Sciences (NIEHS), National Institute for Occupational Safety and Health (NIOSH), U.S. Food and Drug Administration (FDA), the public, and practitioners, as a first step toward establishing an NIH office/department/branch focusing on environmental medicine.
3) Assemble an Environmental Medical Unit (EMU) planning group that includes physicians experienced in the practice of ―exposure medicine," as a prelude to implementing an EMU.
4) Encourage federal agency support of investigations that include the impact of individual choices (e.g., consumer product selection, diet, etc.) on personal exposures and individuals' health.

In the medium term (next two to three years), recommended actions include: 1) prepare EMU design and engineering specifications, operations manual, and clinical research protocols; 2) estimate project costs for construction, staffing, and operation of EMU including direct research cost estimates per patient/day; and 3) identify private and public sources of support for sustained EMU operations including funding for EMU-based research.

Longer term actions include the construction and staffing of a prototype EMU, followed by EMU-based research.

Current status of issues under consideration: Chemical intolerance is disabling for 2-6% of the U.S. population and results in major medical costs and loss of productivity (Caress & Steinemann, 2004; Kreutzer, Neutra & Lashuay, 1999). Approximately 15-30% of Americans report adverse reactions to particular chemical exposures. Groups of individuals in more than a dozen industrialized nations report experiencing multisystem symptoms and new-onset intolerances to structurally diverse chemicals following an identifiable exposure event. However, little is known about prevalence, incidence following exposure events, and individual risk factors for chemical intolerance.

Interdisciplinary research that integrates exposure science and medicine is lacking. There are no appropriate research facilities in the U.S. for the controlled investigation of physiological responses to low-level chemical exposures. Known as EMUs, these research facilities have been a priority recommendation from multiple professional and scientific meetings for more than a decade and are considered critical to advancing our understanding of individual susceptibility (Ashford & Miller, 1998; Association of Occupational and Environmental Clinics, 1992; Miller et al., 1997; National Research Council, 1992). An EMU is an inpatient hospital facility designed to reduce exposures by all routes, in

[9] See http://www.chemicalexposures.org

order to allow patients to achieve a "clean" baseline, or "unmasked state." Researchers can determine the extent to which illness improves with avoidance of potential environmental triggers, and conduct double-blind, placebo-controlled challenges using every day, low-level exposures in the absence of background chemical "noise."

Desired outcomes and implementation:

- A better understanding of individual susceptibility, e.g., children, the aged, and the health compromised, and how it could improve our understanding of community susceptibility.
- A unifying explanation/theory/mechanism of disease, TILT is the distillation of world-wide observations of exposed groups and individuals who develop intolerances following well-documented exposures (Ashford & Miller, 1998). TILT provides a framework for basic and translational research on individual susceptibility which may yield targets for prevention and treatment. These results, obtained through working with chemically-intolerant individuals, including priority groups such as veterans suffering from Gulf War Illness, have the potential to benefit groups with more common conditions such as asthma, autoimmune diseases, and neuropsychological disturbances that may share the same underlying mechanism.

Establish prevalence and incidence of chemical intolerance in exposed and unexposed groups and individuals and pre- and post-illness by assessing symptoms and intolerances at baseline and at serial points following exposures. Identify individual risk factors for susceptibility. Foster collaboration toward interdisciplinary research, including epidemiological, clinical, and animal studies, on individual susceptibility among relevant governmental agencies. Plan, create, and sustain vanguard research facilities based in hospitals and clinics for the systematic investigation of individual differences in response to chemical and mold exposures.

Professional evaluation and tracking of this endeavor is necessary and should follow an accepted framework, e.g., CDC's Framework for Program Evaluation in Public Health (1999), with emphasis on stakeholder involvement at every phase.

Throughout the process, key stakeholders should be involved in an open dialogue to ensure that research programs are translational, leading to research projects with clinical relevance. This should include representatives of affected communities and patient groups, experienced occupational and environmental medicine and other medical practitioners, academic researchers, and various governmental agencies including CDC/ATSDR, NIH/NIEHS/NIOSH, EPA, FDA, health insurance companies, and others as relevant.

C. Recommendations to improve the effectiveness of the scientific methods used by ATSDR and other public health agencies to investigate public health impacts in communities and to increase community involvement in scientific research and decision making

Recommendation 8. Conduct research to identify the limitations, and evaluate the effectiveness, of the scientific methods used by ATSDR and other public health agencies to investigate the public health impacts of community-wide exposures to toxic substances and to improve the science and public health relevance of ATSDR's Public Health Assessment process, epidemiological studies, disease cluster investigations, and exposure investigations.

Recommended actions: Improve the methods used to investigate the public health impacts of community-wide exposures to toxic substances by establishing an independent review panel to evaluate existing approaches and to identify improved approaches. ATSDR should then adopt these approaches. Specific recommended actions include:

In the near term (within 6 months), an independent panel should be established by ATSDR to review the methods used by ATSDR and other public health agencies to investigate the public health impacts of community-wide exposures to toxic substances. The panel would be comprised of agency staff, researchers, residents from affected communities, and representatives from environmental and public health non-governmental organizations and would examine why existing approaches – Public Health Assessments (PHAs), Health Consultations (HCs), Exposure Investigations (EIs), epidemiological studies, disease cluster investigations – may not have worked. Within another 12 to 18 months, the panel would identify and report on case studies of effective ~~"b~~best practices" for assessing exposures and health effects in community-wide settings and for conducting epidemiological studies and disease cluster investigations. In the long term, as better procedures are identified, these best practices should be piloted and incorporated into the PHA Guidance Manual. A new protocol for disease cluster investigations should also be developed which could take another 12 months. Finally, ATSDR staff and cooperative agreement partners in state health departments should receive training and support in implementing these best practices and in mechanisms for community involvement including sensitivity training.

The strengths of this approach are a collaborative process, transparency of government actions, gaining community trust for government actions, and improving the scientific integrity and relevance of results. The weaknesses are the time and infrastructure changes needed to revise approaches used for decades.

Current status of issue under consideration: ATSDR conducts PHAs and HCs, EIs, health studies, and disease cluster investigations in response to requests from the public and from state and tribal agencies. The objectives of the PHAs and HCs are primarily (1) to determine whether people have been, and/or are currently exposed to toxic substances and (2) to assess the likelihood of current and/or future adverse health effects from these exposures. PHAs and HCs may recommend further work, such as EIs or epidemiological studies to assess exposures and adverse health effects. In addition, ATSDR and other public health agencies are often asked to conduct disease cluster investigations because of community concerns about high rates of health problems, such as childhood or adult cancers and birth defects. Community groups across the country have criticized the lack of scientific rigor and effectiveness of PHAs, HCs, EIs, epidemiological studies and disease cluster investigations conducted by ATSDR and other public health agencies, in particular charging that these investigations and studies ~~—~~. lack the ability to properly attribute illness to toxic exposures, and the methodologies used [by ATSDR] to identify suspected environmental exposures to hazardous chemicals are doomed from the start" (Majority Staff of the Subcommittee on Investigations and Oversight of the Committee on Science and Technology, 2009).

The major scientific issue with these investigations is the limited capacity of the methods used to evaluate the public health impacts of community-wide exposures to toxic substances. Methodological limitations include reliance on already-collected data that are insufficient to characterize exposures or assess health outcome rates, failure to adequately assess past exposures, uncertainty concerning the level of exposure that may result in adverse health effects, inadequate accounting of cumulative health risks from multiple exposures, inadequate accounting of variability in susceptibility, and over-reliance on a risk number to determine the safety of exposures without taking into account the uncertainties in the risk number. Disease cluster investigations and epidemiological studies are limited by methodological problems such as exposure and disease misclassification biases, selection bias, possible confounding bias, lack of statistical power, lack of specific hypotheses, and sparse background toxicological and epidemiological data. Research is needed to identify new methods to address exposure and health concerns of communities as well as to improve existing methods for conducting these investigations. The result of this research will provide the scientific basis for adopting new methodologies and improving existing methodologies for assessing health risks in communities.

The major policy issue with these investigations is the lack of community involvement at the "ground-floor" of these activities, including the planning, design, problem-formulation, scoping and conduction of the investigation or study. This lack of community involvement severely limits the focus and relevance of these activities. Additional policy issues limiting the focus and relevance of PHAs and HCs include rigid adherence ("one size fits all") to the PHA guidance manual, lack of necessary expertise among those carrying out the investigations, lack of a "life-cycle" approach involving revised assessments as new information becomes available, and lack of transparency. Moreover, PHAs, HCs, and EIs usually lack external peer review.

Desired outcomes and implementation: ATSDR would establish an independent panel of researchers, residents from affected communities, and representatives from environmental and public health non-governmental organizations to review the methods used by ATSDR and other public health agencies to investigate the public health impacts of community-wide exposures to toxic substances. This process would result in the following outcomes:

1) Best practices for investigating health problems in communities would be identified and adopted improving the way PHAs, HCs, cluster investigations and health studies are conducted by ATSDR and other health agencies.

2) Public confidence in how ATSDR and other health agencies conduct PHAs, HCs, cluster investigations and health studies would be improved.

3) The guidance manual for conducting PHAs would be revised and a new protocol for conducting diseases cluster investigations would be adopted.

4) There would be greater involvement of affected communities in determining the direction and focus of environmental health investigations conducted by ATSDR and other health agencies.

Some exemplary PHAs, HCs, EIs, epidemiological studies and disease cluster investigations should be highlighted and examined as potential role models, and the lessons learned from these investigations should be presented in a report by the independent panel. The lessons learned from model PHAs and HCs should be incorporated into a revised PHA Guidance Manual. An activity's appropriateness for the specific site situation should be taken into account, i.e., the specific site situation should determine which, if any, "tools" (e.g., EI, health study, cluster investigation, etc.) should be recommended by the PHA.

Centers for Disease Control and Prevention/ATSDR, state and local health departments, state and tribal health agencies, residents from affected communities, representatives from environmental and health non-governmental organizations, and citizen groups concerned about shortcomings of past health investigations should implement this recommendation.

D. Recommendations to develop the scientific knowledge needed for decision making to improve public health protection

Recommendation 9. Develop scientific criteria for the application of the precautionary approach, in order to better protect human health and the environment.

Recommended actions: Advancements in scientific understanding will assist in the successful implementation of the precautionary approach. Priority actions include

1) conducting research to establish criteria for using the precautionary approach to chemicals and to support a range of precautionary options,

2) identifying the scientific evidence incorporated into the precautionary approach,

3) identifying the most important and useful data to include in alternatives assessments to implement precautionary decisions,

4) identifying what additional scientific data can be obtained readily that can influence precautionary approach decision making, and

5) refining the analytical methods for integrating the information collected, comparing alternatives, involving the public, and monitoring the consequences of decisions made.

In the near term, examples of scientific data sets could be developed to show how a broader spectrum of scientific information can be integrated into a precautionary approach. It also will be important to develop a comprehensive list of what types of additional data can be helpful in understanding the existence of a threat. Over a longer term, comprehensive examples of how a precautionary approach could assist in decision making will be needed.

Conduct research to establish criteria for applying the precautionary approach to chemicals. Research questions may include: What types of empirical evidence or plausible hypotheses would establish a threat of harm? What scientific information gaps exist and need to be filled to help decision makers apply the precautionary approach? Some examples of threats of harm to be evaluated include chemical persistence or bioaccumulation, endocrine disruption, chemicals similar in structure to chemicals with known toxic characteristics, and the presence of very susceptible or vulnerable populations, e.g., children, the aged, and the health compromised. This research should include early warning signs learned from previous environmental examples as well as best practices in trends, scenario, and life cycle analysis that would inform the application of the precautionary principle. Implementing the precautionary approach also has implications for improving current practices and methodologies in epidemiology and toxicology research.

Conduct research to develop criteria to support a range of precautionary options. Decision makers need to understand the range of options that are available to them under the precautionary approach. These options may include filling information gaps with additional research, reducing exposures, or developing alternative chemicals, processes, or products. These options should be proportional to the levels of potential risk that chemicals may present, and they should be based on scientific criteria, as discussed above.

Current status of issue under consideration: The precautionary approach is a decision and policy making tool which employs scientific rigor and encourages a common-sense approach in the absence of full scientific certainty. The most widely used definition of the precautionary approach comes from the Wingspread Statement on the Precautionary Principle which states that "When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically" (Wingspread Conference on the Precautionary Principle, 1998).[10] This approach is increasingly becoming an important component of public policy decision making worldwide (Martuzzi, 2007), in part because of concerns about the limitations and uncertainties associated with current risk management (RM) approaches that rely primarily on traditional quantitative risk assessment (RA) (O'Brien, 2000; Tickner, 2007).

[10]Please see www.sehn.org/precaution.html for additional definitions and resource information on the precautionary principle.

While RA can be effective in evaluating a single chemical exposure, the ability to evaluate an individual's or community's exposure to a complex mixture of substances, as well as multiple exposures and multiple exposure pathways is extremely difficult due the lack of complete data and the methods to put all the information together. The RA-RM approach requires environmental improvements to be made when a prescribed level of risk is exceeded. This process often places the burden of proof of harm on regulatory agencies or affected communities.

Under a RA paradigm, a lack of toxicity data is often misunderstood as evidence of safety (Thornton, 2000). In contrast, a precautionary approach can shift the burden of proof such that the proponents of a product or project need to show that a chemical will not make the existing situation worse and that a new chemical may actually provide benefits in the context of having considered all reasonable alternatives. Stated another way, the RA-RM paradigm seeks to define how much risk is acceptable while the precautionary approach seeks to determine how much exposure can reasonably be avoided. The precautionary approach also asks the "why" questions – "Why do we need this? Can we do without it? What is the purpose and are there other, safer (less harmful) and more efficient ways to accomplish the same purpose? What are the values and preferences of those who will be affected, and how can the consequences of decisions be monitored?" Because the questions asked are different, some of the scientific information and analytical methods to support the precautionary approach also differ. Lastly, a precautionary approach engages the people who are directly affected by a decision in an extensive public process.

The precautionary approach strives to integrate all available scientific and other relevant information into an understanding of the threat of harm. The information may be quantitative, qualitative or semi-quantitative. Examples of information include animal and *in vitro* studies; epidemiological studies; biomonitoring; disease registries; community knowledge; air monitoring data; scientific tools to determine chemical similarities, such as structure-activity relationships; physical and chemical properties, such as persistence, bioaccumulation, and reactivity; toxic chemical release inventories; physician-submitted illness reports, such as pesticide exposures and workers' compensation claims; behavioral science or psychiatric studies for non-chemical stressors; harm to non-human species; environmental or ecological studies or indicators; land use information; other surveillance data such as noise; comparison with historical instances; sensitivity and vulnerability of potentially exposed populations; and non-chemical stressors that should be considered in the evaluation. The conclusions drawn in the precautionary approach are not merely deductive, but can also be based on inference. (Kriebel et al., 2001; Smith, 2000).

Desired outcomes and implementation: Successful implementation of a precautionary approach, with resulting improvements to public health protection, requires establishment of a strong scientific approach to determining when to use this approach and with what data, analytical methods, and criteria. This is expected to result in a broader spectrum of scientific data being considered in environmental and public health decision making, greater protection of public health and the environment from exposures to toxic chemicals, and a public that is an informed partner in decision making.

Precautionary approaches can become part of the environmental decision making process. As a baseline evaluation it will be important to identify what current environmental decisions were based on the precautionary approach or a RA-RM approach. Future environmental decisions could be based on a precautionary or RA-RM approach. The scientific basis for each decision should be summarized, evaluated, and maintained for future reference.

U.S. Environmental Protection Agency, U.S. Food and Drug Administration, Agency for Toxic Substances and Disease Registry, National Institute of Environmental Health Sciences, state and local

health and environmental protection agencies, and representatives from environmental and health non-governmental organizations are potential actors that should consider implementing this recommendation.

Recommendation 10. Develop standard, scientific protocols for alternatives assessment to support their use to promote the development of safer chemicals and products.

Recommended actions: Advancements in scientific understanding will assist in conducting sound alternatives assessments. Priority actions include:

1) Evaluate existing methodologies and frameworks for conducting alternatives assessment in order to identify key elements of alternatives assessment and to determine the best practices.

2) Ranking chemicals that have been fairly well evaluated on the basis of toxicity, use, and exposure. To do so, it would be important to establish an initial list of toxicological properties, uses, and exposures of concern and to identify chemicals with those known characteristics. Short-term test methods and chemical properties can indicate if chemicals may have the toxicological properties of concern. For example, if the chemical is positive in many genotoxicity tests, but has not been tested for carcinogenicity, there should be concern that the chemical is carcinogenic. If the chemical has not been reported to exhibit that toxicity, indicate if it has been evaluated for it. Use and exposure information can indicate if vulnerable sub-populations, e.g., children, the aged, and the health compromised, are being exposed or if there are sub-populations with high exposures.

3) Establishing scientific principles for identifying safer substitutes (i.e., how to know that a substitute would be less toxic), including methods to address the lack of chemical toxicity data.

4) Establishing a comprehensive database of chemicals, basic toxicities that are known or suspected, and safer substitutes. Include consideration of designing out the need for a chemical of concern in a product, rather than just substituting another chemical.

In the near term, a number of methodologies and frameworks for evaluating and identifying safer chemicals, materials, and products are under development and need refinement and standardization. Washington State Department of Ecology; California Environmental Protection Agency; U.S. Environmental Protection Agency‘s (EPA) Design for the Environment (DfE); Clean Production Action; businesses such as HP, Apple and IBM; and other interested parties are working to create updated alternative assessment methodologies. These efforts should be supported, coordinated, and financed to develop standardized protocols.

Subsequently, alternatives assessment (AA) needs to be integrated into the characterization of chemicals used in commerce that are identified as potential hazards. AA for hazardous chemicals should be conducted in parallel to further toxicological analysis and risk assessments (RAs), rather than only considered once harm from a chemical has been confirmed. Scientific research is needed to understand how to choose alternatives with the least likely hazards.

Current status of issues under consideration: AA provides a systematic, public analysis of the options for addressing a potentially damaging human activity or social arrangement (O‘Brien, 2000). It is a necessary element of a precautionary approach to managing the production, use, clean up and disposal of hazardous and toxic chemicals. AA provides a means to consider attractive, feasible, and safer alternatives, including no action, or designing around the need for a chemical which helps to overcome the gaps in scientific knowledge and uncertainties associated with the use of RA to estimate public health and environmental risks.

Other approaches to environmental decision making such as life cycle analysis, health impact assessment or AA, can be more effective in addressing chemical risks to human health and the environment. AA

focuses more on solutions than problems, stimulates innovation and prevention and can be more efficient at reducing multiple risks in the long term (EPA, 2003). The fundamental components of an AA include the following steps: 1) Presentation of a full range of options, 2) Presentation of potential adverse effects of each option, and 3) Presentation of the potential beneficial effects of each option (O'Brien, 2000).

The Lowell Center for Sustainable Production found that AA would be more effective in addressing environmental problems and has developed an Alternatives Assessment Framework that consists of three core elements: AA foundation, AA processes, and AA evaluation modules. To establish the foundation for AA, guiding principles such as prevention, precaution, substitution and life cycle perspective, along with the scientific information and analyses to support them, are needed. The shift to an AA approach will require the development of scientific methods to identify and assess the effectiveness of strategies to reduce risk. An improved risk assessment process that follows the recommendations of the National Research Council's 2009 report *Science and Decisions: Advancing Risk Assessment* should be an integral part of this AA process. The current RA-RM paradigm focuses on reducing exposures through controls of current processes. The AA approach suggests rethinking the current processes.

Desired outcomes and implementation: Establishment of strong scientific principles and strategies to implement alternatives analysis, along with bringing new scientific information to bear on environmental decision making processes, will result in environmental and public health decisions that provide greater protection of public health and the environment from exposures to toxic chemicals than are provided by current regulatory approaches.

AA would become an important component of decision making. Improved RA methods could be used most effectively in a comparative scenario, comparing various alternatives and giving decision makers a more upstream prevention tool and industry clearer expectations and incentives to produce safer products. One example of an AA approach is the Lowell Center AA Framework, which is ~~"d~~esigned to evaluate and identify environmentally and socially preferable alternatives. "Alternatives' encompass production processes, chemicals, materials, products, economic systems (such as transportation systems), and functions, as well as eliminating the need for a current activity or the function of a product."[11] Benefits include ~~"f~~ocusing on solutions rather than problems…stimulating innovation and prevention…and multi-risk reduction." [Note: The Green Chemistry Principles[12] may also be consistent with this recommendation.]

A website to host AAs would provide an opportunity to share the information and invite input. Milestones for establishing databases of information for the public and industry on the toxicity of chemicals and safer substitutes will need to be developed.

The Agency for Toxic Substances and Disease Registry; EPA; U.S. Food and Drug Administration; Consumer Product Safety Commission; Washington State Department of Ecology; California Environmental Protection Agency; Department of Energy; Clean Product Action; businesses such as HP, Apple, and IBM; and representatives from environmental and health non-governmental organizations should all consider implementing this recommendation.

Recommendation 11. Improve and adapt the procedures for conducting quantitative risk assessment so that it is compatible with and integrated within an overarching precautionary paradigm for decision making, as well as for other decision making paradigms for regulating toxic substances and protecting public health.

[11] See http://www.chemicalspolicy.org/downloads/FinalAltsAssess06.pdf
[12] See http://www.epa.gov/gcc/pubs/principles.html

The enhancements recommended by the NRC's *Science and Decisions*: *Advancing Risk Assessment* report should be implemented by the U.S. Environmental Protection Agency (EPA) and other agencies responsible for risk assessment. These efforts should be undertaken in the context of an open, multi-stakeholder dialogue that addresses public and private sector methods for making decisions using information on risks, including but not limited to how the elements of a precautionary approach can be taken into account. Guidance documents on risk assessment also should be revised as soon as possible. If necessary, risk assessment staff should receive training in order to implement the revised methodologies, including training on how to work effectively and compassionately with exposed communities. NRC recommendations for more stakeholder involvement, especially the involvement (at the "ground floor" and throughout the risk assessment process) of members of exposed communities, should be implemented as soon as possible. Research should also focus on improving existing scientific tools and/or developing new scientific tools that are necessary to complement the risk assessment tool in addressing the anticipated enormous quantities of data and testing expected to result from REACH and the anticipated revision of the Toxic Substances Control Act.

Current status of issues under consideration: A growing number of people from multiple sectors and perspectives have begun to seek more protection from exposure to toxic chemicals than provided by the traditional risk assessment approach which has many limitations and uncertainties. Improved risk assessment can play a role in implementing a precautionary approach as well as in other scientific methods in decision making. Information collected as part of a quantitative risk assessment can be useful when considering exposure and adverse health information, however, the context within which it is used can be improved. Toward this end, it would be useful to improve the uncertainties and limitations of risk assessment, as proposed by the National Research Council in 2009 in their publication *Science and Decisions: Advancing Risk Assessment*. The NRC report acknowledged that risk assessment is "at a crossroads" and that "its credibility is being challenged." The report made a number of recommendations that focused on improving the methodology of risk assessments (e.g., thorough evaluation and communication of uncertainties and variability, unified dose-response approach to cancer and non-cancer endpoints, broadening the assessment of cumulative and interacting health risks and stressors), and improving the relevance or utility of risk assessments for decision making (e.g., involving all stakeholders at the earliest stage of the planning, design and scoping of the risk assessment, and increasing the transparency of the assessment methods and process).

More broadly, the report recommended two major shifts. First, its authors stated "that risk assessment should be viewed as a method for evaluating the relative merits of various options for managing risk," with the risk management questions being "clearly posed, through careful evaluation of the options available to manage environmental problems at hand, similar to what is done in ecologic risk assessment," casting light on "a wider range of decision options than has traditionally been the case." This is consistent with placing risk assessments within the context of alternatives assessment and viewing the results of risk assessments not as absolute risks, but as risks that can be compared and ranked against each other. Second, the NRC recommends closely aligning technical analyses with the problem at hand so that the risk assessment will be relevant to the needs of the decision makers and stakeholders who are addressing the problem. In other words, a "one size fits all" approach to risk assessment will not be appropriate for such very different problems as regulating a chemical and deciding on a site remediation approach.

Desired outcomes and implementation: Adoption of the recommendations in the NRC report should improve risk assessment as a tool for the systematization of the relevant scientific knowledge concerning the hazards, contamination levels and population exposures, dose-response relationships, and cumulative risks (exposures from multiple pathways, complex mixtures, multiple stressors, and factors affecting vulnerability, e.g., children, the aged, and the health compromised), of the environmental problem at hand (e.g., regulation of a chemical or remediation of a site), as well as the evaluation of a wide range of

alternative options (e.g., inherently safer approaches or technologies). Including this information in an alternatives assessment will enhance the choices available to decision makers. EPA has stated its commitment to implement the framework presented in the NRC Report *Toxicity-Pathway-Based Risk Assessment: Preparing for Paradigm Change. A Symposium Summary* (2010).

A monitoring group should be established to track the experiences in communities where improved quantitative risk assessments are used in the context of a precautionary approach, as well as in the context of other decision making paradigms. Issues to be tracked should include improvements in community health, reductions in use of toxic chemicals, and the procedures used in switching to the new approach.

Potential actors include EPA and other regulatory agencies at the federal, tribal, state, and local levels, National Institute of Environmental Health Science, National Toxicology Program, representatives of community and national groups, the regulated community, and the scientific community, especially the scientists who contributed to the two NRC Reports cited.

Recommendation 12: Evaluate short- and long-term effectiveness of containment and institutional controls at Superfund, Brownfields and Resource Conservation and Recovery Act (RCRA) sites.

Recommended actions: A research project should assess successes and failures at National Priorities List (NPL) sites that have containment and institutional controls as their primary remedy. Research studies should begin as soon as possible by U.S. Environmental Protection Agency (EPA) and/or Agency for Toxic Substances and Disease Registry (ATSDR) or an independent oversight organization. This research should document the effectiveness of these measures and determine if health impacts to the communities have occurred. The studies should document any health problems that can be linked to the failures. The costs of remediation and repairs should also be reported. At all sites, members of the affected community should be involved in designing and carrying out the research.

Current status of issues under consideration: Communities are often placed at risk when the remedies selected to protect them from toxic contamination include physical containment such as fences and caps or institutional controls such as deed restrictions and covenants. Reports done by the U.S. Government Accountability Office (GAO, 2005b), Resources for the Future (Oversight Hearing on the Superfund Program, 2006), and the Environmental Law Institute (Pendergrass & Probst, 2005) have documented that these remedies often fail. An understanding of the consequences of such failures, how public health may have been affected, and the costs of repair could help inform more effective and permanent treatments as a remedy.

Desired outcomes and implementation: The aspirational goal is to determine the full cost (i.e., engineering and public health) of remedial actions at Superfund sites, specifically sites that did not treat or remove waste. The expected outcome of this recommendation is to document the health impacts in communities which have NPL sites at which waste has not been treated or removed. If health impacts can be documented, it will strengthen efforts to require permanent treatment at Superfund sites.

Permanent treatment will be more protective of public health and the environment, as well as more cost effective in the long run. There is also potential for creating well paying jobs. Such an approach would have several advantages: (1) contaminants would be removed from the basin environment and the potential for recontamination eliminated, (2) the net cleanup costs would be reduced by the value of the recovered minerals, and (3) such an approach would be one of the few options that would satisfy the preference in CERCLA for remedies that reduce the toxicity of the wastes.

EPA, ATSDR or an independent oversight organization should initiate a team to assess NPL Records of Decision (ROD) in which remedies included containment and institutional controls and assess the

effectiveness of these remedies. ATSDR could simultaneously initiate assessments in these communities to determine reported or documented health impacts. This information should be made available to the public and to others who track the effectiveness of toxic waste clean-ups.

EPA, state governments co-managing Superfund sites, independent government oversight entities such as the Government Accountability Office, tribal nations, Indian Health Service and state health departments are potential actors and should implement this recommendation.

While this recommendation intentionally focuses on the effectiveness of institutional controls at Superfund, Brownfields, and RCRA sites as a high priority, it is also appropriate to generalize this recommendation to studying the short- and long-term effectiveness of all policies and practices intended to reduce chemical exposures and thereby promote public health.

Recommendation 13. Develop standard protocols and tools to characterize potential human exposures to chemicals across the life cycle of chemical products and processes, and across the human life stages.

Recommended Actions: Scientists in all sectors need foundational information and tools to understand the impact of chemicals on humans and ecosystems. This includes access to databases, standard protocols, and assessment tools that measure or predict human exposures to existing and new chemicals and their transformation products. These protocols and assessment tools should address chemical exposures across the life cycle of chemical products and processes, as well as interactions with other chemicals and substances, transformation, transportation, fate in the environment, potential for human exposures, especially in sensitive subpopulations, e.g., children, the aged, and the health compromised, and uptake or absorption by multiple exposure pathways. Tools should also identify alternatives for chemical and product use as well as novel approaches, which, when linked with green chemistry, can be used to minimize risks and promote sustainable chemical use.

In order to efficiently and effectively address chemical risks, exposure tools must be developed and incorporated into integrated evaluation strategies that use tiered approaches ranging from screening-level to the most complex assessments. Within these strategies, exposure and toxicity information must be fully integrated in a way that directly informs well-defined public health decisions, including risk-management approaches.

Exposure information and tools are needed in several critical areas. For example, models are needed to screen chemicals based on exposure. Exposure, dose-response, and biological pathway models must be incorporated into a systems framework for understanding risk. Advanced computational approaches are required to estimate dose and exposure using biomonitoring data. Monitoring methods are needed that easily measure exposure and internal dose of parent compound and metabolites. Internal dose at the target tissue may not be reflected in biological fluids. Thus, opportunities to determine internal dose at the target tissue or tissue dosimetry should be maximized. This could include evaluation of medical samples such as biopsy tissue, surgically obtained tissue, cerebral spinal fluid or autopsy tissue. Finally, novel methods for collecting information on chemical use, human activities, and human decisions must be developed and the resulting information incorporated into easily accessible knowledge bases.

Combined with green chemistry and an array of computational approaches, exposure research offers an opportunity to maximize chemical benefits—by design—while minimizing chemical risks.

Current status of issue under consideration: According to the Environmental Protection Agency, there are over 84,000 chemical substances listed on the TSCA Chemical Substance Inventory

(EPA, 2010a). Of these, although there are significantly fewer for which there is a concern for population exposure, only a small fraction has been assessed adequately for potential risks.

One of the greatest challenges is how to screen chemicals for potential risks so that time and resources can be devoted to the chemicals of greatest concern. Existing chemical testing and exposure measurement protocols are expensive and time consuming (Anastas, Teichman, & Cohen Hubal, 2010). While these testing protocols were designed for hazard identification the current demands for information on subtle effects of long-term low dose exposure requires a re-evaluation of the screening and hazard identification approaches currently in use. Creative advances in exposure science are needed to effectively evaluate, prevent, and manage chemical risks and research is underway to identify and address gaps in required exposure information to meet this challenge (Sheldon & Cohen Hubal, 2009).

For example, researchers have developed tools to predict the inherent properties of chemicals. Research will be directed toward using information on these properties to inform product use, exposure, and chemical substitution. Interest also lies in developing improved tools to more accurately measure exposures. EPA recently implemented its ExpoCast program, which aims to develop novel approaches and metrics to efficiently screen and evaluate chemicals on the basis of biologically relevant human exposures (i.e., exposures that can be directly linked to key events leading to toxic response) (Cohen Hubal, 2009). ExpoCast, combined with information from ToxCast—a battery of rapid screens being studied to determine whether they can predict toxicity (Dix et al., 2007)—can be used in the screening phase of integrated evaluation strategies. The critical component here is the aspect of biological relevance with regards to exposure and to the underlying mechanisms of the toxic response. This integrated link is critical for determining successful approaches for assessing exposures that lead to adverse human health effects.

As another example, exposure and dose models have been developed and linked as an approach for addressing cumulative risks to pyrethroid pesticides. The longitudinal aspects of exposure models provide the ability to estimate not only the magnitude but also the frequency and duration of exposure over the same time period. When the exposure models are linked with dose models, the magnitude, frequency, and duration of internal dose can be predicted for multiple chemicals simultaneously.

Two recent activities have been undertaken by the National Academy of Sciences to address the need for better tools and approaches for measuring, understanding and predicting exposures. In 2009, the NAS initiated a project to develop a long-range vision for exposure science and a strategy to develop an integrated approach to assess risk over the next twenty years. The same year, a workshop was convened, titled ―The Exposome: A Powerful Approach for Evaluating Environmental Exposures and their Influences on Human Disease.‖ The term "exposome" has been defined to represent the long-held concept that effects on health encompass the integration of all environmental exposures from conception onwards, including exposures from chemicals, diet, lifestyle, and endogenous sources (Wild, 2005). The conference highlighted available technologies for establishing methods and advancing this overall approach for environmental exposure assessment and the impact on human health.[13]

Desired outcomes and implementation: Accurate exposure information is critical for preventing, minimizing, and managing risks associated with the manufacture and use of chemicals. Protocols and tools to characterize exposure sources and the pathways of chemicals to unanticipated places are required to provide information not only for direct assessment of human exposure but also to facilitate green chemical and product design, safe use, and prevention of adverse health consequences to people and to the environment. These efforts should include a systems-level understanding of how humans interact with environmental chemicals so as to predict unintended consequences. Initially, this effort will require the

[13] See http://dels.nas.edu/envirohealth/exposome.shtml

collection and evaluation of detailed exposure measurement data on existing chemicals and the use of these data to develop metrics that can be used to predict use and behavior of proposed and emerging chemicals.

Exposure surveillance is required to proactively identify potential risks from chemicals in commerce. Chemicals show up in unexpected places long before their impact on health and the environment is understood or evaluated. As we manufacture and release new chemicals, or existing substances are used in new ways, we need to develop strategic exposure monitoring programs to provide an early indication of a chemical's behavior in our homes, communities, and environment. For example, small-scale biosensors should be developed to detect specific sets of environmental agents in air, water, and food, and even in our bodies. This kind of surveillance can inform interventions to prevent or eliminate unexpected sources of exposure prior to the identification of potential health consequences.

Clear exposure information is required to make educated personal decisions. Good exposure information on chemicals found in the products we use and in our communities enables us, as individuals, to make educated decisions to protect our health and the environment. We need to provide publicly available and accessible exposure information to empower individuals and communities to choose chemical-based products and services that are safe and effective.

V. Conclusion

People are exposed to myriad chemicals every day. While it is important to understand the impacts of these chemicals throughout their life cycles and at different stages in human lives, government agencies still lack critical information about both. In this report, the Scientific Understanding work group has outlined its vision for expanding our knowledge about chemicals and health effects of exposures to them, and calls for improved tools to accomplish this task.

The Scientific Understanding work group recommends taking action in four areas in order to help fill critical gaps for decision makers. First, we must achieve a more complete understanding of chemicals and their health effects. We must also gain a better understanding of individual susceptibility, community vulnerability, and the impacts of low-dose, multiple, and cumulative chemical exposures. In order to better respond to communities‘ needs, we must improve the effectiveness of the scientific methods used by ATSDR and other public health agencies to investigate the public health impacts in communities, and we must increase community engagement in scientific research and decision making. Finally, we must develop the scientific knowledge needed for decision making to improve public health protection.

The Scientific Understanding work group hopes this report contributes to efforts to protect public health, including children and others most vulnerable, from harmful chemical exposures.

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Appendix A
Work group membership[14]

Leadership Team

Kevin Teichman, U.S. Environmental Protection Agency, *Chair*
Ed Murray, Agency for Toxic Substances and Disease Registry, *Senior Liaison*

Members

George V. Alexeeff, California Environmental Protection Agency
Cherri Baysinger, Missouri Department of Health and Senior Services
Nancy Beck, Physicians Committee for Responsible Medicine
Frank Bove, Agency for Toxic Substances and Disease Registry
Mark Buczek, Supresta – retired
Doris Cellarius, community activist
Bob Hamilton, Amway Corporation
Susan Hanson, Shoshone-Bannock Tribe
Gaylia Jean Harry, National Institute of Environmental Health Sciences
Rebecca Head, Monroe County Health Department (MI)
Wade Hill, Alliance of Nurses for Healthy Environments
Jeffrey A. Jacobs, American College of Occupational and Environmental Medicine
Kristi Jacobs, Food and Drug Administration
Stephen Lester, Center for Health, Environment and Justice
Frederick Miller, National Institute of Environmental Health Sciences
Claudia S. Miller, University of Texas Health Science Center at San Antonio
Frank Mirer, Hunter College
Lisa Nagy, The Preventive and Environmental Health Alliance
Richard Niemeier, National Institute for Occupational Safety and Health
Melissa Perry, Harvard University
Stuart Schmitz, Iowa Department of Public Health
Richard Sedlak, American Cleaning Institute
Margaret Shield, Local Hazardous Waste Management Program in King County (WA)

Staff

Gail Bingham, RESOLVE, *Facilitator*
Kim DeFeo, Centers for Disease Control and Prevention/Agency for Toxic Substances and Disease Registry, *Staff*

[14] As noted in footnote 1, members were asked to participate as individuals, rather than on behalf of their organizations or constituencies. Consensus is defined as each member can ~~l~~ive with" the report taken as a whole, rather than as agreement with each recommendation.

Appendix B
Terms and Definitions

Acceptable Risk- the potential for suffering disease or injury that will be tolerated by an individual, group, or society in exchange for the benefits of using a substance or process that will cause such disease or injury. Acceptability of risk depends on scientific data, social, economic, and political factors, and on the perceived benefits arising from a chemical or process that creates the risk in question. (http://www.mondofacto.com/facts/dictionary?acceptable+risk)

Agency for Toxic Substances and Disease Registry (ATSDR) - the principal non-regulatory federal public health agency responsible for addressing health effects associated with toxic exposures.

From statement by Howard Frumkin, Director, National Center for Environmental Health/ Agency for Toxic Substances and Disease Registry, CDC on Scientific Oversight and Management of the Agency for Toxic Substances and Disease Registry before Committee on Science and Technology Subcommittee on Investigations and Oversight United States House of Representatives, March 12, 2009. http://www.hhs.gov/asl/testify/2009/03/t20090312a.html

Bioaccumulation- the accumulation of a substance in a living organism. http://www2.merriam-webster.com/cgi-bin/mwmednlm?book=Medical&va=bioaccumulation

Biomagnification- increase in concentration of a pollutant from one link in a food chain to another.

Biomonitoring- the overall pollutant load and hazardous exposure of an organism is quantitatively determined by monitoring the pollutants themselves, their metabolic products and/or conjugates with protein or DNA, in either serum, urine or other body fluids, as well as tissue samples (hair and nails). http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2695300/

Community- a group or social class who lives together within a larger society or who share certain innate personal characteristics (e.g., gender, race, or ethnicity) (IOM, 1995), health or disability status, or a uniting common interest (HHS, n.d.), occupation, or belief.

Cumulative Risk- the combined risks from aggregate exposures to multiple agents or stressors. Framework for Cumulative Risk Assessment (EPA/630/P-02/001F). Risk Assessment Forum. U.S. Environmental Protection Agency, Washington, DC, May 2003 http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=36941

Cumulative Impacts- exposures, public health or environmental effects from the combined emissions and discharges in a geographic area, including environmental pollution from all sources, whether single or multi-media, routinely, accidentally, or otherwise released. Impacts will take into account sensitive populations and socio-economic factors, where applicable, and to the extent data are available. http://www.calepa.ca.gov/envjustice/ActionPlan/

Environmental Medical Unit (EMU)- a hospital suite comprised of environmentally controlled rooms for studying chemical and food intolerances. Insofar as practical, an EMU would provide clean air, water and food, allowing patients to avoid their usual background exposures for several days and return to a ―clean baseline.‖ Removing background chemical ―noise‖ that can obscure or ―mask‖ a person's responses to individual symptom triggers is necessary for performing double-blind, placebo-controlled challenges. Research subjects would benefit by learning, comprehensively, which exposures they may need to avoid.

Epigenetics- the study of heritable changes in gene functions that do not entail a change in DNA sequence (Dupont, Armant, & Brenner, 2009).

Exposure Assessment- an exposure assessment attempts to answer the following questions for a particular substance or chemical: a) Who or what is exposed (e.g., people, ecosystems)? b) Does the exposure occur through breathing air, drinking water, skin contact or any other routes? c) How much exposure occurs? e) How often and for how long does exposure occur?
www.epa.gov/oppt/exposure/pubs/exposurep.htm

Green Chemistry- the utilization of a set of principles that reduces or eliminates the use or generation of hazardous substances in the design, manufacture, and application of chemical products (Anastas & Warner, 1998).

Minimal Risk Level (MRL)- an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. These substance specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors and other responders to identify contaminants and potential health effects that may be of concern at hazardous waste sites.
http://www.atsdr.cdc.gov/mrls/

National Priorities List (NPL)- The list of national priorities among the known releases or threatened releases of hazardous substances, pollutants, or contaminants throughout the United States and its territories. The NPL is intended primarily to guide the EPA in determining which sites warrant further investigation. Also known as Superfund sites.
http://www.epa.gov/superfund/sites/npl/

Public Health Prevention Hierarchy-

> **Primary Prevention**- the prevention of diseases and conditions before their biological onset.
>
> **Secondary Prevention**- the identification and interdiction of diseases that are present in the body, but that have not progressed to the point of causing signs, symptoms, and dysfunction.
>
> **Tertiary Prevention**- the prevention of disease progression and attendant suffering after it is clinically obvious and a diagnosis established. www.enotes.com/public-health-encyclopedia

Paradigm- A set of assumptions, concepts, values, and practices that constitute a way of viewing reality for the community that shares them, especially in an intellectual discipline. Since the 1960s, paradigm has been used in science to refer to a theoretical framework.
http://dictionary.reference.com/browse/paradigm

Persistent organic pollutants (POPs)- Toxic chemicals that adversely affect human health and the environment around the world. Because they can be transported by wind and water, most POPs generated in one country can and do affect people and wildlife far from where they are used and released. They persist for long periods of time in the environment and can accumulate and pass from one species to the next through the food chain.
http://www.epa.gov/international/toxics/pop.htm#pops

Reference Dose/ Reference Concentration (RfD/RfC)- An estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure/continuous inhalation exposure to the human population

(including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a no-observed-adverse-effect-level (NOAEL), lowest-observed-adverse-effects-level (LOAEL), or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. RfD/RfCs are generally used in EPA's noncancer health assessments. [Durations include acute, short-term, subchronic, and chronic].
http://www.epa.gov/iris/help_gloss.htm#r

Risk Assessment- a scientific analysis that uses information about toxic substances to estimate potential health risks for people who might be exposed to these substances. The four traditional steps of the risk assessment process are:

1. Hazard Identification: The determination of whether a particular chemical is or is not causally linked to particular health effects.
2. Exposure Assessment: The determination of the extent of human exposure before or after application of regulatory controls.
3. Dose-Response: The determination of the relation between the magnitude of exposure and the probability of occurrence of the health effects in question.
4. Risk Characterization: The description of the nature and often the magnitude of human risk, including attendant uncertainty.

Risk Assessment in the Federal Government: Managing the Process
http://books.nap.edu/catalog/366.html, p.3

Toxicant-induced Loss of Tolerance (TILT)- a proposed general mechanism for a class of diseases involving two stages: (1) *Induction*, the loss of former natural or native tolerance following acute, chronic or repeated exposures (e.g., pesticides, solvents, combustion products), and (2) subsequent *triggering* of symptoms by everyday exposures such as fragrances, cleaning chemicals, traffic exhaust, and foods that did not cause problems for the person previously and do not bother most people. Those affected typically report adverse responses to low levels of multiple, *structurally unrelated* substances, a feature distinguishing TILT from usual toxicity or allergy. http://www.chemicalexposures.org