



EMERGING SCIENCE FOR ENVIRONMENTAL HEALTH DECISIONS

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The Exposome: A Powerful Approach for Evaluating Environmental Exposures and Their Influences on Human Disease

On February 25–26, 2010, the National Academies Standing Committee on Use of Emerging Science for Environmental Health Decisions held a public workshop on the exposome, a characterization of a person's lifetime exposures. The workshop examined the concept of the exposome and how it could be used by epidemiologists (scientists who study the health of populations) and laboratory scientists for understanding the cause of human disease. The workshop also addressed the need for resources and technologies that could elaborate the exposome in human populations.

On the first day, speakers and panelists addressed issues related to conceptualization of the human exposome, biomarkers as a mechanism for evaluating exposures, and epidemiologic study design. On the second day, the participants enjoyed an animated discussion of the scientific challenges and public-health questions and of practical first steps to take toward understanding and defining the exposome.

Framing the Issue

David Balshaw, of the National Institute of Environmental Health Sciences (NIEHS), presented opening remarks. He said that participants were there to explore the questions, Why do humans change from healthy to sick? What factors contribute to the transition? Everything from environmental toxicant exposures to genetic vulnerabilities to human behavior and lifestyle choices may contribute to the disease process. Thus, NIEHS defines environmental exposure quite broadly to include chemical exposures, diet, physical activity, stress, pre-existing disease, and use of addictive substances. Balshaw explained that the exposome workshop was convened to address the need for a new way to analyze the environment. Specifically, we need a global view of exposure that spans the entire cascade from source through disease and its variation over time and space, an integrated view of the term environment that includes factors beyond chemical exposures, and a realistic view that considers costs and the application of new technologies to population studies.

Why is evaluating exposure important? If one uses a very broad definition of environment, most of a person's increased risk of cancer and degenerative diseases is the result of environmental rather than genetic factors, said Stephen Rappaport, of the

*A single snapshot, a single point in time, is not
the end-all and be-all of exposure.*

—David Balshaw

University of California, Berkeley. Paolo Vineis, of Imperial College, highlighted one of his recent publications that found that the proportion of cancers worldwide attributable to environmental factors changes wildly with the definition of environmental exposure.¹ Accurate estimates can not easily be provided. Shortcomings in the ability to identify the causes of diseases and to develop preventive strategies are particularly problematic in the developing world, where the greatest increases in cancer would be expected, noted keynote speaker Christopher P. Wild, of the International Agency for Research on Cancer.

In a 2005 editorial, Wild contrasted the effort and dollars that have gone to support genetic research with those spent on exposure studies.² Epidemiologic studies cannot clarify genetic or environmental causes

Saracci R, Vineis P. Disease proportions attributable to environment. *Environ Health* 2007; 6:38.

Wild CP. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. *Cancer Epidemiol Biomarkers Prev* 2005; 14(8):1847–50.

The Current Balance of Research on Genetics vs. the Environment



In *Uca sp.*, the fiddler crab, the male has evolved one huge claw, constituting around 40% of its body weight, to attract females. Wild uses this image to illustrate the effort that has gone into developing high-quality tools for genetic analysis and the relative paucity of effort that has gone into developing measures of exposure to environmental risk factors.

of human disease without accurate measurements of exposure, he emphasized, and the advances in genetics show how much a targeted effort can achieve and what we should expect from a similar targeted effort in exposure science.

To succeed in identifying the combined effects of genetic and environmental factors on chronic diseases, scientists need 21st-century tools to characterize exposures of human populations. There are advanced tools for measuring genetic factors, said Rappaport, but the tools for quantitative exposure assessment have changed little since the 1970s.

Developing a Common Language

The conflicting views within and among disciplines with respect to what constitutes environmental exposure is one of the dominant challenges in exposure science. What is listed as environment not only affects estimates of disease burden but makes comparisons between studies challenging, said Vineis. Rappaport noted that we are not really dealing with the environment as an entity in that epidemiologists and laboratory scientists

The word environment is used in different ways according to different traditions or paradigms.
—Paolo Vineis

measure exposure according to their own definitions. We need to find a common language or Rosetta Stone that would allow us to move forward, said Rappaport.

This common language may be found within the new concept of the exposome. Wild defined exposome in his 2005 editorial as encompassing all environmental exposures, including those associated with diet, lifestyle, and endogenous sources from conception on. The exposome is analogous to the genome in that the genomewide association studies are agnostic and scan the environment broadly for a signal, said Patricia Hartge, of the National Cancer Institute. Rappaport referred to the exposome as “a unifying concept for exposure,” instead of working under the light of a particular lamppost, by studying pollutants from the air, water or the diet, the exposome allows us to include all chemicals, from all sources, all the time, explained Rappaport.

What is the Exposome?

- At its most complete, the exposome encompasses life-course environmental exposures (including lifestyle factors) from the prenatal period onwards.
- A comprehensive measurement of all exposure events (exogenous and endogenous) from conception to death.

Wild noted that characterizing the human exposome may seem overwhelming in the same way characterizing the human genome may have seemed initially. But, he said, exposome science has many opportunities: new tools can be applied to the assessment of environmental exposure, there is international cooperation among scientists, and, most important, there is international access to cohorts (groups of people with a common set of characteristics). Wild emphasized that even a partial characterization of the exposure profile can yield enormous benefits.

Now is the time when we have an opportunity to train young people to speak the languages both of laboratory sciences and of epidemiology.
—Christopher P. Wild

Development of the Exposome through Biomarkers

Workshop participants discussed the integration of laboratory science and technology into population studies, and they looked to molecular and social epidemiology when considering design, measurement, and analytic issues related to the exposome.

Exposures are highly dynamic and therefore difficult to measure. Concentrations of exogenous or endogenous chemicals vary over time within persons and between populations. The scale of variability is enormous, said Rappaport. He and others asked, How do we make sure that we are focusing on the chemicals or periods that are truly important?

Paolo Vineis pointed to a limitation in our measurement techniques: We do not assess long-term exposures. We are reasonably successful in measuring occupational exposures, but measurement error in dietary assessments, for example, is common. Also, we know little about the distribution of exposures within populations and over time, including how exposures change over a person’s lifetime. Vineis noted that our measurement limitations result in misclassification in epidemiologic studies—a problem that commonly leads to false negative results, the failure to identify actual links between exposures and diseases.

Many tools and approaches can be used to refine exposure assessment and advance the ability to measure diverse human exposures accurately, said Wild. Building the exposome will require an integration of approaches, including environmental measurements and validated biomarkers. He focused on the importance of biomarkers

in molecular epidemiology, for studying exposure-disease associations. There will be huge advances in our field if we can bring biomarker technology into both the clinical cancer-research domain and the population-based research domain.

Exposure biomarkers are valuable for

- Refining exposure assessment
- Providing biologic plausibility of exposure-disease associations found in epidemiologic studies
- Identifying susceptible people or groups
- Reducing uncertainties in extrapolating from animals to humans.
- Evaluating interventions

In his keynote talk, Wild identified several important aspects of biomarkers that make them useful for characterizing the human exposome.

Wild pointed to his own research that led to the development of a urinary biomarker of a mycotoxin called deoxynivalenol or vomitoxin that is found on cereals. The biomarker accurately reflects consumption of cereals in the population. His study analyzed the dose-response relationship between exposure and the biomarker and provided information on variation within an individual over time. He emphasized that biomarker development and validation in a structured program of high-priority exposures is an important research step that needs to take place.

Pointing to the importance of biomarkers, Vineis said that it is almost impossible to capture the real association between polychlorinated biphenyls and non-Hodgkin lymphoma by relying solely on traditional exposure assessment and the questionnaires commonly used in epidemiology. A biomarker is necessary.

Elissa Epel, of the University of California, San Francisco, discussed the importance of measuring both external factors and internal biomarkers in evaluating the health effects of psychosocial exposures. Psychosocial exposures fit into the exposome concept if one considers the biologic impacts of stress that people experience in their relationships at home, in school, and in their neighborhoods, said Epel. Stress-related exposures—such as not feeling safe in one’s neighborhood, financial strain, and physical or psychological abuse—are biologically embedded in such biomarkers as allostatic load (biologic responses that result from stress), telomere length at the end of a chromosome, and gene expression. Those biomarkers and others correlate with disease processes and death. Telomere length, for example, is a “master integrator of stressors” that result from a variety of lifestyle and behavioral factors. Epel further explained that telomere length correlates with oxidative stress, insulin

resistance, and stress hormones and may be implicated in the causal pathway of aging-related diseases.

Incorporating Exposure Biomarkers into Population Studies

To take advantage of biomarkers, we need to think about population study designs, said Nathaniel Rothman, of the National Cancer Institute (NCI). But we need to look at diseases, not biomarkers, as the end points. All study designs have something to offer, he said, but we need to think carefully about the questions we can ask in a particular type of design. For example, cross-sectional studies (studies of groups with differing characteristics at a single point in time) usually allow a focus on a few people in great detail, collect a lot of exposure data, and determine what additional information is needed to validate hypothesized exposure-biomarker relationships. Case-control studies can look at exposures that have occurred relatively recently when no relevant biologic samples may be particularly relevant. Rothman described cohort studies (studies of a group with a common set of characteristics over time) as the “crown jewels” in the armamentarium of epidemiology but noted that financial constraints often limit collection of multiple biologic samples.

The different study designs complement one another, said Rothman, and scientists should consider how to integrate them or use them in tandem to get a better picture of exposure. For example, Rothman and colleagues at NCI and the University of California, Berkeley used a series of cross-sectional studies to assess biomarkers of benzene exposure in workers. The studies helped to develop hypotheses that were later tested in a cohort study to follow the workers for disease. Rothman

Every classic design is in the armamentarium of approaches we can use to integrate external exposure data, internal exposure data, and genetic data to try to look at the etiology of a variety of diseases.

—Nathaniel Rothman

also recommended applying the same analytic tools in studies of different types of exposures or classes of exposures. That approach would enable scientists to determine which exposures cause unique signatures or outcomes and which exposures generate more general responses.

Most biomarkers require large amounts of biologic material, such as blood and urine, and so can be difficult to use in cohort studies, cautioned Vineis. As an alternative, Vineis suggested using a mixed design in which biomarkers that are expensive to assess are measured in only a subset of samples and less expensive measurements are done on all the samples. The more expensive tool is then used to

calibrate the less expensive one. Vineis also pointed out that interpreting the findings of biomarker measurements requires the ability to repeat tests on the same cohorts, which means further investment in the cohorts.

Epel described a tiered measurement approach that is similar to Vineis’s mixed design and is commonly used in social epidemiology studies. Tier 1 includes the broadest and easiest measures of social exposures, such as socioeconomic status and major life events. Tier 2 involves daily or monthly measures of perceived stress, typically based on questionnaires that are tightly related to biomarkers, such as telomere length. Tier 3 requires a substudy of participants’ physical or biologic responses to a stress-inducing probe and recovery from its effects. Epel also recommended a nested design, in which intensive substudies involving daily assessments are performed on a smaller sample.

Martyn Smith, of the University of California, Berkeley, observed how different fields of epidemiology—such as social, nutritional, and environmental—use similar techniques and technologies. He noted a need to build a stronger community between the different fields and to encourage the sharing of biomarkers, questionnaires, and other research tools. Enrique Schisterman, of the National Institute of Child Health and Human Development, said that better management of information and resolution of challenges in exposure science will require different disciplines to take an integrated approach either by design or by analysis.

Exposomics

In their discussion of current and future technology, workshop participants explored the use of *-omics* tools (tools for studying biological systems) for biomarker development. What is particularly exciting to Wild is the new generation of research tools, particularly within epigenetics and *-omics*, that are emerging from the growing understanding of the mechanisms of carcinogenesis. These new tools have the potential for use in exposure science. Basic sciences are increasing our knowledge about mechanisms, and we can translate that knowledge into tools that can be used at the population level.

What can *-omics* bring? It can enable us to see unique chemical signatures of exposure, some of which may be persistent or irreversible, said M. Smith. The “holy grail” of molecular epidemiology and the exposome is a biomarker of historical exposure. He discussed recent findings in genomics (the study of genes [DNA] and their functions),

proteomics (the study of proteins expressed by a genome), and transcriptomics (the study of RNA molecules produced by the genome) that constitute preliminary evidence of how *-omics* approaches may be used to discover exposure biomarkers. Using transcriptomics, M. Smith and several collaborators recently identified two potential signatures of benzene exposure—one that is independent of dose and thus might reflect exposure itself and a second that depends on exposure dose and thus might reflect an effect of or response to exposure. As for biomarkers of historical exposure, Avrum Spira and colleagues will soon publish a study that used *-omics* to identify a pattern of irreversibly altered genes by looking at gene expression and microRNA profiles of current, former, and never smokers.

Dean Jones, of Emory University, described two potential pitfalls to avoid as one considers *-omics* approaches for developing the exposome. One pitfall is reducing the exposome research to a small number of agents, either chemical or otherwise. If you study one agent at a time you may miss important potential biomarkers. A second pitfall is to assume that mechanisms of toxicity are common among people; people may all respond to an exposure but respond in different ways.

To study the relationship between environmental exposures and Parkinson’s disease, Jones and his colleagues are taking a “top-down” approach (see illustration). They are using metabolomics (the study of metabolites, produced by cellular processes) to examine all the compounds (potential biomarkers) that they can detect, rather than targeting known compounds, because the identity of half the chemicals in human plasma is unknown. Jones and his colleagues use Fourier transform mass spectrometry (FTMS), which differs slightly from traditional approaches to metabolic profiling. FTMS has the accuracy and resolution to identify 90% of all chemicals on the basis of their mass:charge ratio. They use it for plasma, but it potentially could be used with

Bottom-up Exposomics	vs.	Top-down Exposomics
Evaluate uptake, metabolism, etc., of <i>important</i> agents (to estimate dose).		Measure all analytes in blood from cases and controls.
Test for associations with case status.		Test for associations with case status.
Measure all analytes in air, water, food, etc., from cases and controls.		Identify <i>important</i> agents and determine sources of exposure.

Stephen Rappaport’s comparison of Bottom-up and Top-Down Exposomics.

blood spots. It has moderately high throughput and is very reproducible. Jones also gave examples of the use of this top-down approach to detect differences between pups exposed to ethanol in utero and pups not exposed.

Recognizing the danger of “reductionist thinking” discussed by Jones, Rappaport suggested that it might be possible to reduce the number of chemicals that have to be investigated if research focused on features that commonly make chemicals toxic. In 2006, T. W. Schulz and colleagues reported that most effects attributed to reactive toxicity result from the interaction between an electrophilic chemical and a biologic nucleophile.³ Rappaport described a novel -omics technology, adductomics, the study of adducts produced by a chemical that binds to DNA or blood proteins. Adductomics can be used to characterize exposures to electrophiles, a large class of reactive toxicants that includes aldehydes, quinones, and reactive oxygen species. Electrophiles have a short life span *in vivo* but form stable adducts by reacting with biologic nucleophiles. Triple-quadrupole mass spectrometry with selected reaction monitoring has the necessary sensitivity and specificity for adductomics, said Rappaport.

M. Smith predicted that we are very close to being able to use a systems approach that includes metabolomics, transcriptomics, and adductomics on a set of pilot studies or samples to discern differences between healthy people and diseased patients. We can find DNA in dried blood spots, and within a decade we will potentially be able to elaborate the epigenome and the exposome in a drop of blood, said Rappaport. Rothman said that it would be exciting to use genomic technology to get to the point where adducts, peptides, and other biomarkers can be measured by using very small samples. Wild, however, cautioned that we need to guard against the exposome’s becoming overwhelmed by everything that can be measured. Substantial advances can be made with fairly modest improvements in measurement, he said.

Leveraging Existing Population Research Studies

A session of the workshop focused on existing resources that might be leveraged for exposome research. Tyler Smith, of the Department of Defense (DOD) Center for Deployment Health Research, described current and potential research in the Millennium Cohort Study, DOD’s largest prospective health study ever, which currently includes 152,000 members of all the military services and will eventually add another 50,000. The study is designed to evaluate both subjective and diagnosed chronic health problems in relation to exposures of military concern.

³ Schultz TW, Carlson RE, Cronin MT, Hermens JL, Johnson R, O’Brien PJ, Roberts DW, Siraki A, Wallace KB, Veith GD. A conceptual framework for predicting the toxicity of reactive chemicals: modeling soft electrophilicity. SAR QSAR Environ Res 2006; 17(4):413–28.

A key future research direction is the use of biologic sampling to investigate markers of health outcomes. DOD has the world’s largest serum repository—about 50 million specimens, which have been collected since the late 1980s. It has conducted military-relevant studies with the samples, including a pilot study of dioxin body burden in personnel near a notorious burn pit. DOD also encourages study, by scientists in or outside DOD, of samples collected before and after deployment, according to Craig Postlewaite, of DOD Force Readiness and Health Assurance.

The Millennium Cohort study has a considerable amount of personnel data, including deployment locations, immunization records, job positions, and self-reported exposure data, but there are major limitations of the data, including the inability to access classified information, such as exact location of military personnel, and inaccuracy or inconsistency of exposure assessment. DOD uses environmental monitoring as a surrogate for exposure, but sampling is inconsistent particularly during combat and often does not include information about the time and duration of an exposure, especially with reference to health outcomes. The absence of information often leads to misclassification. T. Smith hoped that information gathered with an exposome approach could help to overcome some of the limitations of current exposure assessment.

Our tasking out of the White House is to create individual exposure records on our personnel, who are deployed around the world. We are looking for the capability to develop records.

—Craig Postlewaite

Patricia Hartge, of NCI, discussed several existing cancer cohort studies and cohort consortia and some considerations that are important in cohort construction. She emphasized the need to consider special exposure cohorts, liken those of the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) and the Sister Study. The PLCO includes 155,000 men and women who have no history of cancer at enrollment. It was designed to develop a biospecimen repository for molecular epidemiology of cancer etiology and early disease detection. The Sister Study includes 50,000 women whose sisters had breast cancer and has an emphasis on underrepresented groups. The Sister Study includes extensive biospecimen sampling, including sampling of urine, blood, and toenails.

Hartge noted that it is important to consider how existing cohorts are constructed when thinking about how to put the exposome into practice. Cohorts of different sizes will be required for studying different outcomes and effects. It is also important to have cohorts of children and adolescents and of multigeneration groups.

Relationships of timing of exposures to outcomes should be considered. For example, there is often a 30-year lag between an exposure and the occurrence of cancer, but that is not necessarily true in other diseases. However, we will still need prospective cohorts with biospecimens to convince ourselves that an association or a lack of association between an environmental exposure and an important outcome, such as breast cancer, is real, explained Hartge.

Hartge also discussed multiple-cohort consortia, which may be powerful resources for answering questions that are common to individual cohorts. The NCI Cohort Consortium consists of 40 cohorts of at least 10,000 participants each. DNA has been collected from about half the cohorts, and serum from probably about two-thirds of those. A recently completed project involving the consortium assessed vitamin D concentrations in prediagnostic blood serum. Vitamin D deficiency is a serious public-health concern. Hartge also mentioned the Asian cohort consortium, which was developed specifically to look at relationships between genes, environmental exposures, and disease. She noted that researchers work hard to put cohorts together and that it is important to develop good communication in and among consortia.

Exposome Vision and Challenges

The second day of the exposome workshop focused on scientific challenges in, public-health value of, and practical next steps for developing the exposome. John Groopman, of Johns Hopkins University, proposed an overarching vision and described scientific and science-policy-related challenges in developing the exposome. A vision for the exposome is to identify, characterize, and quantify the exogenous and endogenous exposures and modifiable risk factors that predispose to and predict diseases throughout a person's life span, said Groopman. He noted that measuring environmental exposures from conception on is a large challenge that requires interdisciplinary research, the hallmark of environmental health research.

Groopman explained that advances in genetics, epigenetics, and human biomarker research show the potential for and challenges in developing the exposome. For example, technology has advanced to the point where we can analyze millions of single-nucleotide polymorphisms (single changes in a gene) in a single assay, in contrast with one in 1997. As a result, we know much more now about relating specific genetic changes to chronic-disease end points, said Groopman. However, the technology increase has created an enormous informatics challenge, he observed.

How we will analyze and use the tremendous amount of data that will come from the new techniques related to the exposome is a challenge that bears repeating, said Elaine Cohen Hubal, of the Environmental Protection

Agency (EPA) National Center for Computational Toxicology. If our goal is improve our understanding of environmental contributions to the cause of disease, we need to think holistically, form an international initiative to bring investigators together, and allow scientists to put their pieces on the map to facilitate integrated interpretation, said Hubal.

Groopman also pointed out that scientists, policy-makers, and funders need to move away from compound-by-compound assessments. That is a particular challenge in that many scientists, including him, have built their careers around single compounds. Linda Birnbaum, director of NIEHS, agreed that we need to move away from the compound-by-compound, dose-response paradigm and start to understand patterns indicative of the processes and exposures

It is our challenge to take these data and to translate them into useful public health policy and impact.

—John Groopman

that lead to disease. Although it is less practical for regulation, we need to find ways to group the many materials that we find in the environment, said Rita Schoeny, of the EPA Office of Science and Technology. EPA is taking incremental steps to look at aggregated risk associated with all routes of exposure and to combine risks posed by materials thought to have the same mode of action. Wild suggested that some of the new tools discussed during the workshop may reveal the cumulative effects of chemicals and their common pathways.

Public Health and Individualized Prevention: Will the Exposome Provide Answers?

In addition to scientific challenges raised by Groopman and others, Howard Frumkin, of the Centers for Disease Control and Prevention, urged participants to consider how the exposome can be applied to issues that regularly arise in public-health practice (see box). Unlike some of the research questions posed during the workshop, the public-health questions facing officials at the federal, state, and local levels are on a short time frame. In communities whose residents perceive high rates of a disease, public health practitioners are asked whether particular community exposures caused the disease. In “fence-line” communities, such as a community near a factory or a group of factories, residents often ask public officials whether they are safe. Exposure assessments might show that individual chemical exposures in a fence-line community are all below regulatory standards, but with multiple exposures present the community clearly is still polluted. Conventional exposure assessment does not yield a complete picture. What is wrong with our science? asked Frumkin. In addition, many communities face much more than chemical exposures. The toxic

**Public-Health Questions—
Will the Exposome Provide Answers?**

1. Can we expect the exposome concept or the tools to which it gives rise to help us answer questions about past exposures in connection with current disease?
2. Can we expect the exposome concept or the tools to which it gives rise to help us answer community questions about whether current exposures are safe?
3. Can the exposome concept or the tools to which it gives rise help us deal with multiple exposures that occur simultaneously at the community level and help us give sensible answers to communities?
4. Can the exposome concept or the tools to which it gives rise help us integrate the cumulative exposure, both chemical and nonchemical, that communities face so that we can assess the combined risk that people face? Can we guide policies so that we know which risks to address and correct to improve the health and well-being of people in the community?

Howard Frumkin asked whether information provided by the exposome could be used to answer key questions that public-health practitioners are frequently asked by federal, state, or local government officials and the public.

exposures must be contextualized, said Frumkin, when they are accompanied by stress, unemployment, lack of access to health care, an ugly neighborhood, and other health challenges. Public health practitioners must weigh the benefits of hazardous waste-site cleanup against other worthy investments, such as schools and health clinics, needed in the community.

William Farland, of Colorado State University, raised the issue of using the exposome to develop individualized prevention. Common toxicity pathways are modulated by and represent differences in individual reactions to exposures, said Farland. Our efforts to understand the exposome build on several National Research Council reports, including *Toxicity Testing in the 21st Century*, which talks about those individual differences. However, many prevention trials have been abysmal failures because we haven't understood compounds' underlying mechanisms. Farland argued that in exposome research we should consider prevention—both reducing the biologically or toxicologically effective dose and reducing the actual exposure.

Frumkin warned that although the genomics revolution has offered great promise with respect to individualized therapeutics, it is a huge leap to go from there to individualized prevention, in part because individual vulnerability varies among populations. Determining who is vulnerable to a chemical and who is not will be resource-intensive, and it may be better for resource investment to try to determine which molecular structures are less toxic and to focus on the production of those molecules instead, said Frumkin.

Helmut Zarbl, of the Robert Wood Johnson Medical School, observed that many exposures cannot be avoided. People face unavoidable exposures in some communities and workplaces. Designing interventions to help with those types of exposures is important, and the exposome is a good way of working toward those interventions, said Zarbl.

Where Do We Go From Here?

The final session of the workshop focused on practical next steps for building and maintaining a national exposome research initiative. The exposome could constitute the next big step in trying to understand human disease, said Tina Bahadori, of the American Chemistry Council. It is important to discuss how to bring visionary leadership and to build capacity, not 10 years from now, but today.

Drawing on a 2003 paper published in *Science* by Francis Collins and on his own experience with the Human Genome Project and other large-scale National Institutes of Health (NIH) research projects, Christopher Austin, of the NIH Chemical Genomics Center, highlighted key aspects of successful large-scale research endeavors.⁴ Austin emphasized the importance of scope, staging, team-building, and public involvement.

The scope and focus must be scientifically based. That is a challenge because one must teach politicians, who are not scientists, what the science is all about. That is best achieved, noted Austin, by people who can easily explain science and can “capture the public imagination and Congress’s imagination.”

An advantage you have over the Human Genome Project, when it was proposed, is that I don't think anybody will argue with the fact that if you succeed in doing the exposome, it is going to be useful.

—Christopher Austin

Staging is critical, emphasized Austin. The project must have clear strategies, explicit milestones, and quality assessments. Data that cannot be reproduced are unacceptable. Also, the project must have three parts: data generation, technology development, and data dissemination.

Building the best teams is important. It is best to have people who want to collaborate and who have a long-term global view. Austin noted that most scientists are taught to be rigorously independent, so it is important to have scientifically driven managers as part of the team. In addition, the project should have international participation. Global participation expands available funding and harnesses scientific resources and knowledge that are not necessarily available in the United States.

⁴ Collins FS, Morgan M, Patrinos A. The human genome project: lessons learned from large-scale biology. *Science* 2003; 300(5617):286–90.

Establishing the exposome as a community resource project is ideal, according to Austin. A community resource project is specifically devised and implemented to create data and other scientific materials whose primary utility will be as a resource for the broad scientific community. In addition, making data freely available to the public helps to garner community support by demonstrating value.

In Summary . . .

Rappaport offered the following summary of key points made by workshop participants.

1. The environmental burden of disease is large, particularly if factors beyond traditional measures of air and water pollution, such as stress, are included. There should be more focus on environmental exposures to improve human health because genetic variations probably play a fairly minor overall role in cancers and degenerative diseases.

Looking to the sources of exposure is what I would call exposure assessment and exposure characterization. If you are interested in taking the exposome and determining its impact on human disease processes, that is what I call exposomics, and that is the beauty of the exposome.

—Stephen Rappaport

2. The exposome puts the primary focus back on human health. It moves exposure science away from studying the relationships between source and receptor and closer to studying the relationships between exposure and some kind of health-related outcome.
3. Developing the exposome will require extraordinary effort in many disciplines. It will need input from exposure science, epidemiology, molecular biology, analytic chemistry, bioinformatics, and engineering.

Those disciplines are not yet connected and will need to develop a common language.

4. There needs to be movement from environmental monitoring to biomonitoring and the use of biomarkers to identify and elaborate the exposome.
5. The exposome can provide quantitative tools for evaluating the many stress-related health risks identified by social epidemiology.
6. Epidemiologic design issues need to be addressed, and the utility of the different designs and available population cohorts need to be considered.
7. Some sectors of -omics technology will be useful in elaborating the exposome. Preliminary -omics research has demonstrated its usefulness for developing biomarkers of historical and current exposures.
8. A top-down exposomics approach is more efficient than a bottom-up approach, and it may be possible to focus on classes of toxicants that have known or suspected associations with human disease.
9. Existing cohort studies and consortia provide access to much questionnaire data and biospecimens that can be used in proof-of-concept studies to characterize and evaluate the exposome. We should encourage support of consortia, longitudinal sampling, and the development of comprehensive cohorts.
10. The exposome effort needs clear strategies and timelines. It will involve identifying the most useful biomarkers, cohorts, and biospecimen repositories. It will be important to emphasize the significance of the exposome for science and human health and to demonstrate its societal benefits.

This newsletter was prepared by Tina Adler, Keegan Sawyer, and Marilee Shelton-Davenport, and edited by Norman Grossblatt.

Related News and Publications

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