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Eunice Kennedy Shriver National Institute of Child Health and Human Development

Scientific Vision Workshop on the Environment

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Workshop White Paper

by Workshop Organizers:
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1. Introduction

The environment—broadly defined as the social, psychological, toxic, and infectious agents to which people can be exposed—deeply affects current and future generations of humans, who in turn affect and shape the environment. It is a leading cause of mortality for mothers and children worldwide and contributes to disabilities and to adverse outcomes for people with disabilities.

Understanding the interplay between the environment and maternal, paternal, child and reproductive health therefore requires a comprehensive approach: an expansive view of what the environment comprises and a broad view of what its effects might be. The causes to be examined go well beyond consideration of particular chemical compounds and the consequences go well beyond the physical health of parents and their children at a single point in time or at single point in the life-span.

NICHD's focus, which includes reproductive health, pregnancy, and child health, gives this institute a unique opportunity and a unique responsibility: exposures to the environment during sensitive developmental windows, including before birth, early childhood, puberty, conception, and pregnancy, have impacts that last over the life course and beyond, to future generations. Advancing our understanding of the environmental impacts, their magnitudes and directions, and their multiple channels of causality will greatly advance our understanding of how these impacts can be mitigated, to the great benefit of public health.

2. The workshop

To address this incredibly rich theme, a multidisciplinary scientific group was invited to a two-day workshop. After kick-off presentations by Scott Gilbert, Michael Greenstone and Greg Duncan and a panel on methods including Barbara Entwistle, Duncan Thomas, Nina Holland and Shumei Sun, participants attended 18 breakout sessions, charged to identify the scientific opportunities and challenges in very specific themes. (The list of breakout sessions is presented in Box 1.)

Each breakout group produced a summary document; these documents form the basis of this paper. The topics and the breakout groups' expertise were extremely deep and wide, which meant that the groups started off with rich and varied lists of potential questions and opportunities. The groups each produced a focused set of overarching questions and opportunities. In this paper, we focus on the breakout groups' conclusions as reported in the summaries, and we present the conclusions in two parts: the scientific opportunities, and how to get there.

BOX 1: LIST OF BREAK OUT SESSIONS

- Toxicity: Food, Soil, Water, etc.
- Healthy Homes
- Impact of Air Pollution on Human Health
- Water Pollution and Human Health
- Multiple Exposures, Mixtures, and Dose Response
- Building *in vitro* Models for Environmental Research
- Early Life Determinants of Neurodevelopment and Mental Health
- Social Behavior and Physical Development in Young Girls in Developed and Developing Countries
- Social Environment: Influences on Child Health and Development
- Economic and Social Barriers to Adoption of Known Preventive Practices
- Eradicating HIV
- Vaccine Development and Delivery
- Environmental Influences on Female Reproduction: Windows of Susceptibility
- Environmental Influences on Male Reproduction: Windows of Susceptibility
- Role of Comparative Biology in Understanding Effects of Environmental Factors on Human Development, Reproduction, Health, and Disease over the Lifecourse
- Womb to Death: A Lifecourse Perspective on How Environmental Factors Influence Health and Development over Time
- Environmental Justice: The Impact of Environment on Health in Vulnerable and Underserved Populations
- Transgenerational Effects of Environmental Exposure

3. Scientific opportunities

Measuring exposures and outcomes

A first key challenge is to improve the measurements of both environmental exposures and their impacts.

The field of toxicity has seen the emergence of new threats, including climate change, geo-engineering, electronic water (magnetic treatment of hard water, also know as anti-scale magnetic treatment or AMT), and nanotechnology and nanoparticles (e.g., in sunscreen). The field is also in its infancy in understanding how multiple exposures interact (e.g., endocrine disruptors). Researchers also have the opportunity to study emerging “marker” diseases; translate the impact of internal doses in animals to expected effects in humans; understand toxicokinetics in pregnant women, developing fetuses and children; and understand interactions with and among other risks (e.g., infection, poverty, prematurity) and toxins.

At the exposure level, tens of thousands of chemicals could potentially be measured. At the moment, measurement is limited to just a few, due both to costs and limitations of technology.

Furthermore, measurement is not harmonized. Can the technology be improved to make it easier, cheaper and less intrusive to measure potentially toxic exposures? There is a comparable need for harmonization in the measurement of non-chemical stressors and the social environment.

The next step would be to explore the possibility of developing effective biomarkers as proxy measures of exposure.

Finally, progress can also be made in getting harmonized measures of the important outcomes, particularly before they turn into clear pathologies: including early markers of neurodevelopment, growth, reproductive dysfunction, mental disorders, precursors of obesity and diabetes, immune and endocrine dysfunction, and cardiovascular and cancer risk.

The time dimension: Window of exposure, long term and trans-generational impacts

A key lesson of epigenetic studies is that environmental exposures, particularly in early life, can induce molecular changes that have long-term effects and can be transmitted from generation to generation. Indeed, to fully understand the impact of a first exposure, multigenerational studies should include at least three generations. Considering that behavioral, nutritional, and chemical factors can each cause modifications to our epigenome, it is important to understand how these factors interact and possibly synergize.

Studies that have followed the long-term effects of pre-natal exposure to an adverse environment (the famine in China, the great flu pandemic, the Chernobyl Disaster) suggest that, in practice, these long-term and cross-generational effects can indeed be very important.

We need to understand better the relevant environment, genome, and epigenetic interactions, and which specific and well-measured exposures trigger these mechanisms. At a broader level, we need to delineate which categories of environmental exposure have “womb to death” relevance, as well as the strength of the effects on later-life outcomes. Because the developmental “susceptibility window” will vary depending on the specific tissue, organ system, and even organism considered, research that describes the period of susceptibility for different exposures and outcomes is critical. A recurring theme for the workshop was that the prenatal period is pivotal. We have relatively poor understanding of how timing of exposure within this period may have an impact on tissue and organ development. Improved understanding of timing will help elucidate biological mechanisms and pinpoint the optimal timing of safeguards, and policy interventions. Furthermore, since rapid development continues after birth, not all effective interventions will be confined to the prenatal period. A challenge will be to identify research designs that support causal inference in the absence of a well-defined postnatal developmental period. Just because “womb to death” linkages are triggered early does not imply that they are irreversible. Behavior in the periods following may mitigate (or accentuate) the impact of a given prenatal environmental exposure. Thus it is equally important to understand the causal effect of possible mitigation intervention(s).

This implies that, when we study the effects of the environment on fathers, mothers and their children, we have to think, about the effect not only during conception, pregnancy and childhood but also over the life course and beyond, to subsequent generations. Taking this very long-run dimension into consideration is not straightforward, given the time lag involved, but is absolutely essential and may hold the key to understanding diseases which are today considered to be "adult" diseases, but may have a root in a pre-natal (or even pre-conception) exposure, potentially in prior generations.

The known unknown and the unknown: old substances with unknown effects; new chemicals; new mixtures; new doses…

The "traditional" approach to toxicity may have been to focus on the effect of large, pathological exposures (to chemicals or to dysfunctional social environments). Those are essential objects of studies, as we were reminded by the nuclear accident at Fukushima—the 2011 Japanese earthquake, tsunami, release of radiation and population trauma and displacement.

But beyond these, we also need a better understanding of the impacts of much lower doses of environmental exposures (chemical and otherwise), which are multiplying in our environment. There are a very large number of chemicals whose effects are entirely unknown. We need to understand the impact of low doses and the way in which these different factors interact with each other.

To properly account for the potential for combination effects from exposure to multiple chemicals, risk evaluation of mixtures should include relevant environmental exposures from chemicals grouped by common adverse outcome (not mechanism/mode of action). Evaluation of single chemicals without accounting for combination effects may underestimate risk. Human exposure to complex mixtures of environmental chemicals is ubiquitous and could lead to an underestimation of the adverse health impact of any single chemical. Pregnant women and children are among the most susceptible populations for adverse effects from these exposures. The exposome of these vulnerable groups should be better characterized, based on relevant sets of chemicals – not chosen for convenience. Methods for evaluating the impact of complex mixtures on human health should be the focus of new innovative thinking.

Understanding the complex causal effects of the environment: from in vitro and animal models to hypothesis generation

One obvious problem with the conclusion of the previous section is that the complexity of the problem seems to have the scope to grow exponentially. This suggests that it may not always be possible to have a detailed pathway linking every specific cause to a specific outcome with human populations. There are, however, other promising paths for future research, some of which are highly practical and others that set the stage for greater understanding and prevention of deleterious effects.

All of these approaches are potentially fruitful: First, use of *in vitro* and animal models, which give us the opportunity of investigating a large number of possible factors, over several generations. Second, a more "global" approach: an environment can be described and studied as a cluster of factors that can be observed in populations over time and space.

1) Non-human research. In vivo, non-human models are required for biomedical research and these models will never be perfect. Experimentation with human subjects is limited by moral and ethical standards and organisms that more closely represent human qualities are constrained by limited numbers as well as expense. However, a wide range of models currently exist and additional models would be beneficial.

The concept of comparative biology in advancing human health falls into three categories of opportunity. First is the recognition of new useful models from the vast array of extant species and the willingness to search for them. The second is the combining of new models with new laboratory and communication technologies. For example, stem cells from humans as well as a variety of divergent species can provide the broadest approach to experimental designs. Finally, the new models that are identified and validated will need to be streamlined and standardized so that academic, regulatory and industry actions can have a more sophisticated approach to chemical screening and/or surveillance.

2). Hypothesis generation. When societies become more industrialized, the quality of air and water change in a variety of ways. Or when a society decides to toughen its environmental regulation, this also produces a cluster of changes. As we already pointed out, evaluating the effects of mixtures of chemical and non-chemical environmental exposures becomes quite complicated quite quickly. To shed light on these issues, it may be necessary to treat changes in the environment as a "package." (This packaging approach has been used fruitfully to study complex systems in other disciplines. For example, engineers study input and output in complex problems, or economists and other social scientists study the "reduced form" or "overall" effect of a cluster of changes in the environment.)

The approach may result in a "black box" that indicates a causal relationship between a complex change in the environment and an output, without explanation. These methods are important for generating hypotheses, which can then be investigated in detail. An approach centered on known mechanisms may miss important effects of mixtures.

The new priorities would include (1) identification of "bad actors" among large sets of chemicals or non-chemical environmental stressors that are purported to be associated with a common adverse outcome; (2) identification of biomarkers of exposure linked to health outcomes; and even (3) determination of which chemicals/stressors or biomarkers of exposure or pathway may be associated with multiple outcomes – or holistic measures of wellness.

Being open-minded on possible causal pathways does not require lowering our standard in terms of what constitutes rigorous proof of a causal effect. Too often, when researchers or policy makers move from the lab to the real world, the standard of what constitutes a causal effect is lowered. There is really no reason for this to be the case, and there would be a tremendous gain in rigorously establishing causal relationships between "complex" changes and overall measure(s) of well being.

How do individuals and societies choose and shape their environment? How can these choices be affected?

With the exception of the fetus and young children, the environment (social or physical) is usually not imposed, without choice, from the outside. Families choose where to live, how to build their houses, and what to expose their children to. Even children choose their environments. As societies, we make collective choices that determine what the environment is going to be.

Understanding how individuals make these choices is essential to our ability to guide public health policy. At the family level, what is the willingness to pay to avoid a particular kind of environmental hazard? Will families in the developing world chose to live in overcrowded cities with no sanitation to ensure that they can get a job, or will they give up a profitable employment opportunity to make sure their children live in a healthier, rural environment? How much do parents pay (e.g., for a doctor visit or an asthma medication) to protect their children from the effect of bad air quality? How are these factors affected by information, opportunities, and public policy (subsidies, compulsion, or “nudges”)? These are the types of questions for which we have very few answers at this stage.

At the societal level, the same question arises, with even more urgency: what is the willingness to regulate (and enforce regulations!) to avoid harmful environmental exposure? What would be the economic costs, if any? As societies, where are we willing to be on this trade-off? How does it depend on the political structure of a particular society or on its level of development? What role does the communication of research results play?

Because this willingness to pay depends on information, this question also interacts with our own work as researchers: Research should be conducted on how to better communicate the potential health risks associated with a complex environment. This message should be science-based, yet presented in terms that the larger community, not just scientists, can understand and could alter behavior accordingly.

What interventions are effective at mitigating environmental effects? How to make sure they are implemented?

Finally, we need a better understanding of how to mitigate environmental effects, in circumstances where the environment itself cannot be modified. Vaccines are a powerful way of mitigating an environment rich with infectious agents: Can new vaccines be developed? Can we invent “epigenetic therapy” to mitigate known exposures and to break transgenerational cycles? Folic acid supplementation (methyl donor), which counteracts the effects of a poor quality diet in pregnancy, is a start, but more needs to be discovered through animal models and then translated to humans. A great question would be, what is the next folic acid? Can we develop interventions both within and between generations – keeping questions of timing in mind? Can intervention in very early life, in pre-school, or in school, counteract the effect of a bad social environment? When do interventions need to happen? How do we demonstrate their effectiveness?

Next, however, we also need to understand how to make sure that these interventions, once developed, are widely adopted. Effective interventions such as vaccinations, insecticide-treated bed nets, water chlorination (in poor countries), exercise, balanced diet (in rich countries), are often underutilized. What stands in the way? Can a social and political environment be created where those behaviors would be the “natural” course of action? Can the interventions themselves be designed with the humans that will use them in mind?

4. How to do get there: Process opportunities

To make progress on these key questions, a number of opportunities came up in most of the summaries of the group discussions.

Cohort Studies and sample banks

Given the long-run nature of the impact of environmental exposures, cohorts that are followed over the long run (across generations) are absolutely critical to our understanding of the environment. There are a number of long-running cohort studies that are invaluable resources. They exist both in the U.S. and abroad. Although costly, it is an efficient and smart use of funds to invest in maintaining cohorts and biorepositories. Maintaining these cohorts, and using them as platforms to collect more data, was viewed as essential. The data should be made widely available to the research community.

Furthermore, improved characterization of exposure to environmental chemicals and non-chemical stressors in those cohort studies (termed the exposome) through pregnancy biospecimens, cord blood, biospecimens for adults of child bearing age, parents, and young children would improve the risk evaluation for important susceptible populations.

Maintaining individual, longitudinal data and especially precious biological banks through the life-course is both costly and unfashionable, but offers large payoffs and crucial research opportunities as new methodologies emerge (e.g., epigenetic markers are time-dependent, and require longitudinal sampling). Therefore, maintaining sample banks is required to ensure that past sample collection work continues to enable new research (e.g., to answer questions that have not yet even been asked.)

Natural experiments

Natural experiments, from disasters to policy changes, particularly in concert with ongoing cohort or panel studies, can open precious windows into the effects of changes in the environment. Sometimes, they will require special data collection in order to collect the right outcomes or individual level exposure data corresponding to a specific experiment. These natural experiments are invaluable because, when they happen in the past, they can give us a long-term perspective. Moreover, carefully constructed analysis of these events allows one to get very robust estimates of causal impact (by comparing carefully constructed affected and unaffected groups).

Harmonization of measurement and data collection

The existing data collection efforts lack common standards to measure both exposures and outcomes: different teams use different methods, and the results are not always comparable. There is an important need for infrastructure work to develop common indicators for both of these types of measures, but without stifling creative new approaches. This needs to be done in consultative ways, with teams involving specialists from different disciplines, to make sure that the resulting instruments are creative, high quality, comprehensive, and widely used and accepted.

With new statistical methods, it is possible to pool data across smaller studies. This may require funds to "work out differences" across institutions, e.g. IRB, contracts and other logistics. These data could then be made available to others, given certain prescribed criteria. New longitudinal birth cohort studies (e.g., the National Children's Study (NCS)) aimed at looking at toxicity should learn from the experiences of these smaller cohorts and past cohorts.

Basic elements of toxicity studies are needed to move the research agenda forward, including transdisciplinary research, central biorepositories with stable funding, and excellent exposure markers that can reflect internal dose. Technological innovation in exposure measurement, e.g., chip and exposome, may make this possible in the near future. Partnerships with industry may be a possible route to increasing accuracy and reducing costs in exposure assessment.

Another important feature of characterizing the exposome of susceptible populations is to evaluate the impact of non-chemical stressors such as diet, exercise, weather, poverty and other external stresses. Ideally, these studies should be longitudinal so that the impact of exposure may be monitored over time; however, even cross-sectional studies are valuable to track trends in exposure.

Randomized trials

Randomized trials allow researchers to establish causal claims with a great level of rigor and certainty. While they are a mainstay of medical research, they remain underused in the public health and social sciences fields. Of course, ethical concerns limit how they can be used. But they are ideal tools, for example, to evaluate the effectiveness of new proposed measures to mitigate environmental damages (e.g., stoves that reduce indoor air pollution in developing countries) or to evaluate the impact of interventions designed to try to increase the adoption of some known effective measures (e.g., information campaigns for vaccines, HIV-AIDs prevention programs, etc.). Following cohorts that were exposed to different interventions over the long run, when possible, would be particularly valuable. Thus, combining randomized control trials with cohort studies, to leverage the data collection apparatus already in place, was identified by several groups as a particularly promising area.

In this context, the NCS was mentioned by several groups, both as a source of fantastic opportunity and with some trepidation. The way the sample is constructed will have a major impact on what can be said about this cohort. Many teams should be encouraged to propose questions. The data should be made widely available as it is collected and there should be a process for inputs from the wider scientific communities.

New sources of data

A number of new data types and sources are becoming available or could become available: video, genetic analysis, social network data, and electronic medical records are but a few examples. Encouraging the development of methods to harvest and productively use these new data sources could dramatically enrich the studies.

Free-living sentinel non-human species are a specific example of such data. They can be used as indicators of real world exposures. Identification of adverse effects in these species presents an untapped resource. Opportunities to use modern communication networks for monitoring non-human populations are an example of how internet connectivity might contribute. Existing archival information on a wide variety of species should be exploited and we should promote and fund meta-analysis of animal data.

Link existing administrative data sources, and make them available to researchers

A wealth of data is already available at our fingertips: governments create comprehensive micro-economic files (e.g., Card, Chetty, Feldstein, Saez, NSF white paper, 2011). A rich archive of information covering most aspects of socio-economic behavior from birth to death, including education, earnings, income, workplace and living place, family composition, health and retirement, is recorded in administrative data. All these administrative data are stored in electronic files that can be used for statistical analysis. Administrative data have large sample sizes, an inherent longitudinal structure, and high quality information. Because of confidentiality and security concerns, administrative data cannot be made publicly available. However, numerous examples—from the Centers for Medicare and Medicaid Services, from other countries, and from a variety of pilot efforts at federal, state, and local government agencies—show that it is possible to provide secure access to de-identified administrative data to researchers. Outside the U.S., many countries have developed systems to allow access to administrative data for research purposes. In Denmark, for example, Statistics Denmark prepares de-identified data by combining information from administrative databases for approved research projects. The data extracts can then be accessed by researchers remotely through a secure server. Researchers apply for data access through accredited “centers” at major universities and access is provided through an open competition process based on scientific merit. Making administrative data available to researchers would provide an incredible wealth of data that can be used to advance research on the effect of the environment and other things.

At the 30,000 foot view, the U. S. should endeavor to construct a population database complete with biologic samples similar to what has been created in Scandinavian countries. We recognize that there are issues of privacy but the workshop group felt that this was essential to monitor the health of our population and the Scandinavian experience shows these issues can be tackled. Health care reform presents a unique opportunity to begin this process. We should assure that there is quality control in data collection, (e.g., data that is reported on birth certificates is collected correctly at all facilities and in the same fashion), and should take advantage of electronic records, involve the end-users (not just clinicians but researchers) in what data should be collected, store biospecimens routinely collected (alpha-fetoprotein (AFP) levels, Guthrie cards; etc.), and allow linkage of administrative data (by a unique identifier) such as birth, death, marriage certificates; criminal justice system, child welfare, and school records, across state lines.

In the meantime (at the 10,000 foot view), we could focus on more reachable populations (e.g., HMO (Kaiser), Department of Defense, Department of Veterans Affairs) to assure that these organizations are collecting data that could be useable for outside researchers, and put in place protocols that allow access to these data based on merit, and in a fashion that preserves patient confidentiality.

Regarding the use of registers in other countries, one of the possibilities discussed was whether access to population register data in other countries might be "routinized" through NICHD involvement (e.g., supporting creation of a de-identified "public use" version for non-citizens). At present, such register data are generally accessed through personal connections with Scandinavian researchers, which obviously limits possibilities to address research questions creatively and cost-effectively.

Comparative biology

In order to identify new non-human models, a deeper understanding of the similarities and differences between humans and existing animal models should be the first goal. For example, studies should be initiated that compare human qualities of social interaction, reproductive function, cognition, biological development, and differentiation with existing animal models.

Achieving these goals will require funding for multidisciplinary consortia—for face-to-face interactions between comparative, wildlife and conservation biologists, veterinarians, human population scientists (behavior, social, clinical, epidemiological), and zoo, aquarium, and wildlife preserve researchers

Once potential new models are identified, they will then need to be validated. At this step one key requirement is to be able to predict how results will change when moving from one model to another. A second factor will be dealing with "wild type" systems in which individual variations in response to treatments will detract from experimental results. To compensate for this between-animal variation, new experimental designs and analyses must be developed.

The mining of comparative biological data should be encouraged to increase the discovery, recognition of, and availability of new model systems. This, in turn will promote the development of procedures for combining models, such as species-specific stem cell studies followed by whole animal and improved chemical screening for industry and surveillance by regulatory agencies. Hopefully, these activities will, in turn, lead to the development of new prevention strategies and superior treatments for adverse effects from toxic exposures.

These advances will not come without overcoming certain challenges. At institutions, there will be a need for new animal facilities, guidelines, and personnel for care and use of new models. There will be a need for resources for training of personnel in broad animal care and welfare. In general, all research will require updated national guidelines (e.g., define neonatal/pubertal period, windows of susceptibility, normal developmental horizons, etc). These would include details of the similarities and differences between humans and animal models as described above.

In vitro models, computational models, tissue engineering

Since human stem cells differentiate into different cells or tissues, they can be used to study the developmental effects of environmental factors on the various organs or tissues, including epigenetic mechanisms that are involved in the differentiation of these cell types. Conversely, since epigenetic patterns are cell-specific and different cells have different patterns, well-characterized homogenous cell lines can be used to study the epigenetic effects of environmental factors.

The power of the computer has been increased tremendously in recent years. This power has already been used in the development of disciplines such as bioinformatics and systems biology and can be further used to develop *in vitro* and computational or *in silico* models in environmental research.

Computational models can be used to predict the interactions between environmental chemicals and their potential cellular targets. In addition, intra- and inter-cellular signaling pathways can be computationally modeled. In conjunction with high-throughput cell or "micro" organ cultures, computational models can also be used to study the "mixture effects" of the thousands of environmental chemicals, such as endocrine-disrupting compounds.

With the advancement of different materials, tissue engineering has made significant progress. When combined with the availability of the human stem cells, tissue engineering can make it possible to develop different tissues, part of organs, or sometimes complete organs. Engineered tissues or organs can be used to test the effects of the developmental exposures to environmental factors. Of course, the effects of the materials that are used as scaffolds within engineered tissues should be tested carefully for their toxicity before their widespread use.

Although the research question at hand must primarily determine whether an *in vivo* or *in vitro* model should be used, building valid *in vitro* models would address the following concerns and would potentially improve public or global health. *In vitro* models will:

a) Speed up screening of environmental toxicants and biological materials.
b) Reduce the cost for evaluation of environmental hazards and drug safety testing.
c) Reduce use of research animals.

In addition, some of the models (e.g., engineered tissue or organs) that are developed for environmental research can also be used for therapeutic purposes.

Multidisciplinary teams and training

The many facets of the environment imply that researchers from different disciplines need to work on similar problems from different angles. Without losing their disciplinary strength, teams could approach, for example, the same cohort study, or the same randomized experiment, from various aspects: measurements of exposures, observations and understanding of individual and collective choices, and measurement of outcomes. Training programs and postdoctoral opportunities that allow young researchers from one field to spend a year in another lab were frequently mentioned.

Increasing interdisciplinary collaborations could prevent research from happening “in silos”; NICHD would be a natural facilitator. Learning methods of other disciplines (e.g., economists, epidemiologists, toxicologists, and statisticians); providing training programs for studying toxicants in pregnancy and early childhood; training (this may require two mentors) in cross-disciplinary sciences (e.g., Robert Wood Johnson, MacArthur Foundation and NIH Clinical and Translational Science Awards models); and providing funding and publishing opportunities for interdisciplinary researchers would also help us achieve our research goals. Also needed is provision of a way to reward rather than punish junior researchers who engage in cross-disciplinary research, since transitioning between disciplines may delay publications (needed towards the tenure clock). Funding and publishing opportunities would ease the way for junior faculty to make a cross-disciplinary transition.

Interagency collaboration and industry partnerships

Several of the efforts proposed by the different groups had a scope that was broader than the NIH. To succeed, these efforts would need collaboration both across agencies and with private foundations, and others in the private sector. There is a gap between the science that is generated by NIH-supported scientists and the data needs and expectations of various regulatory agencies (e.g., the Environmental Protection Agency, the Food and Drug Administration). This gap should be bridged. As examples, two large-scale initiatives were proposed: toxicity testing in the 21st century, and the vaccine institute. Development of efficient, less costly exposome measurement technology is another high priority.

Collaboration with the private sector is particularly important. Part of the environmental exposures, as already noted, is a by-product of new product manufacturing. These new products may be developed without full consideration of what their long terms impacts may be. It should be of the interest to the manufacturers, and to society, to permit independent, high-quality research on these compounds. To ensure researcher independence, a proposal would be to create a fund (e.g., toxicity testing in the 21^{st} century), administered by the NICHD or another federal agency, into which manufacturers could contribute. Proposals would be evaluated purely on scientific merit, and the fund would retain complete independence from the corporate donors, once a map of research is charted.

5. Conclusion: The public health impact

Understanding and mitigating the effects of the environment, from pre-birth and during early childhood, through adolescence, and reproductive life, is likely to be an incredibly cost-effective way to prevent a range of "adult" diseases, as well as improve the health and quality of life of young adults, parents and their children. Given its focus on reproductive health, pregnancy, and child health, the NICHD is uniquely well-placed to take advantage of this opportunity and so advance the health of current and future generations.

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