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Research Agenda for Environmental Reproductive Health in the 21st Century

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Abstract

Scientific indicators of declining reproductive function and increasing rates of reproductive illnesses since the mid-20th century suggest our reproductive health and, ultimately, our reproductive capacity are under strain. Over roughly the same period, human exposure to both natural and synthetic chemicals has dramatically increased. For example, in the United States alone, 3,000 chemicals are manufactured or imported in excess of 1 million pounds each per year. People are exposed to chemicals in the air, water and food supply, and consumer and personal care products, resulting in measurable levels of multiple chemicals in people's bodies. We propose the following Research Agenda for Environmental Reproductive Health to reverse these trends: 1) Enhance methods to identify environmental contaminant risks, including rapid screening techniques, enhanced surveillance, biomarkers of early biological effects, and studies that reflect population variability in factors that influence susceptibility (lifestage, genetics, social and demographic factors) as well as real-world exposure to multiple chemicals simultaneously; 2) Expand methods to rapidly and inexpensively identify sources of exposure; 3) Identify and evaluate interventions that influence market changes, public policies that contribute to effective chemical management and barriers to chemical policy development; and 4) Invest in tools that enhance research productivity and translation of scientific findings to the individual, community and society levels. The ability to lessen the detrimental impact that environmental contaminants have on our reproductive health lies within our hands. Implementing this research agenda will pay large dividends toward preventing harmful chemical exposures and improving the health of this and future generations.

Introduction

At the beginning of the 21st century, we are in a unique but precarious position. Economic globalization, accelerating technological change, expanding industrialization and shifting political and religious forces have provided great opportunities and challenges. Equally important, a growing number of scientific studies and reviews suggest that our reproductive

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health and, ultimately, our reproductive capacity are under strain. These studies report increases in reproductive diseases and decline in reproductive function since the mid-20th century among certain locations and populations, with examples shown in Figure 1 from readily available data primarily from developed countries (Figure 1).[1–4]

Genetic changes can not explain the decline in reproductive health and function and external factors are likely to play a role, with environmental chemicals identified as one suspect risk factor. [3, 5, 6] Over roughly the same period, manufacture and use of both natural and synthetic chemicals has increased by over 20 fold [7], with approximately 87,000 chemical substances registered for use in U.S. commerce as of 2006, and about 3,000 chemicals manufactured or imported in excess of 1 million pounds each. [8] These chemicals contaminate our air, water and food supply; we are also exposed through the use of a wide range of consumer and personal care products. Data from the National Health and Nutrition Examination Survey show that everyone in the United States has measurable levels of multiple environmental contaminants in his/her body. These findings have been mirrored in studies in Europe, and it is expected that exposures are ubiquitous worldwide. [9, 10]

The power of environmental chemicals to impact reproductive health has been dramatically demonstrated through tragic episodes of food contamination and workplace exposure, including severe neurological, reproductive and developmental effects caused by mercury and polychlorinated biphenyl (PCB) poisonings in Japan and Taiwan, and male infertility caused by occupational exposure to the pesticide 1,2-dibromo-3-chloropropane (DBCP) in California. [11–13]

More recently, attention has been placed on evaluating the effects of everyday exposures to environmental contaminants, particularly in light of the declining trends in reproductive health. This growing science shows that reproductive health is particularly susceptible to disruption by environmental contaminants during key periods of development, during which extensive physiological events, such as cellular proliferation and differentiation and rapid shifts in metabolic and hormonal capabilities, occur. Exposures during any of these periods may result in permanent and irreversible adverse effects that can manifest immediately or later in life (labeled the fetal origin of adult disease [14]) and even in subsequent generations. Finally, the influence of environmental chemicals on health can be enhanced or diminished by other external factors such as access to healthy foods, social inequities, poverty, education, race/ethnicity and local environments.

Environmental reproductive health research has also recently expanded its focus on genotoxic or mutagenic chemicals to include effects on gene expression, or epigenetics. Increasing attention has also been placed a class of chemicals called endocrine disrupting chemicals, which interfere with the production, release, transport, metabolism, binding, action or elimination of natural hormones in the body. This research has also strengthened our recognition that exposure to low doses of chemicals can adversely impact reproductive health, that exposure to mixtures of chemicals can have a cumulative effect and that these types of exposures must therefore be studied and considered in chemicals policy. [15, 16] Lastly, the detection of over 200 chemicals in the U.S. population has raised the question of how, exactly, we are being exposed.

Environmental reproductive health research has been defined as the interdisciplinary study of exposures to environmental contaminants, particularly during critical periods in development (such as prior to conception and during pregnancy), and their potential effects on all aspects of future reproductive health throughout the life course, including conception, fertility, pregnancy, child and adolescent development, and adult health.[3] Like many other aspects of the 21st century, the current state of environmental reproductive health research presents great opportunities and challenges. If elements of the environment we create are contributing to the decline in our reproductive health and capacity, then we have, in our hands, the ability to reverse this trend. But, to identify these elements, we must overcome the challenges of studying effects on reproductive health over lifetimes and multiple generations. This requires a research agenda that enhances our understanding of the continuum from sources to exposures to biological perturbations and overt disease. To ensure that meaningful efforts to prevent identified harmful exposures ensue, priority should also be given to technologies that expand research capabilities and understanding of how scientific information is most effectively translated and used for individual, community and society wide efforts to prevent harmful exposures. It is towards these goals that we recommend the following research program, which integrates and builds upon a number of recent research agendas in related disciplines. [2, 3, 17–19]

Identifying Environmental Contaminant Risk

- **Rapid screening techniques for identifying potential harmful chemicals**. Rapid screening techniques are needed to identify the potential health effects of the thousands of chemicals for which only sparse toxicological data exist, and to identify emerging chemicals of concern. One particularly promising screening method is use of *in vitro* toxicology assays based on human stem cells and their derivatives for predictive toxicology. This research would offer significant advantages over current animal models and assays based on primary and/or transformed cell lines, largely due to their improved relevance and greater versatility. [18] Increased use of *in vitro* assays should be accompanied by research to develop statistical techniques that can evaluate the complex resulting data sets and interpret their relevance for human risks.
- **Reproductive diseases and function surveillance**. Data from cancer registries show that rates of hormonally related cancers (e.g., testicular, prostate and breast) have increased dramatically over the past 50 years, yet we have only sparse data on potentially related non-malignant conditions, such as fibroids, endometriosis and infertility. Information on trends in *all* types of reproductive disease and disorders from both developed and developing countries is essential to detecting problems, to developing and testing research hypotheses and to identifying successful prevention activities.
- **Biomarkers of exposure and pre-clinical indicators of disease**. Biomarkers of exposure and pre-clinical disease will help to overcome the time and resource challenges of studying the entire life span because they would lessen the need to track exposure and disease outcomes over extended periods of time and would provide early indicators of overt disease. Support for expanding our

understanding of disease mechanisms, including epigenetics, proteomics and metabolomics, will be essential to this process.

- **Research on low-dose exposure to mixtures of chemicals**. Research on the effects from human-relevant doses of exposure and from exposure to mixtures of chemicals must be expanded if we are to understand the true risks of our low level and simultaneous exposure to hundreds of chemicals.
- **Life-span and transgenerational studies**. Experiences such as the aforementioned mercury and PCB poisonings, combined with the growing evidence of the fetal origins of adult disease, emphasize the importance of considering and studying the entire lifespan as well as multiple generations. In particular, continuing research on existing human cohorts such as the DES Combined Cohort Follow-up Study (www.desfollowupstudy.org) and initiating new cohorts, such as the National Children's Study (www.nationalchildrensstudy.gov), are valuable and unique investments that must be continued and expanded upon.
- **Inclusion of other determinants of health**. Research on the relationship between sources, exposures and increases in reproductive health risks should consider the influence of other extrinsic factors that can modify the influence of environmental chemicals, including access to healthy foods, social inequities, poverty, education, race/ethnicity and local environments.

Assessing Exposure

- **Rapid, low-cost, easy-to-use, real-time methods for measuring environmental contaminants in environmental media and human biological samples**. Development of these tools will provide the data necessary for ep idemiologic and exposure assessment studies to identify leading sources of exposure contributing to our chemical body burden.
- **Expanded chemical biomonitoring programs**. In addition to expanding the number of chemicals measured, support is necessary for ongoing biomonitoring of sub-populations known to be particularly vulnerable to effects from chemical exposures, including pregnant women, infants, children and elderly populations.

Enhancing Research Productivity

- **Minor investments to amplify research gains**. Minor investments in tools to support materials-sharing between investigators – for example, support for biological specimen banks, tissue sharing efforts and expansion of national surveys to include measures of reproductive health – will vastly expand the amount we can learn from existing research studies at a comparatively minimal cost.
- **Technologies to support multidisciplinary and multi-stakeholder consortiums**. Real-time, interactive, flexible, low-cost and more environmentally neutral technologies, such as wikis, blogs and web conferencing, offer

unprecedented opportunities to form collaborations and share information with geographically disparate members of multidisciplinary teams. Such teams, which can include multiple research disciplines and partners, such as clinical medicine, and community based partners, will be needed to address and interpret the studies identified above.

Making the Findings Matter

- **Research on effective public and economic policies**. Support for research that identifies and evaluates interventions that influence market changes, public policies that contribute to effective chemical management and barriers to effective chemical policy development will support more informed and effective policy and decision making.
- **Research on translating environmental reproductive health**. Identifying the most effective means of educating and translating environmental health information from the scientific and research arenas to policy makers, clinicians and the general public will enable scientific discoveries to make broader contributions to our health.
- **Communication and Collaboration**. The array of stakeholders who must work together in this process – researchers, health care providers, policy makers, community and advocacy groups, national and international agencies – have traditionally been separated by institutional and cultural divides. Each of these fields speaks a different, highly specialized language and communicates in a way that assumes a background expertise. Communication and collaboration are therefore as essential as the pursuit of knowledge and understanding through research.
- **Measuring Effectiveness**. Developing and implementing environmental reproductive health indicators – quantitative, ongoing, and longitudinal measures of sources, exposures and disease outcomes – is key to identifying successful interventions and prioritizing areas of future efforts. In addition, equal attention should be put toward developing other methods to evaluate research and prevention-oriented efforts at the personal, community and system-wide level to ensure efficient and effective use of resources.

Conclusion

We are fortunate that the ability to lessen the detrimental impact that environmental contaminants have on our reproductive health lies within our hands. A research effort that improves our ability to understand the continuum from sources, to exposures to disease etiologies and how to effectively utilize this knowledge is a critical component of efforts to create an environment in which future generations thrive.

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An Agenda for Environmental Reproductive Health Research in the 21st Century

Identify Environmental Contaminant Risk

- Rapid screening techniques for identifying potential harmful chemicals
- Surveillance of reproductive diseases and function
- Biomarkers of exposure and pre-clinical indicators of disease
- Research on low-dose exposure to mixtures of chemicals
- Life-span and transgenerational studies
- Inclusion of other determinants of health

Assess Exposure

- Rapid, low-cost, easy-to-use, real-time methods for measuring environmental contaminants in environmental media and human biological samples
- Expanded chemical biomonitoring programs

Enhance Research Productivity

- Amplify research gains with minor investments in existing studies
- Utilize technology to support multidisciplinary and multi-stakeholder consortiums

Make Findings Matter

- Research effective public and economic policies
- Research on translating environmental reproductive health science
- Create, foster and participate in interdisciplinary collaboration and communication
- Develop and measure environmental reproductive health indicators.

Reproductive Diseases/Disorders	Increase	Period	Location	Ref.
Testicular cancer	1– 6%	1953 - 1999	Europe	[20]
Testicular cancer	60%	1973 - 2003	USA	[21]
Certain childhood cancers	20 – 24%	1976 - 2005	USA	[22]
Autism	700–800%	1990 - 2006	California	[23]
Attention Deficit Hyperactivity Disorder	3% per year	1997 - 2006	USA	[24]
Birth defects:				
Cryptorchidism	200%	1970 - 1993	USA	[25]
Gastroschisis	300%	1978 - 2005	California	[26]
Congenital hypothyroidism	138%	1987 - 2003	New York	[27]
Reproductive Function		**Time**	**Location**	**Ref.**
Reported difficulty conceiving and maintaining pregnancy				
All ages	60% more women	1982; 2002	USA	[28, 29]
<25 years old	200% more women	1982; 2002	USA	[28, 29]
Prematurity	2.9% shorter gestation	1992 - 2002	USA	[30]
Pre-eclampsia	19-36%	1968-2002	Norway	[31]
Gestational Diabetes	122%	1989-2004	USA	[32]
Premature puberty:				
Age at onset of breast development	1 – 2 years younger	1940 - 1994	USA, Denmark	[6, 33]
Age at onset of menstruation	2.5 – 4 months younger	1940 - 1994	USA	[6]
Sperm count	~1% decline per year	1931 - 1994	Western countries	[34, 35]
Serum testosterone	1% decline per year	1987 - 2004	Boston, USA	[36, 37]

Figure 1:
Examples of recent trends in select reproductive disease, disorders and function.