NIEHS
Global Environmental Health Conference

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This report represents the deliberations of the workshop participants and should not be construed to represent the opinion of NIEHS.

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Executive Summary

The vision of the National Institute of Environmental Health Sciences (NIEHS) is to prevent disease and improve human health by using environmental sciences to understand human biology and human disease. To achieve this vision and to have the greatest impact on preventing disease and improving human health; the NIEHS focuses on basic science, disease-oriented research, population-based research, and multidisciplinary training and career development for researchers. As part of its new strategic plan, NIEHS has prioritized Global Environmental Health (GEH). To consider the opportunities in GEH, on January 10, 2007, the NIEHS convened a distinguished panel of scientists in San Francisco, California, to participate in a working conference on global environmental health. The overall goal of this conference was to provide advice and guidance to NIEHS Senior Staff on potential research strategies as they enter into this new arena of environmental health science.

The NIEHS Global Environmental Health Conference objectives were to: (1) inform NIEHS of opportunities in global environmental health (GEH); (2) evaluate the opportunities in GEH within the context of NIEHS's strategic priorities; (3) determine the current barriers for NIEHS/NIH to effectively conduct GEH research; and (4) determine the process for establishing effective strategic partnerships in GEH.

The conference was organized around a life course model that consisted of three independent working groups: Group A: Environmental Components of Maternal and Perinatal Health; Group B: Environmental Components of Child Health; and Group C: Environmental Components of Adult Health. Each group was asked to address five key tasks:

1. Identify diseases where environment plausibly constitutes a significant contributor to human disease

2. Identify specific, key methodological approaches for advancing research and interventions/therapies on this topic

3. Identify methods for connecting NIEHS/NIH funded researchers with communities and researchers in the developing world

4. Identify barriers and alternatives for breaking them down to successful and meaningful research in global environmental health

5. Identify partnership possibilities within NIH, across federal agencies, as well as public-private partnerships with academic institutions, private foundations or industries to support or conduct GEH research.

Throughout the conference, each working group presented their interim findings and summaries for comment and modification but the entire group of conference participants. The format and writing style of each working group was unique to that group and represented the consensus approach to the 5 key tasks.

1. Environmental Components of Maternal and Perinatal Health

Background:
Environmental factors cause or influence an array of conditions that lead to illness and death among mothers and children. Worldwide, mothers and children are the populations at greatest risk for premature death and illness. In addition, these populations are also heavily exposed to environmental factors that affect overall health and contribute to a broad spectrum of diseases. Exposure to solvents, combustion products, metals, arsenic, iodine, endocrine disrupting chemicals, pesticides and combinations of these can influence reproductive and developmental environmental health. Exposures experienced by a mother or father can damage their health and the lifelong wellbeing of their developing fetus. Exposures during pregnancy can influence maternal conditions during pregnancy, such as asthma, anemia, and infectious disease susceptibility, and result in adverse pregnancy outcomes, such as miscarriage, intra-uterine growth retardation, prematurity. These exposures can also adversely affect long-term health outcomes for the offspring, such as suboptimal neurobehavioral development, cancer, and other chronic diseases.
Environmental exposures of particular relevance to maternal and perinatal health include: combustion products, arsenic and other metals, the indoor environment, and endocrine disrupters. There are a number of reproductive and adverse pregnancy outcomes such as infertility and spontaneous miscarriage that are associated with periconceptual and perinatal chemical exposures. Exposure to environmental contaminants (e.g.: endocrine disruptors) can result in adverse pregnancy outcomes such as preterm delivery and low birth weight. Preterm delivery is one of the leading causes of perinatal mortality and babies who survive preterm birth have higher rates of morbidity in childhood and adulthood and shorter life spans.

Another concern is birth defects secondary to dysfunctional organogenesis. Birth defects are one of the leading causes of infant mortality and can compromise the long term health of the developing child and future adult. Finally, neurodevelopmental detects may arise due to prenatal exposures with the potential for lifelong sequelae.

***Priority Research Areas in Parental and Neonatal Environmental Health*:**

(1) Relationship between indoor combustion of biomass and adverse pregnancy outcomes (examples: Preterm birth and Intrauterine Growth Reaction (IUGR))
(2) Arsenic in drinking water (example: deficits in IQ in young Children)
(3) Interaction between management of malaria, DDT and other pesticide interventions, neurodevelopmental and pregnancy outcomes
(4) Understanding environmental risk factors that influence susceptibility to infectious diseases through modulation of the immune response
(5) Endocrine Disruptors (example: preterm delivery, fertility risk, cancer, risk)
(6) Taking advantage of rapid industrial growth to identify important environmental exposures

2. Environmental Components of Child Health

Background:
The environment together with other factors contributes to major pediatric diseases in both developed and developing countries.

Over the past two hundred years, the environment of developed nations has improved greatly. Consequently, patterns of disease and death have changed in parallel. Modern advancements in the delivery of safe drinking water; provision of sufficient and wholesome food; removal of sewage; control of insect vectors; and the construction of decent housing are the principal drivers of this transition. Today, the major diseases confronting children in developed nations are: acute respiratory illness, asthma; diarrheal disease; neurodevelopmental disorders such as dyslexia, mental retardation, attention deficit1 hyperactivity disorder (ADHD) and autism; leukemia and brain cancer in children and testicular cancer in adolescents; and obesity and type 2 diabetes.

However, the burden of childhood diseases with major environmental contributions is not spread evenly around the globe. In developing countries need exists to improve both childhood survival from common infections and malnutrition and to improve the health and well-being of those children who survive. In addition, the environmental exposures contributing to childhood diseases differ between developing and developed countries. For example, the major pollutants contributing to acute lower respiratory infections/pneumonia in children in developing countries are combustion-related products from burning biomass/solid fuels; whereas in developed countries these illnesses are more related to traffic-related pollutants.

Developmental-stage specific exposures and windows of susceptibility are critically important in child health since the effects of any given exposure are determined largely by the time in the developmental and maturational process when exposure occurs and the duration of the exposure.

Gene-environment interactions are also powerful determinants of disease. Current evidence indicates that only 10-20% of disease in children is determined by genetic factors, while a majority is now understood to arise from interactions between environmental exposures and genetically determined variations in individual susceptibility. Understanding the mechanisms responsible for susceptibility and the consequences of adverse exposures during these times will help us investigate the effects of environmental exposures on child health.

Environmental Exposures of Importance:

Exposures in the home
Indoor air pollution resulting from biomass solid fuel burning, environmental tobacco smoke, volatile organic compounds, formaldehyde, pesticides/household chemicals, and contaminated water and food;

Exposures in the ambient environment
Traffic-related pollutants and other ambient pollutant sources; neurotoxicants including heavy metals, especially lead and methylmercury, and
PCBs; water contaminants, including arsenic, fluoride and infective agents; tobacco-related pollutants resulting from active and passive smoking.

Priority Research Areas in Child Environmental Health

(1) Acute Respiratory Infection (ARI) and Pneumonia, including Otitis Media
(2) Asthma
(3) Neurobehavioral disorders (NBDs)
(4) Diarrheal Diseases
(5) Malaria
(6) Diabetes

3. Environmental Components of Adult Health

Background:
Adulthood spans a broad spectrum of life. The Adult Working Group developed three age categories of adult life: (1) 10-35 years; (2) 35-60 years; and (3) 60-100 years. Within these overlapping categories are issues related to work-life and reproductive health status, each of which may contribute to increased risk from environmental exposures.

By 2050, approximately half of the world's population will come from five countries (China, India, Bangladesh, Indonesia and Pakistan). The aging populations in these countries are rapidly growing. This clearly suggests that by mid-century, most of the elderly in the world will be located in these countries. As a consequence, many chronic diseases, such as cardiovascular disease and cancer, which are currently prevalent in the United States and Europe, will be dramatically overrepresented in these Asian countries within the next 40 years. Similarly, as the demographics change in the United States, there will be an increase in the number of young people or young adults. This increase will be due to immigration primarily from Latin and Central America. Therefore, the changing patterns of work life, adult experiences, and changing patterns of exposure will have an impact on health across the globe.

Priority Research Areas in Adult Environmental Health:

(1) Asthma and respiratory allergies
(2) Chronic Obstructive Pulmonary Disease
(3) Cardiovascular disease and diabetes/metabolic syndrome
(4) Liver Cancer
(5) Hormonally mediated cancers
(6) Lung Cancer
(7) Neurological disorders

Innovative Research Methods

(1) Gene-Environment Interaction Studies.
Not all individuals are equally susceptible to the adverse environmental consequences of exposure. With the advent of high-throughput technologies for the identification of environmental contaminants in carefully collected environmental and biological samples, there exists a range of equally powerful high-throughput genomic based technologies (mass spectroscopy, microarray, Q-PCR, global methylation platforms) to thoroughly interrogate genetic variation in order to identify single gene polymorphisms (SNPs) and mutations that determine an individual's susceptibility to an adverse health outcome.

(2) Animal Models for Validation and Intervention Studies
To validate potential gene targets or whole gene pathways and to develop testable intervention strategies, it will be essential to utilize animal model systems that closely parallel the human situation, both from an underlying molecular basis, but also with respect to the delivery system of the environmental contaminants.

(3) 'Omics Approaches
Understanding the molecular mechanisms of biological responses to environmental exposures would lead to efficient identification of effective biomarkers for exposure assessment. The recent advent in technology of genomics, proteomics, and metabolomics provide powerful tools to conduct high-throughput screening for biomarkers of exposure assessment

(4) Statistical Analysis for Understanding Gene-Environment and Gene-Gene-Environment- Environment Interaction.
As new exposure and biologic assessment methods are developed, numerous measures of exposure, genetic markers, nutritional factors, maternal-fetal interactions, and other covariates in research studies will be acquired. Due to limited budgets, small scale epidemiological studies may be used. Therefore, new statistical methods are needed to analyze these data with maximum power.

(5) Rapid and Cost-Effective Screening of Biological and Environmental Samples
In many of the proposed areas of research, a pressing need exists for developing methods that can be used to rapidly and cheaply screen both biological and environmental samples.

(6) Culturally-Appropriate Assessment of Sequelae of Environmental Exposures
Tools for assessment should be developed in appropriate languages and standardized for cultural differences in specific populations.

4. Breaking down Research Barriers, Facilitating Partnerships and Connecting Researchers

(1) Research Barriers

- Lack of trained Environmental Health Researchers in developing countries
- Lack of resources of collection, processing, transport, annotation of samples and analyses
- Challenge with cultural obstetrical practices in developing countries
- Few large international cohort studies on environmental health
- Institutional and cultural differences in how research is approached
- Environmental health science not viewed as an academic discipline in developing countries
- Environmental health viewed as barrier to industrial growth

(2) Bringing Researcher Partners Together

- Fogarty International Center can provide foreign partnership opportunities
- NIEHS should take advantage of CDC's US/India cooperative working groups and NICHDs working group on child and maternal health
- NIEHS should use the international meeting to encourage research partnerships between developing and developed country researchers
- Competitive travel and conference grants could be used for US research teams to visit developing countries to identify collaborators and build partnerships.
- NIEHS should convene federal working groups to discuss training opportunities and identify partnerships among the agencies. Agencies may include: NIAID, NICHD, NCI, HG, Fogerty, CDC, USGS, NOA, NASA, EPA, USAID, NSF, and DOD
- NIEHS should develop a non-federal partnership working group to best assess development of strategic partnerships with WHO and NGO's such as the philanthropic foundations committed to global health.

5. Summary

The purpose of the meeting was to advise the NIEHS as to strategies and priorities to consider for the effective use of resources in the arena of global environmental health. Participants joined one of three working groups, focused on the environmental components of Maternal and Perinatal, Child, or Adult Health.

Each working group was charged to develop recommendations based on the five key tasks and to focus these recommendations on goals attainable within a 10 year period.

At the end of the workshop, the three working groups consolidated their research priority lists into a single list. Additionally, there was a discussion of likely successful short-term strategies that NIEHS could consider to further its interests in global

environmental health in the next year. The priorities were then rank ordered for each group and the results are shown below.

Although the workshop accomplished almost all of its stated goals, there was insufficient time to address task 3 related to connecting US researchers with investigators and communities elsewhere in the world. In addition, not all working groups completed the task related to identification of barriers and strategic partnerships. The document represents a summary opinion of the three working groups regarding these areas. The next steps for NIEHS will be to pursue further comment regarding the workshop summary by the public and scientific community.

Report from the
NIEHS Global Environmental Health Conference

Overview

1 Introduction

In January 2007, the NIEHS gathered a distinguished panel of scientists in San Francisco, California to participate in a working conference on global environmental health. The conference was designed to provide advice and guidance to NIEHS staff on how the institute might most strategically allocate resources as it begins to support research in global environmental health. As a working conference, participants joined one of three working groups, each of which drafted guidance documents for the NIEHS during the conference itself. Plenary sessions that included a few formal talks were interspersed with meetings of the three concurrent working groups. This conference design provided an environment for articulating a strategy for global environmental health (GEH) research.

1.1 Purpose of the Meeting

NIEHS has prioritized global environmental health in its strategic plan, but is currently trying to determine how it might most appropriately enter the arena of global environmental health research. Such an effort must be undertaken with careful forethought and planning, especially given the circumstances of flat funding under which the National Institutes of Health currently operates. Thus NIEHS chose to call together leading experts from the field to provide advice and guidance on potential strategies for the NIEHS to consider.

The purpose of the NIEHS Global Environmental Health Conference was to:

- inform NIEHS of opportunities in global environmental health (GEH)
- evaluate the opportunities in GEH within the context of NIEHS's strategic priorities
- determine the current barriers for NIEHS/NIH to effectively conduct GEH research
- determine the process for establishing effective strategic partnerships in GEH

1.2 Meeting Organization

The conference was intentionally organized around a life course model. Thus three working groups were delineated:

- Working Group A: Environmental Components of Maternal and Perinatal Health
- Working Group B: Environmental Components of Child Health
- Working Group C: Environmental Components of Adult Health

Conference participants were asked to address five key tasks:

1. Identify diseases where environment plausibly constitutes a significant contributor to human disease

2. Identify specific, key methodological approaches for advancing research and interventions/therapies on this topic

3. Identify methods for connecting NIEHS/NIH funded researchers with communities and researchers in the developing world

4. Identify barriers and alternatives for breaking them down to successful and meaningful research in global environmental health

5. Identify partnership possibilities within NIH, across federal agencies, as well as public-private partnerships with academic institutions, private foundations or industries to support or conduct GEH research

The co-chairs of each working group were charged with guiding the group in developing responses to the five key tasks identified above. NIEHS was especially interested in garnering scientific input on the first two questions (diseases and methodological approaches). In focusing on these tasks, participants were encouraged to focus on: scientific impact; public health impact; relevance to mission of NIEHS; whether disease is treatable and/or preventable; if successful, estimated number of lives and quality life-years saved; research and translation should be feasible within 10 years.

Each working group produced a précis addressing the five key tasks. Early versions were presented in plenary session in order to promote cross communication. This report represents a summary of all three groups' work.

2 Environmental Components of Maternal and Perinatal Health

2.1 Background

Worldwide, mothers and children are the populations at greatest risk for premature death and illness. These populations also are heavily exposed to environmental factors that affect overall health and contribute to a broad spectrum of diseases. Environmental health research targeting these populations, particularly in developing countries, has been inadequate. Therefore, as a priority, NIEHS should support discovery and translational research targeting the development of effective, affordable and appropriate interventions that significantly reduce adverse reproductive and pregnancy outcomes and perinatal mortality and morbidity.

Environmental factors cause or influence an array of conditions that lead to illness and death among mothers and children. Exposure to solvents, combustion products, metals, arsenic, iodine, endocrine disrupting chemicals, pesticides and combinations of these can influence reproductive and developmental environmental health. Exposures experienced by a mother or a father can damage their health and the lifelong wellbeing of their developing fetus. Exposures during pregnancy can influence maternal conditions during pregnancy, such as asthma, anemia, and infectious disease susceptibility, and result in adverse pregnancy outcomes, such as miscarriage, intra-uterine growth retardation, prematurity. These exposures can also adversely affect long-term health outcomes for the offspring, such as suboptimal neurobehavioral development, cancer, and other chronic diseases. NIEHS is uniquely qualified to design and support studies that address these factors within the complex life-cycle stages of conception, pregnancy, birth and first weeks of childhood. It is also during this period of life when genetic and nutritional factors can interact with environmental influences to profoundly influence inter-generational health.

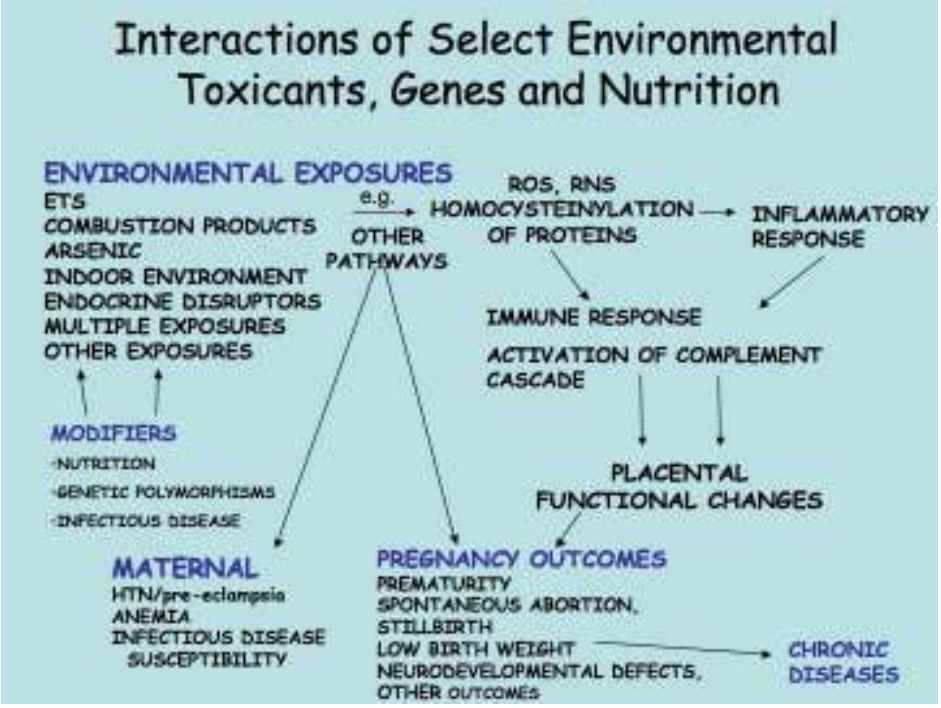

Figure 1 illustrates the complex relationships between environmental exposures and other factors that determine health outcomes. The figure represents a broad view of the interconnected and often complex relationships that are often common to environmental contaminants and their adverse effects on parents and offspring, including a myriad of lifelong chronic disease and disability. Environmental exposures of particular relevance to maternal and perinatal health include: combustion products, arsenic and other metals, the indoor environment, and endocrine disruptors. They can exert their adverse effects through physiological pathways that are modified by the maternal-fetal genotypes and the nutritional milieu of the uterus. These environmental agents and their modifiers can work through multiple pathways. One well-defined pathway is the development of reactive oxidative stress (ROS) that induces an inflammatory response, resulting in the production of maternal auto-antibodies, as well as an activation of the complement cascade resulting in subsequent induction of placental functional changes that may contribute to one of many adverse pregnancy

outcomes, including IUGR, prematurity, low birth weight, congenital and neurodevelopmental defects.

At each point in the Figure 1, there are opportunities for scientific inquiry, including both population-based and mechanistic, hypothesis-driven investigation. For environmentally at-risk populations, such as those identified in the developing world, it is conceptually possible to propose population based studies that include high-throughput analysis of environmental and biological samples that are subsequently subjected to genomic, proteomic and chemical analysis to determine the toxicants and those genetic and protein pathways that regulate susceptibility. These can then be further dissected mechanistically with the use of animal models that take advantage of knock-in and knock-out technologies to provide unique models for human exposure and response. These model systems can be interrogated at the molecular, cellular and morphological levels to validate the findings in the population studies and to suggest intervention strategies for new translational studies.

There are a number of reproductive and adverse pregnancy outcomes associated with periconceptual and perinatal chemical exposures. Infertility, the inability to conceive offspring, can occur due to male or female factors; time to pregnancy (TTP), the time required for successful conception, is a measure of subfertility. Another cause of subfertility is spontaneous miscarriage, which occurs normally in 15-25% of pregnancy and is often unrecognized. The mechanisms for infertility, spontaneous miscarriage and prolonged TTP include abnormal sperm and semen, ovulatory dysfunction, failure of implantation, and chromosomal abnormalities of ova or sperm.

Exposure to environmental contaminants can result in adverse pregnancy outcomes. Preterm delivery is one of the leading causes of perinatal mortality and babies who survive preterm birth have higher rates of morbidity in childhood and adulthood and shorter life spans. Theoretically, environmental exposures to chemicals such as endocrine disruptors that interfere with hormonal signals may be associated with preterm delivery; possible confounders include cigarette smoke and psychosocial stress. Babies born Small for Gestational Age (SGA) or with Intrauterine Growth Restriction (IUGR) are smaller than expectation based on gestational age-specific growth curves. Parameters that can be measured include weight, length, head circumference, as well as several fetal ultrasound measures during gestation and at birth. Babies born with IUGR are at higher risk for perinatal morbidity and mortality as well as a number of adult conditions such as obesity, diabetes, hypertension, and cardiovascular disease. Numerous environmental exposures have an impact on intrauterine growth, and endocrine disruption could be involved as a pathway. Low birth weight (LBW) is one of the major conditions responsible for the burden of disease in poor countries as it is directly responsible for about 1.3 million deaths annually in young children (10% of DALYs). In addition, a wide range of other health problems in childhood and probably later in life are associated with LBW. Nearly all of this burden is found in the poorest countries.

Another concern is with birth defects, such as organogenesis. Examples include major structural birth defects, such as of the limb and major organs, and more subtle birth defects, such as development of the male reproductive tract. Birth defects are one of the leading causes of infant mortality and can compromise the long term health of the developing child and future adult. Whether such effects occur at lower doses in humans needs further assessment although some human evidence exists. Such effects would potentially affect male fertility and cancer risk to both sexes over a lifetime. Finally, studies show potential for neurodevelopmental effects due to prenatal exposures, with the potential for lifelong sequelae.

Chemicals can be measured in biological samples such as semen, ovarian follicular fluid, amniotic fluid, umbilical cord blood, urine, and breast milk. From the earliest developmental period throughout life, humans are exposed to a wide variety and mixture of chemicals.

2.2 Priority Research Areas in Parental and Neonatal Environmental Health

The potentially long term public health consequences of environmental exposures in combination with exquisitely vulnerable windows of exposure during the maternal and perinatal period help to identify priority research areas during this life stage.

2.2.1 Relationship between indoor combustion of biomass and adverse pregnancy outcomes

The indoor burning of solid fuels (biomass and coal) in developing countries produces exposures to a range of products of incomplete combustion that have toxic properties potentially hazardous to pregnancy outcomes and normal fetal development. Prominent among these is carbon monoxide, which is clearly related to reduced oxygen transport to the fetus in human and animal studies. Multiple studies of active and passive exposures of pregnant women to tobacco smoke, the most well-studied biomass smoke, show adverse impacts on birth weight and fetal lung development, which are known risk factors for a host of diseases in later life.

Given that half of the world's population is exposed, and the importance of these birth outcomes, we recommend that research be conducted to quantify the risks of these exposures for adverse birth outcomes including preterm birth and IUGR. Such studies would also provide excellent opportunities to develop and validate biomarkers in maternal and cord blood and the placenta, as well as to quantitatively examine interactions with poor nutrition and other risk factors. Moreover, the contribution of IUGR to the overall problem of low birth weight could be disentangled. Exposure-response information obtained by monitoring indoor air pollutant exposure during pregnancy would also assist in the development of future interventions aimed at an array of other adverse health outcomes, and may ultimately allow scientists to parse out the relative health impact of the multiple pollutants in smoke. In that regard, there are numerous fundamental biological questions pertaining to the pathophysiology of smoke-induced lung disease, elevated blood pressure, and cardiovascular disease that lend

themselves to study. For example, the relative roles of pulmonary inflammation and fibrosis remain to be elucidated, while the impact of smoke on endothelial cell function and blood pressure regulation could be studied via the monitoring of biomarkers of endothelial cell function.

The quantification of indoor air pollutants during pregnancy is necessary to properly focus further research and intervention. The relatively high rate of LBW in the developing world and the relative shortness of the relevant exposure period make feasible the use of case-control studies, and/or randomized controlled clinical trials aimed at minimizing exposure. Additional adverse outcomes, including hypoxic and chemical insults to the fetal brain and other tissues and mechanisms underlying these are important areas of investigation, as are effects of indoor air pollutants on implantation and placental physiology and vascularization.

2.2.2 Arsenic in drinking water

Current estimates indicate that as many as 100 million people in India, Bangladesh, Vietnam, Cambodia and Nepal are drinking water with arsenic (As) concentrations up to 100 times the World Health Organization (WHO) guideline of 10 ug per liter. Other regions of the world, including China, Taiwan, Mexico, Chile and the United States, also have naturally occurring As in groundwater. Today, in South Asia, a generation of women of child-bearing age has been exposed to As for their entire lives. Trans-placental transfer of As and its most toxic metabolites is known to occur, and evidence of arsenicosis, once thought to require two decades of exposure, is now evident in young children. Moreover, deficits in intelligence in young children have been attributed to naturally occurring elevated As and manganese (Mn) concentrations in drinking water.

There are major inter-individual differences in the human biological response to As exposure that appear to be due to fundamental gene-environment and nutrition-environment interactions. For example, both folate and selenium appear to be protective against As toxicity, and polymorphisms in the metabolism of folate enhance As toxicity. These represent but two of many possible genetic pathways in which variants may regulate susceptibility to As toxicity. Folate supplementation enhances As methylation and urinary elimination in folate deficient populations, but it is not known whether such supplementation would accomplish this in those who are not folate deficient. Selenium (Se) forms a complex with As and glutathione in the liver, and thereby enhances biliary As excretion. It too, however, can be methylated and excreted, and it is not known what effects folate supplementation might have on Se metabolism and elimination. It therefore appears that therapeutic trials of various nutritional interventions, perhaps in women of child-bearing age, hold promise in reducing As toxicity and burden in pregnant women and their offspring. In addition, current strategies to provide As remediation – such as dug wells, pond sand filters, As-removal technologies and deep wells – need to be fully evaluated with regard to social acceptance, efficacy in reducing As exposure, and possible re-introduction of microbial disease risks.

In February 2007, the National Academy of Engineering, with support from the Grainger Foundation, will award prizes of $1M, $200K, and $100K for first, second, and third place, for the design and creation of a sustainable, economical point-of-use water treatment system to remove As from drinking water in South Asian countries. For the most part, finalists are large corporations. Thus, both the prize winners and the Grainger Foundation are possible partners for this work.

2.2.3 Interaction between management of malaria, DDT and other pesticide interventions, neurodevelopmental and pregnancy outcomes

Malaria is a major killer of children and a risk factor for adverse outcomes of pregnancy. DDT Indoor Residual Spraying (IRS) and other pesticide interventions (pyrethroid IRS and pesticide impregnated bednets) have been identified by WHO as key elements of their new malaria strategy. There is much enthusiasm by international and NGO donors to support WHO in this strategy and large scale intervention programs are underway in several sub-Saharan African countries. At the same time, there is enormous concern that we are reintroducing a “bad actor” to control an infectious disease. These new DDT initiatives represent enormous scientific and public health opportunities to understand the potential impact of DDT exposure and malaria on the developing child, as well as the interaction of infectious and environmental agents. If DDT is going to be a major tool for malaria control, we need to identify methods to minimize exposure to pregnant women and children.

DDT is persistent and lipophilic. It is relatively well known that persistent organic pollutants like DDT are hormonally active. Studies in animals indicate that DDT is a reproductive and neurodevelopmental toxicant. Two recent studies published in Pediatrics and the American Journal of Epidemiology indicate there is evidence that maternal serum levels of DDT during pregnancy are associated with adverse neurodevelopmental outcomes in young children. These outcomes have been found at serum levels that are likely to be lower than levels where DDT is still in use. After birth, DDT is present in human milk; lactation is the most important source of nutrition for babies, especially those in developing countries where the malaria risks are highest. Two studies have suggested that the principal metabolite of DDT, DDE, is associated with shortened duration of lactation. It is also possible that DDT has an impact on immunity, a critical component of survival of malaria infection, and thereby a direct biological interaction between infection and prevention measures.

There is a paucity of data on exposure to human populations to DDT following IRS and additional information is desperately needed to better understand risk-risk tradeoffs. Studies in association with malaria control would assess maternal exposure and human milk levels to DDT, DDE and other pesticides associated with treatment, and their potential adverse reproductive and developmental outcomes. Because of the recent change in worldwide policy decisions, this study topic is particularly timely and is likely to attract partners from both within the U.S. Government and international organizations.

2.2.4 Understanding environmental risk factors that influence susceptibility to infectious diseases through modulation of the immune response

Globally, some of the most important causes of mortality and morbidity among mothers and neonates are infectious diseases, particularly malaria, tuberculosis (TB) and diarrheal diseases. The extent to which numerous environmental exposures may modify the immune system to interact with these infections and lead to adverse pregnancy outcomes provides a rich set of research questions. Exposures to chemicals during pregnancy that may affect the immune system generally and inflammatory processes in particular are especially important because the immune system is already endogenously suppressed during pregnancy. Since fluctuations in immune function during pregnancy are not well understood, studies of exposed and non-exposed populations offer an opportunity to elucidate fundamental mechanisms underlying immune function and dysfunction during pregnancy. NIEHS could make a substantive contribution to this field by motivating research in this area, since investigators may find it difficult individually to navigate between the multiple NIH institutes that would have interest in these areas (NIAID, NICHD, etc.)

We suggest the NIEHS consider investigation of the impact of environmental factors such as immunotoxicants on immune system function and inflammation – particularly to better understand their interaction with and influence on infectious disease acquisition, transmission, and natural history, along with resulting adverse pregnancy outcomes. The effort to identify the specific environmental toxins in a setting could be part of the efforts to apply rapid environmental screening methods. For example, does exposure to particular indoor air pollutants, pesticides, heavy metals or combinations of these make women or neonates more susceptible to TB, malaria, or diarrheal diseases.

Immunotoxicology is a relatively new area in environmental health, but there is emerging evidence that a number of environmental exposures – such as components of combustion, air pollution, mercury, and certain pesticides – are associated with alterations in inflammatory processes. This is especially important in fetal and early life because:

- developing fetal immune systems may be sensitive to reprogramming initiated by perturbations in inflammatory responses (e.g. hygiene hypothesis);
- altered immune responses may increase susceptibility to/severity of communicable diseases;
- infection and inflammation in mothers is associated with numerous adverse outcomes in the child

Malaria is an example of a disease that has a major global impact with particularly severe impacts on pregnant women and young children. Mercury exposure is known to be a risk factor for malarial infection, but there may be other important exposures (air pollution/pesticides) and diseases (TB, infectious diarrhea) that could be additional risks

factors for susceptibility and targets of investigation. In addition, there may be important direct and indirect roles for infectious diseases in preterm birth:

- **Direct**: Babies born preterm consistently have higher levels of IL-6 in cord blood along with other pro-inflammatory cytokines observed in some studies (TGF-alpha 1, TNF-alpha; IL-8).
- **Indirect**: Infection can have negative impacts on maternal nutritional status that may in turn lead to adverse pregnancy outcomes.

Malnutrition is also a known risk factor for preterm delivery, as well as low birth weight, adverse neurodevelopment, spontaneous abortion, and other endpoints. Also, infections can exacerbate underlying nutritional deficiencies.

NIEHS could partner with other agencies to support basic research into the mechanisms of inflammatory response during pregnancy and infection (including animal models) and how environmental exposures alter these responses. While human studies would best be launched in the developing world where the prevalence of these conditions is high, the understanding gained about inflammation during pregnancy would have immediate and obvious value for the rest of the world.

2.2.5 Endocrine Disruptors

Numerous organohalogen compounds in the human environment have been identified as endocrine disruptors (e.g., having effects via modes of action involving estrogen, anti androgen, thyroid, or AhR mediation). Some of these compounds are no longer in use but persist in the environment; others are unintentionally released (e.g., dioxins); and new ones continue to be introduced into the environment (e.g., persistent organohalogens such as PBDEs and non persistent compounds such as perfluorinated compounds, phthalates, bisphenol A, perchlorate and some organophosphate pesticides). Exposures are likely to be higher in developing countries where many such compounds have been used more recently; where control over releases and workplace exposures has been weaker; and where levels of such chemicals in food and other sources of exposure may be higher. Toxicology studies and limited epidemiological evidence suggest that endocrine disruption can exert adverse effects on a population level, for example, adverse effects on male and female fertility; sex ratio; sex differentiation; neurodevelopment; maternal and fetal thyroid function; increased cancer risk to both the mother and the child; and development of the male reproductive tract, resulting in alterations such as reduced anogenital distance, decreased sperm, smaller testicles and penis and increased risk of prostate and testicular cancers later in life.

Additionally, there are birth outcomes that may be associated with perinatal exposures to endocrine disrupting chemicals, such as preterm delivery, SGA, IUGR, and birth defects. Organogenesis may be a unique concern with EDCs, especially development of the male reproductive tract. Animal studies have found that chemicals with anti androgen and/or estrogenic agonist effects perturb the development of the male reproductive tract. Whether such effects occur at lower doses in humans needs further

assessment although there is some human evidence. Such effects would potentially affect male fertility and cancer risk to both sexes over a lifetime.

Generally the timing of exposure, gender of the fetus, co-exposures to other substances, and the genetic makeup of the individual are likely to modify the impact of an exposure. An obvious challenge is that multiple exposures occur, and we know little about their mechanisms of action and potential interactions, either in *in vitro*, animal or human models. We propose a program of research that would focus on multiple exposures to endocrine disruptors in highly exposed populations globally along with laboratory investigations such as high throughput screening of individual compounds and mixtures for endocrine receptor activity and "omics" alterations as well as targeted toxicology assessments of mixtures that reflect combinations of exposures that are found in human populations.

2.2.6 Taking advantage of rapid industrial growth to identify important environmental exposures

International research settings and collaborations offer unusual and promising opportunities to examine the impact of environmental exposures over time on various populations, especially women and children, and individually as well as in combinations. As a consequence of rapid urbanization and development, even while the environment is generally improving, there are situations where there are great increases in exposures to toxic substances such as metals (lead, mercury, cadmium, arsenic), solvents (benzene, formaldehyde), air pollutants (from burning fuel and from traffic), and pesticides. Such situations arise from a variety of exposure scenarios, including occupation and work in the informal sector, improper waste management, scavenging and burning, poorly formulated consumer products, and industrial releases. To bring such exposures under control, the reality is that most countries need evidence of adverse effects within their own regions in order to be persuaded that there is a problem. Outcomes of concern are adverse pregnancy outcomes particularly preterm birth and low birth weight for gestational age as well as structural birth defects and developmental neurotoxicity. Which mechanisms would be of interest would depend on which exposures are selected for study. These circumstances provide an opportunity for health researchers to discover new health effects from these exposures individually and in combination given higher exposure levels in developing countries. This is advantageous when one is attempting to evaluate dose-response relationships. However, in these populations there can be serious confounding and/or effect modification by other factors such as nutrition, cultural practices, co-exposures, and disease states. We are suggesting that despite these caveats, these situations should be considered by the NIEHS as opportunities to identify environmental etiologies of adverse pregnancy outcomes.

2.3 Summary

As outlined below, the research priorities NIEHS should focus on to improve maternal and neonatal health will directly contribute to the achievement of six of the ten most important international health goals identified in the Disease Control Priorities Project.

These include the prevention of neonatal mortality, ensuring the health of mothers and children, decreasing cardiovascular disease, addressing AIDS, TB and malaria, and reducing the health impact of tobacco use. To undertake this work, significant methodological challenges must be resolved and institutional, resource and cultural barriers will need to be understood and overcome. In addition, partnerships with a wide array of researchers, funding institutions and international collaborators (public and private) will be needed to address the inter-disciplinary nature of this area of research. NIEHS is uniquely qualified to lead this complex effort and meet these challenges.

3 Environmental Components of Child Health

3.1 Background

The environment contributes to causation of major pediatric diseases in both developed and developing countries. This recognition had its origins in episodes that involved high-dose exposures that caused clinically obvious illness. Deeper understanding of the unique vulnerability of infants and children derives from studies showing that pre- and perinatal factors can predispose to later development of disease and to lifelong disability. Impaired fetal growth has, for example, been related to increased risk of cardiovascular disease, hypertension, and diabetes in adult life, and accelerated growth in childhood has been associated with subsequent risk of female breast cancer as well as of impaired glucose tolerance.

The environment of the developed nations has changed greatly in the past two hundred years, and patterns of disease and death have changed in parallel. Broad-scale improvements – delivery of safe drinking water; provision of sufficient, wholesome food; removal of sewage; control of insect vectors; and the construction of decent housing – are the principal drivers of this transition. Today, the major diseases confronting children in developed nations are: acute respiratory illness, asthma (which has more than doubled in frequency since 1980, especially among underserved children residing in inner-city communities); diarrheal disease; neurodevelopmental disorders, such as dyslexia, mental retardation, attention deficit/ hyperactivity disorder (ADHD) and autism; leukemia and brain cancer in children and testicular cancer in adolescents; and obesity and type 2 diabetes. As a result of these changes, the focus of child health in developed nations has changed from simply improving childhood survival to addressing specific fatal conditions (e.g., leukemia) and loss of health through non-fatal conditions.

However, the burden of childhood diseases with major environmental contributions is not spread evenly around the globe. The majority of the childhood burden of disease falls on those living in developing countries where significant need exists to improve both child survival at the population level and to improve the health and well-being of those children who survive. In addition, the environmental exposures contributing to childhood diseases differ between developing and developed countries. For example, the major pollutants contributing to acute lower respiratory infections/pneumonia in children in low-income developing countries are combustion-related products from burning biomass/solid fuels; whereas in the mega-cities in emerging countries these

illnesses are more related to traffic-related pollutants; and in developed countries exposures to environmental tobacco smoke and volatile organic compounds inside houses are important.

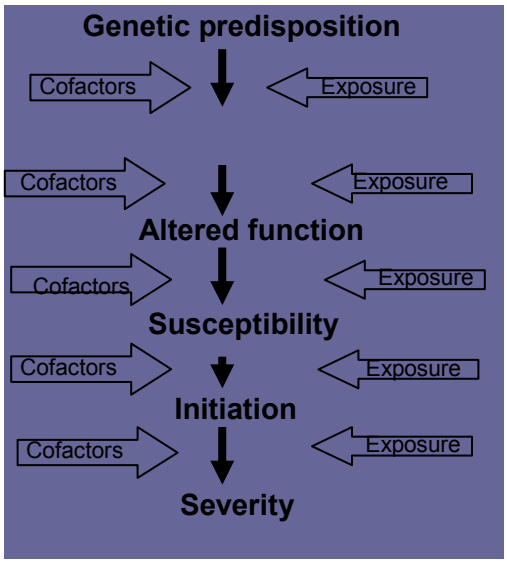

Figure 2

Environmental exposures can cause a dose-dependent continuum of toxicity, in which clinically obvious effects have subclinical counterparts. *In utero* and early childhood exposures to environmental agents have become a particular focus of concern. The timing of exposure is critically important, because at certain times during development, various organ systems are particularly vulnerable to environmental exposures; these are known as "windows of susceptibility". Exposures sustained during windows of susceptibility, even to low levels of toxic materials, can cause lasting damage. Gene-environment interactions are also powerful determinants of disease. Current evidence indicates that only 10-20% of disease in children is determined by genetic factors, while a majority is now understood to arise from interactions between environmental exposures and genetically determined variations in individual susceptibility. Elucidation of mechanisms responsible for susceptibility and consequences of adverse exposures during these times will be essential for more complete understanding about effects of environmental exposures on child health.

In its deliberations, the Environmental Components of Child Health Working Group paid particular attention to the importance of developmental-stage specific exposures and windows of susceptibility, which are particularly important, since the effects of any given exposure are determined largely by the time in the developmental and maturational process when exposure occurs (see figure 2). Developmental susceptibility refers to two basic concepts:

- The outcome of the exposure depends on where in the developmental process an exposure occurs (i.e., an exposure occurring early in gestation during organogenesis can result in structural alterations); and
- The extent of the exposure itself may be altered by the stage of maturity (i.e., the absorption, distribution, metabolism and elimination of chemicals is likely to be influences by the stage of maturation of the child).

The Child Health Working Group also recognized the early origins of chronic diseases in adults, such as COPD, hypertension, and cardiac disease. Although the Child Health Working Group did not consider these diseases specifically, it focused on environmental impacts on lung growth, since poor lung growth is likely to have a major influence on the risk of both acute and chronic lung diseases at various stages of life.

The Child Health Working Group considered the following specific environmental exposures of particular importance:

- Exposures in the home, including indoor air pollution resulting from biomass/solid fuel burning, environmental tobacco smoke, volatile organic compounds/formaldehyde, pesticides/household chemicals, and contaminated water and food;
- Exposures in the ambient environment including traffic-related pollutants and other ambient pollutant sources;
- Neurotoxicants including heavy metals, especially lead and methylmercury, and PCBs;
- Water contaminants, including arsenic, fluoride and infective agents;
- Tobacco-related pollutants resulting from active and passive smoking.

Other aspects that were considered included: the complex causal pathways of pediatric diseases as they result from genetic susceptibility and environmental exposure; different etiological factors, such as: congenital, developmental, infectious, environmental, genetic, and mixed – where there is one or more primary factor. Although it was not a major focus of deliberations by the Child Health Working Group, climate change was also recognized as a possible contributor affecting child health in a number of ways. These effects include immediate environmental consequences of processes that cause climate change, such as burning of fossil fuels and forests. Direct impacts of altered climate, would also include health risks associated with heat waves, a greater intensity and frequency of natural catastrophes, indirect impacts caused by ecological disturbance, increased production of pollens and fungal spores that exacerbate allergic conditions (e.g. asthma, allergic rhinitis), and higher temperatures and increased flooding that expand areas of vector-borne diseases.

The first task of the working group was to identify diseases where environment plausibly constitutes a significant contributor to human (childhood disease). The working group initially identified:
a. childhood diseases where environmental plausibly constitutes a significant contributor. These included infectious and parasitic diseases, neurobehavioral dysfunction, non-communicable respiratory diseases, metabolic and endocrine diseases and childhood cancers;
b. disturbances of growth and development, including body and organ growth and socio-emotional well-being;
c. effects of chemicals and mixtures of known toxicity, e.g., arsenic exposure in ground water in Bangladesh and India, environmental asbestos exposure globally;
d. effects of exposures to chemicals and to mixtures with unknown toxicity, e.g., children living on or near toxic waste sites.

The working group developed a conceptual model that underpinned the environmental contribution to major childhood diseases (table 1).

Table 1

Environmental Threat – Infectious Diseases	Global Burden Children	Potential Major Impact 10 yrs	Measurable Outcomes?	What is known	Most relevant category of research	Region(s) Most Affected	Priority	Institution involved
Diarrheal Diseases	High	High	Y	A lot	1,2	SSA Asia	med	NICHD NIAID CDC USAID WHO EPA
ALRI	High	High	Y	A lot - But need more	1,2	SSA	high	NHLBI CDC EPA USAID
Malaria	High	High	Y	A lot	1,2 3 Exposure to DDT	SSA Asia Latin America	Med* DDT	NHCID NIAID EPA CDC WHO (SAMRC)
Vector borne disease	Med	Med	Y	Not much	3		Med	NIAID CDC WHO EPA
TB	Med?	Low	Y, difficult		?	S Asia, SSA,	no	

Table 1 (cont)

Environmental Threat –NBD	Global Burden Children	Potential Major Impact 10 yrs	Measurable Outcomes?	What is known	Most relevant category of research	Region(s) Most Affected	Priority to NIEHS	Institution involved
NBD Cognitive deficit	**Potentially high**	**High on morbidity in new cases**	**Y**	**A lot more needed**	**1,2,3**	**Global**	**y**	**NINDS**
ADH			**Need standardization**	**Chemical specific**	**New chemical and ETS**			**NIEDBS**
Behavioral problems								**CDC, EPA, NICHD, WHO**
Mental Health							**no**	
Neuro-degenaritive diseases							**no**	
Environmental Threats – respiratory Non Communicable	**Global Burden to Children**	**Potential for Major Impact in 10 years**	**Measurable Outcomes?**	**What is known**	**Most relevant category of research**	**Regions Most Affected**	**Priority to NIEHS**	**Institutions involved**
Asthma	Med (growing)	Med	Y	A lot but more needed	1,2,3	global	Y	NIAID…..
Environmental Threats – Metabolic and endocrine disruptors	**Global Burden to Children**	**Potential for Major Impact in 10 years**	**Measurable Outcomes?**	**What is know**	**Most relevant category of research**	**Regions Most Affected**	**Priority to NIEHS**	**Institution involved**
Diabetes	Growing	Small	y	Little in relation with toxicants	3	global	Related to chemical and build environment	
Reproductive health effects	unknown	unknown	y	little	3	global	Related to chemical	

The working group classified the type of research that would be required to address priorities in children's environmental health into three categories:

- **Type 1** - Translational research to test proven interventions for their effectiveness in the community setting (i.e., where effective interventions are known and research efforts should concentrate on studies to determine factors related to acceptability and sustainability of the interventions)

- **Type 2** – Research to develop and test the efficacy of plausible interventions, including consideration of co-factors (i.e., where knowledge about underlying mechanisms is sufficient to develop intervention studies but where more studies are required to understand the mechanisms underlying disease modifying co-factors, gene-environment interactions and epigenetic phenomena)

- **Type 3** – Research to understand the mechanisms and the biological basis of environmentally-related disease, including epigenetics, especially where insufficient knowledge exists to plan large-scale intervention studies (i.e., where studies are required to understand the mechanisms involved in disease causation, including the impact of disease modifying co-factors, gene-environment interactions and epigenetic phenomena)

3.2 Priority Research Areas in Child Environmental Health

The Child Health Working Group identified six priority areas for environmental health research: 1) acute respiratory infection/pneumonia, including otitis media; 2) asthma; 3) neurobehavioural deficits; 4) diarrhreal disease; 5) malaria; and 6) diabetes. The first three represent childhood diseases where NIEHS can play a critical and major role; the latter three where NIEHS can play a critical but limited role.

3.2.1 Acute respiratory infection (ARI) and pneumonia

Exposure to indoor air pollution, including environmental tobacco smoke, increases the risk of ARI/pneumonia, especially in low-income developing countries. Additionally, exposure to outdoor air pollutants increases infant mortality and the risk of ARI/ pneumonia. Potentially exacerbating the problem, poor lung growth increases dosing of pollutants, and inflammatory stimuli in pollutants in turn decrease lung growth. Key co-factors involved with ARI/pneumonia include: low birth weight; malnutrition, especially micronutrient deficiency; gene-environment interactions (e.g., Phase II metabolic enzymes); poor lung growth; and delayed immune system maturation. Figure 3 illustrates the relationships between lung development and immune function as determined by environmental exposures to the risk of ARI and COPD.

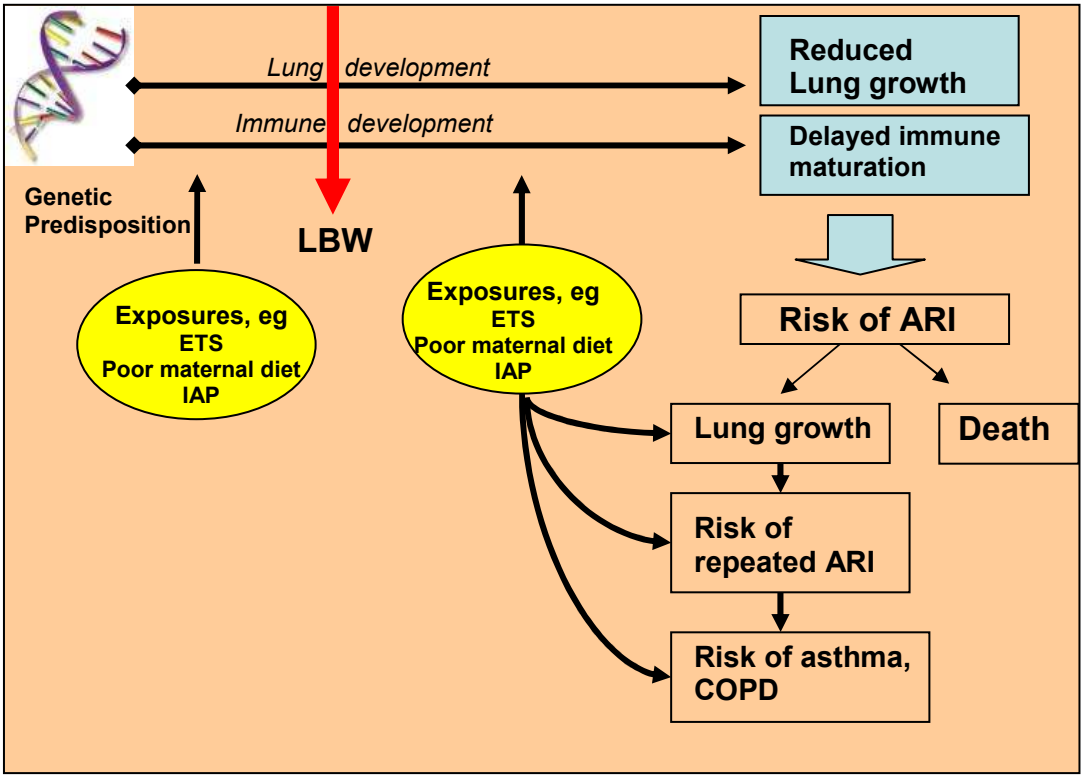

Figure 3

Using the Research Type taxonomy described above, the Child Health Working Group identified multiple research approaches on ARI/pneumonia.

- **Type 1**: Determination of factors related to acceptability and sustainability of biomass combustion exposure reduction programs, while simultaneously investigating disease- modifying and susceptibility factors.
- **Type 2**: Examining the effect of repeated ARI/pneumonia on lung growth and future respiratory health. Measurement of the impact of exposure reduction on long-term respiratory health. Prospective studies to quantify exposure-response relationships to indoor air pollution along the range of exposures. Randomized clinical trial of novel interventions to reduce exposure (e.g., liquefied biomass-based fuels or improved stoves). Quantify the health impacts of public health initiatives to improve ambient air quality (e.g., removal of diesel fuel from buses in Delhi as a natural experiment). Intervention study of anti-oxidant and micronutrient supplementation during pregnancy and first 2 years of life, including studying modifying effects of co-factors and gene-environment interactions.
- **Type 3**: Development and validation of biomarkers of lung injury for use in large cohort studies (e.g., CC16, SPA/SPD). Direct studies measuring the impact of pollutant exposure on lung growth (i.e., lung volumes and lung function in early life, together with the development of indices of lung growth suitable for use in large cohort studies). Determining the impact of delayed immune development on lung growth and risk for ARI/pneumonia. Identifying key indicator pollutants to facilitate research aimed at exposure reduction. Determining the health consequences of reduction of individual components of IAP. Exploring the

relevance of animal models in evaluating the health effects of exposure to indoor air pollution.

3.2.2 Asthma

Slow post-natal maturation of innate and adaptive immune function, especially in the ability to mount adequate Th-1 responses, is a significant risk factor for the development of asthma. In addition, the early onset of persistent atopy is a major risk factor for persistent asthma. More severe atopy in childhood is more likely to be associated with persistent and more severe asthma and bronchial hyper responsiveness (BHR). Viral lower respiratory illnesses, especially in the first year of life, are risk factors for asthma in childhood, and there is a synergistic interaction between early LRI and atopy in the risk for asthma. In addition, asthmatics mount a lower anti-viral response (e.g., lower type I interferons in response to viral infections). Defects in the anti-oxidant defense system (phase II metabolic enzymes) increase the risk of and severity of asthma in children.

In terms of environmental contributors, environmental tobacco smoke exposure, especially maternal smoking during pregnancy, is a major risk factor for asthma in childhood. Exposure to air pollution and bioaerosols increases the prevalence of and severity of asthma in children. Important co-factors include low birth weight, malnutrition, exposure to inflammatory stimuli, gene-environment interactions and epigenetic phenomena. (see also figure 3)

Using the Research Type taxonomy described above, the Child Health Working Group identified multiple research approaches on asthma.

- **Type 2**: Birth cohorts, preferably of high risk children, concentrating on environmental exposures and disease-modifying co-factors in a variety of environmental settings. These studies should include mechanistic components to determine how co-factors modify disease risk. Randomized clinical trial of increased anti-oxidant intake to reduce severity of asthma. Randomized clinical trial of “anti-inflammatory” substances to reduce severity of asthma. Primary prevention studies in high risk children aimed at: prevention of allergic sensitization/persistent atopy using immunological approaches (e.g., high-zone tolerance, Th-2 antagonists, anti-IgE, and prevention of viral LRI using monoclonal antibodies or vaccines.
- **Type 3**: Direct studies on infant immune system maturation (e.g., bio-banked T-cells) with well characterized environmental exposures. Development of methods for T-cell stimulation suitable for large scale epidemiology and field studies.

3.2.3 Neurobehavioral disorders (NBDs)

One in every six children born worldwide has a developmental disability. In most cases, these disabilities are the consequence of pre- or postnatal injury to the developing

nervous system. Although NBDs are not usually major causes of death, they account for much morbidity and for diminution of function that can have negative effects on the economic productivity and stability of entire societies. They induce reductions in intelligence, disruptions of behavior, increased impulsivity and a tendency to violence, increased risk for disorders of mental health, and possible predisposition to progressive neurodegenerative disorders in later life. The most common neurodevelopmental disorders of childhood include mental retardation, learning disabilities, sensory deficits, developmental delays, attention deficit/hyperactivity disorder (ADHD), and cerebral palsy. Treatment of these disorders is difficult, and the disabilities they cause can be permanent. They are therefore very costly to families and to society.

Evidence has been accumulating over several decades that industrial chemicals can cause neurodevelopmental damage and that subclinical stages of these disorders might be common. The possibility of a link between chemicals and widespread neurobehavioural changes was first raised by research showing that lead was toxic to the developing brain across a wide range of exposures.

Developmental neurotoxicity in children exposed to industrial chemicals is often first identified through recognition of obvious functional abnormalities after high-dose exposure that clearly caused poisoning. Research later documented the presence of less striking, but nonetheless serious adverse effects at low doses of exposure. This research typically joined epidemiological study with the application of biological markers of exposure and of subclinical effects that often derived from basic biological investigations. These studies have provided fundamental biological insights about the vulnerability of the developing nervous system and the differential susceptibility to external exposures that exists at various developmental stages. Figure 4 illustrates the temporal and spatial complexity between neurodevelopment and environmental exposures in the risk of neurodevelopmental diseases.

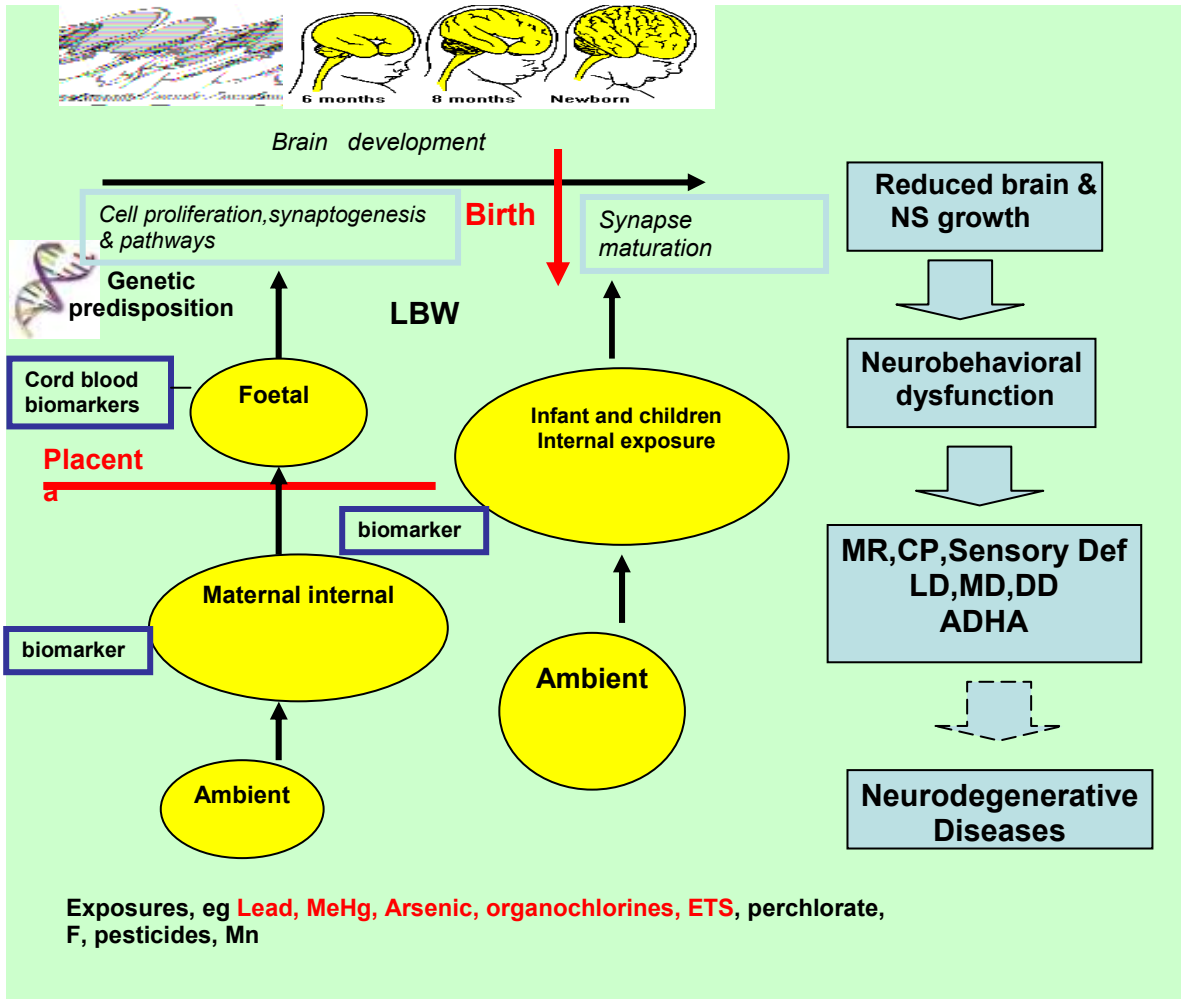

Figure 4

This sequence of discovery led to the recognition that environmental pollutants exert a range of adverse effects – some are clinically evident, but others can be discerned only through special testing and are not evident on standard examination (hence the term subclinical toxicity). The full extent to which these chemicals contribute to neurodevelopmental disorders and subclinical neurotoxicity is still unknown. This lack of information is due, in part, to the fact that the overwhelming majority of chemicals in commerce have not been tested for potential to cause neurodevelopmental toxicity. Despite this, the developmental neurotoxicity of lead, methylmercury, arsenic, polychlorinated biphenyls, solvents, pesticides, and environmental tobacco smoke may be considered proven. Developmental neurotoxicity is suspected, but not yet fully established, for certain pesticides, including organophosphates and organochlorines, manganese, fluoride, perchlorate.

The evidence for the neurodevelopmental neurotoxicity of these materials derives from animal as well as human studies. These studies have documented:

- Existence of dose-response relationships that include subclinical toxicity at lower levels of exposure;

- Importance of timing of exposure. Exposures at different developmental stages have differential potency and can cause qualitatively different effects.
- Possibility of successful interventions for reducing exposure, e.g., the removal of lead from gasoline with subsequent 90% reduction in blood lead levels and society-wide increases in intelligence and economic productivity.
- Co-factors. Nutritional status particularly iron deficiency and stunting, malaria and possibly other infectious diseases, educational stimulation all have the potential to interact with chemical exposures and to modulate the impact of industrial chemicals on the developing nervous system.

Neurobehavioural damage caused by industrial chemicals is, in theory, preventable. An essential prerequisite to prevention is recognition of a chemical's ability to harm the developing brain. Knowledge that a chemical is neurotoxic can prompt efforts to restrict its use and to control exposure.

Specific needs and opportunities for research include, but are not limited to:

- Epidemiological studies – cross-sectional, case-control, and prospective birth cohort studies – of populations at high risk of exposure and disease. Such studies could be done in partnership with FIC Centers of Excellence, CDC, national ministries of health, NGOs, or WHO. They could focus on groups currently exposed, on groups at risk of newly emergent exposures (e.g., Mn in gasoline), or on groups where exposure is diminishing. They could document the relative effectiveness of various strategies for intervention.
- Basic laboratory studies to identify and elucidate mechanisms and models of toxicity, as well as new biological markers of exposure and effect.
- New high throughput technologies for toxicity testing.
- Better quantification of the role of risk factors (e.g. highly undernourished populations).
- Development of techniques/instruments for valid and consistent outcome measurement for a range of physiological, cognitive, and other outcomes. Assessment of higher CNS function such as language and behaviour will require development of validated instruments that are linguistically and culturally appropriate.
- Development of new approaches for assessing the developmental neurotoxicity of pollutant mixtures from specific sources (combustion products; specific chemical/industrial products and processes).

3.2.4 Diarrheal Diseases

Despite the availability of proven interventions for their prevention and effective treatment, diarrheal diseases continue to kill more than two million children every year, mainly in sub-Saharan Africa and Asia. This number has been largely unchanged for the past decade. Diarrheal diseases are the third-leading risk factor for the burden of disease in high-mortality developing regions. The vast majority of the morbidity and mortality burden is linked to environmental factors, mainly unsafe water and inadequate sanitation and hygiene.

Epidemiologic studies and meta-analyses have confirmed the impact of improved water quality, water quantity, hand washing, and effective sanitation on diarrhea. Generally accepted impacts for the individual interventions are on the order of 30-50% with a broader range of reported impacts. The evidence for synergistic impacts of multiple interventions is mixed, though such synergy is plausible, based upon the known mechanisms of fecal-oral transmission. There is also limited emerging evidence of the association of diarrhea with toxic substance exposure, especially pesticides. While important infectious diseases associated with specific pathogens – such as cholera, shigella dysentery, and typhoid fever – contribute to the diarrheal disease burden, most diarrhea is endemic and associated with commonly circulating pathogens.

Malnutrition both complicates and is caused by diarrhea. Micronutrient deficiencies and other immune system impacts (plausibly including environmental exposures) also affect the incidence, severity, and duration of disease. Low birth weight and maternal breastfeeding status also play important roles in modifying the impact of exposure to diarrheal disease pathogens.

The major research need is translational research to support more effective implementation of interventions of proven efficacy in community and household settings. Key questions focus on the acceptance and use of technology and related hygiene behaviors. There is also an ongoing need to test the efficacy of emerging technologies for household water treatment and sanitation.

Using the Research Type taxonomy described above, the Child Health Working Group identified multiple research approaches.

- **Type 1**: Social and behavioral research to better understand barriers to adoption and effective use of key household water supply, sanitation, and hygiene technologies. Translational research to test the effectiveness of innovative technologies, such as various household water filters, in community and household settings.
- **Type 2**: Intervention trials of new technologies, such as household biosand filters, testing efficacy in terms of diarrheal disease impacts in children. Intervention trials of clustered hygiene interventions, including improved household water management (treatment and storage), hand washing promotion, and sanitation using both diarrheal disease prevalence and overall under-five mortality as outcomes of interest.
- **Type 3**: Investigations to better understand the impact of toxic substance exposure on diarrhea, including the impact of exposure to infectious agents as well as alternate etiologies. Investigation to better understand the interface of diarrhea with the development of pneumonia.

3.2.5 Malaria

Malaria is a major killer of children, especially in Africa and Southeast Asia. In addition, malaria is likely to become more of a problem as a result of global warming, as habitat for mosquitoes grows. DDT is currently one of the most effective agents for malaria

prevention and is still being used both as a bed-net spray and for indoor residual spraying on walls in homes in endemic countries. DDT can have serious health consequences, especially in children. In fact, new research documents risk of learning disabilities in children, as well as risk of diabetes and disruption of endocrine function (both sex hormones and thyroid hormones). DDT is rated by IARC and EPA as a probably human carcinogen. Key co-factors include malnutrition and parasitic and other infections

Using the Research Type taxonomy described above, the Child Health Working Group identified multiple research approaches on malaria.

- **Type 1**: Develop insecticides that are effective against malarial mosquitoes but without having the toxic actions of DDT/DDE. Find ways in which DDT can be used in high risk areas with less risk of human exposure.
- **Type 2**: Investigation of rates of diabetes, neurobehavioral function and sexual development and reproductive function in exposed vs. less exposed populations.
- **Type 3**: Study of mechanism whereby DDT/DDE exposure perturbs glucose regulation. Study of mechanisms and effects of DDT/DDE exposure on estrogenic and androgenic hormone actions. Determine whether low dose DDT can be used safely without affecting the ecosystem.

3.2.6 Diabetes

Diabetes is increasing at epidemic proportions in developed countries. Major known risk factors for Type II diabetes are inactivity, excessive caloric intake, and genetic predisposition. Concomitantly, Type II diabetes is becoming increasingly common in children. Type II diabetes is a major (perhaps the major) component of metabolic syndrome, which is characterized by associated cardiovascular disease, hypertension, hyperlipemia and abdominal obesity. Recent studies have demonstrated convincingly that exposure to persistent organic pollutants, such as dioxins/furans, PCBs, and chlorinated pesticides significantly increases the risk of developing diabetes, with significant adjusted odds ratios as high as 38. These recent studies suggest obesity alone is not a risk factor for diabetes, but rather is frequently correlated with diabetes because obesity reflects the excessive intake of animal fats containing persistent organic pollutants.

Using the Research Type taxonomy described above, the Child Health Working Group identified multiple research approaches on diabetes.

- **Type 1**: Evaluate means of reduced consumption of contaminated animal fats in children. Evaluate means to reduce the recycling of contaminated animal fats into the food fed to animals meant for human consumption. Evaluate means for promoting exercise, as well as reducing time spent watching TV and playing video games among children. Evaluate means of promoting consumption of fat-free milk, fruit, and vegetables by children.
- **Type 2**: Perform additional epidemiological studies to confirm the relationship between environmental exposures and development of diabetes. Perform

epidemiological studies to explore possible protective factors, such as omega-3 fatty acids or other dietary interventions.

- **Type 3**: In animal studies, determine effects of exposure to various persistent organochlorine compounds on fasting glucose, blood pressure and serum lipids. Determine genes up or down regulated upon exposure to these compounds. Explore the relationships between diabetes and exposure to different dioxin/furan and PCB congeners and various organochlorine pesticides to determine which specific compounds are responsible

4 Environmental Components of Adult Health

4.1 Background

Adulthood spans a broad spectrum of life, with multiple definitions – both legal and biological. The Adult Working Group considered whether there were unique circumstances of environmental exposures that would confer differential risk in the different parts of the adult life course. The Adult Working Group developed three categories of adult life: 1) 10-35 years; 2) 18-60 years; and 3) 60-100 years. Within these overlapping categories are issues related to work-life and reproductive health status, each of which may contribute to increased risk from environmental exposures.

Five countries (China, India, Bangladesh, Indonesia and Pakistan) will represent about half the world's population in the year 2050. These are rapidly growing and aging populations such that most of the elderly in the world will be located in these countries by mid-century. As a consequence, many of the chronic diseases, such as cardiovascular disease and cancer, which are prevalent in the United States and Europe, will be dramatically overrepresented in these Asian countries in the next 40 years. Similarly, there is a changing demography in the United States where there will be an increase in the number of young people or young adults, due to immigration primarily from Latin and Central America. Therefore, the changing patterns of work life, adult experiences, and changing patterns of exposure will have an impact on health across the globe.

Biological Research Questions for Consideration:

The adult working group addressed the 5 tasks by focusing on biologically based research questions for the individual diseases enumerated in the following Table. The working group concluded that environmental exposure, epigenetic changes mediated by those exposures and the underlying inflammatory response provides a unifying base for moving the biological research agenda forward.

See following Table summary: **1= lowest, 5=highest

High Environmental Contribution	*Global Burden 10-35 yrs*	*Global Burden 18-60 yrs*	*Global Burden 60-100yrs*	*Potential Major Impact 10 yrs*	*Biological Model Available? (1-5)Hu/Exp*	*Measurable Outcomes?*	*Unique NIEHS Opportunity*	*Regions Most Affected*
PULMONARY DISEASE								
Asthma	**High**	**High**	**High**	**High**	**5 (Hu, exp)**	**Yes**	**Yes (LHF) Cent. Amer, Asia, Africa**	**Global**
COPD	**Low**	**Med**	**High**	**High**	**3 (Hu, exp)**	**Yes**	**Yes (LHF) Local Regions in Asia/Lat Am**	**Global**
CVD AND METABOLIC SYNDROME								
CVD	**Low**	**Med**	**High**	**High**	**5 (Hu, exp)**	**Yes**	**Yes (LHF) Local Regions in S. Asia/Lat Am, India**	**Global**
Endocr/ Metab Syndrome	**Emerge**	**Med**	**High**	**High**	**??**	**Yes**	**Yes Asia, Mexico**	**Global**
CANCER								
Liver	**Med**	**High**	**High**	**High**	**5 (Hu) 3 (Exp)**	**Yes**	**Yes (LHF) E. Asia, Africa**	**Global**
Hormonal Mediated	**Low**	**Med/ High**	**High**	**??**	**2 (Hu) 3 (Exp)**	**Yes**	**Yes, NCI partnership?**	**Emerging Global**
Lung	**Low**	**Med/ High**	**High**	**High**	**5 (Hu) 3-4 (Exp)**	**Yes**	**Yes, non-smokers, NCI?**	**Global**
NEUROLOGICAL								
Non-progressive	**High**	**High**	**High**	**High**	**5 (Hu) 5 (Exp)**	**Yes**	**Yes, NINDS, (LHF)**	**Global, Asia, Africa**
Progressive	**Low**	**Med**	**High**	**High**	**5 (Hu) 4 (Exp)**	**Yes (some)**	**Yes, NINDS, NIA, (LHF)**	**Global**

4.2 Priority Research Areas in Adult Environmental Health

4.2.1 Asthma and respiratory allergies

Asthma is a major global environmental problem worldwide. Asthma is defined as reversible airways obstruction that tends to occur in relation to environmental stimuli. In children, it is most frequently allergic; adult onset asthma is somewhat more frequently non-allergic. Environmental risk factors for asthma, especially in children, include living

in a more developed country. The reason for this international variation is not completely understood, but does not appear to be due to diagnostic practices. A major hypothesis proposed to explain the international variation in asthma rates is the hygiene hypothesis, which posits that the greater burden of early infections in developing countries leads to immune development in directions that protect against allergic responses to the common allergens in the environment. However, inhaled pollutants, which tend to be higher in urban developing country settings and in areas where biomass is burned for domestic fuel, clearly exacerbate asthma and are also risk factors for its development. Understanding the balance between these potential protective and provocative aspects of the environment in relation to asthma is a major challenge and opportunity that could lead to improved therapies for the disease and avenues for prevention.

In adults in the developing world, occupational exposures are a major cause of asthma and result in an important health burden. Environmental tobacco smoke is also an important risk factor. Increasing data suggests that dietary factors can reduce the effects of environmental exposures on asthma severity and induction, but dietary factors may also be involved in increasing risk. There is a strong genetic component to asthma risk, and a few genes have been clearly identified. However, few genetic studies have seriously considered environmental exposures, and it is clear that interactions are paramount in asthma causation.

A high potential for major public health impact in 10 years exists for asthma. Reduction of harmful exposures could have rapid effects on reducing new cases of asthma and reducing the severity of existing cases. Further, asthma in childhood and early adulthood is a risk factor for COPD in later adulthood.

Strong biologic models are available for allergic asthma and for the role of environmental exposures in triggering asthma phenotypes. Mouse models exist for allergic airway inflammation that share many features with human asthma. Models for non-allergic asthma are less strong. There are guinea models that have been used to examine effects of pesticides on muscarinic function, a non-allergic pathway.

Asthma is highly amenable to study because outcomes are measurable and standardized. The combination of symptoms and lung function testing with challenge enables fairly reliable classification. Atopic status is easily characterized by blood tests or skin tests enabling further classification of asthma. Further classification can be done by investigating specific triggering agents and by specific inhalation challenge. This is done for diagnostic purposes in the occupational setting but has not been widely used in population studies to date.

Asthma represents a unique opportunity for NIEHS. Although other NIH institutes such as NHLBI and NIAID study asthma and their environmental triggers, especially allergens, NIEHS has historically taken the lead in studying the effects of inhaled combustion products on asthma. The marked international differences clearly suggest environmental causes and gene-environment interactions. Understanding the reasons

for the lower risks of asthma in the developing world would provide great new insights into asthma etiology. Studies of the effects of reducing indoor burning of solid fuels on asthma-related phenotypes provide an excellent opportunity. These exposure changes can be encouraged by development of low-cost alternatives for heating and cooking that supplant the burning of biomass or drastically reduce emissions. At the moment, excellent alternatives do not exist although studies of changing to other fuels that remain higher cost (LP, charcoal) could be done to document changes in respiratory status. It would be important to identify whether reduction of biomass burning results in improvements in adult respiratory parameters and also to identify whether perhaps allergic illness is increase with lower exposure. If so, this would suggest that components of biomass combustion alter immune function so as to reduce the development of allergy in response to common antigens. Relatively short-term studies could be done of both children and parents and potentially grandparents living in the same home to quantify clinical and biologic changes resulting from improvements. Other benefits that would accrue from this intervention could include reduction in CVD and lung cancer, and potentially neurologic dysfunction. Birth outcomes would also likely be improved. Opportunities to study the interactions among genetics, diet, and indoor biomass burning exist within infectious diseases cohorts and intervention studies, including TB and HIV studies.

Global studies also offer the opportunity to examine occupational factors for asthma that may not be common in the US. This might help to identify the components of ambient air pollution that are responsible for asthma exacerbation and incidence in non-occupationally exposed populations, including in the United States.

Possible partners include NHLBI, NIAID, NOAA, NIOSH, NSF, CDC, and the governments of China and India. Engineering advances might come from partnership with local industries in the host countries.

4.2.2 Chronic Obstructive Pulmonary Disease

Chronic obstructive pulmonary disease (COPD) is among the top five causes of death in the US and is high worldwide and thus represents a truly global problem. COPD is defined as airway obstruction that has a chronic or nonreversible component. The global burden of COPD is higher after middle age. Respiratory symptoms precede demonstrable COPD in middle age and constitute an important cause of morbidity and impaired quality of life. Smoking is the major risk factor in developed countries. Exposures other than smoking are very important in the developing world. Understanding the role of exposures other than smoking in developing countries can help to identify causes that may play an important role in the developed world as well.

Risk factors, other than smoking, include ambient and indoor air pollution, as well as occupational exposures. These other factors may also increase the risk of developing COPD among smokers. Genetic factors influence the risk from environmental exposures, including smoking, but less penetrant genes than *A1AT* (alpha-1 antitrypsin deficiency) are yet to be clearly identified, creating opportunities for studies with

excellent exposure characterization. There may be dietary factors involved in risk and prevention. Interaction between environmental exposure and infections is also important but has not been well-studied.

Potential for major impact in 10 years is high because exposure reduction would result in rapid changes in the profile of severity as well as the development of new cases. Evidence from smoking research clearly shows that cessation modifies the progression of established disease. Reduction in COPD prevalence and severity also would positively impact cardiovascular mortality and lung cancer, as well as prevent cognitive impairment in affected individuals.

Biological models exist for smoking-induced emphysema and to a lesser extent bronchitis. There is a need for better experimental models. International standard criteria for COPD diagnosis exist (GOLD criteria) and are easily implemented. Additional modalities including imaging techniques (HRCT) are now available for human studies.

There are unique opportunities for NIEHS. Large female nonsmoking populations in Asia, Latin America and Africa with high levels of exposures provide important research opportunities.

4.2.3 Cardiovascular disease and diabetes/metabolic syndrome

Cardiovascular diseases are the leading cause of death globally. Ischemic heart disease (17.9% of deaths) and cerebrovascular disease (10.7%) are the two leading causes of death in high income countries. In addition, these are also the two leading causes of death in low to middle income countries (ischemic heart disease 17.9% of deaths, and cerebrovascular disease 10.7%). As these countries transition from high infectious to chronic diseases, the proportion of deaths attributable to cardiovascular disease will continue to rise.

Metabolic syndrome and Type II diabetes are increasing rapidly in the developed world. Murray and Lopez reported that diabetes was responsible for 2.3% of deaths in high income countries and 2.4% of DALYs. While diabetes was not identified as one of the leading (top 15) causes of death (or DALYs) in low to middle income countries, the increasing prevalence of obesity as these countries develop means that diabetes and diseases associated with metabolic syndrome will become a larger contributor to death and morbidity.

Systemic inflammation has been shown to be a powerful risk factor for cardiovascular events. Many environmental exposures have been shown to act through systemic inflammation and oxidative stress.

Current research demonstrates that air pollution is associated with acute and chronic cardiovascular events. There is evidence that inhalation of particulate air pollution creates and exacerbates both pulmonary and systemic inflammation and oxidative stress, leading to direct vascular injury, atherosclerosis, and autonomic dysfunction.

Particulate air pollution has been found to lead to rapid and significant increases in fibrinogen, plasma viscosity, platelet activation, and release of endothelins, a family of potent vasoconstrictor molecules. Build-up of atherosclerotic plaque, measured by carotid intima-media thickness, is higher in communities with higher mean $PM_{2.5}$ concentrations. A wide range of other environmental exposures have been associated with increased risk of cardiovascular risks including environmental tobacco smoke, carbon monoxide, lead and other metals, solvents, and endotoxins.

While the public health burden of cardiovascular disease attributable to air pollution could be large, the evidence suggests that individual risks are modest. If studies of unique populations can identify intrinsic and acquired individual factors that lead to increased adverse cardiovascular responses to environmental exposures, then it should be possible to offer focused interventions to those at greatest risk and thereby ameliorate at least some of the patient-specific damages of air pollution.

If air pollution and potentially other environmental agents acutely induce an inflammatory or oxidative stress response, potentially contributing to acute cardiovascular events, then subgroups within the population who have elevated inflammatory levels may be at increased risk to respond to acute environmental challenges. Chronic exposure to air pollution can lead to chronic pulmonary inflammatory states. We now understand that obesity is also an inflammatory condition.

Populations who have reduced ability to deal with inflammation or oxidative stress, either through genetic or epigenetic characteristics, dietary deficiencies, or co-morbidities, may provide insights into the mechanisms of these acute air pollution effects. On the other side are individuals with enhanced anti-inflammatory/anti-oxidant response.

The experience from tobacco smoke is that cessation of exposure leads to rapid improvements. Potential for unique studies of some aspects of CVD (such as inflammatory markers) exist within natural experiments, such as the expected reduction in air pollution surrounding the 2008 Beijing Olympics. There are highly developed objective measures of cardiovascular events and clinical status, as well as for some of the inflammatory markers (e.g. CRP). While extensive CVD research is ongoing, the focus is typically on therapeutic interventions and individual risk factors. Investigations in the developing world present NIEHS with the opportunity to assess associations in populations with unique host characteristics.

4.2.4 Liver cancer

Liver cancer is the fifth most common cancer on a worldwide basis. Eighty percent of the cases occur in the developing world; the high-risk countries are those in sub-Saharan Africa and East and Southeast Asia. China has the highest burden of this rapidly fatal disease; close to half of all newly diagnosed cases annually in the world are in China. Almost all liver cancer occurring in high risk regions are hepatocellular carcinomas (HCC), with the exception of certain pockets of Southeast Asia where cholangiocarcinomas are prevalent, due to parasitic infection.

Unlike most other epithelial cancers which are rare in persons under age 50, HCC is a common cause of death in middle-age men in many parts of the high-risk regions. Thus, this disease has a significant adverse impact on the local economy and development.

NIH-funded collaborative research in high-risk regions in the past 3 decades has established chronic infection by the hepatitis B virus (either vertical transmission from carrier mother or horizontal transmission in the first few years of life as dominant modes of transmission) and lifelong exposure to aflatoxins through ingestion of contaminated foods as the two most important causal factors for HCC in these parts of the world. Although hepatitis C virus plays a relatively minor role in the present occurrence of liver cancer in high-risk regions, there is reason to speculate that its importance will increase over time.

Cancer registry data from pockets of newly affluent parts of Asia have shown decreasing local rates of liver cancer that parallels the communities' recent, rapid progress in economic development. These observations suggest that reduction in aflatoxin exposure can lead to reduced burden of liver cancer within a relatively short time period.

Other established or probable risk factors for HCC include heavy alcohol intake, cigarette smoking, and a history of diabetes. In parts of Asia where liver cancer is prevalent, tobacco and alcohol use has been increasing at an alarming rate. In addition, a combination of less physical activity (due to higher availability of motor vehicles) and more abundant and varied food supply have led to increased body size in historically very lean populations. Data from newly affluent parts of Asia have documented increased rates of diabetes in the local populations.

The changes in risk factor profiles outlined above offer unique opportunities to NIEHS investigators in elucidating the etiology of liver cancer in humans as well as in reducing this common, rapidly fatal disease that impact disproportionately the developing world.

Specific research questions include:

- What will be the effects of diabetes, cigarette smoking and excessive alcohol intake against a high background rate of chronic viral hepatitis and continuing exposure to aflatoxins on the development of HCC in the developing world? What are the underlying causal mechanisms for the observed effects?
- Epidemiologic studies conducted in high risk regions have established that the interaction effects between viral hepatitis and aflatoxin exposure in affecting HCC development are highly synergistic (two-fold higher than the multiplicative product of individual effects). What are the biological underpinnings for such dramatic synergism between a viral and a chemical carcinogen?
- Limited epidemiologic observations have suggested a major late stage effect by aflatoxins on HCC development. This offers a unique opportunity to significantly reduce HCC burden in the developing world within a relatively short time frame. Can we identify effective intervention strategies that do not depend on the

region's eventual rise to economic affluence (which may take some time) with consequential cleanup of its food supplies?

4.2.5 Hormonally mediated cancers

The two major hormonally driven cancers are breast cancer and prostate cancer. Large-scale epidemiologic studies of migration patterns around the world have demonstrated that both of these cancers change very rapidly within one to two generations. These data form a very strong basis for suggesting environmental exposures play an important role in the increased incidence of both of these diseases. In both cases, estrogen and other hormones appear to play an important role in their etiology and development. Extensive molecular investigations demonstrate the underlying modes of action of these hormones in biological systems. This offers tremendous opportunity for the basic science community to partner with NIEHS on the problems of breast and prostate cancer. Further, historic interest and expertise of NIEHS in the role of environmental estrogenic compounds offers a tremendous opportunity to investigate the role that these exogenous estrogens play in the development of the hormonally mediated cancers. Research opportunities employing experimental models and epidemiologic investigations with associated biological samples provide important venues for collaborative investigations.

4.2.6 Lung cancer

The contribution of environmental exposures to lung cancer is well-established. Although tobacco smoking accounts for the majority of lung cancer in the world, in various parts of the world other exposures are well-known. Examples include a number of occupational exposures, as well as second-hand smoke. In East Asia, the lung is the most common site of cancer, and a substantial proportion of lung cancer, especially among women, is not related to tobacco smoking. The burden of this disease is huge, with at least 1.2 million deaths per year, and projected to grow enormously over the next several decades. Although these changes are mostly accounted for by the change in smoking prevalence, other carcinogen exposures (such as indoor air pollution, ambient air pollution, occupational exposures, arsenic, PAHs and second hand smoke) are rising as well.

Lung cancer places its greatest burden in the mature and older adult population. There are excellent human models, and more recently, good animal models (especially for non-small cell carcinoma). There are also measurable outcomes, with standardized (WHO) pathologic classification of the major types. There are some unique opportunities for research on non-smoking related environmental causes of lung cancer. For example, Chinese women in Mainland China, Taiwan, Hong Kong, and Singapore have very high rates of non-small cell lung cancer, with Thailand intermediate between western and Chinese rates. Thus these locations provide excellent opportunities for future epidemiologic investigations of nonsmokers.

There are excellent opportunities for partnerships with NCI and EPA, as well as governmental agencies (such as the Chinese National Science Foundation) and research institutions in these countries for investigations that focus on elucidating the environmental determinants of lung cancer in non-smokers, and the relevant effect modifiers (such as diet, and energy balance).

4.2.7 Neurological disorders

Neurological disorders known to be associated with environmental factors include (1) neurodegenerative diseases that probably begin to evolve early in life, clinically appear later, and progress to fatal outcomes (ALS, Parkinson's, Alzheimer's, diabetic autonomic neuropathy), and (2) non-progressive neurological disorders across the span of life that result in physically and cognitively crippling disease. Examples include diet-related conditions (e.g. cassava-related konzo), and pesticide, solvent, and metal (e.g. As, Mn, Hg) neurotoxicity. Some of the latter impair brain development persistently; others compromise productive life during the working years.

"Low-hanging fruit" opportunities to assess unusual populations include western Pacific ALS-P-D, chemical-induced neurotoxicity associated with rapidly industrializing societies (Asia), konzo (Africa, India), and over-zealous pesticide use in agriculture. Much less is known about the environmental contribution to adult-onset psychiatric disorders, but cognitive and behavioral perturbation has been linked to occupational pesticide, manganese, and solvent exposures. Only small percentages of individuals within a population exposed to neurotoxic chemicals succumb to neurologic disease, but very little is known regarding genetic susceptibilities. Similarly, only a small proportion of neurodegenerative disease can be explained by heritable factors, raising the possibility that gene-environment interactions are important for the bulk of spontaneous cases. One valuable approach has been to focus on high-incidence clusters of neurological diseases, the understanding of which can shed light on look-alike disorders globally. For example, informal study of a cluster of parkinsonism among young-adult U.S. drug addicts led to the discovery of MPTP, which became the standard method of inducing experimental parkinsonism and promoted interest in possibly related environmental exposures (e.g. paraquat). The burden of neurological disorders with environmental components is global and, for progressive neurodegenerative disease, will increase with community development and the attendant extension of life. While there are precise tools to define neurologic disease, the development of biomarkers of impending disease in biological fluids is in its infancy. Animal and tissue culture models of neurological diseases are mostly well developed. Possible U.S. NIH partners include NINDS and NIA.

5 Innovative research methods

To implement a meaningful research program in global environmental health, the NIEHS should take advantage of a suite of highly-relevant innovative research methods. Key methodological approaches involve the coordinated application of existing and emerging chemical and biological technologies that will relate exposure to disease

outcome. Additionally, it is a mandate of our charge to identify wherever possible approaches that help uncover the mechanistic underpinnings of environmental disease.

Given that exposures will most often be multi-factoral, the most statistically robust relationships will be established if measurements can be done on individuals, who are then tracked for either end stage disease or for reliable biomarkers that predict end stage disease. Once again, because the exposures are likely to be complex, and the basic mechanisms underlying the diseases are often not known, it is wise to cast a broad net when looking for disease biomarkers. Both genetic and non-genetic endpoints should be monitored.

5.1 Gene-Environment Interaction Studies

Any proposed investigations on global environmental health issues must be built upon the premise that not all individuals are equally susceptible to the adverse environmental consequences of exposure. With the advent of high-throughput technologies for the identification of environmental contaminants in carefully collected environmental and biological samples, there exists a range of equally powerful high-throughput genomic based technologies (mass spectroscopy, microarray, Q-PCR, global methylation platforms) to thoroughly interrogate genetic variation in order to identify single gene polymorphisms (SNPs) and mutations that determine an individual's susceptibility to an adverse health outcome. While it is possible now to interrogate individual genomes for up to one million SNPs on commercially available platforms, in the very near future it will be possible to sequence entire individual genomes in a very cost-effective manner to discern all gene variants contributing to susceptibility. The ability of statistical geneticists, working in concert with molecular epidemiologists to analyze these massive datasets is currently lagging behind our ability to generate the data. Informative algorithms must be developed for fully exploit these developing genomic and proteomic approaches to understand the underlying biology rendering individuals susceptible to environmentally-induced disease.

5.2 Animal Models for Validation and Intervention Studies:

The high-throughput genotyping studies envisioned for this GEH program will identify potential gene targets or whole gene pathways whose ability to function properly are compromised by environmental exposure. In order to validate these observations and to develop testable intervention strategies, it will be essential to utilize animal model systems that closely parallel the human situation, both from an underlying molecular basis, but also with respect to the delivery system of the environmental contaminants. With several international consortia working to develop gene inactivation for every gene in the mouse (See: www.tigm.org), it will be possible to use both gene knockout and gene knock-in (putting a known human mutation identified in the high throughput genotyping studies described above) approaches to develop mouse models with the precise genetic factors that render specific haplotypes susceptible to adverse health effects following exposure to environmental toxicants. Specifically, mice can be created that carry heterozygous mutations for 2-10 genes that may influence a number of

different developmental or signaling pathways that were shown to be responsive to the environmental factors in question. Understanding the underlying biology of these compromised systems will enable strategic decisions to be made for interventions that may restore the physiological homeostasis such as providing protection against the environmental exposure in question. With solid validation data of the proposed intervention strategy developed in a highly specific animal model in place, it will be possible to consider performing the translational studies in high-risk human populations.

5.3 'Omics Approaches

Understanding the molecular mechanisms of biological responses to environmental exposures would lead to efficient identification of effective biomarkers for exposure assessment. Recent advent in technology of genomics, proteomics, and metabolomics provide powerful tools to conduct high-throughput screening of such biomarkers by exposing cell lines and animal models with the chemical pollutants and their combinations. Such screening can be conducted under the exposure of chemical pollutants and their combinations at various concentrations and various durations. The molecules (genes, proteins, or metabolites) that are subject to the change in exposure will be selected as the candidates for biomarkers upon further verification and validation, and they too may shed light on the underlying biological processes. Such markers can also serve as endo-phenotypes or intermediate phenotypes in delineating the relationship between the genetic variation, environmental exposure, and phenotypes. Phenotypes would be prioritized based on research opportunities identified above, in particular immune and endocrine responses. Bioinformatics tools for data hosting, manipulating, and analyzing are imperative to the success of the aforementioned high-throughput screening approaches.

5.4 Statistical Analysis for Understanding Gene-Environment and Gene-Gene-Environment-Environment Interaction

Most phenotypic variations and differences in exposure response are caused by complex and joint actions of multiple genetic and environmental factors, through dynamic, epigenetic, and regulatory mechanisms. A comprehensive delineation of the complicated interplay between genetic and environmental factors that influences complex traits will require characterization of DNA variation in the population, collection of individuals' histories of environmental exposure, and the development of mathematical tools for unraveling the dynamic interaction between genetic variation and environmental exposures. Despite growing consensus on importance of gene-environment interaction in the genetic studies of complex traits, we still have limited tools to detect interaction between gene and environments. It is therefore important to develop powerful statistical methods to determine how genes and environmental exposures interact to influence the development of the diseases.

As new exposure and biologic assessment methods are developed, we will acquire numerous measures of exposure, genetic markers, nutritional factors, maternal-fetal interactions, and other covariates in research studies. These studies may be of limited

sample size given the cost of epidemiologic research. New statistical methods are needed to analyze this data with maximum power. Although this issue is not specific to research on global health, it may be a particular problem in these populations where there may be numerous exposures and other factors that impact health.

5.5 Rapid and Cost-Effective Screening of Biological and Environmental Samples

In many of the proposed areas of research, a pressing need exists for methods that could be used to rapidly and cheaply screen both biological and environmental samples. For example, there are good methods for the assessment of human exposure to many persistent compounds. However, assessment of exposure to less persistent compounds poses a challenge. Methods need to be perfected and others need to be developed to assess chronic exposures to non-persistent compounds. Furthermore, it is difficult to estimate exposures based on measurements of environmental contaminants in biological samples from pregnant women because very little is known about how pregnancy alters the pharmacokinetics. Methods are needed to develop efficient methods for using pharmacokinetics to estimate exposures in pregnant women. Animal experiments in this area could provide important insights.

Another example is the development of a microarray chip with which the presence of thousands of potential pathogens could be quickly screened (using known DNA and RNA fragments) or chemicals would allow significant advances in the measurement of exposure to and/or infection with infectious agents. Ideally, such chips would be able to screen both environmental (e.g. air and/or water) and human (e.g. stool, serum, saliva) samples.

Working groups also considered the development of reliable, inexpensive, datalogging, personal air quality monitors using advanced sensors, microprocessing, and wireless communication technologies. Such monitors could revolutionize the ability to understand environmental risks by greatly reducing uncertainty in exposure assessment. In addition, if appropriately inexpensive, they would make possible studies in developing-country settings with little infrastructure, including the trained personnel and laboratory back-up needed, where such work is difficult at present.

The importance of developing such techniques with high sensitivity is especially important for analyzing the limited sample sizes that can typically be obtained from infants and children. In addition, techniques should be relatively affordable and usable in field settings in developing world research. Such techniques would of course have direct application to similar studies in the United States.

5.6 Culturally-Appropriate Assessment of Sequelae of Environmental Exposures

These are important sequelae of a number of environmental exposures, yet there are few tools available except in English. Moreover, tools for assessment available in appropriate languages all too often have not been standardized for the populations

where they are to be used. For example, a Wechsler Intelligence Scale standardized in Spain may not be appropriate for use in Mexico and Costa Rica, where there will be both language and cultural differences. Up to now, most neurodevelopmental assessments in the face of this challenge have resorted to nonverbal assessment, neglecting an important domain of intellectual function.

6 Breaking Down Research Barriers, Partnerships, and Connecting Researchers

6.1 Research Barriers

Environmental health training. Environmental health researchers are very few in the developing world, even in proportion to other health scientists in the same countries. Scientists that understand and conduct research on exposures and associated morbidities of pregnancy and the perinatal period are even rarer. Both the science and implementation of global environmental health are greatly limited by this paucity of collaborators and on-site expertise. Identification of key problems, access to populations, storage, analysis of samples, and interpretation of data, as well as the sustainability of any proposed intervention are unlikely to be successful in the long term without knowledgeable local scientists.

Substantial gains to the global environmental health research community can be made by greater investments in training foreign scientists, particularly in the context of research activities. Training can and should take multiple forms. Mentored research training at the graduate and post-graduate level can be incorporated into funded research projects at priority sites, and existing efforts such as the Fogarty International Center's training program on Environmental and Occupational Health could be expanded and oriented more tightly to research.

Lack of resources of collection, processing, transport, annotation of samples and analyses. Improvements in the detection of environmental chemicals in blood often lead to major advances in our knowledge concerning the impact of exposure on health. Examples include the detection of blood lead concentrations < 60 ug/dl (around 1960) by atomic absorption spectrophotometry, the detection of an array of pesticides in cord blood by GC-MS (late 1990s), and the recent detection of As and its metabolites in cord blood by ICP-MS in 2006. Since biological specimens are typically available in very small amounts, particularly in the developing world where there is an aversion to both blood sampling and transport (across borders), the development of sensitive "low-tech" (i.e., in country) methods for the detection of environmental chemicals is a high priority,

Cultural obstetrical practices. In much of the developing world, cultural obstetric practices pose a major challenge to the conduct of research targeted at the impact of environmental exposures on the newborn, and the subsequent short and long-term effects of such exposures. In many parts of the world, women deliver at home; while in other regions, births occur in relatively primitive birthing clinics. Often electricity is

absent or intermittent. The collection, processing and appropriate storage of maternal and umbilical cord blood samples in regions of particular interest to environmental health scientists will require the establishment of appropriate partnerships and the provision of adequate resources for a research infrastructure.

Few large international cohort studies on environmental health. Birth cohort studies provide an efficient design to examine environmental threats to children's development and health. Such studies among global populations with high levels of a wide range of environmental exposures are particularly important to provide: 1) an increased understanding of the impact of the environment on prenatal and postnatal health and development of children who may already be compromised by infections, malnutrition, and other consequences of persistent poverty; 2) data to identify and assess the relationships between multiple environmental and non-environmental exposures and multiple outcomes; 3) provide opportunities to explore the effects of multiple exposures, including cumulative exposures on the health and development of children across various stages of development and 4) provide a sound basis for the further assessment of environmental and socioeconomic factors as determinants of child health and development.

Currently, a number of studies are being planned or undertaken globally to study the effects of the environment on children's health and development. In addition, there are a number of large birth cohorts already underway to which environmental assessment components could be added that would link environmental exposures to later outcomes. Finally, harmonization of data collection methods to assess environmental exposures and outcomes across cohorts need to be established

Institutional and cultural differences in how research is approached. A host of challenges related to cross-cultural context of environmental health research are particularly important to work in developing countries. In particular, the cultural sensitivities to the birth process in traditional societies, for instance in Africa, make access for observation and sampling an enormous challenge for scientists in general. Other social and ethical challenges derive from traditional organization of societies, and sometimes limit access to women generally, and in some societies genetic studies are greatly constrained by concerns of commercial exploitation and sometimes cultural/religious prohibitions. Environmental sampling can be constrained in high concentration environments by local political anxieties for multiple reasons, including the fear of political activists, potential impacts on tourism and business interests, among others, and may be both local and regional in nature.

These challenges require particular and local attention to the local political social/cultural and ethical context that is generally beyond the regulatory approach of IRBs. International and local researchers engaged in the research are often the most knowledgeable individuals in navigating these issues, but often need to consult or even incorporate social scientists and research ethicists in the design and execution of projects. Particular attention to communication with individuals, communities, universities, and government authorities from the earliest stages of a project and

continue through and after its completion. This is true for basic research and increases in importance as one moves toward interventions.

Clinical studies addressing neonatal or maternal exposures to environmental factors face particular difficulties in many developing country settings. In many developing countries, the majority of women rarely receives prenatal care and delivers in rural settings attended by midwives or traditional birth attendants far from medical facilities. Enrollment of women in studies can be hampered by lack of literacy and lack of personal authority for giving informed consent. Determination of birth outcomes, e.g. stillbirth, subtle birth defects, delayed development may be difficult. In addition, collection of samples (placenta, blood samples) and their transport and storage provide additional technological challenges.

Establishing culturally sensitive teams to approaches to obtaining buy-in by the community and development of informed consent forms that take into account the understanding of risks involved by the woman and ensuring that appropriate community responsible individuals are critical, as are training of birth attendants in collection and storage of specimen and development of methods for collection and storage and transport that address rural areas. In addition, local infrastructure to help establish regional cores and centers of excellence will greatly enhance global environmental health research. This would best build on regional centers that already have NIH funding, could include expertise and facilities related to laboratory-based science, data management and establishment of community based partnerships. To ensure sustainability, it is best to partner with other agencies and international partners.

Environmental health science not viewed as an academic discipline in developing countries. Environmental health science is not viewed as an academic discipline in most developing countries; rather it is treated as a public health management topic. As such, there are few research programs, minimal career paths for research oriented scientists, and minimal research investments by national governments, relative to other health sciences. A Global Environmental Health program led by the NIEHS could do much to stimulate the field, lending it prestige in developing countries in a number of cost-effective ways. These include: helping to develop indigenous environmental health journals such as Environmental Health Perspectives, stimulating development of local professional societies or interest groups of relevant international societies, and sponsoring symposia at international societies. Indigenous intellectual leadership may be found in the alumni of the Fogarty-NIEHS training program (ITREOH) and in the expatriate community in the United States, among other places.

Environmental health viewed as barrier to industrial growth. A barrier to environmental research is reluctance on the part of developing and emerging industrial countries to engage in research that can result in environmental regulations that could be perceived as hindering industrial growth. However, research from the high income, industrialized countries, such as the US, have shown that measures to reduce exposures to environmental contaminants has provided higher health benefits compared to costs of environmental regulations. These lessons are important for

countries to know when considering the importance of investing in environmental health issues. NIEHS should develop ways to convey the health benefits of environmental intervention opportunities in other countries.

6.2 Bringing Research Partners Together

It is highly likely that multiple federal and non-federal partnerships will be required to develop a global environmental health program for NIEHS. Potential federal partners include other institutes and centers (IC's) of NIH such as Fogarty, NICHD, NIAID, NCI, and others. In addition, non-NIH partners may include CDC, EPA, USAID, DOD, USGS, NOA, NASA and NSF. Equally critical would be organizations such as WHO, other United Nations – related agencies, as well The World Bank, Gates Foundation and myriad NGO's in both developing and developed countries. One illustration of how NIEHS might develop a sustainable strategic partnership is with the Fogarty International Center.

Fogarty International Center - Fogarty can provide a number of partnership opportunities for NIEHS as it has a long history of establishing partnerships between US and foreign investigators. NIEHS should use existing partnerships on global maternal and perinatal to expand training and research to questions of the effects of environmental impacts. NIEHS and Fogarty could also encourage new partnerships in this area. In addition, NIEHS should utilize other Fogarty health related programs for training in global environmental health. For example, NIEHS could supplement the Aids International Training and Research Program in Africa (AITRP) to include environmental issues. In addition, NIEHS could partner with NICHD's Global network for women's and children's health research to further environmental research

NIEHS could also partner with Fogarty and other relevant institutes to fund Regional Centers of Excellence in Research and Training in Global Environmental Health in the Developing World. These should be partnered with several developing and developed country institutions.

NIEHS can take advantage of the US/India cooperative working groups, in particular the working group on environmental health (run by CDC) and the working group on child and maternal health (run by NICHD) to discuss priorities for US/India cooperative environmental research on perinatal and maternal health issues.

NIEHS should use convening's to encourage research partnerships between developing and developed country researchers. NIEHS should identify research priorities and target specific appropriate meetings to bring together health and environment researchers. This could include meetings of existing professional international societies, such as the International Society of Environmental Epidemiology (ISEE), International Society of Exposure Assessment (ISEA). In addition, international

societies focused on particularly relevant disease endpoints could also be important, such as International Congress on Birth Defects and Developmental Disabilities in Developing Countries, and International Brain Research Organization. Another venue would be for NIEHS to organize an international stand alone conference on priority research topics.

NIEHS can also provide competitive travel and conference grants for US research teams to visit specific countries to identify collaborators and build partnerships related environmental health research and training.

NIEHS and the Fogarty International Center should have level high engagement, including visits, with partners in key governments (for example India and China) to identify research and training priorities, as well as research resources in global environmental health.

NIEHS should convene a federal working group on global environmental health research to discuss research and training priorities and identify partnerships among the agencies in this area. Members of the group could include NIAID, NICHD, NCI, HG, Fogarty, CDC, USGS, NOA, NASA, EPA, USAID, NSF, and DOD.

In some cases research capacity may be facilitated through the existing Fogarty International Center's training and research in environmental and occupational health program, which is cosponsored by both the NIEHS and NIOSH. In other cases, research capacity may build on research and research training investments made by both the Fogarty international program in the National Institutes of Health in areas of science or through a new NIEHS and Fogarty international collaboration under the global health initiative research program. In this case scientists from the low and middle income countries trained in the US and under at the NIEHS grants will be able to provide for reentry support under GRIP. Research capacity also requires preparing the next generation of US scientists to participate in global environmental health research. Towards this end, existing Fogarty international programs are available to help in this regard, the Fogarty -- Ellison program (recently renamed the international clinical scholars program) and the Fogarty international research scientist development award program as well as the new K/99 pathways to independence trans- NIH program in which both the NIEHS and a fully international program participates.
To be effective, research capacity must be built upon collaborations among individual scientists as well as long-term partnerships among institutions in the developed and developing world. In all likelihood, research capacity strategies will need to be designed to fit the specific needs of the research being undertaken under NIEHS's global environment health initiatives. These priorities must reflect both important scientific questions and a response to local needs.

Summary - NIEHS should explore potential for partnering with foundations to support efforts in global environmental health research. These could include the Wellcome Trust, Suzy Buffett, and David and Lucille Packard Foundation, and other foundations that work through the Health and Environment Funders Network. NIEHS should also

explore using the SBIR model for supporting appropriate technology development (e.g., storing blood/serum at room temperature) in the developing world.

Regardless of what research priorities are ultimately selected under the global environmental health investment, strengthening research capacity is essential. Research capacity is a prerequisite for successful research. Perhaps even more importantly, for global environmental health, it provides the opportunity for scientists from low and middle income countries to participate as equal partners with colleagues from the developed world in the planning and implementation of research, including detailing the necessary community agreements and government approvals needed before the research is begun. Research capacity is also important in facilitating the ability of the country to translate the results of this research into practical benefits for its citizens. The success of both the research and research training initiatives will require NIEHS to carefully consider multiple strategic partnerships to provide a sustainable and culturally sensitive program that would endure for decades. This workshop is an excellent first step on that long road.

7 Summary

The purpose of the meeting was to advise the NIEHS as to strategies and priorities to consider for the effective use of resources in the arena of global environmental health. Participants joined one of three working groups, focused on the environmental components of Maternal and Perinatal, Child, or Adult Health. Each working group was charged to develop recommendations based on the five key tasks and to focus these recommendations on goals attainable within a 10 year period. While each group had identified diseases that specifically affected their age/life group, the recommendations on research focus, approaches, barriers and partnerships were applicable to all.

At the end of the workshop, the three working groups consolidated their research priority lists into a single list. Additionally, there was a discussion of likely successful short-term strategies that NIEHS could consider to further its interests in global environmental health in the next year. The priorities were then rank ordered for each group and the results are shown in the appendix and are summarized below.
The top six research areas recommended for the NIEHS include: 1) Biomass combustion and poor pregnancy and birth outcomes, 2) Acute respiratory infections, asthma, & IAP/OAP, 3) Arsenic in drinking water & poor health outcomes, 4) Neurobehavioral deficits & PCBs/pesticides/metals, 5) Susceptibility to ID through environmentally-mediated modulation of immune response, 6) Lung cancer & nonsmokers in Asia.

The top six short term strategic approaches recommended for NIEHS to be considered for next year include: 1) Adding environmental questions to demographic health surveys, 2) Adding environmental components to existing projects, 3) Contribute to established research stations/centers, 4) Co-investing with Fogarty on specific new topics/Research training in environmental health, 5) Exploratory grants, 6) Travel funds.

Some common barriers to successful environmental health research include: 1) Too few environmental health scientists. Increase numbers through training and mentoring of graduate students and post-doctoral fellows; and promote environmental health as an academic discipline in developing countries, 2) Too few resources for the collection, processing, transport, annotation of samples and analyses. This will require the establishment of appropriate partnerships and the provision of adequate resources for a research infrastructure. NIEHS should also explore using the SBIR model for supporting appropriate technology development (e.g., storing blood/serum at room temperature) in the developing world, 3) Institutional and cultural differences in how research is approached. Clinical studies addressing neonatal or maternal exposures to environmental factors face particular difficulties in many developing country settings. Culturally sensitive research teams are needed, 4) Environmental health viewed as barrier to industrial growth in emerging industrial countries. There is reluctance on the part of such countries to engage in research that can result in environmental regulations that could be perceived as hindering industrial growth.

There were several suggestions on how NIEHS could increase development of partnerships. 1) NIEHS should encourage research partnerships between developing and developed country researchers through sponsoring and funding meetings and taking advantage of existing US/India cooperative working groups, and international societies focused on particularly relevant disease endpoints, 2) NIEHS should convene a federal working group on global environmental health research to discuss research and training priorities and identify partnerships among the agencies in this area. This should include other institutes within the NIH, CDC, USGS, NOA, EPA, NSF and other global foundations such as the Wellcome Trust, Suzy Buffet, and David and Lucille Packard Foundation, 3) NIEHS should develop a non-federal partnership working group to best assess development of strategic partnerships with WHO and NGO's such as philanthropic foundations committed to global health.

Although the workshop accomplished almost all of its stated goals, there was insufficient time to address task 3 related to connecting US researchers with investigators and communities elsewhere in the world. In addition, not all working groups completed the tasks related to identification of barriers and strategic partnerships. The document represents a summary opinion of the three working groups regarding these areas. The next steps for NIEHS will be to pursue further comment regarding the workshop summary by the public and scientific community

Appendix

Rank Order of Research Projects and Short Term Strategies

Rank Order of Research Projects

	Environment-Disease Research Option	Point Total	# Positive Votes
1	Biomass combustion and poor pregnancy and birth outcomes	480	23
2	Acute respiratory infections & IAP/OAP	370	15
3	Arsenic in drinking water & poor health outcomes	330	20
4	Neurobehavioral deficits & PCBs/pesticides/metals	310	15
5	Asthma & IAP/OAP	280	16
6	Susceptibility to ID through environmentally-mediated modulation of immune response	270	15
7	Lung cancer & nonsmokers in Asia	260	12
8	Malaria/DDT & neurodevelopment & pregnancy outcomes	190	13
9	CVD & air pollution	190	11
10	Liver cancer & smoking/alcohol/infection	180	8
11	COPD & IAP/OAP (nonsmoker)	140	9
12	Neurological disease related developmental & adult exposures	140	10
13	Endocrine disruptors & adverse reproductive & pregnancy outcomes	100	7
14	Diarrheal disease & contaminated water	90	6
15	Diabetes & DDT/other chemicals	40	4
16	Rapid industrial growth	30	2

Rank Order of Short Term Strategies

		Point Total	# Positive Votes
1	Adding environmental questions to demographic health surveys	430	19
2	Adding environmental components to existing projects	400	20
3	Contribute to established research stations/centers	390	19
4	Co-investing with Fogarty on specific new topics	280	17
5	Exploratory grants	270	16
6	Research training in environmental health	260	20
7	Travel funds	250	20
8	Topic-specific workshops in regions	230	15
9	Collaborate with existing networks	210	12
10	Web-based, update-able inventory of infrastructure and research projects	180	12
11	Pilot epi study	170	10
12	Field guides/SOPs for measurement sample storage	120	8
13	Investigator-initiated networking	110	7

*** The exercise of rank ordering projects and strategies occurred at the end of the workshop and not all participants were available at that time.**

Meeting Participants and Contributors

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