Environmental Health Summit Report: Research Blueprint for the 21st Century

Carol M. Baldwin

University of Arizona Health Sciences Center, College of Medicine, Tucson, AZ 85724 USA

The Environmental Health Summit was held 1–4 June 1995 at Biosphere 2 in Oracle, 30 miles north of Tucson, Arizona. Nearly 30 scientists from across the country gathered to formulate a new national blueprint for addressing the nation's most urgent environmental health research priorities. The priorities were addressed by five committees: 1) children's health, 2) respiratory system, 3) immune system, 4) nervous system, and 5) reproductive system. The summit was a public–private partnership between nonprofit Environmental Health Foundation, the National Institute of Environmental Health Sciences, the Agency for Toxic Substances and Disease Registry (ATSDR), and the University of Arizona Health Sciences Center. This meeting report provides a summary of research recommendations from each of the summit committees.

Children's Health

The differences in examining the effects of environmental toxicants between children and adults include differing patterns of exposure, breathing, and dietary intake, as well as differing biology of absorption, distribution, metabolism, and excretion of these agents (implying different exposure–dose relationships), rapid growth and development of organ systems (implying different dose–response relationships); and the projected longer life span of children (1–4). These differences prompted the committee to formulate the following recommendations.

Endocrine modifiers. The committee stressed the need for increased research on environmental endocrine modifiers in children, especially the effects of early exposure and intrauterine exposure in particular. Outcomes of interest include sexual maturation, altered thyroid function, and gender-specific behaviors.

Neurodevelopmental outcomes. Research should be conducted on the effects of exposures to environmental agents in infants and children and their neurodevelopmental outcomes. Of particular interest are outcomes for which there is already some limited evidence of environmental contributors: attention deficit hyperactivity disorder (ADHD), mood disorders (depression and bipolar disorder), hyperagression and criminal behaviors, and infantile autism.

The agents of greatest interest for this research should include metals, including lead, mercury, cadmium, and manganese; halogenated hydrocarbons, particularly dioxins, organochlorine pesticides, and PCBs; organic solvents, such as trichloroethylene (TCE) and benzene; air pollutants, particularly their interactions with infectious agents, such as respiratory syncytial virus (RSV), and certain fungal agents; and other environmental factors, such as electromagnetic fields (EMF), radon gas, ultraviolet light (UV), and sound (especially repeated exposure to high frequencies).

Lung development. Studies need to be done regarding potential for permanent impairment of lung function and structure due to exposure to environmental hazardous pollutants during infancy and early childhood. Because the lung, like the nervous system, has certain critical periods of development and maturation, specific timing of lung injury could lead to permanent morphologic alterations. Such alterations may set the stage for lifelong impairment and future susceptibility to adult lung diseases such as asthma, emphysema, bronchiectasis, and bronchiectasis.

Health and social costs. The committee strongly recommended studies to determine the total costs to American society of diseases related to environmental exposures in children. This analysis should assess all costs to include, but not be limited to lost productivity over the lifetime of the child, household costs such as lost parental wages, costs of household disruption and divorce, and costs of special education and the many other corollary costs of the often permanent injuries that children suffer. (The committee noted that in severely neurologically damaged children, families often have a divorce rate greater than 90%, which has devastating human and economic consequences.) As a step toward understanding the economic consequences of environmental inequality, the committee also urged that research be conducted on the interactions between environmental injuries and malnutrition, poverty, and social disadvantage. Some important target effects would include the nervous system, lung injury, and environmental carcinogenesis.

Respiratory System

Lung diseases, when combined, are the third leading cause of death in the United States and are a leading cause of illness and disability (5). Morbidity and mortality from asthma are well-documented (5), and associated health care costs exceed $6 billion. Since the major contribution to lung diseases is cigarette smoking, these diseases are inherently controllable, providing a huge opportunity for prevention (6–8). Accordingly, this committee focused on research leading to a better understanding of what environmental exposure factors are important in the etiology of lung disease. All research should be human-oriented, interdisciplinary research that contains careful, rigorous study design and exposure assessment, including estimates of target tissue dose and specific effects. The committee on the Respiratory System recommended these research foci:

Complex exposures. In today's environment, people are exposed to air pollution, pollen, and contaminant-containing materials such as carpets, upholstery, and drapes. Questions that arise from these complex exposures include: How do these exposures interact? Is it important for one exposure to precede another? What triggers lung disease? Multidisciplinary studies of exposure to complex mixtures of pollutants and bioaerosols (including both allergens and infectious agents) are necessary, both in actual environments and in exposure chambers, to better understand the dose–response relationships, additive effects, adjuvant effects, cumulative exposure and dose, time and disease outcome, as well as the respiratory consequences of the exposures to environmental pollutants (particularly in asthma). These studies should have appropriate indoor and outdoor assessments of the pollutant exposures, including particles and gases, volatile organic compounds (VOCs), pesticides, and bioaerosols.

Host factors. Some people will react to exposure, some will not. Identifying important host factors (predispositions/susceptibilities) can help us understand the expo-

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sure–dose relationships in humans and help identify other factors that may be overlooked in some segments of the population, such as genetics, nutritional status, sociocultural factors, and socioeconomic status. This research will help identify the specific factors in the agent–host–environment interaction in disease etiology, which will lead to preventive strategies and environmental equity. There should be research on host susceptibility and gene–environment interactions in relation to asthma and other lung diseases in those individuals with physiological and immunological hyperresponsiveness, including nutritional factors and familial and genetic factors.

Markers in the disease process. The committee suggested that indicators of the disease process also be included in research. The committee addressed the problem of relating effects of acute exposures to effects of chronic exposures and understanding the complete process in order to link the question of low-level exposures to environmental pollutants to the possibility of chronic pulmonary effects.

Environmentally induced lung diseases are the result of a process leading from exposure, pollutant deposition, preclinical biochemical and physiological effects, to overt symptoms of diseases, including lung cancer, chronic bronchitis, asthma, hypersensitivity pneumonitis, and pulmonary fibrosis. To prevent and treat such lung diseases, biologic indicators of each step in this process need to be developed. Such markers of exposure, dose, early effects, and susceptibility need to be used in epidemiologic and clinical studies of these diseases.

It was also recommended that the methodology for banking tissue specimens for later molecular marker studies be developed to study markers of exposure, host susceptibility, and these disease processes. In conjunction, we need to address the complex scientific and ethical issues facing such analyses and the use of their results.

Evaluation of environmental controls and new sources. In addition to specific pharmaceutical treatments for lung diseases, an entire industry promoting environmental controls (with, for example, air cleaners, cleaning of ventilation systems) has emerged. The efficiency of environmental controls has yet to be established. Studies examining the utility of environmental control methods are needed. The scope would necessarily include both engineering and clinical efficacy. Research should also include monitoring of the respiratory effects of pollutants from existing and new sources, specifically construction and furnishing materials (for example, new synthetic fibers) and consumer products in populations.

Immune System

The committee on the immune system addressed three categories of immune-related dysfunction: 1) immune suppression associated with decreased resistance to external pathogens and cancer, 2) autoimmunity, and 3) inappropriate responses (hypersensitivity) that may result in allergy and/or autoimmunity (1,6,7,9,10,13).

Immunosuppression. Research on immunosuppression should consist of studies to determine whether low-level (background or near-background) exposures are sufficient to affect the immune system in humans. Such studies will require well-designed, prospective immunono-epidemiologic studies that include sensitive, validated immunodiagnostic techniques and standardized case definitions.

The committee addressed developmental and susceptibility issues by emphasizing that special consideration should be given to potentially sensitive populations such as the elderly, the very young, and possibly underserved minorities, as well as the contribution of genetic predisposition, malnutrition, and stress.

In studies of dose–response relationships on immunosuppression, the committee suggested that, in order to determine the biological relevance of small changes in immune function, additional data will be needed on the quantitative relationships of exposure–dose with immune function relationships and clinical disease outcomes, as well as on the dose effects with intervention (e.g., vaccine effectiveness). From an epidemiological standpoint, even slight changes in immune functions could equate to significant increases in disease.

The committee recommended that consideration should be given to both systemic as well as regional immunosuppression and the potential clinical consequences. For example, there is evidence that breathing ozone alters lung immune function, resulting in increased infections, and UV exposure decreases the ability of the immune system to inhibit skin cancers.

The committee emphasized that appropriate methodology is critical in assessing environmentally induced diseases. The use of assays of soluble immune and inflammatory medications, immunoactive substances (e.g., low-molecular weight agents, cytokines) is encouraged. Methods should be used to obtain small-volume samples that ease subject burden, using molecular methods that maximize information return. In addition to appropriate laboratory methods, it is critical that appropriate control populations be studied.

Autoimmunity. With the exception of heavy metals (e.g., mercury, cadmium, chromium), there are insufficient animal data and still fewer human studies that evaluate specific chemicals (such as halogenated hydrocarbons, pesticides, solvents), complex mixtures (such as diesel and gasoline exhaust, tobacco smoke, alone or in combination with antigens), genetic predisposition, and molecular mechanisms that would better explain toxic pollutants and immune function interactions. Based on the studies that do exist, which implicate an immunologic mechanism after exposure (such as occupational asthma due to low molecular weight chemicals, chromium allergy, formaldehyde sensitization), and the possibility that other exposures result in autoimmune illnesses (e.g., systemic lupus erythematos; SLE), the committee posed the following questions: 1) Are specific substances associated with an increased incidence or severity of autoimmune disorders? For instance, are alkenes such as TCE and/or other solvents related to SLE? Similar relationships could be found with environmental agents as with drugs. 2) Are there regional increases in autoantibodies, and are they related to environmental exposures? If so, are these autoantibodies clinically relevant? How would we determine if they lead to autoimmune diseases? For instance, do known neurotoxic solvents, alone or in conjunction with viruses or vaccines, also induce cellular changes leading to autoantibody production, neural damage (e.g., demyelination), and disease? Are neurotoxins adjuvants for viral-related autoimmunity (e.g., multiple sclerosis)? 3) If exposure–autoimmunity relations were determined, what are the possible immune mechanisms by which environmental toxic agents or UVB produce autoimmunity? Also, what is the molecular basis of such autoimmunity? 4) Can existing or new animal models of autoimmune disorders be used to study induction or exacerbation of autoimmune diseases by environmental agents?

Hypersensitivity. The committee recommended that hypersensitivity research be conducted to determine which indoor air pollutants trigger immune responses and how these responses are related to symptoms or illness. Questions concerning the role of indoor air pollution in chronic fatigue, headaches, depression, chemical sensitivity, asthma, and allergy need to be answered. There is a high degree of public awareness and concern with respect to these possible associations, and many of these concerns have chemophobic overtones. Thus, the committee strongly recommended that hypersensitivity research address the following areas in a definitive manner: 1) Research should incorporate human epidemiological...
studies, both prospective and retrospective, which take advantage of unfortunate "natural experiments" (e.g., involving "problem buildings) and which include measures of specific and general immune response. 2) Hypersensitivity research, which lends itself to multidisciplinary, controlled exposure studies with humans, can provide strong experimental evidence for an immune effect. Both aclimatization and increased sensitivity should be taken into account in these double-blinded, placebo-controlled challenged studies. 3) Attention should be given in all human studies to the responses of groups of individuals who appear more sensitive to one or more substances, since they may serve as sentinels for the general population. 4) Relevant, objective biological markers, including immunological, neurological, biochemical, and other measures which may correlate with symptoms should be sought. 5) Relevant animal models for research and possible use as sentinels also need to be developed.

**Nervous System**

It is widely recognized that neurotoxicant effects can be measured at multiple levels of nervous system organization. Cognitive, motor, and sensory impairments are among the most debilitating of conditions and can lead to reductions in job productivity, increased accident risk, and contribute to poor quality of life (1,3). Environmental exposures to substances such as n-hexane and toluene have also been implicated in neurodegenerative disorders such as Parkinson’s disease, Alzheimer’s disease, and amyotrophic lateral sclerosis (ALS) (11). Such impairments increase societal costs, as they are major factors in nursing home placement, disability, and loss of independence. In addition, psychiatric problems affect up to 40% of the American population over a lifetime. Psychiatric epidemiological research has generally not considered the possible role of neurotoxicants. (Findings in occupational samples are often confounded by litigation issues.) Understanding the relationship between environmental toxicants and the biochemical and physiological neuropsychiatric diseases requires concerted epidemiological analysis. The committee on the nervous system prefaced their research recommendations with six general themes: 1) importance of studying long-term, delayed, or latent, rather than acute effects of both high and low doses of neurotoxicants; 2) need for evaluating subtle nervous system effects, especially those from low-dose exposures; 3) importance of assessing individual differences and cross-species differences in susceptibility; 4) importance of understanding the modulation of neurotoxicant effects by other factors, such as age, gender, nutritional status, and disease states; 5) the interdisciplinary and cost-effective approach for studying the effects of neurotoxicants by using existing human population-based studies of neurotoxicant exposures, and incorporating studies of health effects, including measures of cognition, behavior, and effect; and 6) significance of using cross-species technologies and resolution of mechanisms of neurotoxication, facilitated by multidisciplinary approaches. These themes led to the following recommendations.

**Neurodegenerative disorders.** Research should be conducted to characterize the role of environmental neurotoxicants in the initiation, progression, and/or exacerbation of neurodegenerative disorders. The disorders should include, but not be limited to, Parkinson’s disease, Alzheimer’s disease, and ALS.

**Quality of life.** Research should apply repeated-meaures methodologies in novel ways to detect and evaluate the long-term cognitive, motor, and sensory effects of neurotoxicants across species. It is of paramount importance to study the impact of toxic exposures on impairment of functions of daily living (such as driving, shopping, using the telephone, performing one’s job responsibilities) and overall quality of life. There are problems with using only standard neuropsychological tests, which are designed to detect deficits on a one-time
basis, and which also have limitations for detecting deficits in persons with above-average intelligence (such as might be found in sick building syndrome populations). The committee suggested the use of sensitive tests amenable to repetition over time within a single session, or over multiple sessions close in time that can measure and track subtle and progressive neuropsychological and neurophysiological changes with time; and application of repeated-measures approaches applied to studying the long-term effects of acute, high-dose exposures (e.g., accidental chemical spills) and chronic, low-dose exposures (e.g., indoor air pollution).

**Psychiatric and behavioral disorders.** Research should be done to determine the role of environmental neurotoxins in the initiation, progression, and/or exacerbation of psychiatric and behavioral disorders, including major depression, chronic low-grade depression, panic disorder, other anxiety disorders, and impulse control disorders involving irritability and violence. The committee stressed the need for neuropsychiatric research to be included in epidemiological studies of the incidence, prevalence, and course of such disorders in existing population-based samples in whom levels of neurotoxicant exposures have already been characterized. There is a need for epidemiological research evaluating the association between neurotoxicant exposures and neuropsychiatric disorders in samples with not only high-level, but also chronic low-level neurotoxicant exposures and population-based samples without motivational confounders. In the event that epidemiological associations between specific neurotoxins and a subset of neurological and psychiatric disorders are found, and drawing upon prior research in animal models, neurochemical and other neurobiological mechanisms can be used to develop more specific pharmacologic treatments for these illnesses than is currently possible.

**Reproductive System**

The Committee on the Reproductive System considered health trends in human reproduction, which included the following reports (13-15): in men, a 40% decrease in semen count over the last 20-50 years, an increase in testicular cancer, a two- to threefold increase in undescended testes, and increases in cancers of the prostate and breast; in women, an increase in breast cancer; "benign" uterine diseases such as endometriosis and uterine fibroids are estimated to affect close to 20% of women between puberty and menopause; premature ovarian failure is also of concern. Questions remain as to how these diseases and dysfunctions are initiated. The best known example of “endocrine-disrupting” chemicals are those associated with, or mimicking, female sex hormone activity, the “environmental estrogens.” Since a number of common environmental chemicals have been shown to behave as weak-acting estrogens (or, in some cases, antiestrogens), these environmental factors have been proposed as possible contributors to these reproductive dysfunctions.

**Adverse and beneficial effects of environmental chemicals.** The committee’s first research recommendation is pragmatic, with an emphasis on disease prevention and treatment. Research should be conducted on the application of fundamental biology and chemistry to reproductive sciences and clinical needs. Studies of the reproductive system lag behind other sciences in using the most modern of biotechnologies. Further, the research on human reproduction should specifically address the adverse as well as the beneficial effects of chemicals in the environment (including dietary factors) which interact with hormones that have reproductive significance. These effects could include chemicals that mimic hormones, block hormone action, change the metabolism of natural hormones, and/or change a hormonally important process (such as increase or decrease a hormone receptor). The difficulties of assessing the balance of these estrogenic and antiestrogenic effects of agents and complex mixtures will require novel research approaches. The study of the impact of environmental estrogens on human reproductive health would benefit from various basic, clinical, and epidemiological approaches, and an understanding of the effects of environmental factors working like female sex hormones is central to the issue of the environment and women’s health. In addition, the committee suggested that the role of hormonally active xenobiotics in the development of the reproductive system should be emphasized.

**Development of exposure/effect biomarkers.** Finally, the committee encouraged the development and use of appropriate biomarkers of exposure and effect for environmental agents acting on the reproductive system. This is a critically needed area which could build on the knowledge gained in the previous research recommendations and be applied to human reproductive wellness in two important ways: the fundamental new knowledge of the biology and chemistry of reproductive organs and processes should be used in a predictive sense, and such an approach should lead to biomarkers that reflect early alterations in reproductive processes and tissues, thus allowing for the successful development of intervention or prevention strategies for the enhancement of reproductive health.

**Conclusion**

All research should be interdisciplinary with careful and rigorous study design and exposure assessment, including estimations of target-tissue dose, toxicokinetics, and specific health effects. Interactions of environmental toxic agents and genes should be an important research priority. At-risk groups, such as children and the elderly, as well as other factors such as gender, nutritional status, and socioeconomic status need to become a focus in environmental health research. All research proposals should undergo rigorous peer review.

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