ENVIRONMENTAL HEALTH SCIENCE FOR REGULATORY DECISIONMAKING

LINDA S. BIRNBAUM, PAUL JUNG, SHEILA A. NEWTON*

I. INTRODUCTION

Environmental health science has made tremendous strides since the creation of the Environmental Protection Agency (EPA) in 1970 and even since the original passage of the Toxic Substances Control Act of 1976 (TSCA).[1] This paper will discuss the role of the National Institute of Environmental Health Sciences (NIEHS) in supporting the scientific underpinnings of regulatory decisionmaking by EPA and other agencies through NIEHS's commitment to conducting and funding outstanding research in environmental health sciences. Herein we present and describe the NIEHS, its mission, and its research program; discuss some basic ideas in environmental health; and then outline some of the major new concepts in the field and explain how they may affect regulatory science.

A. National Institute of Environmental Health Sciences

The NIEHS is one of the twenty-seven institutes and centers of the National Institutes of Health (NIH), an agency in the U.S. Department of Health and Human Services (HHS).[2] The mission of the NIEHS is "to reduce the burden of human illness and disability by understanding how the environment influences the development and progression of human disease."[3] Established in 1966, NIEHS is the premier environmental health sciences research institution in the world, comprising intramural laboratories and extramural funding

* Linda S. Birnbaum, Ph.D., A.T.S., D.A.B.T., Director, National Institute of Environmental Health Sciences and National Toxicology Program; Paul Jung, M.D., M.P.H., Chief of Staff, National Institute of Environmental Health Sciences; Sheila A. Newton, Ph.D., Director, Office of Policy, Planning & Evaluation, National Institute of Environmental Health Sciences.

1. Reorganization Plan No. 3 of 1970, 35 Fed. Reg. 15,623, 84 Stat. 2086; Toxic Substances Control Act of 1976, Pub. L. No. 94-469, 90 Stat. 2003.

2. *About NIEHS*, NAT'L INST. OF ENVTL. HEALTH SCI., http://www.niehs.nih.gov/about/index.cfm (last visited Apr. 27, 2011).

3. *Id.*

programs.[4] Like most NIH institutes, the greatest share of NIEHS funding goes to support so-called "extramural" research and training activities in universities and research institutions across the nation.[5] In addition, federal scientists employed directly by NIEHS in its "intramural" research program also conduct significant research activities, many of which are high-risk, high-profile, or otherwise mission-critical.[6]

NIEHS also houses the National Toxicology Program (NTP).[7] Along with the NIEHS Superfund Program,[8] described below, the NTP is distinguished by its problem-solving or applied focus.[9] The NTP is a cross-agency organization designed to coordinate toxicity testing across the federal government.[10]

B. National Toxicology Program

The National Toxicology Program (NTP) is a unique program that brings together the toxicology study functions of three sub-agencies of HHS—NIEHS within NIH, the National Institute for Occupational Safety and Health (NIOSH) within the Centers for Disease Control and Prevention (CDC), and the National Center for Toxicological Research within the Food and Drug Administration (FDA)—as a sort of "virtual agency."[11] The NTP's Executive Committee draws on the leadership of those organizations as well as of other federal agencies, including EPA.[12] This structure may sound unwieldy, but it works because the focus of the effort is very tightly defined: to conduct studies to determine the toxicity of specific

4. Thomas R. Hawkins, *A History of Progress: NIEHS, The First 20 Years (1966 to 1986)*, 75 ENVTL. HEALTH PERSP. 7, 7 (1987); *Research*, NAT'L INST. OF ENVTL. HEALTH SCI., http://www.niehs.nih.gov/research/index.cfm (last visited Apr. 27, 2011).

5. *Budget Authority by Activity*, NAT'L INST. OF ENVTL. HEALTH SCI, http://www.niehs.nih.gov/about/congress/justification/2012/2012cj/budgetprogram/index.cfm (last visited Sept. 23, 2011).

6. *Research at NIEHS – Division of Intramural Research*, NAT'L INST. OF ENVTL. HEALTH SCI, http://www.niehs.nih.gov/research/atniehs/index.cfm (last visited Apr. 27, 2011).

7. NAT'L TOXICOLOGY PROGRAM, http://ntp.niehs.nih.gov/ (last visited Apr. 27, 2011).

8. *Superfund Research Program Home Page*, NAT'L INST. OF ENVTL. HEALTH SCI., http://www.niehs.nih.gov/research/supported/srp/ (last visited Apr. 27, 2011).

9. *About the NTP – National Toxicology Program*, NAT'L TOXICOLOGY PROGRAM, http://ntp.niehs.nih.gov/?objectid=7201637B-BDB7-CEBA-F57E39896A08F1BB (last visited Apr. 27, 2011).

10. *Id.*

11. *See NTP Executive Committee*, NAT'L TOXICOLOGY PROGRAM, http://ntp.niehs.nih.gov/INDEX9E40_2.HTM?objectid=72016475-BDB7-CEBA-F6D3AEBDF2C8CED7 (last visited June 15, 2011).

12. *Id.*

environmental agents and to develop and validate study methods.[13] The NTP's mission is to evaluate agents of public health concern by developing and applying tools of modern toxicology and molecular biology.[14] The NTP is the principal HHS collaboration on toxicology and chemical exposures—the NTP's mandated mission includes coordinating toxicology testing activities across the federal government. In fact, at this time, the Executive Committee of the NTP involves the leadership of the EPA, CPSC (Consumer Product Safety Commission), OSHA (Occupational Safety and Health Administration), NIOSH, ATSDR (Agency for Toxic Substances and Disease Registry), FDA, and NCI (National Cancer Institute).[15]

Building on the cancer bioassay studies done at the National Cancer Institute decades ago, NTP has brought forward the two-species, both-gender rat and mouse studies to a level of sophistication and uniformity that has made its series of technical reports the gold standard of such testing in the world.[16] Moreover, the laboratory data, tissues in paraffin blocks, and other biological samples from these studies are meticulously archived for further use as new resources and science become available. These archives are regularly and extensively used both by NTP and NIEHS investigators and by other scientists. From these studies, combined with a comprehensive review of experimental results from throughout the world, NTP produces the congressionally mandated Report on Carcinogens which identifies chemicals categorized as "known to be" or "reasonably anticipated to be" human carcinogens.[17] These categorizations of substances of concern are updated in republications of new editions; the list is regularly updated, with substances added (and in some cases, de-listed) as the science moves forward.[18]

Cancer is not the only endpoint of interest to environmental health scientists. The NTP has recently established new criteria for

13. *See Partnerships*, NAT'L TOXICOLOGY PROGRAM, http://ntp.niehs.nih.gov/INDEX4964.HTM?objectid=7201664A-BDB7-CEBA-FA921231DE6023E8 (last visited June 15, 2011).

14. *Id.*

15. *NTP Executive Committee*, *supra* note 11.

16. Linda Birnbaum, Dir., Nat'l Inst. of Envtl. Health Sci., Remarks at National Conversation on Public Health and Chemical Exposures Kickoff Meeting: Launching the Conversation 18 (June 26, 2009) (transcript available at http://www.atsdr.cdc.gov/nationalconversation/docs/062609_transcript3.pdf).

17. *Questions & Answers about the RoC*, NAT'L TOXICOLOGY PROGRAM, http://ntp.niehs.nih.gov/INDEX5F4E.HTM (last visited June 15, 2011).

18. Birnbaum, *supra* note 16, at 18.

evaluating the results of chemicals tested in immunotoxicology, reproductive, and developmental studies, bringing the same rigorous standards it uses for classifying the outcomes of its cancer studies to many of its non-cancer studies.[19]

The NTP is the home of the Office of Health Assessment and Translation (OHAT), formerly known as the Center for Evaluation of Risks to Human Reproduction, or CERHR.[20] OHAT conducts evaluations to assess the evidence in the scientific literature that substances in the environment (environmental chemicals, physical substances, or mixtures) cause adverse health effects. OHAT's monographs offer opinions on whether these substances may be of concern, given what is known about current exposure levels for human populations. CERHR, the predecessor of OHAT, carried out these assessments from 1998 to 2010. In 2008, CERHR released its assessment monograph on Bisphenol A, or BPA as it is commonly known.[21] The effect of the BPA monograph and the dissemination of its findings was to prompt a widespread discussion among the general public and the regulatory community about the potential effects of exposure to this ubiquitous chemical, resulting in interagency action to develop an agenda for further research.[22]

The NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) makes continual progress toward reducing, refining, and replacing animal use in toxicity testing.[23] NICEATM also oversees the functioning of the fifteen-

19. NAT'L TOXICOLOGY PROGRAM, NTP UNVEILS NEW NON-CANCER EVALUATION CRITERIA 1 (2009), *available at* http://www.niehs.nih.gov/news/assets/docs_f_o/ntp_criteria_for_hazard_identification_in_noncancer_studies.pdf.

20. *Health Assessment and Translation*, NAT'L TOXICOLOGY PROGRAM, http://ntp.niehs.nih.gov/?objectid=497BF6E6-D00C-C4E6-423E8917D64B6A20 (last visited Sept. 23, 2011).

21. *See* CTR. FOR THE EVALUATION OF THE RISKS TO HUMAN REPRODUCTION, NAT'L TOXICOLOGY PROGRAM, NIH PUB. NO. 08-5994, NTP-CERHR MONOGRAPH ON THE POTENTIAL HUMAN REPRODUCTIVE AND DEVELOPMENTAL EFFECTS OF BISPHENOL A (2008) [hereinafter BISPHENOL A MONOGRAPH], *available at* http://ntp.niehs.nih.gov/ntp/ohat/bisphenol/bisphenol.pdf.

22. *Bisphenol A (BPA): Expanding Research to Impact Human Health.* NAT'L INST. OF ENVTL. HEALTH SCI., http://www.niehs.nih.gov/recovery/critical/bpa.cfm (last visited Sept. 23, 2011); *Research Consortium for 2-Year Bisphenol A Toxicity Study (U01).* NAT'L INST. OF ENVTL. HEALTH SCI., http://grants.nih.gov/grants/guide/rfa-files/RFA-ES-10-009.html (last visited Sept. 23, 2011).

23. *NICEATM-ICCVAM–Home*, NAT'L TOXICOLOGY PROGRAM, http://iccvam.niehs.nih.gov/ (last visited Aug. 10, 2011).

member Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM).[24]

The NTP has been a steadfast and key asset in the public health arsenal. The NTP functions at the intersection of basic biology and public health and works to provide definitive data on which to base public health decisions.

C. Superfund Research Program

The second "problem-solving" program within NIEHS is the Superfund Research Program (SRP), a university-based research and training program mandated to develop methods and technologies to detect, assess, and reduce the amount and toxicity of hazardous substances and to evaluate the risks and effects on human health.[25] This multidisciplinary program funds research on all aspects of hazardous substances, from health effects to cleanup technologies.[26] The SRP's university grantees also train graduate students and post-doctoral researchers—the next generation of scientists in charge of solving the health and environmental issues resulting from the legacy of Superfund sites.[27]

There are clear relationships and complementary missions between the NIEHS SRP and its sister Superfund agencies, EPA and the Agency for Toxic Substances and Disease Registry (ATSDR), a part of the CDC.[28] When Congress created the SRP in 1986 under the Superfund Amendments and Reauthorization Act, it was the legislature's intent that the research conducted under the SRP would complement the more applied activities of EPA's and ATSDR's Superfund programs.[29]

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24. *Id. See also* INTERAGENCY COORDINATING COMM. ON THE VALIDATION OF ALTERNATIVE METHODS [ICCVAM], MEMBER ROSTER (2011), *available at* http://iccvam.niehs.nih.gov/docs/about_docs/DetailRoster.pdf (providing the contact information for the representatives from the fifteen member institutions).

25. *Program Mandates—Superfund Research Program*, NAT'L INST. OF ENVTL. HEALTH SCI., http://www.niehs.nih.gov/research/supported/srp/about/index.cfm (last visited Nov. 5, 2011).

26. *See Who We Fund—Superfund Research Program*, NAT'L INST. OF ENVTL. HEALTH SCI., http://tools.niehs.nih.gov/srp/programs/index.cfm (last visited Aug. 10, 2010).

27. *Training—Superfund Research Program*, NAT'L INST. OF ENVTL. HEALTH SCI., http://www.niehs.nih.gov/research/supported/srp/training/index.cfm (last visited Aug. 10, 2011).

28. AGENCY FOR TOXIC SUBSTANCES & DISEASE REGISTRY, http://www.atsdr.cdc.gov/ (last visited Aug. 10, 2011); *Superfund Research Program*, NAT'L INST. OF ENVTL. HEALTH SCI., http://www.niehs.nih.gov/research/supported/srp/index.cfm (last visited Aug. 10, 2011).

29. *See* Superfund Amendments and Reauthorization Act of 1986, 42 U.S.C. § 9601 (2006).

A defining vision for the SRP has been that the program be an accountable enterprise—that its research must be directed towards solving practical problems relating to hazardous substances.[30] Within the SRP's signature program of interdisciplinary multi-project grants, basic hypothesis-driven biomedical research is married to population-based research, environmental engineering, remediation technology development, fate and transport studies, and other disciplines as needed.[31] For a program such as the SRP to meet its full potential, there must be an ongoing evolution and maturation of the basic research that leads to opportunities for the results to develop into applied, "product-oriented" research directions.

The Worker Education and Training Program (WETP), also created under the Superfund Amendments and Reauthorization Act of 1986, is an assistance program for training workers in how best to protect themselves and their communities from exposure to hazardous materials encountered during hazardous waste operations, hazardous materials transportation, environmental restoration of contaminated facilities, or chemical emergency response.[32]

The WETP has conducted training in all fifty states, Puerto Rico, and the Pacific territories;[33] it has trained over 2.5 million workers in high-risk occupations such as toxic waste cleanup and chemical emergency response.[34] During 2008 to 2009 alone, over 155,000 workers received 1,487,050 contact hours of training in 8,662 classes.[35]

D. NIEHS Summary

Our environment is one of the most important determinants of our health and our quality of life. The mission of the NIEHS is to "reduce the burden of human illness and disability by understanding how the environment influences the development and progression of

30. *See* NAT'L INST. OF ENVTL. HEALTH SCI., SRP STRATEGIC PLAN (2010), *available at* http://tools.niehs.nih.gov/srp/about/Strategic%20Plan.pdf.

31. *See Currently Funded—Superfund Research Program*, NAT'L INST. OF ENVTL. HEALTH SCI., http://tools.niehs.nih.gov/srp/programs/index267.cfm (last visited Aug. 10, 2011).

32. *General Summary of Training Activities*, NAT'L INST. OF ENVTL. HEALTH SCI., http://www.niehs.nih.gov/careers/hazmat/about_wetp/training_activities/index.cfm (last visited Aug. 10, 2011).

33. *Justification of Budget Request,* NAT'L INST. OF ENVTL. HEALTH SCI., http://www.niehs.nih.gov/about/congress/justification/2012/2012scj/justification/index.cfm (last visited Sept. 23, 2011).

34. NAT'L INST. OF ENVTL. HEALTH SCI., NIEHS WORKER EDUCATION & TRAINING PROGRAM (2011) (unpublished) (on file with author).

35. For these numbers, please see internal agency data (on file with author).

human disease."[36] This is one of the most ambitious missions of all the institutes of the NIH, embracing the need to understand all aspects of interaction of human health and biology with a wide range of environmental factors. Understanding the health-environment relationship is critical to help prevent disease and transform new scientific knowledge into improvements in human health. Under the standard biomedical paradigm, translational research is defined in the medical community as contributing to the standard biomedical pathway leading to new drugs or lifestyle interventions.[37] By analogy, NIEHS environmental health sciences research establishes a different translational pathway—one that provides a foundation for population-based public health interventions. The NIEHS provides a major contribution to the knowledge base for regulatory action in the protection of public health. Thousands of lives are saved and diseases prevented in the United States every year as a result of standards created under the Clean Air Act, the Safe Drinking Water Act, and others on the basis of NIEHS research results.[38]

It should be made explicitly clear that the NIEHS and NTP are not regulatory agencies, and rules or regulations related to the environment are not formulated there. However, the NIEHS and NTP are instrumental in creating the science that serves as the basis for regulatory decisions made by agencies such as the EPA, the FDA, the Consumer Product Safety Commission, and the Occupational Safety and Health Administration.

II. OLD AND NEW PARADIGMS

The science of environmental health is changing rapidly. Our old assumptions about toxicants and how they affect our bodies are being changed by modern science. Toxicologists used to say, "The dose makes the poison."[39] In other words, higher doses of a given hazardous substance were assumed to be uniformly and self-evidently more hazardous, while a lower dose of the same substance was

36. NAT'L INST. OF ENVTL. HEALTH SCI., http://www.niehs.nih.gov/ (last visited Apr. 4, 2011).

37. *See About Translational Research*, INST. OF TRANSLATIONAL HEALTH SCI., https://www.iths.org/about/translational (last visited Aug. 10, 2011).

38. U.S. ENVTL. PROT. AGENCY, EPA-410-R-99-001, THE BENEFITS AND COSTS OF THE CLEAN AIR ACT 1990 TO 2010: EPA REPORT TO CONGRESS 423–30 (1999), *available at* http://www.epa.gov/air/sect812/1990-2010/fullrept.pdf.

39. Nancy Trautmann, *The Dose Makes the Poison – Or Does It?*, AM. INST. OF BIOLOGICAL SCI. (Jan. 2005), http://www.actionbioscience.org/environment/trautmann.html.

considered not as bad or possibly even not bad at all.[40] Scientists now know that low-dose effects from some chemicals can have a substantial impact on our health.[41] Clearly, there are still many places around the world where the most important problems with respect to environmental health are excessive exposures to highly toxic heavy metals, pesticides, or other substances. However, an emerging new understanding of how low-level, widespread exposures contribute to the development of common disorders like diabetes, developmental delays, and other modern epidemics, is changing the traditional paradigm of toxicology. Studies have shown that the timing of exposure, as much as the dose, is critical for the kinds of effects that can result from that exposure.[42] Moreover, toxic exposures can, in some cases, also induce observable impacts over several subsequent generations.[43]

Traditionally, both the biomedical and environmental health research communities have thought of disease etiology in two primary ways—either genes cause disease, or exposures cause disease. The genetic revolution in science has prompted many to opt for a gene-centric approach, in which a single gene mutation alters a single protein, which alters a single cellular activity, which ultimately causes disease.[44] Similarly, an environment-centric approach to disease holds that exposure to a single toxicant alters a gene or protein, which then alters a single cellular activity, causing disease.[45] Both approaches are

40. *Id.*

41. Examples include lead, estrogens, and bisphenol A. *See* Bruce B. Lanphear et al., *Low-Level Environmental Lead Exposure and Children's Intellectual Function: An International Pooled Analysis*, 113 EVNTL. HEALTH PERSP. 894 (2005) (lead); Catherine A. Richter et al., *In Vivo Effects of Bisphenol A in Laboratory Rodent Studies*. 24 REPROD. TOXICOLOGY 199 (2007) (bisphenol A); D.M. Sheehan et al., *No Threshold Dose for Estradiol-Induced Sex Reversal of Turtle Embryos: How Little Is Too Much?*, 107 ENVTL. HEALTH PERSP. 155 (1999) (estrogen).

42. *See* Dana C. Dolinoy et al., *Epigenetic Gene Regulation: Linking Early Developmental Environment to Adult Disease*, 23 REPROD. TOXICOLOGY 297 (2007); Walter J. Rogan & N. Beth Ragan, *Evidence of Effects of Environmental Chemicals on the Endocrine System in Children*, 112 PEDIATRICS 247 (2003).

43. Retha R. Newbold et al., *Adverse Effects of the Model Environmental Estrogen Diethylstilbestrol are Transmitted to Subsequent Generations*, 147 ENDOCRINOLOGY S11 (2006).

44. Sickle cell anemia and Huntington's disease are two examples of disease resulting from genetic mutations. More information about these diseases are available at *NINDS Huntington's Disease Information Page*, NAT'L INST. OF NEUROLOGICAL DISORDERS & STROKE, http://www.ninds.nih.gov/disorders/huntington/huntington.htm (last updated Aug. 13, 2010) and *Sickle Cell Anemia*, NAT'L HEART LUNG & BLOOD INST. http://www.nhlbi.nih.gov/health/dci/Diseases/Sca/SCA_WhatIs.html (last revised Feb. 2011).

45. *See, e.g.*, Eliezer Bermúdez et al., *Environmental Tobacco Smoke Is Just as Damaging to DNA as Mainstream Smoke*, 102 ENVTL. HEALTH PERSP. 870, 873–74 (1994); Frederica

too simplistic. Even in cases of "genetic diseases" such as cystic fibrosis, exposure is known to exacerbate symptoms;[46] on the other hand, in many "environmental diseases" such as asbestosis, genetic susceptibility can influence disease severity.[47] Instead, it should be recognized that both exposure and genetic variation are important parts of the disease process. However, if we want to understand the real underpinnings of disease, we need to understand the complete context of the human organism—all exposures, co-existing diseases, developmental stage, nutritional status, and societal factors such as socioeconomic status, stress, and physical activity—and how all these factors interact to influence the individual's risk of developing disease.

Given this background of rapidly changing science, an environmental health research strategy must consider the breadth, scope, tools, methods, technologies, and goals for a multi-disciplinary science, the results of which may significantly impact human health in the twenty-first century. This includes consideration of data and information needs of the multiple audiences and stakeholders who use environmental health sciences data.

It is important, as part of this discussion, to consider what we mean by the term "environment." In terms of human health, most people simplistically define "environment" to mean air and water pollutants, industrial and agricultural chemicals and the like, but this is an overly narrow view. The environment also includes physical agents such as heat, noise, light, and ionizing radiation; by-products of combustion and industrial processes (e.g., dioxin); foods and nutrients; prescription drugs; lifestyle factors (e.g., substance abuse); some social and economic factors; and various environmental stressors such as psychosocial stress, physical activity, climate, and even infections. As we learn more about the interconnectedness of the biological systems that modulate the responses to this wide range of agents, we begin to see that a more inclusive definition of the

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Perera et al., *In Utero DNA Damage from Environmental Pollution is Associated with Somatic Gene Mutation in Newborns*, 11 CANCER EPIDEMIOLOGY, BIOMARKERS & PREVENTION 1134, 1136 (2002).

46. *See, e.g.*, Bruce K. Rubin, *Exposure of Children with Cystic Fibrosis to Environmental Tobacco Smoke*, 323 NEW ENG. J. MED. 782, 782 (1990); Michael S. Schechter, *Non-Genetic Influences on Cystic Fibrosis Lung Disease: The Role of Sociodemographic Characteristics, Environmental Exposures, and Healthcare Interventions*, 26 PEDIATRIC PULMONOLOGY S82 (2004).

47. M. Neri et al., *Genetic Susceptibility to Malignant Pleural Mesothelioma and Other Asbestos-Associated Diseases*, 659 MUTATION RES. 126, 134 (2008).

environment will improve our ability to make sense of the connections of these exposures to human health and disease. For example, if we learn that an antimicrobial chemical in hand soap and a chemical in a food additive both act on the same hormonal pathway, this information informs our understanding of biological effects and can lead to the development of effective public health interventions. The idea is not to create an ever-expanding definition of environmental health, but rather to ensure that science captures all possibilities in exploring various causes and relationships between the environment and human health.

Not only can multiple stressors influence a specific outcome, but many different outcomes can also result from a single environmental exposure. The list of diseases or dysfunctions with environmental etiology is long. Diseases with a known or suspected environmental component include cancers,[48] birth defects (cleft palate, cardiac malformations),[49] reproductive dysfunction (infertility, subfertility),[50] lung dysfunction (asthma, asbestosis, COPD),[51] neurodegenerative diseases (Parkinson's),[52] and neurodevelopmental disorders (autism).[53] As our view of the environment grows more nuanced, and our understanding of biological mechanisms more sophisticated, we will likely discover additional conditions with substantial environmental components; this, in turn, will result in greater understanding of the cause of disease and more effective

48. Juan Alguacil et al., *Risk of Pancreatic Cancer and Occupational Exposures in Spain*, 44 ANNALS OCCUPATIONAL HYGIENE 391, 400 (2000) (pancreatic cancer); Yvonne Marie Coyle, *The Effect of Environment on Breast Cancer Risk*, 84 BREAST CANCER RES. & TREATMENT 273, 273–75, 282 (2004) (breast cancer); Jose M. Ramon et al., *Dietary Factors and Gastric Cancer Risk: A Case-Control Study in Spain*, 71 CANCER 1731, 1731 (1993) (gastric cancer).

49. James J. Nora, *Multifactorial Inheritance Hypothesis for the Etiology of Congenital Heart Diseases: The Genetic-Environmental Interaction*, 38 CIRCULATION 604, 604 (1968) (cardiac malformations); Joanna S. Zeiger et al., *Oral Clefts, Maternal Smoking, and TGFA: A Meta-Analysis of Gene-Environmental Interaction*, 42 CLEFT PALATE–CRANIOFACIAL J. 58, 58 (2005) (cleft palate).

50. Frank Michal et al., *Impact of the Environment on Reproductive Health: Executive Summary*, 101 ENVTL. HEALTH PERSP. (SUPP.) 159, 159 (1993).

51. Stephen I. Rennard, *COPD: Overview of Definitions, Epidemiology, and Factors Influencing Its Development*, 113 CHEST 235S (1998); Victor L. Roggli, *Human Disease Consequences of Fiber Exposures: A Review of Human Lung Pathology and Fiber Burden Data*, 88 ENVTL. HEALTH PERSP. 295 (1990); Padmaja Subbarao et al., *Asthma: Epidemiology, Etiology and Risk Factors*, 181 CAN. MED. ASS'N J. E181, E181 (2009).

52. Donato A. Di Monte, Mitra Lavasani & Amy B. Manning-Bog, *Environmental Factors in Parkinson's Disease*, 23 NEUROTOXICOLOGY 487, 487 (2002).

53. Eric London & Ruth A. Etzel, *The Environment as an Etiologic Factor in Autism: A New Direction for Research*, 108 ENVTL. HEALTH PERSP. 401, 401 (2000).

interventions to reduce disease. An expanded understanding of environment should result in better prevention, education, and, ultimately, regulatory policy.

This new paradigm is exemplified by some of the major advances in environmental health science, including epigenetics[54] and the concept of "windows of susceptibility."[55] These new biological insights are discussed in more detail below.

III. COMPLEX DISEASES HAVE COMPLEX ETIOLOGIES

Cancer, cardiopulmonary disease, autoimmune disease, diabetes, neurodevelopmental disorders, schizophrenia, addiction, and depression are just some of the diseases for which we know that the environment plays a significant role in their development.[56] In this section, we discuss some of the ways in which our understanding of the biological processes underlying environmental effects has greatly outstripped what we thought we knew in decades past. This new knowledge provides a framework for assessing risk from exposures, mixtures of exposures, and levels of exposures that is vastly different from the framework to which EPA and other regulatory agencies have been held as a result of their various statutory authorities.[57] It is critically important to use the results of the best, most recent research results to frame appropriate regulatory responses.

A. Gene-Environment Interactions

We have all observed that individuals can react very differently to the same exposure. For some types of chemicals and health effects, there may be excess risk to some individuals due to interaction of an

54. Alan P. Wolffe & Marjori A. Matzke, *Epigenetics: Regulation Through Repression*, 286 SCIENCE 481, 481 (1999) ("Epigenetics is the study of heritable changes in gene expression that occur without a change in DNA sequence.").

55. Sherry G. Selevan et al., *Identifying Critical Windows of Exposure for Children's Health*, 108 ENVTL. HEALTH PERSP. 451, 451 (2000) ("The same exposure at different times would create a different spectrum of, in this case, malformations due to the timing of the development of different organ systems.").

56. Rob Stein, *Theory Says Disease Tendencies Begin in Womb*, WASH. POST, July 7, 2003, at A4.

57. Frederick S. vom Saal & John Peterson Myers, *Bisphenol A and Risk of Metabolic Disorders*, 300 J. AM. MED. ASS'N 1353, 1354 (2008) ("Despite decades of published observations by endocrinologists reporting nonmonotonic dose-response curves for hormonally active compounds, the core assumption used by the FDA, the Environmental Protection Agency, and the European Food Safety Authority in estimating ADIs for environmental chemicals is still based on a concept first articulated in the 16th century: 'The dose makes the poison'; *i.e.*, dose response curves are assumed to be monotonic for environmental chemicals.").

exposure with specific genes or gene variants. For example, the level of a person's risk of bladder cancer from smoking has been shown to depend in part on whether that individual's genome contains variants in the coding for specific detoxification enzymes.[58]

The regulatory framework that is used to set acceptable or target levels of environmental pollutants includes safety factors that recognize these differences.[59] These factors are incorporated into setting environmental standards based on the completeness and certainty of the underlying data, including unknown but assumed individual susceptibilities. The robust research efforts on gene-environment interactions by NIEHS and other NIH institutes are providing critical knowledge of how these interactions work at the biological level.[60] The existence of these subtle variations in susceptibility must be factored into overall toxicity assessments.

B. Epigenetics

Our understanding of chemical toxicity has been challenged by the new science of epigenetics, which is the study of heritable changes in DNA expression that are independent of the DNA sequence itself.[61] Although a person's DNA base sequence does not change, the expression of that DNA into a person's phenotype can be altered by direct chemical modification (e.g., methylation), modification of the histones which package the DNA into chromatin, and control of chromatin structure via micro-RNA.[62] The operations of and

58. Douglas A. Bell et al., *Genetic Risk and Carcinogen Exposure: A Common Inherited Defect of the Carcinogen-Metabolism Gene Glutathione S-Transferase M1 (GSTM1) That Increases Susceptibility to Bladder Cancer*, 85 J. NAT'L CANCER INST. 1159, 1159 (1993).

59. *See, e.g.,* OFFICE OF PESTICIDE PROGRAMS, U.S. ENVTL. PROT. AGENCY, DOCKET NO. OPP-00757, DETERMINATION OF THE APPROPRIATE FQPA FACTOR(S) IN TOLERANCE ASSESSMENT (Feb. 29, 2002), *available at* http://www.epa.gov/pesticides/trac/science/determ.pdf; Peter M. Chapman et al., *A Critical Evaluation of Safety (Uncertainty) Factors for Ecological Risk Assessment*, 17 ENVTL. TOXICOLOGY & CHEMISTRY 99, 99 (1998); Palarp Sinhaseni & Ornrat Samatiwat, *Toxicokinetics and Safety Factors in Risk Assessment*, 23 J. TOXICOLOGICAL SCI. 209, 209 (1998); Theo Vermeire et al., *Assessment Factors for Human Health Risk Assessment: A Discussion Paper*, 29 CRITICAL REVS. TOXICOLOGY 459 (1999).

60. *See* John W. Hollingsworth et al., *Ozone Activates Pulmonary Dendritic Cells and Promotes Allergic Sensitization Through a Toll-Like Receptor 4-Dependent Mechanism*, 125 J. ALLERGY & CLINICAL IMMUNOLOGY 1167, 1170 (2010); Joshua F. Robinson et al., *Integrating Genetic and Toxicogenomic Information for Determining Underlying Susceptibility to Developmental Disorders*, 88 BIRTH DEFECTS RES. A: CLINICAL & MOLECULAR TERATOLOGY 920, 929 (2010).

61. Wolffe & Matzke, *supra* note 54, at 481.

62. *Id.* at 481–83; M. Fabbri & G.A. Calin, *Epigenetics and miRNAs in Human Cancer*, 70 ADVANCES IN GENETICS 87 (2010); Peter A. Jones & Daiya Takai, The Role of DNA Methylation in Mammalian Epigenetics, 293 SCIENCE 1068 (2001).

modifications to this system—collectively referred to as the epigenome—provide a sensitive means for cells and organisms to provide delicate control of gene expression during development and throughout life. However, the same sensitivity and pliability of the epigenome that make it useful for developmental regulation also make it vulnerable to environmental perturbation.

There is good evidence of the importance of epigenetic mechanisms in both animal models and in humans. Alterations in DNA methylation in specific regulatory "imprinted" genes are present in people exposed in utero to famine conditions decades earlier.[63] It is thought that this effect is adaptive for an environment of malnourishment; however, the effects appear to carry forward into adulthood, long after the resumption of a normal nutrition environment, and show a correlation with some disease states later in life, such as cancer, schizophrenia, and cardiovascular disease.[64] Even the children of in-utero-famine-exposed parents are at high risk for cancer, autoimmune diseases, and neonatal adiposity (excess fat deposition).[65]

Clearly, epigenetics is creating a new paradigm in our understanding of disease. Whereas in the past, we believed that there was a simple relationship between environmental exposures and disease—that is, you get exposed and somehow the exposure causes disease—we now understand that the effects are more complex. Exposure to an environmental chemical does not have to result in a direct DNA sequence mutation to have an effect. Rather, we now know that there is extremely complicated molecular machinery that

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63. P. D. Gluckman et al., *Effect of In Utero and Early-Life Conditions on Adult Health and Disease*, 359 NEW ENG. J. MED. 61 (2008).

64. H. M. Abdolmaleky et al., *Genetics and Epigenetics in Major Psychiatric Disorders: Dilemmas, Achievements, Applications, and Future Scope* 5 AM. J. PHARMACOGENOMICS 149 (2005); S. Akbarian, *Epigenetics of Schizophrenia*, 4 CURRENT TOPICS BEHAVIORAL NEUROSCIENCE 611 (2010); David J.P. Barker et al., *Growth and Living Conditions in Childhood and Hypertension in Adult Life: A Longitudinal Study* 20 J. HYPERTENSION 1951 (2002) (attributing the correlation between low birthweight and hypertension to reduced number of nephrons, as determined *in utero*); David J.P. Barker & Phillipa M. Clark, *Fetal Undernutrition and Disease in Later Life*, 2 REV. REPROD. 105 (1997) (cancer); Johan Eriksson et al., *Fetal and Childhood Growth and Hypertension in Adult Life*, 36 J. HYPERTENSION 790 (2000) (cardiovascular disease); T.J. Roseboom et al., *Coronary Heart Disease After Prenatal Exposure to the Dutch Famine*, *1944–45*, 84 HEART 595 (2000) (cardiovascular disease); R.P. Sharma, *Schizophrenia, Epigenetics and Ligand-Activated Nuclear Receptors: A Framework for Chromatin Therapeutics* 72 SCHIZOPHRENIA RES. 79 (2005).

65. Autumn J. Bernal & Randy L. Jirtle, *Epigenomic Disruption: The Effects of Early Developmental Exposures*, 88 BIRTH DEFECTS RES. A: CLINICAL & MOLECULAR TERATOLOGY 938, 938–43 (2010).

governs the decisions about which genes get expressed all the time, which genes only get expressed at certain times or under certain conditions, and which genes are totally silenced.[66] In theory, an environmental agent can exert its effect at any, and all, of these stages, which would result in changes in gene expression that could drive other types of adverse health effects.

As we come to terms with the profound implications of the existence of these epigenetic mechanisms, we can also see this new understanding as an opportunity. For example, these changes may actually be reversible; currently there are several chemotherapeutic agents in use that affect DNA methylation.[67] And some adverse epigenetic effects may also be preventable. For example, it has been suggested that the prevention of neural tube defects through periconceptional folate supplementation occurs via an epigenetic mechanism whereby folate contributes to DNA methylation.[68]

This means that if the field develops a better understanding of the epigenetic mechanisms of disease, the opportunity arises for prevention and targeted therapeutics. Thus, environmental health science goals in epigenetics should be to determine epigenetic targets in the genome that are sensitive to modification by environmental exposures, examine changes in epigenetic markers over time and correlate these changes with environmental exposures, identify genes whose imprint is modified by environmental exposures on paternal or maternal genomes, determine genes modulated by environmental exposures that are targets for activation or inactivation by DNA methylation and chromatin remodeling, and, finally, determine predictive biomarkers of altered epigenetic regulation due to exposures to environmental chemicals.

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66. Sayyed K. Zaidi et al., *Bookmarking the Genome: Maintenance of Epigenetic Information*, 286 J. BIOLOGICAL CHEMISTRY 18,355 (2011).

67. Peter W. Laird, *The Power and the Promise of DNA Methylation Markers*, 3 NATURE REVS. CANCER 253, 262 (2003) ("The development of DNA methylation markers that are predictive of a response to chemotherapy is still in its infancy. Several studies have reported associations between DNA methylation markers and response to chemotherapy . . . Others have expressed reservations regarding the conclusions that can be drawn from such retrospective multidrug studies.").

68. Henk J. Blom et al., *Neural Tube Defects and Folate: Case Far from Closed*, 7 NATURE REVS. NEUROSCIENCE 724, 724 (2006) ("It has been known for more than 20 years that women can reduce their risk of having an NTD-affected pregnancy by taking folic acid supplements. However, the underlying mechanisms by which folic acid contributes to a reduction in the risk of an infant being born with an NTD or other types of malformation are unclear. . . . Biochemical, genetic and epidemiological observations have led to the development of the methylation hypothesis, which suggests that folic acid prevents neural tube defects by stimulating cellular methylation reactions.")

If the first ten years of this century were all about the genome, it may well be that the next ten years will be all about the epigenome.

C. Time of Exposure and "Windows of Susceptibility"

The concept of "windows of susceptibility" is based on research that has revealed the heightened vulnerability of fetal, infant, and child developmental processes to disruption from relatively low doses of certain chemicals.[69] Established first for neurodevelopmental toxicants like polychlorinated biphenyls (PCBs), lead, and other metals,[70] this concept also applies to hormonally active agents, or endocrine disrupting chemicals.[71] The "windows of susceptibility" concept is related to epigenetics in that the biological mechanisms leading to differential gene expression that characterizes some of these "windows" are epigenetic mechanisms.

The Barker Hypothesis proposed that sub-optimal developmental nutrition could lead to increased susceptibility to disease later in life.[72] For decades, we have been aware of the acutely sensitive nature of the developmental period to environmental perturbations.[73] The developing organism (fetus and neonate) is extremely sensitive to perturbation by chemicals because its tissues and organs are still forming; there is a lack of DNA repair ability, poor liver metabolism, an immature (and programmable) immune system, and a lack of a blood-brain barrier.[74] However, until recently, the focus was on obvious teratological outcomes such as death, birth defects, and low birth weight as the result of developmental exposures.

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69. *Cf.* Lanphear et al., *supra* note 41, at 898 ("We found evidence of lead-related intellectual deficits among children who had maximal blood lead levels < 7.5 μg/dL. Indeed, we found no evidence of a threshold. . . . Nevertheless, . . . we cannot entirely resolve the question of whether children are more vulnerable to lead exposure during the first 2 years of life.").

70. *See, e.g.,* P. Grandjean & P.J. Landrigan, *Developmental Neurotoxicity of Industrial Chemicals*, 368 LANCET 2167, 2171–74 (2006) (PCBs, lead, mercury, etc.); Todd A. Jusko et al., *Blood Lead Concentrations < 10 microg/dL and Child Intelligence at 6 Years of Age*, 116 ENVTL. HEALTH PERSP. 243, 243 (2008) (lead); Gary J. Myers et al., *Postnatal Exposure to Methyl Mercury from Fish Consumption: A Review and New Data from the Seychelles Child Development Study*, 30 NEUROTOXICOLOGY 338, 338 (2009) (mercury).

71. Susan L. Schantz & John. J. Widholm, *Cognitive Effects of Endocrine-Disrupting Chemicals in Animals*, 109 ENVTL. HEALTH PERSP. 1197, 1197 (2001).

72. Jerrold J. Heindel, Editorial, *Role of Exposure to Environmental chemicals in the Developmental Basis of Disease and Dysfunction*, 23 REPROD. TOXICOLOGY 257, 257 (2007).

73. *Id.*

74. *Id.* at 258.

The breakthrough came with "-omics" technology. "Omics" is shorthand for the technology-driven revolution in biomedical research that permits scientists to examine system-wide, comprehensive biological changes across a cell, tissue, or organism, rather than confining their observations to one gene, molecule, protein, or pathway at a time. A full spectrum of "omics" tools is now available to biological scientists: genomics (analysis of the whole genome, not just limited individual genes), transcriptomics (study of gene expression patterns across the genome), proteomics (the study of the full complement of proteins, as opposed to a single protein), and metabolomics (comprehensive analysis of metabolites). Through this technology, scientists are able to "see" functional changes in the full suite of a cell's or tissue's proteins without having to wait for the complete organism to exhibit signs of disease.[75] Transcriptomics and proteomics allow for analysis of abnormal function at the gene expression and protein level while outwardly everything appears normal—essentially finding disease processes prior to the full clinical expression of disease symptoms.

This technology also facilitated research that revealed the heightened vulnerability of fetal, infant, and child developmental processes to disruption from relatively low doses of certain chemicals.[76] Such disruptions can result in functional changes without typical teratology endpoints such as cleft lip or palate, cardiac ventricular septal defect, anencephaly, and dysmelia, suggesting a developmental basis of disease based on a wide range of environmental exposures, not just poor fetal nutrition.[77]

During in utero and neonatal development, environmental stressors cause functional changes, such as altered gene expression, altered protein activity, and/or altered number of cells.[78] These functional changes or aberrant developmental programming permanently alter gland, organ, or system potential that persists after the environmental stress is gone.[79] We have seen that even decades later, exposures during developmental time "windows" result in

75. *Id.* at 257–58.

76. *NICEATM-ICCVAM Home, supra* note 23. *See generally* BISPHENOL A MONOGRAPH, *supra* note 21.

77. *See* Lanphear et al., *supra* note 41, at 899 ("Still, in studies that did examine other relevant covariates, such as breast-feeding and iron status, the estimated effect of lead was not altered appreciably.").

78. Bernal & Jirtle, *supra* note 65, at 938–43.

79. *Id.*

increased risk of disease later in life.[80] These functional changes are not detected in typical teratology studies, so we need studies that test developmental exposures combined with lifetime examinations for multiple disease outcomes. Toxicant-induced responses are most likely the result of altered gene expression or altered protein regulation (functional change) due to epigenetic changes.[81] When "lifetime examination" is too lengthy, "-omics" endpoints are another way to ensure that we test for the most appropriate endpoints.

Established first for neurodevelopmental toxicants like PCBs, lead, and other metals, this "windows of susceptibility" concept also applies to endocrine disrupting chemicals. Development is a highly integrated process, and it is during this time that epigenetic marks can be set, or "programmed," causing functional changes. The gene and the cell may look normal; however, at the molecular level, one might find altered gene expression (leading to altered proteins), altered protein activity, and an altered number of cells—changes *that persist long after the stress is gone* and can lead to increased sensitivity to disease later in life. Therefore, with regard to exposures during development, in opposition to classical toxicology, *the harm is not proportionate to the dose*.

In addition to fetal and neonatal development, puberty is also a critical window, since rapid developmental changes during this period offer different targets for environmental agents to disrupt gene expression and other processes in ways that cannot be repaired once the time window is over.[82] NIEHS is exploring this "window" in our NIEHS Breast Cancer and Environment Research Program, co-funded with the National Cancer Institute.[83] Researchers are investigating whether periods of susceptibility exist in the development of the mammary gland—periods when exposures to environmental agents may impact the breast and endocrine systems that can influence breast cancer risk in adulthood.[84]

D. Persistence of Biological Effects

The other side of the "windows of susceptibility" coin is that the health effects of a "window" exposure to chemicals such as endocrine

80. *Id.*

81. *Id.*

82. *Background Information*, BREAST CANCER & THE ENV'T RESEARCH PROGRAM, http://www.bcerc.org/about.htm (last visited Apr. 19, 2011).

83. *Id.*

84. *Id.*

disruptors can be observed long after the actual exposure has stopped.[85] This is a high priority area for NIEHS-funded research; for example, scientists are conducting human studies on the latent effects of endocrine disruptor exposure, including studies of children with behavioral, mental, and/or physical challenges who were exposed to phthalates or PBDEs (polybrominated diphenyl ethers) before birth.[86]

Preliminary data also suggests that developmental exposure at the time of germ cell development and erasure of epigenetic marks can lead to "carry over" of altered epigenetic programming across generations (as many as three generations).[87] If this is true, then what your mother was exposed to during pregnancy can affect your health as well as your children's health. This potential impact is huge—this paradigm changes the focus for investigating the cause of disease from adulthood to the developmental stage, it focuses on the perinatal period as a window of opportunity for disease prevention, it changes the focus from curing a disease to prevention and intervention strategies to reduce disease incidence, and it provides an epigenetic "imprint" left by developmental programming that may be useful for identification of exposed individuals and as a biomarker for disease susceptibility.

This knowledge has far-reaching implications for risk assessment and risk management. When we consider the harm done to an individual or group from a hazardous exposure, we cannot simply dismiss the possibility just because the exposure is not occurring at present. From a policy perspective, we must also be alert to the potential for unrealized impacts of earlier exposures as we try to solve a public health problem manifesting itself in the present. If, for example, fetal exposures to some chemicals predispose the exposed individuals to a health effect such as obesity in childhood and later life, then all of our policy emphasis on exercise and proper nutrition, while beneficial, will not be addressing the root problem.

85. Julie B. Herbstman et al., *Prenatal Exposure to PBDEs and Neurodevelopment,* 118 ENVTL. HEALTH PERSP. 712, 712 (2010).

86. *Cf. id.*; *Key Findings & Interventions*, COLUMBIA CTR. FOR CHILDREN'S ENVTL. HEALTH, http://www.cumc.columbia.edu/dept/mailman/ccceh/findings.html (last visited Aug. 10, 2011).

87. Matthew D. Anway & Michael K. Skinner, *Epigenetic Transgenerational Actions of Endocrine Disruptors*, 147 ENDOCRINOLOGY (SUPP.) S43, S45–46 (2006).

IV. WIDE RANGE OF HEALTH EFFECTS

With our growing awareness of previously unanticipated effects of exposure to toxic chemicals, we recognize that our research must extend to health endpoints beyond cancer and birth defects. In fact, these studies are some of the most exciting in the environmental health sciences field.[88] Complex, chronic diseases have complex origins; for most common diseases, there is an intricate interplay among biological pathways or systems and different environmental factors.

Endocrine disruption is a good example of this interplay. Endocrine signals govern every organ and process in the body.[89] This means that when chemicals interfere with endocrine signaling, the effects can be seen in many different conditions and diseases.[90] Early work on endocrine disruption focused mostly on health problems such as reproductive cancers that were known to be hormonally sensitive.[91] More recently, the universe of potential health effects has grown to include immune function,[92] metabolism,[93] brain development,[94] and behavior.[95] Animal studies have identified how exposure to environmental endocrine disruptors, such as tributyltin, genistein, and diethylstilbestrol (DES), can cause weight gain later in life.[96] Endocrine disruptors have also been linked to cancers, altered

88. Retha R. Newbold, Elizabeth Padilla-Banks & Wendy N. Jefferson, *Environmental Estrogens and Obesity,* 304 MOLECULAR & CELLULAR ENDOCRINOLOGY 84, 85 (2009).

89. *Id.*

90. Felix Grun & Bruce Blumberg, *Environmental Obsogens: Organotins and Endocrine Disruption via Nuclear Receptor Signaling*, 147 ENDOCRINOLOGY S50, S50 (2006).

91. Dana C. Dolinoy, Jennifer R. Wedman & Randy L. Jirtle, *Epigenetic Gene Regulation: Linking Early Developmental Environment to Adult Disease*, 23 REPROD. TOXICOLOGY 297, 298 (2007).

92. *See* C.G. Bornehag & E. Nanberg, *Phthalate Exposure and Asthma in Children*, 33 INT'L J. ANDROLOGY 333, 333 (2010); Rodney R. Dietert & Judith T. Zelikoff, *Early-life Environment, Developmental Immunotoxicology, and the Risk of Pediatric Allergic Disease Including Asthma*, 83 BIRTH DEFECTS RES. PART B: DEVELOPMENTAL & REPROD. TOXICOLOGY 547, 547 (2008).

93. Cristina Casals-Casas & Beatrice Desvergne, *Endocrine Disruptors: From Endocrine to Metabolic Disruption*, 73 ANN. REV. PHYSIOLOLOGY 135, 135 (2011).

94. Bernard Weiss, *Endocrine Disruptors as a Threat to Neurological Function*, 305 J. NEUROLOGICAL SCI. 11 (2011).

95. Amir Miodovnik et al., *Endocrine Disruptors and Childhood Social Impairment*, 32 NEUROTOXICOLOGY. 261 (2011).

96. Newbold, Padilla-Banks & Jefferson, *supra* note 88, at 84.

behavior, diabetes, immune dysfunction, reproductive dysfunction, and cardiovascular disease.[97]

A. Early Puberty

A U.S. consensus panel, which included scientists from EPA and NIEHS, published its findings in 2008, in which there was general agreement, given the existing science, that the age of puberty has decreased, specifically as manifested by earlier breast development and onset of menarche.[98] There was also agreement that the studies suggest that endocrine-disrupting chemicals are associated with this altered timing of puberty.[99]

B. Obesity

NIEHS is supporting research on the developmental origins of obesity and the theory that environmental exposures during development play an important role in the current epidemic of obesity, diabetes, and metabolic syndrome.[100] There are data showing weight gain in rats or mice after developmental exposure to a number of different substances, including DDT, polychlorinated biphenyls, fire retardants, phthalates, bisphenol A, and metal compounds such as tributyltin.[101] Thus, we need to start thinking about obesity not just in terms of genetics and lifestyle, but also in terms of exposures. These kinds of outcomes will need to be considered in assessment of toxicity.

C. Neurodevelopment

More than a dozen chemicals (alcohol, lead, mercury, etc.) have been closely associated with human cognitive impairment,[102] and more than 200 chemicals have been shown to be neurotoxic in man.[103] And

97. Evanthia Diamanti-Kandarakis et al., *Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement*, 30 ENDOCRINE REVS. 293 (2009).

98. Susan Y. Euling et al., *Examination of US Puberty-Timing Data from 1940 to 1994 for Secular Trends: Panel Findings*, 121 PEDIATRICS S172 (2008).

99. *Id.*

100. *Estimates of Funding for Various Research Condition, and Disease Categories*, NAT'L INSTS. OF HEALTH RESEARCH PORTFOLIO ONLINE REPORTING TOOLS (Feb. 14, 2011), http://report.nih.gov/rcdc/categories/. *See also Project Listing by Category*, NAT'L INSTS. OF HEALTH RESEARCH PORTFOLIO ONLINE REPORTING TOOLS (Feb. 14, 2011), http://report.nih.gov/rcdc/categories/ProjectSearch.aspx?FY=2010&ARRA=N&DCat=Obesity.

101. *See* Michele La Merrill & Linda S. Birnbaum, *Childhood Obesity and Environmental Chemicals*, 78 MOUNT SINAI J. MED. 22 (2011).

102. Schantz & Widholm, *supra* note 71, at 1197.

103. Grandjean & Landrigan, *supra* note 70, at 1, 9.

yet, the vast majority of chemicals in commerce remain untested for their impacts on neurodevelopment.[104] The 2008 report from the NTP's Center for the Evaluation of Risks to Human Reproduction (CERHR) on the potential human reproductive and developmental effects of bisphenol A, a ubiquitous chemical found in many plastics, was confirmed by the NTP's finding of "some concern for effects on the brain, behavior, and prostate gland in fetuses, infants, and children at current human exposures to bisphenol A."[105] This example demonstrates that the chemicals that can have deleterious effects on the developing brain are not just the typical smokestack pollutants, but also common chemicals that are found in children's toys, in the food that we eat, and even in household furniture and appliances.

V. EXPOSURE MEASUREMENT AND EXPOSURE SCIENCE

The field of environmental health science is in desperate need of a breakthrough in the science of exposure measurement and exposure assessment. Identifying and characterizing past environmental exposures is still very difficult, if not impossible, for many agents of concern. The methodologies for detection and measurement of an actual exposure sustained by a specific organism are often weak and imprecise, especially when the systemic half-life of the substance is short.[106] These issues have bedeviled environmental health researchers for years, and scientists have engineered various approaches to address the problem: using biological measurements when feasible (for stable molecules or their metabolites),[107] extrapolating from questionnaire data,[108] or inferring exposure levels from data on ambient pollutants.[109] The fact remains that accurate, personalized measures of many exposures of interest are still not obtainable. This problem is made even more obvious when we compare our exposure measurement capabilities to the robust tools we employ in the fields of genetics and genomics.

NIEHS has been engaged in an exciting effort aimed at addressing some of the gaps in personalized exposure measurement.

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104. *Id.*

105. *Since You Asked–Bisphenol A,* NAT'L INST. OF ENVTL. HEALTH SCI., http://www.niehs.nih.gov/news/sya/sya-bpa/ (lats reviewed Sept. 8, 2011).

106. Paul J. Lioy, *Exposure Science: A View of the Past and Milestones for the Future*, 118 ENVTL. HEALTH PERSP. 1081, 1081 (2010).

107. *Id.* at 1083.

108. *Id.*

109. *Id.*

NIEHS has been a leading partner in the Genes, Environment and Health Initiative (GEI), a five-year NIH initiative to understand the interactions of genetics and the environment with respect to influences on asthma, diabetes, cancer, and other common illnesses.[110] The initiative is supporting the development of new procedures for analyzing genetic variation in groups of patients with specific illnesses, along with new technologies for measuring exposures to chemical and biological agents, dietary intakes, physical activity, psychosocial stress, and addictive substances.[111] On the exposure-measurement side, through our extramural grants program, NIEHS-funded scientists are involved in developing an array of tools to more precisely measure the myriad of environmental agents and situations we encounter in daily life.[112] Some of these exposure measurement tools are being readied for validation studies.[113]

A. Mixtures

Exposures do not occur singly, although that is how they are usually tested in the lab. All of us are exposed to many different chemicals at the same time. Scientists have labored to come up with ways to estimate risk from combinations of exposures. One example was the method used for dioxin and related compounds. Dioxin is an environmental contaminant and known human carcinogen.[114] Scientists believe that other related chemicals, such as some PCBs and furans, cause cancer in a similar manner.[115] The question for public health officials is how health standards can be adjusted to take into account the fact that people are always exposed to mixtures of dioxin-like compounds, not just to one compound at a time.

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110. *Genes, Environment and Health Initiative,* NAT'L INSTS. OF HEALTH, http://www.gei.nih.gov/ (last updated Feb. 4, 2010).

111. *Id.*

112. *See, e.g.*, Eddy Ball, *Air-Sampling Robot on Florida Beach,* ENVTL. FACTOR, Oct. 2007, http://www.niehs.nih.gov/news/newsletter/2007/october/robot.cfm; *see also Sensor Technologies for Environmental Exposure Assessment,* GENES, ENV'T & HEALTH INITIATIVE, http://www.gei.nih.gov/exposurebiology/program/sensor.asp (last updated Oct. 6, 2008).

113. *See Validation and Field Testing of New Tools for Characterizing the Personal Environment,* NAT'L INSTS. OF HEALTH, http://grants.nih.gov/grants/guide/rfa-files/RFA-ES-10-007.html (last visited Apr. 22, 2011).

114. *Dioxins,* NAT'L INST. OF ENVTL. HEALTH SCI., http://www.niehs.nih.gov/health/topics/agents/dioxins/index.cfm (last updated Feb. 7, 2011).

115. *Known and Probable Human Carcinogens,* AM. CANCER SOC'Y, http://www.cancer.org/Cancer/CancerCauses/OtherCarcinogens/GeneralInformationaboutCarcinogens/known-and-probable-human-carcinogens (last updated Feb. 17, 2011).

To address this problem, a large body of work led to the development of a method to estimate toxicity of mixtures of dioxin-like compounds based upon toxic equivalency factors (TEFs).[116] To estimate the overall toxicity of a mixture, the contaminants' weighted contributions are added together, adjusting for the fact that some compounds are more toxic than others.[117] The additive methodology has been tested and confirmed by studies done by the NTP, EPA, and others.[118] TEF methodology has also been extended to other health endpoints, including reproductive, developmental, immune, and neurological,[119] and the approach is also being used for other classes of chemicals that have a common mechanism of action—for example, organophosphates and other pesticides.[120]

Another challenge related to mixtures is that commercial products such as pesticides, pharmaceuticals, and personal care products contain both "active" and "inert" ingredients. The inert ingredients are key to the effectiveness of these products, but federal law does not require all such ingredients to be identified by percentage—or for pesticides, even by name—on the label.[121] Not all

116. *See Dioxin Toxicity Equivalency Factors for Human Health,* OFFICE OF THE SCI. ADVISOR, U.S. ENVTL. PROT. AGENCY, http://www.epa.gov/raf/hhtefguidance/ (last updated Mar. 1, 2011).

117. OFFICE OF THE SCI. ADVISOR, U.S. ENVTL. PROT. AGENCY, EPA/600/R-10/005 RECOMMENDED TOXICITY EQUIVALENCE FACTORS (TEFS) FOR HUMAN HEALTH RISK ASSESSMENTS OF 2,3,7,8-TETRACHLORODIBENZO-*P*-DIOXIN AND DIOXIN-LIKE COMPOUNDS 2 (2010), *available at* http://www.epa.gov/osa/raf/files/tefs-for-dioxin-epa-00-r-10-005-final.pdf.

118. *See* NAT'L TOXICOLOGY PROGRAM, DEP'T OF HEALTH AND HUMAN SERVICES, NTP TR 526, NIH PUB. NO. 06-4462, NTP TECHNICAL REPORT ON THE TOXICOLOGY AND CARCINOGENESIS STUDIES OF A MIXTURE OF 2,3,7,8-TETRACHLORODIBENZO-P-DIOXIN (TCDD) (CAS NO. 1746-01-6), 2,3,4,7,8-PENTACHLORODIBENZOFURAN (PECDF) (CAS NO. 57117-31-4), AND 3,3',4,4',5-PENTACHLOROBIPHENYL (PCB 126) (CAS NO. 57465-28-8) IN FEMALE HARLAN SPRAGUE-DAWLEY RATS (GAVAGE STUDIES) (2006), *available at* http://ntp.niehs.nih.gov/files/526_Web_Final.pdf.

119. *See* Martin Van den Berg et al., *The 2005 World Health Organization Reevaluation of Human and Mammalian Toxic Equivalency Factors for Dioxins and Dioxin-Like Compounds,* 93 TOXICOLOGICAL SCI., 223, 225–26.

120. *See Organophosphate Pesticides: Revised Cumulative Risk Assessment,* U.S. ENVTL. PROT. AGENCY, http://www.epa.gov/pesticides/cumulative/rra-op/ (last updated Apr. 22, 2011).

121. Michael H. Surgan, *Toxicity Tests: "Inert" and Active Ingredients*, 113 ENVTL. HEALTH PERSP. A657-58, A658 (2005) ("[F]or many pesticide products, little or no information about the identity of inert ingredients is publicly available. . . . [T]he identity of inert ingredients is rarely revealed in the open literature, publicly available regulatory documents, or product labels."). *See also, e.g.*, 21 C.F.R. § 701.3(a) (2011) ("The label on each package of a cosmetic shall bear a declaration of the name of each ingredient in descending order of predominance"). *See also generally* R.E. Baynes & J.E. Riviere, *Influence of Inert Ingredients in Pesticide Formulations on Dermal Absorption of Carbaryl*, 59 AM. J. VETERINARY RES. 168 (1998) (pesticides); K. Noiles & R. Vender, *Are Excipients Really Inert Ingredients? A Review of Adverse Reactions to*

inert ingredients are non-toxic—but many are uncharacterized for toxicity.[122] The lack of safety testing for inert ingredients, and mixtures of inert and active ingredients, leaves open the question of the effects from mixtures of these ingredients.

B. Low-Dose Exposure

As discussed in section II ("Complex Diseases Have Complex Etiologies"), it is important that our research on exposures, exposure measurement, and dose effects address results of low-dose exposures. We know, for example, that our endocrine system works on tiny amounts of hormones that have profound effects on development and normal health.[123] As a result, exposures to endocrine-active chemicals, even at low doses, can disrupt the body's delicate endocrine system and create a mechanism for disease.[124]

For some endocrine-disrupting chemicals, biological effects can occur at low doses, but different effects, typically cytotoxicity, occur at high doses.[125] This is different from the usual dose-response curve, which shows continually increasing responses with increases in dose.[126] As an example, studies have shown that low doses of BPA, an endocrine disruptor, change brain structure, function, and behavior in rats and mice exposed during critical periods of development.[127]

The question remains, however: What is the definition of "low dose"? Although there is no consensus, we propose that "low dose" equals the smallest dose to which people are typically exposed that results in measurable physiological effects.

Excipients in Oral Dermatologic Medications in Canada, 14 J. CUTANEOUS MED. & SURGERY 105 (2010) (pesticides); *Cosmetic Labeling Manual*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/Cosmetics/CosmeticLabelingLabelClaims/CosmeticLabelingManual/default.htm (last updated May 13, 2009) (cosmetics).

122. Sophie Richard et al., *Differential Effects of Glyphosate and Roundup on Human Placental Cells and Aromatase*, 113 ENVTL. HEALTH PERSP. 716 (2005); Gilles-Eric Seralini, *"Inert" and Active Ingredients: Seralini Responds*, 113 ENVTL. HEALTH PERSP. A658, A658 (2005); Surgan, *supra* note 121, at A658 ("It has been long known that the adjuvants (commonly and misleadingly called "inert" ingredients) may be toxic and may enhance or supplement the toxic effects of the active pesticidal ingredient.").

123. Miodovnik et al., *supra* note 95, at 265.

124. *Id. See also* Laura N. Vandenberg et al., *Bisphenol-A and the Great Divide: a Review of Controversies in the Field of Endocrine Disruption*, 30 ENDOCRINE REV. 75, 75 (2009).

125. Wade V. Welshons, et al., *Large Effects from Small Exposures. I. Mechanisms for Endocrine-Disrupting Chemicals with Estrogenic Activity,* 11 ENVTL. HEALTH PERSP. 994, 994 (2003).

126. *Id.*

127. *See* BISPHENOL A MONOGRAPH, *supra* note 21.

C. Routes of Exposure

Differences in routes of exposure may result in considerable differences in effects. For example, hexavalent chromium compounds have been shown to cause lung cancer in humans when inhaled,[128] but it was not known how these compounds behaved when ingested. Hexavalent chromium was tested by the NTP because of concerns over its presence in drinking water.[129] The NTP studies showed that a compound containing hexavalent chromium causes cancer in laboratory animals following oral administration in drinking water, confirming the need to protect people from oral, as well as inhalational, exposure.[130]

VI. TRANSLATING SCIENCE INTO RISK ASSESSMENT AND REGULATORY ACTION

NIEHS research is opening new opportunities for expanding and deepening our understanding of the effects of environmental agents on biological systems and on health and disease. NIEHS also places a high priority on ensuring that our state-of-the-art research is used to inform real-world solutions for issues and problems in environmental health.[131] Some of the examples below describe this science "translation": providing critical data for EPA's use in setting regulatory standards; taking advantage of new science and new tools to create High Throughput Screening (HTS) approaches to testing; following up on the effects of emerging exposures such as nanoparticles and the changes in human exposures that are anticipated as a result of climate change.

A. Arsenic

The impact of new scientific information on the effects of environmental chemicals can be seen in the EPA's arsenic standards for drinking water, which were enforced in 2006.[132] The NIEHS Superfund Research Program funded scientists who played a vital

128. NAT'L TOXICOLOGY PROGRAM, HEXAVALENT CHROMIUM 1 (2007), *available at* http://ntp.niehs.nih.gov/files/NTPHexaVChrmFactR5.pdf.

129. *Id.*

130. *Id.*

131. *See* NAT'L INST. OF ENVTL. HEALTH SCI., NEW FRONTIERS IN ENVIRONMENTAL SCIENCES AND HUMAN HEALTH: THE 2006-2011 NIEHS STRATEGIC PLAN 2 (2006*) available at* http://www.niehs.nih.gov/about/od/strategicplan/strategicplan2006/strategic-plan06.pdf.

132. *See Arsenic Rule*, U.S. ENVTL. PROT. AGENCY, http://water.epa.gov/lawsregs/rulesregs/sdwa/arsenic/regulations.cfm (last visited Sept. 24, 2011).

role in the development of these standards through research on health effects of arsenic in drinking water.[133] This research included studies of arsenic metabolism, mechanistic research on disease pathogenesis by arsenic, and both molecular and traditional epidemiology with detailed exposure assessment.[134] These studies provided the scientific underpinnings for a standard that protects the health of Americans against long-term effects of arsenic exposure, which include cancer, diabetes, neurological, and cardiovascular disease.[135]

B. High-Throughput Screening

We are poised to move forward into an era of a new kind of toxicological testing that is less expensive, uses fewer animals, and gives us an improved understanding of the actual effects on humans. Toxicology is advancing from a mostly observational science using disease-specific models to a more predictive science focused upon broad inclusion of target-specific, mechanism-based biological observations. This entails using alternative assays targeting the key pathways, molecular events, or processes linked to disease or injury and incorporating them into a research and testing framework. The NTP is laying the foundation for this testing paradigm in partnership with the National Human Genome Research Institute, EPA, and FDA to promote the use of quantitative high-throughput screening assays to test a large number of chemicals.[136] The resulting data are deposited into publicly accessible relational databases.[137] Analyses of these results will set the stage for a new framework for toxicity testing.

C. Nanomaterials

Engineered nanomaterials are already making their way into commerce—through industrial processes, paints and coatings, pharmaceuticals, and personal use products like lotions, cosmetics,

133. See *Arsenic Drinking Water Standard,* NAT'L INST. OF ENVTL. HEALTH SCI., http://www.niehs.nih.gov/research/supported/srp/products/products2_s2_s1.cfm (last visited Aug. 10, 2011).

134. See *id.*

135. See *id.*

136. *High Throughput Screening Initiative,* NAT'L TOXICOLOGY PROGRAM, http://ntp.niehs.nih.gov/?objectid=05F80E15-F1F6-975E-77DDEDBDF3B941CD (last visited Aug. 10, 2011).

137. *Id.*

and sunscreens.[138] FDA, EPA, NIOSH, and CPSC currently do not have the knowledge base they need to regulate these substances appropriately.

NIEHS began a nanomaterials initiative to examine the fundamental physicochemical interactions of engineered nanomaterials with biological systems at the molecular, cellular, and organ levels, as well as with associated pathophysiologic processes.[139]

Ultimately, we want to identify the biologically and clinically relevant properties of engineered nanomaterials to help create rules for design of these materials to maximize benefits and minimize risks.

D. Climate Change and Human Health

The Intergovernmental Panel on Climate Change's Fourth Assessment Report (AR4), issued in 2007,[140] marked a turning point in the global scientific and policy discussion of climate change. Before then, the scientific community was focused on whether climate change was actually occurring, whether greenhouse gases emitted by human activities were the primary cause of climate change, and whether these effects were quantifiable.[141] The Fourth Assessment Report concluded that the answer to all of these questions was a definitive "Yes."[142]

With these issues resolved, the immediate questions become ones of both science and policy: How can we determine the urgency and severity of climate change effects? Do we have the means to mitigate GHG emissions to slow or ultimately reverse the process? And, most significantly for the near-term, what can we do to help human and natural systems adapt to these changes in order to prevent the worst consequences, build population resiliency, and protect health? These questions are particularly critical and urgent for those most vulnerable populations, both in the United States and around

138. *See Frequently Asked Questions: Nanotechnology,* NAT'L NANOTECHNOLOGY INITIATIVE, http://www.nano.gov/html/facts/faqs.html (last visited Apr. 19, 2011). *See also Analysis,* PROJECT ON EMERGING NANOTECHNOLOGIES, http://www.nanotechproject.org/inventories/consumer/analysis_draft/ (last visited Apr. 19, 2011).

139. NAT'L INST. OF ENVIRONMENTAL HEALTH SERVICES, NAT'L INSTS. OF HEALTH & U.S. DEP'T OF HUMAN HEALTH SERVICES, NANOHEALTH ENTERPRISE INITIATIVE 2, *available at* http://www.niehs.nih.gov/research/supported/programs/nanohealth/docs/nanohealth-initiative2.pdf.

140. *See* INTERGOVERNMENTAL PANEL ON CLIMATE CHANGE, CLIMATE CHANGE 2007: SYNTHESIS REPORT (2007), *available at* http://www.ipcc.ch/pdf/assessment-report/ar4/syr/ar4_syr.pdf.

141. *See id*.

142. *Id*. at 72–73.

the world, who bear a disproportionate burden of illness from climate change in relation to their contribution to the problem.

In response, NIEHS created and led the Interagency Working Group on Climate Change and Health,[143] which includes members from the NIH Fogarty International Center, the U.S. EPA, the National Oceanic and Atmospheric Administration, the U.S. Department of Agriculture, the U.S. Department of State, and the White House Office of Science and Technology Policy, with support and input from the U.S. Global Change Research Program, among others.[144]

On Earth Day last year, this group published a white paper in the NIEHS journal, *Environmental Health Perspectives* (*EHP*), describing what we know about the actual and likely impacts on human health from climate change, both directly and indirectly, and the research that is needed to fill in the gaps of what we do not yet know for eleven categories of health consequences.[145] It is important to note that the research needs outlined in this document incorporate and reference prior important work in this area by groups such as the Intergovernmental Panel on Climate Change, the U.S. Global Change Research Program, the National Research Council, and peer-reviewed literature.[146]

The projected health consequences of climate change are numerous and significant, including asthma, respiratory allergies, airway diseases, cancer, cardiovascular disease, stroke, foodborne illnesses, heat-related morbidity and mortality, human developmental effects, mental health and stress-related disorders, neurological diseases and disorders, vector-borne and zoonotic diseases, waterborne diseases, and weather-related morbidity and mortality.[147]

Crosscutting issues relevant to preventing or avoiding many of the potential health impacts of climate change include identifying susceptible, vulnerable, and displaced populations; enhancing public health and health care infrastructure; developing capacities and skills in modeling and prediction; and improving risk communication and

143. *Climate Change & Human Health,* NAT'L INST. OF ENVTL. HEALTH SCI., http://www.niehs.nih.gov/about/od/programs/climatechange/index.cfm (last visited Apr. 8, 2011).

144. *Id*.

145. ENVTL. HEALTH PERSPECTIVES & NAT'L INST. OF ENVTL. HEALTH SCI., A HUMAN HEALTH PERSPECTIVE ON CLIMATE CHANGE, at v (2010), *available at* http://www.niehs.nih.gov/climatereport.

146. *See id*.

147. *Id*. at 7.

public health education.[148] Research in these areas will lead to more effective early warning systems and greater public awareness of an individual's or community's health risk from climate change, which should translate into more successful mitigation and adaptation strategies.

While the Interagency Working Group on Climate Change and Health identified many research needs, it deliberately did not prioritize them, recognizing that many diverse scientifically and socially weighted factors must be considered.[149] The intent of this paper was to provide a starting point for the federal government, as well as partners in academia, industry, non-governmental organizations, and particularly local, state, regional, and tribal governments, to begin to define their own appropriate agendas and priorities for research action.[150]

VII. PARTNERSHIPS FOR EFFECTIVE ENVIRONMENTAL HEALTH STRATEGIES

A. Community Partnerships

Environmental health science does not occur in a vacuum. Our environment is where we live, work, and play. At NIEHS we value the two-way dialogue necessary for effective research, interventions, and grant programs.

NIEHS has established a new integrated, unified program to coordinate NIEHS's extramural activities in environmental public health, the Partnerships for Environmental Public Health (PEPH).[151] PEPH is an umbrella program that brings together scientists, community members, educators, health care providers, public health officials, and policy makers in the shared goal of advancing the impact of environmental public health research at local, regional, and national levels.[152] A major focus of the PEPH program is to encourage community participation in the research process, from development of research questions through translating and disseminating research

148. *Id*. at vii.

149. *Id*.

150. *Id*.

151. *Partnerships for Environmental Public Health (PEPH): Background,* NAT'L INST. OF ENVTL. HEALTH SCI., http://www.niehs.nih.gov/research/supported/programs/peph/about/background.cfm (last visited Sept. 8, 2011).

152. *Partnerships for Environmental Public Health (PEPH): About PEPH,* NAT'L INST. OF ENVTL. HEALTH SCI., http://www.niehs.nih.gov/research/supported/programs/peph/about/index.cfm (last visited Sept. 8, 2011).

findings.[153] Community participation can enhance research in many ways. Benefits include community input to help inform the science and/or refine the research focus of the project, increased trust between community members and researchers, participation of community members in the research process, access to community members to help collect exposure data, improved access to the multiple exposure environments experienced by vulnerable populations (home, work, and school), more effective translation and dissemination of research findings, increased awareness of environmental hazards and community empowerment, and improved recruitment and retention of study participants.[154]

NIEHS has a long history of involvement with community-based activities.[155] A "research to action" program is designed to bring together community members with environmental and occupational health researchers to investigate the potential health risks of environmental and occupational exposures that are of concern to their communities.[156] Longstanding programs in community-based participatory research and environmental justice enhance and strengthen community-university partnerships in the pursuit of addressing environmental health research and interventions, with a particular focus on addressing environmental justice concerns and health disparities.[157]

As part of many of our grant programs, we require our grantees to develop Community Engagement Cores as a means to establish "bi-directional" communication with their target audience to understand their needs and how best to address them.[158] These Cores help facilitate communication between community groups and research center members.

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153. *Partnerships for Environmental Public Health (PEPH): Background,* NAT'L INST. OF ENVTL. HEALTH SCI., http://www.niehs.nih.gov/research/supported/programs/peph/about/background.cfm (last visited Sept. 8, 2011).

154. *Partnerships for Environmental Public Health (PEPH): Communication and Dissemination Research,* NAT'L INST. OF ENVTL. HEALTH SCI., http://www.niehs.nih.gov/research/supported/programs/peph/about/communication.cfm (last visited Sept. 8, 2011).

155. *Research to Action,* NAT'L INST. OF ENVTL. HEALTH SCI. http://www.niehs.nih.gov/research/supported/programs/peph/prog/rta/ (last visited Sept. 8, 2011).

156. *Id*.

157. *Environmental Justice & Community-Based Participatory Research: Select Program Highlights,* NAT'L INST. OF ENVTL. HEALTH SCI., http://www.niehs.nih.gov/research/supported/programs/justice/highlights.cfm (last visited Sept. 8, 2011).

158. *Environmental Health Sciences Core Centers Community Outreach & Engagement Program,* NAT'L INST. OF ENVTL. HEALTH SCI., http://www.niehs.nih.gov/research/supported/centers/core/coe/index.cfm (last visited Sept. 8, 2011).

Our strategies for fostering "bi-directional" communication involve numerous groups, including the Public Interest Partners, a formal group of community and advocacy representatives that includes groups such as the Alliance for Health Homes, the American Cancer Society, the American Public Health Association, Physicians for Social Responsibility, Cure Autism Now, and the Environmental Defense Fund.[159] Working with the Public Interest Partners allows the NIEHS to learn more about the priorities of these organizations, and helps to shape the Institute's research agenda. In turn, these organizations learn about the NIEHS research enterprise and about the other partner organizations. As a group, the Public Interest Partners are a powerful voice for environmental health issues. The Friends of NIEHS is another organization that has been revitalized to advocate on behalf of NIEHS to Congress.[160]

NIEHS has held Community Forums across the country in order to hear about real issues of importance to local residents. Recent meetings were held in Piscataway, N.J.; Milwaukee, Wis.; Sausalito, Cal.; West Harlem, N.Y.; Louisville, Ky.; and New Orleans, La.[161] In each meeting, NIEHS representatives heard different concerns about different public health issues. Such community level engagement is integral to NIEHS's mission to produce valuable research and policy solutions that respond to public priorities.

B. Expanded Federal Partnerships

An additional way to expand the reach of environmental health science in meaningful ways is through our expanded federal partnerships with agencies where health has not traditionally been considered part of their mission or mandate, although health issues are clearly evident in their decisionmaking. For example, the Department of Transportation makes rules about trucks, and these rules may impact air pollution levels near highways, thereby increasing exposure to particulate matter that causes or exacerbates

159. *Public Interest Partners,* NAT'L INST. OF ENVTL. HEALTH SCI., http://www.niehs.nih.gov/about/community/publicinterest/ (last visited Sept. 8, 2011).

160. LINDA S. BIRNBAUM, NAT'L INST. OF ENVTL. HEALTH SCI., REPORT TO THE NATIONAL ADVISORY ENVIRONMENTAL HEALTH SCIENCES COUNCIL 3 (2011), *available at* http://www.niehs.nih.gov/about/boards/naehsc/agenda/may2011/report_of_the_director_niehs.pdf.

161. *Community Forums,* NAT'L INST. OF ENVTL. HEALTH SCI., http://www.niehs.nih.gov/about/community/communityforums/index.cfm (last visited Sept. 8, 2011).

disease;[162] the Department of Energy has a mandate to develop alternative energy sources,[163] and these may have new or unanticipated environmental and human health consequences.

The connection between environmental health science and public health can be thought of as a loop that links basic biology and bench research to public health outcomes. By "closing the loop," we can frame our research goals and priorities to ensure that environmental health science is best positioned to improve public health. This framework allows research to be considered from a multi-stakeholder perspective, developing hypotheses that provide data for multiple uses, including regulatory policy, legislative action, and transparent communication strategies addressing concerns of the general public. In the simplest terms, environmental health research must have a positive outcome on people's actual health. For this to happen, a robust relationship between NIEHS and its partners is vital.

VIII. CASE STUDY OF SCIENCE FOR POLICY: GULF OIL SPILL

NIEHS staff visited the Gulf very early in the oil spill response and took the initiative to corral the other parts of HHS into an Interagency Oil Spill Health Monitoring and Research Workgroup.[164] The workgroup consists of NIEHS (NIH), NIOSH and ATSDR (CDC), the Substance Abuse and Mental Health Services Administration, as well as the HHS Assistant Secretary for Preparedness and Response.[165] The workgroup is intended to coordinate and facilitate public health efforts associated with the Gulf oil spill.[166] This workgroup has been very effective at helping the Department of Health and Human Services respond to the spill by engaging stakeholders, including federal, state, and local agencies,

162. *Rules & Regulations – Fed. Motor Carrier Safety Admin,* FED. MOTOR CARRIER SAFETY ADMIN., http://www.fmcsa.dot.gov/rules-regulations/rules-regulations.htm (last visited Apr. 8, 2011).

163. *Energy Sources,* ENERGY.GOV, http://energy.gov/science-innovation/energy-sources (last visited Sept. 21, 2011).

164. Aubrey Keith Miller, *NIEHS Activities Related to the Gulf Oil Spill,* U.S. DEP'T OF HEALTH & HUMAN SERVS., http://www.hhs.gov/asl/testify/2010/06/t20100615i.html (last visited Sept. 8, 2011).

165. NAT'L INST. OF ENVTL. HEALTH SCI., NATIONAL TOXICOLOGY PROGRAM BOARD OF SCIENTIFIC COUNSELORS SUMMARY MINUTES JUNE 21–22, 2010, at 5, *available at* http://ntp.niehs.nih.gov/ntp/About_NTP/BSC/2010/June/Minutes20100622.pdf.

166. Miller, *supra* note 164.

academia, and relevant non-governmental organizations.[167] This has been viewed as an integral part of the Department's response.

As of December 2010, more than 100,000 people on the Gulf Coast have been trained using NIEHS/Worker Training Program materials.[168] Various levels of training are available, including an intensive forty-hour course on Hazardous Waste Operations and Emergency Response, commonly known as HAZWOPER training,[169] four-hour courses for workers doing on-shore cleanup,[170] additional training to workers on Vessels of Opportunity (local commercial and charter fishing vessels contracted by British Petroleum to assist with oil cleanup) ,[171] and safety briefings for dock workers.[172] The courses have been provided in English, Spanish, and Vietnamese.[173] The NIEHS Worker Education Training Program created pocket-sized booklets with vital information about oil spill exposures, hazards, and risks and printed and distributed 5,000 of these booklets to oil spill cleanup workers within days.[174]

While experts agree there is potential for human health effects from the oil spill, understanding and quantifying these effects requires further study. NIH Director Francis Collins announced $10 million to support research into the potential health effects of the oil spill.[175]

The NIEHS Gulf Long-term Followup (GuLF) cohort study of oil cleanup workers and volunteers is being designed with input from local, state, and federal agencies, and community partners.[176] It is expected to evaluate about 55,000 cleanup workers for a range of

167. *Id*.

168. *Deepwater Horizon Oil Spill HHS Efforts Factsheet*, DEP'T OF HEALTH & HUMAN SERVS., http://www.hhs.gov/gulfoilspill/factsheet_gulfoilspill_12092010.html (last visited Sept. 8, 2011).

169. *Deepwater Oil Spill, July 23, 2010: HHS Efforts Fact Sheet*, DEP'T OF HEALTH & HUMAN SERVS., http://www.hhs.gov/gulfoilspill/factshhet_gulfoilspill_07232010.html (last visited Sept. 8, 2011).

170. *Id*.

171. *Id*.

172. *Id*.

173. Ed Kang, *NIEHS Oil Spill Response Intensifies,* ENVTL. FACTOR, July 2010, http://www.niehs.nih.gov/news/newsletter/2010/july/spotlight-niehs.cfm.

174. *Id*.

175. *Id*.

176. *GuLF STUDY*, NAT'L INST. OF ENVTL. HEALTH SCI., http://www.niehs.nih.gov/about/od/programs/gulfspill/gulfstudy/index.cfm (last visited Sept. 8, 2011).

possible health effects, including respiratory, neurobehavioral, carcinogenic, immunological, and mental health disorders.[177]

The National Toxicology Program is engaged in studies that will include a mixture of literature evaluations, analytical chemistry activities, toxicity pathway screens, and targeted testing in rodent studies to confirm and extend our understanding of the hazards presented by the complex materials released during the spill and cleanup.[178] This includes a literature search and maintenance of toxicity information, chemical analysis of oil and dispersant samples, medium throughput screens, and targeted short-term animal studies.[179]

NIEHS's extramural program is leading eight other NIH institutes in forming consortia of research programs including environmental monitoring and characterization, toxicity testing, exposure assessment for individuals and populations, health effects research, risk assessment, and communication and outreach, all utilizing the NIH research infrastructure.[180]

IX. CONCLUSION

Regulatory decisionmaking needs to account for the ways in which our understanding of the effects of chemical exposures has deepened and improved over the past forty years. We must have the ability to harness new technologies and a growing knowledge base of underlying biology, receptor and other host pathways, variations in susceptibility, and routes and timing of exposure to obtain a clearer and more accurate picture of the risks posed by these chemicals, both to individuals and to the population. EPA, in common with all government regulatory agencies, depends on the availability of well-conducted, unbiased, high-quality science to fulfill its mission to set appropriate environmental regulations that protect human health and the environment. NIEHS, despite its organizational position outside the EPA and within a separate Cabinet department (the Department

177. Press Release, Nat'l Inst. of Envtl. Health Sci., NIH Launches Largest Oil Spill Health Study (Feb. 28, 2011), *available at* http://www.nih.gov/news/health/feb2011/niehs-28.htm.

178. *Gulf Oil Spill Response Efforts,* NAT'L INST. OF ENVTL. HEALTH SCI., http://www.niehs.nih.gov/about/od/programs/gulfspill/ (last visited Sept. 8, 2011).

179. SCOTT A. MASTEN, NAT'L TOXICOLOGY PROGRAM, NATIONAL TOXICOLOGY PROGRAM ACTIVITIES RELATED TO THE GULF OIL SPILL (2010), *available at* http://www.niehs.nih.gov/about/od/programs/gulfspill/masten-ntp-nieh121010.pdf.

180. NAT'L ADVISORY ENVTL. HEALTH SCI. COUNCIL, THE ENVIRONMENTAL HEALTH SCIENCES CENTRALIZED KNOWLEDGEBASE, (2010), *available at* http://www.niehs.nih.gov/about/orgstructure/boards/naehsc/agenda/sep2010/ehs-kb-maull.pdf.

of Health and Human Services), is a major supplier of the overall base of scientific knowledge on which EPA bases its decisions. Our new tools must provide for research and development to create the comprehensive testing envisioned. NIEHS is ready and willing to be a vital partner to EPA, bringing our strengths as a builder of the environmental health sciences enterprise that can help provide the quality knowledge and state-of-the-art tools for EPA to do its job effectively. Ultimately, our shared goal is the protection of the health and environment of the American people.

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