EPA
United States
Environmental Protection
Agency

NIEHS
National Institute of
Environmental Health Sciences

PEHSU
Pediatric Environmental
Health Specialty Units

Proceedings of the 2007 Children's Environmental Health Workshop: Discover, Treat, Prevent, Prepare

OCTOBER 10–13, 2007
THE HAMILTON HOTEL
14TH AND K STREETS, NW
WASHINGTON, DC 20005

National Center for Environmental Research
Science To Achieve Results (STAR) Research Program

2007 Children's Environmental Health Workshop: Discover, Treat, Prevent, Prepare

Hamilton Crowne Plaza
1001 14th Street, NW
Washington, DC

October 11–12, 2007

Agenda

Purpose:
This workshop brings together the expertise and experience of the Pediatric Environmental Health Specialty Units (PEHSU) of North America and the Children's Environmental Health Centers to explore the latest research findings and their practical application in community settings. This workshop is sponsored by the U.S. Environmental Protection Agency (EPA) (Office of Research and Development and Office of Children's Health Protection and Environmental Education), the Department of Health and Human Services (Agency for Toxic Substances and Disease Registry of the Centers for Disease Control and Prevention and the National Institute of Environmental Health Sciences), and the Association of Occupational and Environmental Clinics in recognition of 10 years of federal effort to protect children's environmental health as called for in Executive Order 13045, Protection of Children from Environmental Health Risks and Safety Risks.
This anniversary provides the children's environmental health community with an opportunity to reflect on the progress that has been made and to formulate our vision for the future of children's environmental health.

Thursday, October 11, 2007

7:30 – 8:15 a.m. **Breakfast and Registration**

8:15 – 9:00 a.m. **Welcome/Review of Agenda**
William H. Sanders III, Dr.P.H.
Director, National Center for Environmental Research, EPA

***Dona DeLeon**, Acting Director, Office of Children's Health Protection and Environmental Education, EPA*

Kevin Y. Teichman, Ph.D.
Acting Deputy Assistant Administrator for Science, EPA

Children's Environmental Health: Looking Backward, Looking Forward
Howard Frumkin, M.D., Dr.P.H., M.P.H.
Director, National Center for Environmental Health, Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention

***Gwen Collman, Ph.D.,** Chief, Susceptibility and Population Health Branch, Division of Extramural Research and Training, National Institute for Environmental Health Sciences*

9:00 – 10:45 a.m. **Session I: Evolution of Biomarkers for Pesticides: Examples From the Agricultural Setting**

Co-Chairs: ***Catherine Karr, M.D., Ph.D.,*** *Director, Northwest PEHSU*
Elaine Faustman, Ph.D., *Director, Center for Child Environmental Health Risks Research*

In the late 1990s, an epidemic of initially unrecognized organophosphate (OP) poisoning affecting families in eight states helped motivate the development of the PEHSU network to increase the capacity of physicians to identify and prevent adverse effects of environmental toxicants. In recent years, concern has focused on the potential child health implications from chronic, lower level exposure and are a focus of ongoing longitudinal birth cohort studies and exposure pathway studies within the EPA/NIEHS Children's Centers Program. An accumulating evidence base led to recent restrictions in residential use of these products; however, organophosphate insecticides continue to have extensive use in many agricultural settings.

In research and clinical settings, biomarkers of organophosphate exposure, toxicity, and susceptibility have contributed to improved understanding of exposure pathways and adverse health outcomes. The session will discuss: (a) use of pesticide metabolite concentrations to estimate exposure type, extent, and source attribution based on EPA/NIEHS-sponsored studies and CDC population surveillance; (b) strengths and pitfalls regarding the determination of cholinesterase enzyme activity in clinical practice, occupational surveillance, and research as a marker of OP toxicity; and (c) evolving insight into the importance of gene-environment interaction in OP toxicity using recent findings based on paraoxonase 1 studies in the Children's Centers.

The key areas for discussion will include the current stage of validation of these OP-related biomarkers and critical missing data/applications to consider in moving the translation of each biomarker forward for clinical and public health relevance. The links between research, education, and risk communication activities from PEHSU and the Children's Centers will be highlighted.

Presenters:

Elaine Faustman, Ph.D.
Catherine Karr, M.D., Ph.D.
Kim Harley, Ph.D., *University of California at Berkeley, Center for Children's Environmental Health Research*
John Furman, *Washington State Department of Labor and Industries*
Bill Griffith, Ph.D., *Center for Child Environmental Health Risks Research*
Frederica Perera, Dr.PH, *Columbia Center for Children's Environmental Health*

10:45 – 11:00 a.m. **Break**

11:00 a.m. – 12:45 p.m. **Session II: Phthalates Exposure in Childhood: Is There Evidence of Harm?**

Chair: ***Maida P. Galvez, M.D., M.P.H.****, Mount Sinai PEHSU, and Mount Sinai Center for Inner City Toxics and Children's Health*

Phthalates are chemicals added to plastics that impart flexibility and act as a scent stabilizer for a wide range of products—from food packaging and children's toys to personal hygiene products such as shampoos, fragrances, and nail polish. Concerns exist about the potential for phthalates to act as endocrine disruptors, largely based on animal studies and a small but growing body of evidence in human studies.

Several countries around the world, beginning with the European Union, have subsequently banned phthalates in children's products. Since then, widespread media reports on the potential harms of toxic toys and other children's products containing phthalates have raised parental anxiety about the impact of environmental exposures on their children.

Primary care pediatricians are subsequently faced with clinical questions that are often difficult to answer given the limited medical school training in children's environmental health, particularly in newly emerging exposures of concern such as phthalates.

This session will present clinical scenarios commonly encountered by general pediatricians and PEHSUs regarding questions about phthalates. The goal of this session is to describe: (a) exposure levels in pregnant women, toddlers, and school-aged children; (b) sources of exposure; and (c) known and potential health outcomes. Data will be shared from three cohorts: A cohort of pregnant women in New York (Dr. Robin Whyatt, Columbia University Center for Children's Environmental Health); a cohort of 6 to 24-month-old infants from California, Minnesota, and Missouri (Dr. Sheela Sathyanarayana, University of Washington, Seattle, Northwest PEHSU); and a cohort of 6 to 8-year-old New York City children (Drs. Mary Wolff and Maida Galvez, Mount Sinai Center for Children's Environmental Health and Mount Sinai PEHSU).

Key areas for discussion will include: (1) What is the current evidence for adverse health outcomes? (2) What are the research gaps? (3) What health messages on phthalates can we share with families now? (4) What policy issues remain unresolved?

Presenters: ***Maida P. Galvez, M.D., M.P.H.****, Mount Sinai PEHSU, and Mount Sinai Center for Inner City Toxics and Children's Health*
Robin Whyatt, Dr.P.H., *Deputy Director, Columbia Center for Children's Environmental Health*
Sheela Sathyanarayana, M.D., *Northwest PEHSU*
Mary Wolff, Ph.D.*, Director, Mount Sinai Center for Inner City Toxics and Children's Health*

12:45 – 2:00 p.m. Lunch (on your own)

2:00 – 3:15 p.m. **Session III: The Evolving Science and Practice of Environmental Management for Asthma Prevention and Care**

Co-Chairs: ***Kimberly Gray,*** *Ph.D., National Institute of Environmental Health Sciences*
Leyla E. McCurdy, *National Environmental Education Foundation*

Asthma is a chronic respiratory disease characterized by episodes of inflammation and narrowing of small airways. Childhood asthma, in particular, continues to be a major, vexing public health problem in the United States. Low-income populations, minorities, and children living in inner cities still experience disproportionately higher morbidity and mortality due to asthma. Asthma's effects on children and adolescents account for millions of lost days of school missed annually and cost more than $3 billion per year to treat. According to the Centers for Disease Control and Prevention in 2005, prevalence rates for childhood asthma peaked at 8.9 percent; more than 6 million of the nation's children. Even so, there have been important gains recently, including a reduction in childhood deaths from asthma attacks, a leveling of hospitalizations, improved patient education, and evidence of earlier clinical recognition and treatment.

Currently, there are neither known preventions nor cures for asthma. However, avoiding environmental agents that promote or exacerbate asthma attacks is one of

the primary goals of good asthma management. Considerable research within the EPA/NIEHS Children's Centers has primarily focused on four areas: (1) household interventions and avoidance of environmental triggers, (2) exposure and effects of air pollution, (3) gene-environment interactions, and (4) mechanisms of early immune deregulation and subsequent asthma risk.
This session will: (1) review potential mechanisms (immune, epigenetic) for the effects of prenatal and early postnatal exposure on asthma outcomes, and the ongoing mechanistic work being performed by the Children's Centers; and (2) highlight currently recommended household environmental management strategies most useful for clinical settings based on the 3rd Expert Panel Report of Guidelines on Asthma issued August 2007.

The discussion will broaden to include recent research findings of Children's Centers, including the impact of chronic exposure to air pollution and the contribution of genetic vulnerabilities in an open-session format.

Presenters: ***David Rowson****, Office of Air and Radiation, EPA*
Rachel Miller, M.D., FAAAAI, *Columbia Center for Children's Environmental Health*

Discussant: ***Elizabeth Matsui, M.D., M.H.S.****, Center for Childhood Asthma in the Urban Environment*
James M. Seltzer, M.D.*, University of California, PEHSU*

3:15 – 3:30 p.m. **Break**

3:30 – 5:15 p.m. **Session IV: Early Life Exposures to Metals and Neurotoxic Outcomes**
Co-Chairs: ***Isaac Pessah, Ph.D.****, Director, University of California at Davis, Center for Children's Environmental Health*
Nigel A. Fields, M.S.P.H.*, National Center for Environmental Research, EPA*

There has been significant public health progress in reducing chronic high level exposures to metals, such as lead and mercury, which can cause neurological damage at any age. For instance, today most children in the United States maintain average blood lead levels well below the action level of 10 µg/dL. This has been accomplished largely through state and local education and advisories, multimedia public health campaigns, and federal regulation. However, there is increasing evidence that early life exposures to toxic metals, particularly during fetal development, may contribute to behavioral effects and adversely affect cognitive functioning well into adult life. There also is growing concern regarding the social context of exposure, or non-chemical stressors, which may modify the uptake and neurotoxic effect of metals such as lead, mercury, and manganese, both pre- and post-natally. Yet, currently there is limited ability to identify and translate clinically significant prenatal biomarkers of exposure, susceptibility, and effect that could better elucidate risks of metal exposures during pregnancy.

The purpose of this session is to: highlight recent findings of the long-term effects of metals and metal mixtures; discuss the utility of perinatal biomarkers of lead and mercury; and consider modifying factors that might offer additional protection or confer additional risk to children. Based on three longitudinal cohorts and one case-control study, this session will explore: (1) the plausible interactive effects of metals and psychosocial stresses on neurodevelopment; (2) the use of new mercury exposure biomarkers and epidemiological approaches in autism etiology research; (3) the long-term behavioral consequences of fetal and childhood exposures to lead, resulting in criminality and increased societal risks; (4) the impact of early exposure to lead on adult cerebral cortical anatomy and function as revealed by advanced neuro-imaging techniques; and (5) the interactive effects of exposure to multiple metals on neurodevelopment.

Panel and Audience Discussion Questions: What are the key window periods of concern for fetal exposure to metals? What factors confer added protection or increased risk from early life exposures to metals? How should the long-term effects of metal exposures inform public health actions during early childhood development?

Presenters: ***Irva Hertz Piciotto, Ph.D.,*** *Deputy Director, University of California at Davis, Center for Children's Environmental Health*
Robert Wright, M.D., *New England PEHSU and Harvard Center for Metal Mixtures and Children's Health*
Kim Dietrich, Ph.D., *Cincinnati Children's Environmental Health Center*

5:30 p.m. **Reception and 3rd Annual EPA Children's Environmental Health Excellence Award Ceremony** *(Open Invitation)*

Dr. William H. Sanders III, Presiding

The Children's Environmental Health Excellence Awards recognize ongoing and sustainable dedication to, and notable leadership in, protecting children from environmental health risks at the local, regional, national, and international level. Excellence Awards are presented to groups or individuals that exemplify invaluable leadership in the protection of children from environmental health risks. There are 10 winners in 2007, 7 in the health care provider category, 1 for schools, 1 for corporate leadership, and 1 for research.

The Children's Environmental Health Champion is an honorary award presented to individuals to recognize their outstanding efforts and commitment to advancing environmental health issues. The 2006 Children's Environmental Health Champion award was presented to Philip J. Landrigan, M.D., M.Sc., and in 2005 our Champion Award winner was Ramona Trovato.

Who will it be for 2007? Join us and find out!

Friday, October 12, 2007

7:30 a.m. Breakfast

8:30 – 9:30 a.m. **Session V: Transportation, the Built Environment, and Children's Health**

Moderator: ***Joanne Rodman,*** *Acting Director, Child and Aging Health Protection Division, OCHPEE*

This session will explore trends in population demographics, how and where development occurs, the explosive growth in international trade, and the anticipated impacts on public health, the environment, transportation, and infrastructure planning. There will be a more detailed look at trends in school siting with relationship to roadways and other factors and discussion of the implications of those trends on efforts to develop healthy communities. The session will examine how a school's site and its context within a community can affect children's health, as well as the environment, economic development, land use, and transportation. Recent studies on proximity to traffic and adverse health effects will be discussed, as well the health and community impacts of port and "goods movement" (freight transportation) expansion in many U.S. cities. Possible points of intervention for the public health community on this issue also will be discussed.

***Tim Torma**, EPA, Office of Policy, Economics and Innovation*
***Andrea M. Hricko, M.P.H.**, University of Southern California, Center for Children's Environmental Health*

9:30 – 10:00 a.m. **The National Children's Study: Opportunities for Adjunct Studies**
***Marion Balsam, M.D.,** Research Partnerships Program Director, National Children's Study*

As the National Children's Study proceeds, scientific knowledge will evolve and the Study will serve as an appropriate platform on which to build additional scientific studies. Investigators from various sectors will propose adjunct studies. Such studies will enhance the breadth, depth, and value of the Study and will assure continued interest of a diverse group of investigators, which is critical to the overall success of the Study.

An adjunct study involves a portion of the National Children's Study cohort, utilizing individually or in combination, any of the following: The Study participants, their bio-specimens, or their environmental samples. Adjunct studies can take place at one or more Study Centers, on all or a portion of their Center participants. Adjunct studies generally will be initiated and planned outside of the Study protocol planning process and funded with non-Study funding; that is, by such mechanisms as government grants (for example, R01) applied for by the initiator, by intramural federal resources, through public private partnerships, or from other sources. To preserve the quality and integrity of the National Children's Study, all proposals for adjunct studies will receive rigorous review. This presentation will include a brief overview of adjunct studies and of the review and approval process.

10:00 – 10:15 a.m. **Break**

10:15 – 11:15 a.m. **Session VI: Children's Protection in the Aftermath of a Natural Disaster: Tools for Recovery and Communicating Risks**
Chair: ***Debra Cherry, M.D., M.S.,** University of Texas Health Center at Tyler, Southwest PEHSU*

Hurricane Katrina, which struck the Gulf Coast on August 29, 2005, has been called the most devastating natural environmental calamity in U.S. history. More than 354,000 homes along the Gulf Coast were destroyed or damaged beyond repair. Katrina damaged more than 200 sewage treatment plants and 140 oil and gas platforms and leached hazardous chemicals and fuels from hundreds of small businesses as the floodwaters passed over them. Rampant mold growth, mountains of debris, and widespread cleanup, demolition, and construction projects followed. Some residents were housed "temporarily" in FEMA trailers with hastily assembled indoor materials that off gassed high levels of formaldehyde. Many New Orleans residents left the area permanently.

This session will describe some of the efforts of a Gulf Coast pediatrician, NIEHS scientists, and PEHSU clinicians to respond to this calamity. Dr. Scott Needle (pediatrician, relocated from Bay St. Louis, Mississippi to Florida) will describe via Web conference his experience on the front lines of the disaster, the disaster preparedness document he prepared on behalf of AAP, and his federal testimony on the health effects of formaldehyde in FEMA trailers. Dr. Marie Lynn Miranda (scientist and GIS expert, Duke University) will describe the NIEHS Hurricane Response Portal, a research and planning tool for the Gulf Coast, which overlays multiple geographic and demographic features, such as location of hazardous waste sites, racial composition, and extent of flooding. Dr. Debra Cherry (occupational medicine physician from the Southwest PEHSU) will briefly present fact sheets on sludge, formaldehyde, and mold, as well as the PEHSU/AAP guidelines for returning children to previously flooded areas.

Key areas for discussion will include: (1) How should federal agencies communicate with local clinicians in the aftermath of a natural disaster? (2) What types of tools are most useful? (3) What environmental health risks were overblown, and which were understated in the aftermath of Hurricanes Katrina and Rita?

Presenters: ***Debra Cherry, M.D., M.S.,*** *University of Texas Health Center at Tyler, Southwest PEHSU*
Marie Lynn Miranda, Ph.D., *Director, Duke University Southern Center for Environmentally-Driven Disparities in Birth Outcomes*
Scott Needle, M.D., *Pediatrician, formally of Bay St. Louis, MS*

11:15 a.m. – 12:15 p.m. **The National Forum on Children and Nature**

Key Note Address: ***Lawrence A. Selzer****, President and Chief Executive Officer, Conservation Fund*
Introduction and Discussant: ***Howard Frumkin, M.D., Dr.P.H., M.P.H.***

Launched in June 2007, the National Forum on Children and Nature will involve governors, mayors, corporate CEOs, heads of environmental organizations, and leaders from health and education institutions, and will invest several million dollars in projects with on-the-ground tangible results that address the issue of children's isolation from nature. The Forum will identify 20 nationally significant demonstration projects in four key areas of health, education, the built environment, and media/culture that, individually and collectively, will provide substantial steps toward improved children's health and environmental stewardship.

12:15 – 12:30 p.m. **Closing Remarks: *Dr. William H. Sanders III, EPA***

Acknowledgments

Many thanks to the honorary workshop co-chairs: William Sanders and Howard Frumkin

Also special thanks to the workshop planning committee: Nora Conlon, Elaine Faustman, Maida Galvez, Kimberly Gray, Michael Hatcher, Catherine Karr, Leyla McCurdy, Ketna Mistry, Jerome Paulson, Isaac Pessah, and Maryann Suero

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MEETING SUMMARY

OCTOBER 11, 2007

INTRODUCTION AND OVERVIEW

The U.S. Environmental Protection Agency (EPA) 2007 Children's Environmental Health Workshop: Discover, Treat, Prevent, Prepare was held on October 11–12, 2007, in Washington, DC. The workshop brought together a diverse group of clinicians, researchers, and health advocates from academic, government, and nonprofit organizations. Participants discussed issues in clinical practice, ongoing research in children's environmental health, and opportunities for translating scientific findings. The workshop also served as a stimulus for increased collaborations among the Pediatric Environmental Health Specialty Units (PEHSUs) and the Centers for Children's Environmental Health and Disease Prevention Research. Approximately 133 individuals attended.

Welcome and Review of the Agenda
Nigel Fields, William H. Sanders, III, Dona DeLeon, and Kevin Y. Teichman, U.S. EPA; Paula Davis, Association of Occupational and Environmental Clinics (AOEC)

Mr. Fields thanked attendees for their participation. He noted that the 10th anniversary of Executive Order 13045, Protection of Children from Environmental Health Risks and Safety Risks, was an opportune time to celebrate the progress made in children's environmental health (CEH) and to align perspectives for the future of this field. He invited participants to engage workshop speakers in their discussions about how to further CEH protection.

Ms. Davis, Coordinator of the Pediatric Environmental Health Specialty Units Program (PEHSU) welcomed presenters and workshop participants. She expressed her interest in collaborating with PEHSU colleagues and other scientists involved in CEH to help bridge the gap between research and practice.

Before his recent appointment as Director of the National Center for Environmental Research (NCER), Dr. Sanders previously worked directly with the PEHSUs and indirectly with the Children's Environmental Health Centers (CEHC) in his role as Acting Director of the Office of Children's Health Protection and Environmental Education. He noted the variety of constituents in attendance and remarked that it is a great opportunity for bringing together representatives from the PEHSUs with the CEHC Directors in a central venue. He presented an overview of the workshop agenda, explaining the nature of each session. Dr. Sanders also invited participants to attend the Third Annual Excellence Awards Ceremony at end of the first day.

Ms. DeLeon explained that she is new to the Office of Children's Health Protection and Environmental Education but has spent many years at EPA, including working with and examining the delivery system at

the state and local levels. Implementation of environmental policy is taking place at the local level; how regulation implementation is translated at the local level and communicated to the public is critical to keep environmental progress moving forward. This audience plays an important role in communicating health risks and promoting the science that underlies decision-making to the public working with families and children. She congratulated attendees for the progress that has been made and thanked them for their continuation of these efforts. She welcomed the international visitors and commented that she looks forward to learning more about children's environmental health issues and how EPA can assist researchers in advancing these issues.

Dr. Teichman welcomed participants and remarked that the CEH protection community experienced another tremendous year of growth; he noted that it was appropriate that the workshop was held during Children's Health Month. He also welcomed Dr. William Sanders to EPA's Office of Research and Development (ORD) and expressed his gratitude to the Center for Children's Environmental Health and Disease Prevention Research; the National Institute of Environmental Health Sciences (NIEHS); PEHSUs; the Agency for Toxic Substances and Disease Registry (ATSDR); AOEC; and the new health care provider capacity-building grantees and Children's Environmental Health Champion Award winners.

The mission of EPA is to protect human health and the environment. In attempting to achieve this goal, the Agency is examining one of the most vulnerable populations with increased specificity. There is a wide range of genetic susceptibility among newborns and young children to exposure from household or agricultural pesticides. Where a child lives within the urban environment may significantly influence or impact his or her exposures and health outcomes. With the passing of several federal mandates, EPA has emphasized the identification of child-specific exposures, health risks, and protective actions for more than a decade. Within ORD, these mandates have stimulated a wide array of research activities, with the purposes of studying how chemical exposures change across life stages; gaining a greater understanding about the genetic factors that contribute to children's vulnerability to air pollution, pesticide exposures, and heavy metals; validating novel methods for both aggregate and cumulative exposures to single and multiple chemical, biological, and radiological agents; discovering, translating, and employing biomarkers of exposure effect and susceptibility; and promoting cost-effective sustainable household- and community-level interventions.

EPA scientists and their academic partners have applied their expertise to these efforts because children may be at increased risk from environmental influences as a result of their vulnerable developing systems and enhanced exposures to many agents. These environmental influences include the quality of air, ingested lead, and exposures to chemicals and mold; all of these factors are within society's power to control. ORD researchers have contributed to improving CEH in many ways. The Stochastic Human Exposure and Dose Simulation Multiscale Model is now used as a primary tool for simulating exposures to a variety of chemicals that enter the body to determine how best to advise the public on reducing children's exposures to toxic compounds. During the past 10 years, EPA has improved the ability to monitor chemical exposures and assess the effects based on the development, validation, and implementation of biological markers. EPA scientists and those supported by the Agency are leading efforts to validate noninvasive biomarkers and to apply them in epidemiologic studies and clinical settings. ORD also is contributing to the Agency's next *Report on the Environment* by developing the scientific basis for the use of health outcomes to measure and evaluate environmental policy decisions.

ORD is only one contributor to improving the understanding of CEH; community partners play a critical role in informing, implementing, and translating research findings. Workshop participants have the opportunity to discuss findings and clinical experiences and translate those experiences for advancing more protective medical guidance in environmental policy into the future. Today's sessions, which focus on the translation of research and clinical insights regarding organophosphates (OPs), phthalates, asthma, and exposures to metals, will specifically concentrate on prenatal and early life exposures and the

subsequent health effects associated with these exposures. The next day's sessions will examine what lies ahead for researchers, clinicians, and health advocates as increasingly complex public health challenges that also will impact children's health emerge. These challenges include persistently high rates of low birth weight and preterm births; increasing rates of neurobehavioral disorders in young children, such as autism and attention deficit hyperactivity disorder (ADHD); increasing body burdens of potentially endocrine-disrupting compounds; escalating prevalence rates for obesity and type II diabetes; growing disparities between low-income and minority groups to chemical exposures; the risks of climate change; the emergence and application of nanotechnology; and complex trends in urbanization. EPA will need partners in determining the environmental factors and related health outcomes of these issues.

ORD will continue to work closely with the Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), and international collaborators such as the World Health Organization (WHO) to systematically discover ways to protect children in a rapidly evolving world. The National Children's Study (NCS) holds much promise for gaining a deeper understanding of these complex issues and to make better, more targeted decisions for promoting healthier environments. The NCS represents a truly unprecedented collaboration among government agencies, private industry and foundations, community leaders, and university-based scientists around the nation devoted to improving children's health. EPA conducted and supported much of the science that laid the foundation for this ambitious study. Researchers from the CEHCs participated in workgroups that developed the core hypotheses for the studies, and the Centers also collectively published "Lessons Learned" papers to offer guidance to the NCS for practical approaches to sustaining long-term studies and interpreting complex data.

Last week, EPA joined the National Institute of Child Health and Development (NICHD) in announcing the 22 Health Study Center awards, which joined the previously awarded Vanguard Centers in officially launching the study next year. As the research community moves forward to build on the past decade of success, it is clear that meeting these challenges will require strong, committed partnerships that better link research questions, health care practice, and environmental health.

Children's Environmental Health: Looking Backward, Looking Forward
Howard Frumkin, CDC, and Gwen Collman, NIEHS

In 1993, the National Academy of Sciences published *Pesticides in the Diets of Infants and Children*. This report helped establish the scientific basis for the CEH movement. Executive Order 13045 is a milestone in the movement, but since its enactment, the world has changed in many ways. For instance, 10 years ago, people did not routinely discuss the enhanced vulnerability of children, and preparedness was not a commonly used term in the public health world. Much work has been accomplished in the CEH field during the past 10 years in the areas of research, education, and service. Disease-specific research, community-based participatory research, research on the combination of genetic and environmental factors, and studies on vulnerable populations have expanded. Education has been extended to include fellowship training, and the field has seen an increase in the publication of books, papers, and Web sites related to CEH. The development of community networks, PEHSUs, and technical tools have added to the list of services that the scientific community provides to the public, but it is time to evaluate these accomplishments by asking what they have achieved in terms of improving children's health. Are children healthier now? Do health care providers and parents know how to provide children with safe and wholesome environments more effectively than they did 10 years ago? Has there been a continuing record of policy-making reflecting the importance of CEH?

This month, October 2007, marks the 10th anniversary of the Executive Order, and the CEH community is entering a new decade with the chance to reinvent, reinvigorate, and re-expand efforts and move from an individual clinical approach to a more encompassing legacy approach of caring for future generations. Biomonitoring is a well-established tool for determining known toxicants in the bodies of children. This

tool will be instrumental in focusing future research trends by measuring decreases in current chemicals of concern and identifying possible emerging toxicants. Genetic science will transform the field as research continues and scientists deepen their understanding of gene-environment interactions. In addition, there appears to be a change in the political climate that is more sympathetic to CEH. The child health community must take advantage of these advances to confront current and future challenges. Challenges during the next 10 years include poverty, changing chemical toxicity, dealing with the built environment, climate change, mental health burdens, and communication.

Poverty and lack of insurance are two of the most important threats to children's health, as underscored by the American Cancer Society's 2007 public relations theme, "Access to Health Care." The built environment has impacted children's health by engineering physical activity out of neighborhoods and communities. Children and adults now must drive to most destinations, including grocery stores, pharmacies, shopping malls, and schools. Low physical activity has been linked to childhood obesity and an increase in diabetes, and the increase in vehicle traffic is adding to environmental pollution. The built environment also discourages childrens from spending time outside. The author of *Last Child in the Woods* advocates "saving our kids from nature-deficit disorder" and maintains that spending time in natural settings is an important part of a healthy childhood. One of the mechanisms of the benefits of nature contact seems to be through attention-restoration theory, which states that attention is focused and distractions are minimized when children have the chance to be outside. This book has given rise to some very interesting efforts. The Children and Nature Network links people working to promote initiatives at the state level, including the "Leave No Child Inside" initiative. A number of federal agencies, such as the U.S. Fish and Wildlife Service, have developed programs about reconnecting children and nature. An initiative called "The National Forum on Children and Nature" seeks to support 20 nationally significant demonstration projects across the country that will restore kids into national settings, with a focus on underserved and minority children. Research on the health evidence of these initiatives should be part of the CEH portfolio.

Climate change is an important and growing environmental health concern. In addition to potential physical effects, children now face potential psychological effects, including some effects that may stem from the fear associated with global warming. Other psychological effects already have been seen in the aftermath of recent hurricanes, which are predicted to become more severe with global warming. This kind of message in the media is becoming more common now, with rather apocalyptic narratives about climate change. Journalistic accounts of schools have described evidence of terror in children about the world and what it has in store for them. This must be considered because climate change is an issue that is going to remain for a long time. The manner in which it is discussed either will scare and immobilize people, or it will spur them to constructive action; the right message must be promoted. The reactions of adults influence children's reactions. Aftereffects of climate-related events must be considered as well; the biggest health burden of Hurricane Katrina, in retrospect, is the mental health burden. The anticipation of bad things happening, the aftermath, and the post-traumatic phase are serious mental health concerns that threaten children, and this needs to be part of CEH thinking.

"The Death of Environmentalism," an essay by Ted Nordhaus and Michael Shellenberger, was considered a "big picture" piece on environmentalism. It challenged some of the basic assumptions of contemporary environmentalism. The book-length expansion of that essay, *Breakthrough*, is provocative reading, and some of its points are very relevant to children's environmental health. Many CEH messages are negative: stopping the bad rather than creating the good. The authors recommend articulating a positive, compelling image of a healthy, wholesome world, rather than focusing so much on the negative. Positive messages are compelling and motivating to the public. Additionally, the challenge of climate change is so massive, global, and complex that it can only be overcome if the issue categories of the past are discarded and an aspirational vision of the future is embraced. According to the authors, environmentalists should think about job creation, economic development, law enforcement, and other important issues traditionally

outside the environmental arena. A similar approach may well be advisable for CEH. In communities where toxic exposures for children are a concern, poor education, joblessness, or squalor in the physical environment often are more important problems than the toxic exposures. The more globally children's problems can be addressed, the better they will be managed; broad thinking and getting outside of traditional categories can be beneficial. Climate change calls for expanded thinking.

One method by which CEH research portfolios can be expanded is to leverage opportunities with other partners, such as the U.S. Fish and Wildlife Service, which is actively involved in getting children back into the outdoors; the U.S. Department of Housing and Urban Development (HUD), which attempts to improve the quality of housing; and the U.S. Department of Education, which is concerned with healthy schools. Leveraging of opportunities and development of new partnerships must be creative, as concerns increase without increasing resources.

Dr. Collman explained that NIEHS has a strong portfolio in research areas that are now classically part of the rubric of CEH, such as basic mechanisms of toxicity during development, early life, and in organ systems related to diseases. The executive orders, reports, and regulations provided an impetus for moving the science forward and moving individual scientific inquiries in individual laboratories to partners across a spectrum of science. These efforts were furthered by the creation of the CEHCs, which bring together scientists of different disciplines to work with local health advocates and community partners. Through multidisciplinary research and outreach projects, the Centers are investigating environmental health challenges facing children and families in their community settings. These partnerships would not be complete without the health care community. Today, this collective network of research, community, and clinical partners can be proud of the training and development programs that are preparing future scientists and health care professionals, including residents, fellows, and academic physicians in becoming tomorrow's experts and leaders in CEH.

SESSION I: EVOLUTION OF BIOMARKERS FOR PESTICIDES: EXAMPLES FROM THE AGRICULTURAL SETTING

Co-Chairs: Catherine Karr and Elaine Faustman, University of Washington

Dr. Karr stated that it was a pleasure to open the first workshop session. The topic of the session is the evolution of biomarkers for pesticides with examples from agricultural settings. The session speakers are accomplished leaders from the public health, research, and clinical sectors who will discuss their experiences with biomarkers with the focus on a specific group of pesticides, the OP insecticides. Despite recent decreases in home and garden use, these insecticides continue to be used heavily in agriculture and are of great interest in the Pacific Northwest because of orchard crop production that relies intensively on OP use. OPs also are of interest because of their legacy of acute toxicity in humans; they are the pesticides most often implicated in symptomatic illness. Another reason to consider OP exposures is the accumulating evidence of neurodevelopmental toxicity related to relatively low chronic exposures in children. This provides a framework for considering the application and use of biomarkers. Biomarkers provide a context for understanding the pathway from release of an organopesticide in a child's environment to the potential for development of clinically significant disease or prognosis. This session will explore biomarkers of exposure in terms of internal dose measures using urinary metabolite monitoring, biomarkers of biologically effective dose or early biological effect, and biomarkers of susceptibility based on genetic polymorphisms in the population.

PEHSUs receive a number of questions from parents, pediatricians, public health officers, federal agency leaders, and policy-makers from "Should I have my child tested?" to "Should we have a national monitoring program for agricultural workers?" Today researchers are at the stage of validating biomarkers and must concentrate their efforts on finding ways for various sectors to utilize these data.

Efforts to use biomarkers in population-based monitoring in the States of Washington and California for occupational surveillance may inform the following questions: Should we have a national medical monitoring program for agriculturally exposed workers? What would such a program constitute? Lastly, from a risk assessment perspective, policy-makers may ask researchers: Can we use biomonitoring to evaluate whether regulation of diazanon and chlorpyrifos (CPF) has reduced exposure in at-risk populations such as children? Policy-makers may follow the unfolding story of the paraoxonase gene (*PON1*) as an effect modifier and ask: Should regulatory decision-making incorporate evaluation and protection of the most genetically vulnerable subset of the population? These are questions to consider during the presentations. The presenters will provide insight into progress toward validation of biomarkers and their utility as well as various limitations and knowledge gaps that need to be overcome, so that researchers can move forward to increase the clinical public health and risk assessment relevancy of biomarkers.

Biomarkers of Pesticide Exposure: Lessons for Children in Agricultural Communities
Elaine Faustman, University of Washington

Dr. Faustman stated that her presentation would focus on some of the biomarkers of pesticide exposure and some of the lessons for children in agricultural communities, including exposure to internal dose, biologically effective does, early biological effect, altered structure and function, clinical disease, and the relationship with biomarkers of exposure and biomarkers of effect. In Washington State, OPs are used on apple and potato crops. OPs have various structures that differ by ethyl and methyl moieties, and up to 40 different OPs are in common use. The differences in patterns of the methyl and ethyl group metabolites can allow for the tracking of sources and attributable uses of these pesticides. Linking this information within the exposure response biomarker paradigm is important. Agricultural pesticides and contributions of occupational factors to home, adult, and child contamination will be discussed.

The complex series of metabolites that are formed following OP exposure presents a challenge to examining and interpreting what a biomarker of exposure might mean from the environment versus an internal dose of biomarker (e.g., urinary metabolites). Genetic polymorphism in the enzymes involved in the metabolism of these compounds present significant challenges, but modeling approaches that measure specific and nonspecific metabolites from OPs allow researchers to compare exposure markers. National Health and Nutrition Examination Survey (NHANES) data show U.S. population averages and show that children's exposures are higher than average adult exposures, and this becomes important if the exposures remain elevated over multiple years. In terms of assessing children's exposure based on the take-home pathway, this is the hypothesis that was put forth: Adult workplace exposure increases pesticides in dust in vehicles and homes and, therefore, to children through direct physical contact with the adults and indirectly through contaminated homes and cars. For example, a study of homes and vehicles of farmworkers in the Pacific Northwest found that the workers had higher levels of pesticides in the dust of their vehicles and homes and OP markers one to two orders of magnitude higher than U.S. averages. Their children's levels also were skewed to higher values compared with NHANES data. Modeling across specific metabolites allows researchers to detect high-risk exposure subgroups. Another study examined various crops and the distributions of specific metabolites in nonfarmworkers and farmworkers adults and children. Results showed a higher association of OP metabolites among those working with pome fruit, and this was identified as a potential place for intervention. All of the correlations were positive, illustrating a strong workplace take-home pathway. Using these models, sources of where the metabolite was attributable to child exposure were identified. These data have informed decisions about intervention procedures and allows targeting of populations that have been neglected in terms of public health intervention.

Two longitudinal studies measuring OP metabolites revealed another issue involved in biomarker analyses: variability. The variability was less between children than the variability within an individual

child; metabolites will vary considerably following repeated sampling of children. Within-person distributions are wider than distributions among a whole population. This has important ramifications in understanding the potential environmental effects of certain agents. Because there are a variety of factors (e.g., half-life, dynamics of exposure, and continued exposure), sampling approaches must be considered that increase understanding of how individuals versus populations are being exposed.

Biomarkers of exposure cannot be used for all types of studies, but they are very useful for understanding the patterns of exposures and source attribution. Other studies may be necessary to identify highly exposed groups and plan interventions. EPA studies will allow researchers to link multiple sampling of exposure and internal dose with potential early markers of response, such as enzyme changes and gene expression markers. Physiologically based toxicokinetic models are being built for OPs, with polymorphic information being added at multiple stages for the myriad of enzymes that are involved in OP metabolism. This is important so that genotypes can be used to help identify at-risk populations and to determine what these differences may mean for exposure and responses. Once these tools are further developed, they can be used for research and clinical applications. Dr. Faustman's group will be testing the hypotheses of how much knowledge about the genotype-phenotype makes a difference in understanding differences in between-person variability and how much knowledge about gene expression contributes to understanding responses within the same person over time. Future work includes identifying the genotype and phenotype for key genes that metabolize OPs to improve prediction of exposure response and at-risk individuals in agricultural communities. Learning more about polymorphisms of oxidant responsive pathways will allow researchers to better evaluate the potential for genomic biomarkers of early response to be linked with OP metabolites of exposure, better predict relationship of biomarkers of effect (e.g., acetylcholine) to respond in a dose-response manner to OP exposures in adults and children, and better predict whether "omic" biomarkers of disease are correlated with OP exposure.

Discussion

A participant requested clarification on the comment regarding how exposure measurement techniques may need to be modified for assessment of chemicals with short chemical half-lives. Dr. Faustman replied that the NCS holds a lot of promise to look at longitudinal exposures, but there are unique questions for some agents, for which the exposure and compounds are dynamic enough that additional assessments could be used in the NCS to answer some of these more specific questions. Her presentation illustrated the kind of information that can be gained from longitudinal studies versus specific studies and how this information can be integrated to build a cohesive picture.

A participant asked if the study examined children under age 6. Dr. Faustman replied that the study included younger children but did not examine crawling behavior.

A participant asked Dr. Faustman to discuss intervention and evaluation studies regarding the take-home pathway conducted at the University of Washington Center. Dr. Faustman indicated that a paired study was conducted where interventions were performed at the community- and household-level. The data are being analyzed, but early results show positive associations with intervention actions taken in the homes.

OP Pesticide Exposures and Neurodevelopment in Children From Farmworker Families
Kim Harley, University of California at Berkeley

The Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) study is a longitudinal birth cohort study of Mexican farmworker children and their mothers in the agricultural Salinas Valley region of California. The goals of this study were to: (1) estimate source and pathways of

OP pesticide exposure and levels of *in utero* and postnatal pesticide exposures in children living in agricultural communities; and (2) determine the relationship of this exposure with neurodevelopment, growth, and respiratory disease. The Berkeley team measured biomarkers of OP exposure using dialkylphosphate (DAP) metabolites measured in maternal and child urine. Increasing age, proximity to agricultural fields, and increased consumption of fresh fruits and vegetables were associated with higher DAP levels in young children in this cohort. Prenatal and child DAP levels were compared with early childhood neurodevelopmental and neurobehavioral outcomes using the Brazelton Neonatal Behavioral Assessment Scale, Bayley Scales of Infant Development, the Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III), and the Child Behavior Checklist (CBCL). Reflexes in neonates were more likely to be abnormal in association with high maternal DAPs, but no associations were established between prenatal DAPs and six of the other seven Brazelton clusters. In addition, as the mothers' prenatal levels increased, Bayley Mental Development Index scores decreased in children at 24 months of age. Higher prenatal DAPs were also associated with increased likelihood of Pervasive Developmental Disorder, as assessed by the CBCL at 24 and 42 months of age. Findings were driven primarily by the dimethylphosphate, as opposed to diethylphosphate metabolites. These results were compared with similar studies at Mt. Sinai Hospital and Columbia University in New York City (NYC). Although these studies looked at different populations, the results mirrored results found in California. The NYC cohorts were made up of Mexican, Puerto Rican, and Dominican Hispanics; African Americans; and non-Hispanic Whites in an urban environment. The majority of the Berkeley cohort was comprised of Mexican Hispanics from an agricultural environment. Despite these differences, some patterns have emerged across these three cohort studies. Prenatal OP exposures in two cohorts were associated with increased odds of abnormal reflexes in neonates, and in all three cohorts with poorer mental development in 2- and 3-year-olds and poorer verbal IQ in 3.5–5-year-olds. Increased odds of pervasive developmental disorder was found in the two cohorts that examined this outcome.

Discussion

A participant asked if fruit and vegetable consumption could explain better performance in children. Dr. Harley responded that fruit and vegetable consumption was factored into the model and did not account for any differences.

A participant asked about potential confounders in the study. Dr. Harley answered that the study adjusted for factors that could have a bearing on development and intellect (e.g., parental IQ, socioeconomics, etc.).

A participant commented about the findings of a rat study that showed higher performance levels associated with CPF exposure and suggested that the researchers examine the higher performing children in the study to determine if they had higher prenatal exposures.

Cholinesterase Monitoring in Washington State
John Furman, **Washington State Department of Labor and Industries**

In 2003, the Washington State Department of Labor and Industries began an occupational medical surveillance program of agricultural pesticide handlers that measured cholinesterase (ChE) levels throughout the pesticide application season to detect overexposure to pesticides and prevent illness, increase hazard awareness, identify unsafe environments, and fix problems. Symptoms of ChE illness range from mild to severe and include dizziness, blurred vision, nausea, headache, stomach cramps, diarrhea, hypotension, and seizures; often, many of these symptoms are misdiagnosed.

Acetylcholinesterase is an enzyme that removes the chemical neurotransmitter acetylcholine from the neuronal synapse. Humans, insects, and other species have this basic acetylcholine system.

Cholinesterase-inhibiting pesticides have been developed to kill insects, but overexposure in humans results in sustained levels of acetylcholine and overstimulation of neuronal pathways and eventual exhaustion of neuronal pathways. Pesticide handlers of Toxicity Class I and II pesticides are monitored for ChE levels in red blood cells (RBCs) and serum. Exposure-free baselines are established annually during periods when handlers have not handled pesticides for at least 30 days. Analyses are conducted within the same laboratory to control for interlaboratory variations. Employees who handle these pesticides for more than 30 hours in any 30-day span are tested every 30 days. Employees may decline participation but must undergo an informed consent process with a medical provider if they opt out. ChE depression of 20 percent or more from baseline requires the employer to perform a work practice evaluation and intervene to reduce any chances of further exposure. Depression of 30 percent or more in RBC CheE or 40 percent or more in serum ChE requires the employee to be removed from handling until their levels return to within 20 percent of baseline. In addition to monitoring and enforcement, the program also provides follow-up services for those with significant ChE depression and consultation services to employers to help them reduce further exposures, reduce possible risk of long-term adverse health effects, and decrease take-home exposures. These follow-up efforts are offered to employees and employers even if they no longer participate in the program. The program has led to increased knowledge on the use of these pesticides, increased hazard awareness, changes in pest management practices, greater access to medical services, and more informed diagnoses and treatment of pesticide-related illness. Additionally, the findings of this program are being integrated into a state-wide pesticide handler training program.

Discussion

A participant requested clarification on the percentage of employees declining participation with the program. Dr. Furman replied that the program is averaging a 12 percent declination rate, and there has been a sustained participation during the past 3 years.

A participant asked about the change in minimum hours of handling for workers to be tested. Dr. Furman responded that the initial recommendation by the researchers was 30 hours, but political intervention arrived at the 50-hour minimum. No significant correlations were found between handling hours and ChE depression after 3 years of testing; however, a legal suit forced the issue, and the hours have been changed to the initial recommended minimum of 30.

A participant asked if OP pesticides are being replaced by other pesticides. Dr. Furman answered that part of the program follow-up procedures capture this information, and a significant number of employers who were previously engaged in the program have switched to safer products.

A participant asked about published findings that demonstrate that these types of interventions lead to health outcomes and behavior change. Dr. Furman replied that research reports for each of the 3 years are posted at http://www.lni.wa.gov/Safety/Topics/AtoZ/Cholinesterase/default.asp.

Biomarkers of Pesticide Exposure: Lessons for Children in Agricultural Communities
Catherine Karr, University of Washington

Dr. Karr discussed the utility of ChE testing in clinical practice as a diagnostic tool for identifying pesticide poisoning in children. Although significant exposure occurs in agricultural workplaces, playgrounds, and orchards in agricultural Pacific Northwest, poisoning is not always considered by pediatricians. When it is suspected, it is difficult to interpret cholinesterase tests because there often is no baseline with which to compare it. Additionally, while cholinesterase tests are useful for diagnosing or confirming OP poisoning, there is no test for detecting chronic exposure, which may have health implications. In addition, while the symptoms in classic adult occupational poisoning have been

identified, in children they are not so clear, making diagnoses in children more difficult. Overexposed children are much more likely to manifest central nervous system (CNS) symptoms, and very young children cannot verbalize these symptoms and often present with subtle signs. Children are more likely to develop seizures as a result of OP poisoning. The classic hypersecretion (e.g., tearing, diarrhea, urinary incontinence, sweating) seen in adults often is not seen in children, and the poisoning is misdiagnosed as a more common infectious illness, such as flu or gastroenteritis.

Although there is great variability in the normal population, ChE testing still can play a role in the context of post-exposure followup testing, which can discern if there were significant changes in an individual. ChE testing is useful for acute OP poisoning via the cholinergic pathway, but there is evidence that neurodevelopmental toxicity can occur by alternate mechanisms. *In vivo* embryonic and neonatal rat models and neuronal rat cell line studies show effects seen throughout brain regions, including those with very little cholinergic innervation. Cell loss and apoptosis occurs immediately after exposure, neural deficits appear later in adolescent and adult animals, brain cell numbers are reduced, and neurite projections and synaptic communications are disrupted. This translates into a disruption of signaling pathways that are very important for normal neurological development in children and immature animals, and it is thought that these may underlie some of these observations in the epidemiological studies, such as effects on performance, attention, and behavior in humans.

A targeted survey in Washington State was conducted of healthcare providers and *promotoras* (lay health providers) who serve farm families and farmworkers in agricultural regions. Results showed that 49 percent of respondents had received any training on pesticides and health, and 22 percent had received child-specific information on pesticides and health. Based on these findings, the Washington PEHSU, in collaboration with the Pacific Northwest Agricultural Safety and Health Center, developed a Web-based CME product, "OP Pesticides and Child Health: A Primer for Healthcare Providers," which includes translation of findings from the NIEHS/EPA CEHCs regarding chronic toxicity. Additionally, in-person training has been conducted for *promotoras* who did not show an interest in the Web product.

Dr. Karr ended her presentation by raising some questions to motivate moving beyond ChE testing and focusing further on noncholinergic endpoints. She indicated the need for more rapid tests that can be used in clinical practice to confirm acute exposure to OPs and help provide indication for preventive guidance to parents. Finally, she urged participants to begin thinking about OP exposures in children with neurodevelopmental disabilities (e.g., ADHD or autism). In addition to potential etiologic relationships, these subgroups may be particularly vulnerable to the toxicity of OP exposure.

Integrated Pest Management in New York City Public Housing
Frederica Perera, Columbia University

Dr. Perera outlined some of the studies being conducted at the Columbia Center for Children's Environmental Health. Based on high levels of CPF exposure, as measured by plasma concentrations in mothers and newborns in the Columbia cohort, the researchers instituted: (1) an educational intervention with newsletters to members of the cohort and community; (2) an integrated pest management (IPM) project; and (3) an effort to develop an early life reference dose (RfD) of OPs. Levels of use of CPF are down, following the EPA phaseout for residential use, and the Columbia study recorded a significant drop in plasma levels of chlorpyrifos in umbilical cord blood. High prenatal exposure, as measured by elevated umbilical cord levels, was associated with a decrease in developmental scores at 3 years using the Bayley Scales at age 3, and at 5 years using the WPPSI. The adverse effect was observed with the highest concentrations of CPF occurring before the EPA ban.

The IPM intervention was formed through a partnership with the NYC Department of Health and Mental Hygiene and the NYC Housing Authority. It involved professional cleaning to remove food sources and

cockroach frass (fecal matter) in kitchens and bathrooms of 194 intervention and 129 control apartments. Following intervention, cockroach populations were decreased, allergens were significantly decreased, and nearly a 50 percent decrease was seen in the use of bombs and sprays by the IPM group. Effects on asthma symptoms are being evaluated. Based on these results, the housing authority is expanding the IPM to other building sites in NYC.

Use of Biomarkers and Physiologically Based Pharmacokinetic (PBPK) Modeling in Risk Analysis for Developmental Effects of Chlorpyrifos
Robin Whyatt, Columbia University

The newly received EPA Science To Achieve Results grant is designed to use the exposure response relationship seen in the Columbia study and, using PBPK modeling, derive an RfD dose for CPF based on the developmental effects of the maternal dose during pregnancy. The study approach is enhancing an already-developed CPF PBPK model to estimate dosimetry during pregnancy. It will incorporate human interindividual variability in key metabolic parameters, based in part on newer metabolism measurements in human livers and exposure time pattern data to convert observed CPF levels in cord and maternal blood to both intake doses and internal concentrations of active metabolite for benchmark modeling. The specific measurements to be used from the Columbia study include cord blood levels of CPF at delivery, maternal blood levels 1–2 days following delivery, indoor and personal air levels of CPF, and urinary levels of a CPF metabolite (TCPY). These data will be used with NHANES data to estimate what percentage of the population in the United States has detectable levels of CPF in their urine. More information on this study can be found at http://www.mailman.hs.columbia.edu/ccceh/about.html.

Discussion

A representative from the New England Asthma Regional Council offered information about research on the effectiveness of IPM, particularly for homes in low-income populations, that was translated into policies and procedures. In conjunction with HUD, the New England Council will be releasing a DVD for tenants and housing managers on how to use IPM. In addition, over the next few months, the Council will be releasing a toolkit for policy-makers on how to promote IPM from a policy level on federal, state, and local levels and a toolkit for housing managers on how to work with their tenants to put IPM into place using the Boston Housing Authority's successful model. More information can be found at the New England Asthma Regional Council Web Site (http://www.asthmaregionalcouncil.org).

SESSION II: PHTHALATES EXPOSURE IN CHILDHOOD: IS THERE EVIDENCE OF HARM?
Chair: Maida P. Galvez, Mount Sinai School of Medicine

The goals of this presentation were to describe phthalate exposure levels in pregnant women, toddlers, and school age children; identify important sources of exposure in these populations; and understand the known and potential health outcomes. Based on exposure studies in animals, there is evidence for adverse birth outcomes, from fetal demise to modulation of gestational age to adverse impacts on the male reproductive system, including decreased anogenital distance in male infants and decreased testicular function and fertility. Phthalates are found in a wide range of products, and there is potential for inhalation, ingestion, and dermal absorption, the major pathways of exposure. The premature baby population, which is exposed through medical IV tubing in intensive care units (ICUs), is considered highly sensitive to exposures. The potential of phthalates to act as endocrine disruptors is a concern, based on animal studies and a small but growing body of evidence in human studies.

Legislation banning phthalate use in children's toys was first implemented in the European Union, and subsequent media reports raised parental anxiety about a number of items in their homes that may potentially expose their children. Primary pediatric physicians are in a difficult position, faced with

clinical questions that are difficult to answer. Pediatricians receive limited training in CEH in medical school, have limited knowledge of emerging exposures of concern such as phthalates, and are exposed to conflicting messages in the media. Dr. Galvez concluded her presentation by introducing the speakers for this session.

Phthalate Exposures During Pregnancy
Robin Whyatt, Columbia University

The Columbia Center for Children's Environmental Health is conducting research on phthalate exposure during pregnancy from inner city communities in NYC because it is a universal issue in the United States. A number of phthalates are endocrine disruptors, including those acting as anti-androgens. Experimental and epidemiological evidence indicates that a number of phthalates are reproductive toxicants and are associated with malformation in the developing male reproductive tract and other reproductive outcomes. Recent epidemiologic data indicate that prenatal exposure may modulate the timing of labor.

The specific aims of the research are to: (1) characterize phthalate exposures during pregnancy among NYC African American and Dominican women (n = 350); (2) examine effects of prenatal phthalate exposures on modulation of gene expression in placental tissue; and (3) examine the effects of prenatal phthalate exposure on gestational age and fetal growth. This cohort is comprised of 300 mother-newborn pairs from a larger 725-person cohort and has the same inclusion/exclusion residential criteria as the full cohort. Phthalates were measured in personal air samples during pregnancy, and biological samples and gene expression were examined. The conclusions of this study are that phthalate exposures are widespread among NYC African Americans and Dominicans during pregnancy; phthalates are detected in 85–100 percent of indoor air, personal air and maternal urine samples; indoor air levels appear stable over time and are significantly correlated with personal air levels in most cases; there is a significant correlation between air and urine levels in two phthalates; and di(2-ethylhexyl)phthalate (DEHP) exposures may be modulating gestational age.

Discussion

A participant asked about data on the time of urine collection in relation to when the mothers may have been using cosmetics. Dr. Whyatt responded that these data have not been analyzed for diurnal variability.

A participant asked about air fresheners, because many of them contain phthalates, including those labeled as "all natural." Dr. Whyatt indicated that they collected extensive questionnaire data related to product use, but the data have not been analyzed in relation to outcome measures. There is such variability between products and within brands of products that the questionnaires may not be capturing the intended information.

A participant asked if the study will be expanded beyond minority populations. Dr. Whyatt explained that there are no plans to extend the study beyond the Center's cohort, but phthalate studies are being planned for the Krakow cohort.

Infant Phthalate Exposures and Potential Developmental Impacts
Sheela Sathyanarayana, University of Washington

The University of Washington and Northwest PEHSU, in concert with the University of Rochester, examined data from the Study for Future Families, a mother-baby cohort study in Missouri, California, and Minnesota, to determine whether infant personal care product use was associated with urine pthalate concentrations and whether maternal phthalate exposure was associated with developmental outcomes in infants. The demographic characteristics of the cohort study included 163 infants ages 2–24 months, with

an even distribution between genders; a racial profile of 80 percent white and 11 percent Hispanic and Latino; high socioeconomic status; 50 percent of participants from Minnesota and 25 percent each from Missouri and California; and 91 percent of families reporting health insurance. Infant urine samples were tested for detectable concentrations of nine known phthalate metabolites, and all infants samples contained at least one detectable phthalate metabolite. More than 80 percent had detectable concentrations for seven of the metabolites, and over 50 percent showed detectable concentrations for all nine. These concentrations are similar to or lower than children 6–11 years of age in NHANES data. This may be because younger children are not as involved in their environments unless they are walking or crawling; therefore, most of their exposures come from their parents and diet. Metabolites were measured to test for an association with reported use of a variety of baby products, including baby powder, baby lotion, baby shampoo, diaper cream, and baby wipes. Infants whose mothers reported using baby lotion, shampoo, and powder showed increases in urine phthalate metabolites compared to infants who were not exposed. Results of this study suggest that phthalate exposure in infants is widespread, distribution is varied in infants, and dermally applied baby care products may significantly contribute to infant phthalate body burden. Reported exposure to baby lotion, baby powder, and baby shampoo was significantly associated with increased urinary concentrations of monoethyl (MEP), monobutyl (MMP), and monoisobutyl, and the associations were stronger in younger infants.

To determine whether maternal phthalate exposure was associated with developmental outcomes in infants, the researchers examined anogenital distance as a marker in infants because of animal model evidence that abnormal anogenital distance is associated with phthalate exposure and genital tract abnormalities. Exposure in rodents is related to shorter anogenital distance, impaired testicular descent, hypospadia, low sperm count, and sometimes testicular tumors. Because short anogenital distance is the most important marker, the researchers first created a model estimating the standard for distance associated with age and weight. The phthalates associated with the shorter distance included MBP, MEP, and DEHP phthalate metabolites. Increasing phthalate metabolite concentrations were associated with decreasing anogenital distance in a dose-response manner. The clinical implications of these findings associated exposure with a shorter anogenital distance and suggest that phthalates may act through an endocrine disrupting mechanism to affect hormonal development of genital structures. Researchers also found an association between increased phthalate metabolite concentrations, decreased testicular descent, and smaller penile volume, but these were not significant. Further research is needed to determine if distance is a marker of abnormal male reproductive development in humans.

Discussion

A participant asked why an earlier study did not find a metabolite effect. Dr. Sathyanarayana indicated that the sample size was not large enough for that study, and that they had used the anogenital index, which was not an appropriate statistical model for predicting the expected distance. Based on feedback to the earlier study regarding these issues, the research team for this study constructed a new age- and weight-based model for conducting analyses, but the results of this study have not yet been published.

A participant requested clarification on the hormone involved in these studies and asked if phthalates could be tested for with amniocentesis. Dr. Sathyanarayana explained that the theory is that androgen decreases overall *in utero* as a result of exposure, but it is difficult to determine whether it is testosterone or some other hormone. One problem with using amniocentesis for phthalate detection is that the procedure is not a standard test, and it is usually carried out on high-risk pregnancies, decreasing its feasibility as an accurate marker for the general population.

A participant asked about the specific components of the baby products that are associated with phthalate exposures. Dr. Sathyanarayana replied that there is no method to determine the components because there are no labeling requirements for chemicals, which is why studies that identify phthalate-associated

products are important. California is beginning to mandate disclosure of phthalates and other reproductive and carcinogenic compounds for products sold in that state. In addition, phthalates are plasticizers that help bind other compounds together, so it is possible that the manufacturing process may be responsible, not necessarily the product components.

A participant asked whether synthetic hormone use during pregnancy was controlled for and whether any of the male infants had hypospadias or cryptorchidism. Dr. Sathyanarayana responded that the mothers were asked about hormone use during pregnancy, and all reported no use. None of the boys had frank phenotypic abnormalities.

A participant asked whether the U.S. Food and Drug Administration (FDA) had examined this study and set a maximum level in all these products. Dr. Sathyanarayana answered that the FDA has evaluated phthalates previously and has not set any concentration levels, but as the results of this study have not been published, the FDA has not examined the data. The FDA did register a warning to health care providers that concentrations might be high in neonatal ICUs because of IV tubing, but the agency has not set any mandatory requirements for testing or RfDs. EPA will be undertaking a larger review soon. Another participant clarified that the FDA receives advice from a separate industry-run organization but does not have authority over cosmetic products. The European Union has banned phthalates in many of these products, which may be pushing U.S. industries to produce phthalate-free products because they market to the European Union. One cautionary note regarding phthalate-free products on the market is that consumer companies still find detectable levels in these products; there must be a higher level of enforcement at some point.

Inner City Toxicants, Child Growth and Development
Mary Wolff, Mount Sinai School of Medicine

Dr. Wolff mentioned a monograph published by *Environmental Health Perspectives* in the 1970s that proved phthalates are not toxic. The issue now is that the levels of phthalates are very high and that some of the newer generations of bioassays have revealed hormonal effects. She summarized preliminary data from the Mt. Sinai birth cohort, a multiracial cohort that included 100 boys and 300 girls from 6–8 years of age. The researchers conducted exposure assessments in mothers during their third trimesters and outcome measurements of the children. In a cohort of school-age children, levels and variability have been assessed to determine feasibility of a single urinary biomarker for these chemicals. Preliminary results showed exposures similar to the Columbia study for MEP. The mothers had higher levels of some phthalate metabolites than the Columbia and NHANES cohorts, but were consistent with NHANES for minorities. Results of temporality studies suggest that some of these biomarkers can be used as predictors of these metabolites for up to 1 year, and of the three families of chemicals studied, phthalates were the most reproducible. The Mt. Sinai team also summed groups of phthalates based on molecular weight and found significant levels of low molecular-weight phthalates among the minority populations and higher molecular weights among whites. Product use questionnaires revealed some borderline associations of the DEHP metabolites with nail polish and hair products, but they were not significant in preliminary data from a small number of subjects.

Because there currently is much interest in body mass index (BMI) and phthalates because of cross-sectional data published by NHANES, the researchers examined gestational age. In relation to phthalate metabolites, the researchers found very weak associations between phthalate exposure and longer gestation. The researchers currently are evaluating these biomarkers with respect to neurodevelopment.

Discussion

Dr. Maida Galvez summarized the presentations before opening the floor to discussion. Phthalate exposures are widespread. In this session, evidence was presented from three different cohorts, ranging from exposures in pregnancy, a particularly vulnerable time period, through early childhood and beyond. The two cohorts of pregnant women from NYC showed similar levels of exposure, despite the fact that the populations were very different in racial and ethnic demographics. This is a contrast to exposures in infancy and early childhood in a predominantly white cohort, with relatively low exposures when compared to the inner city populations. The sources of exposure were varied, from voluntary use of products to contamination of indoor air from dust generated from phthalate products. Through measurement of the available biomarkers, there is now limited evidence from human studies demonstrating possible modulation of gestational age and potential impact on anogenital distance. These cohorts will continue, and effects on body size, particularly BMI and waist-hip ratio; potential associations with asthma; and other developmental outcomes will be examined. What to tell the parents asking for advice is a challenging situation, but it is usually best to give them an action item in the face of clinical uncertainty. Mt. Sinai's Community Outreach Translational Core developed a pocket guide to plastics for easy reference. In the absence of legislation mandating correct labeling of products, these wallet-size cards can help families identify phthalate-containing products. In general, the plastics to avoid are labeled 3, 6, and 7 for recycling purposes. The CEH community needs to work together to determine the best health messages to relay to families and what policy issues to advocate.

A participant asked about the Mt. Sinai study participants' access to results. Dr. Wolff explained that participants were provided with summary data when available on request. Families also would be told how their levels compared to the entire study population on request, but no individual data would be shared with the participants. The researchers were prepared to respond to questions through a potential collaboration with the PEHSUs, but no requests have been received. Study participants did express concern that environmental factors may be related to long-term health outcomes such as obesity and puberty. The same question was posed to Dr. Sathyanarayana, who replied that study participants received a one-page handout of the previously published study because the current study results are not complete. Dr. Wolff's team will not be submitting individual data, but its cohort was educated about group findings versus individual findings at enrollment. The participants were told that if harm is found on a group basis, the entire cohort would be notified about those findings and receive information on what they could do on an individual basis to reduce the exposure.

A participant asked about the issue of potential "sleeper biomarkers" that have been identified in animal models but have not been tested in humans. One of the session speakers answered that some studies are underway, and an issue remains regarding validation involved in anthropological types of markers, such as anogenital distance. Some clinicians successfully use the finger ration with certain conditions (autism, etc.) and the results are very interesting but difficult to measure scientifically. Another participant added that a new mulitcenter cohort study is underway that uses anogenital distance to examine dysmorphology.

A participant asked for clarification on what the focus was of the pocket guide. Dr. Wolff explained that the pocket guide identifies plastics that are associated with phthalates and other chemical exposures from food packaging. Because dietary sources are considered to be the major pathway of phthalate exposure, the card also includes some information about leaching.

A participant questioned the usefulness of cautioning the public about phthalate-free products, because although organic food contains detectable levels of pesticides, it is still considered better because the levels are relatively lower. Dr. Galvez indicated that, from the limited consumer product testing, phthalate-free products do contain relatively lower levels of phthalates, but the study participants received cautioning as a process of full disclosure so they could make informed decisions.

A participant asked, given the relatively small effect size in much of the presented data regarding which plastic containers or which kind of fragrant-free products to use, where clinicians should put this issue on the list of priorities when discussing hazards with parents. A session speaker explained that, although there is no definitive answer regarding humans, it is not a good idea to put phthalates on the bottom of the priority list in a clinic setting. Animal toxicity data exist, and more studies are planned. Full disclosure about what is known and what is not known is better than no disclosure.

A participant commented that the benefit of the CEHCs is that they bring clinicians and the community together in an academic setting where there is integration of mechanistic and animal scientists. Anogenital distance studies were prompted by animal studies. Increased collaboration between animal scientists and human health and environmental researchers will increase opportunities for the CEH community to learn about biomarkers. Perhaps more of the animal models will be adapted to human studies for more definitive purposes.

A participant asked if there is a safer substitute for phthalates. A session speaker explained that there are other plasticizers and other technologies that do not use a plasticizer, but there are enormous data gaps on the substitutes. Nonplasticizers do not leach as much as plasticizers, so that may be a significant advantage. Dr. Wolff's team is preparing to submit a paper examining substitutions in the neonatal ICU because that is where exposures are higher. The paper examines every substitute to date and what is known about them.

SESSION III: THE EVOLVING SCIENCE AND PRACTICE OF ENVIRONMENTAL MANAGEMENT FOR ASTHMA PREVENTION AND CARE

Co-Chairs: Kimberly Gray, NIEHS, and Leyla E. McCurdy, National Environmental Education Foundation

Improving Asthma Outcomes: 2007 NAEPP Guidelines Focus Attention on Education and Environmental Interventions

David Rowson, U.S. EPA

Mr. Rowson provided an overview of the 2007 National Asthma Education and Prevention Program **(**NAEPP) Guidelines for the diagnosis and management of asthma. The new guidelines focus on monitoring asthma control as the goal for asthma therapy and distinguishing between asthma severity and monitoring asthma control. Treatment should be initiated based on severity assessment and then adjusted based on control. There is a new focus on impairment and risk. Impairment includes the frequency and intensity of symptoms, low lung function, and activity limitations. Future risk includes the risks of exacerbation, progressive loss of lung function, or adverse side effects from medications. Clinicians need to increase the consistency of asthma monitoring, assessment, and care. There are new modifications to the step-wise approach to long-term management of asthma. Treatment is partitioned into three different age groups, and there are six specific steps of care that span from intermittent to severe. The new guidelines incorporate updated approaches to patient education and control of environmental factors and co-morbid conditions that affect asthma. Finally, there are modifications to treatment strategies for managing and classifying asthma exacerbations. The guidelines are built around a framework of four essential components that include: (1) assessment and monitoring of asthma severity and control; (2) education for a partnership in asthma care; (3) control of environmental factors and co-morbid conditions; and (4) medications.

The new guidelines have increased attention on self-management and education of family and individuals regarding the environment, noting many potential sites for asthma education and care: homes, schools, and community settings. The guidelines recommend patients receive education in an integrated,

multifaceted method in multiple settings. Written action plans are highlighted as a central component of asthma care, with a focus on multicultural ethnic factors and health literacy to enhance adherence to physician advice and medication regimens. Provider education also is highlighted as an essential component. Automated assistance helps clinicians to adhere to the guidelines, so these systems are being put into place to support them. The most important actions patients should take include avoiding environmental triggers that exacerbate symptoms and cause asthma attacks. The guidelines list potential triggers and a series of steps to follow for controlling individual environments. The guidelines recommend testing individuals for sensitivities so that intervention steps can be tailored to individual needs. The guidelines also stress the importance of an active lifestyle. With proper control, exercise should be possible; if an individual cannot exercise because of symptoms, that should be considered a benchmark for a change in treatment.

Although asthma rates appear to be steadying nationally, they remain at an all-time high, and there are significant disparities in morbidity and mortality. *Healthy People 2010* goals contain a range of important indicators; some of those goals are close to being reached, whereas others are farther off. The new guidelines highlight critical areas to help reach those goals. For instance, the guidelines suggest more written asthma action plans, increasing adherence with treatment, and controlling for environmental triggers—all goals of *HP2010*.

To support the delivery of evidence-based care at the community level, EPA is supporting the Communities in Action for Asthma Friendly Environments Network (CAAFE). Grounded in the results of the Asthma Health Outcomes Project and conducted by the University of Michigan, a centerpiece of CAAFE is the Change Package—a compendium of practical, day-to-day best practices program strategies that deliver positive health outcomes. CAAFE is supported by an interactive Web site developed to facilitate real-time learning and sharing of best practices, as well as an annual National Asthma Forum. More information on the CAAFE and the National Asthma Forum can be found at http://www.asthmacommunitynetwork.org.

Prenatal and Early Postnatal Exposures and Asthma Risk—How?
Rachel Miller, Columbia University

Dr. Miller provided a review of mechanistic data that begin to address the question of how prenatal and postnatal exposures may affect asthma risk. Asthma is a complex disease mediated by genetic predisposition, environmental exposures, and host factors (e.g., obesity, psychosocial issues, infections). Prenatal and early postnatal exposure (e.g., traffic, diesel, roaches, dust mite allergens, pollens) can modify asthma risk, and there is evidence that exposure during pregnancy is very important in modifying or protecting for asthma. A review of epidemiologic data shows that prenatal exposure can affect asthma risk, and the strongest evidence is related to prenatal exposure to environmental tobacco smoke (ETS). Prenatal ETS exposure is associated with impaired respiratory function, transient wheeze, asthma, and respiratory infections in infants and young children. Additional exposures during pregnancy that appear to be associated with an increased risk of asthma include low maternal intake of vitamin E and zinc during pregnancy, antibiotic use, and several types of maternal infection. Furthermore, respiratory infection during pregnancy has been shown to be an independent factor that may increase later asthma risk. Recent data also suggest that ambient air pollution and polycyclic aromatic hydrocarbons may increase risk later on in life for children. Early postnatal exposure to traffic and combustion-related pollutants has been associated with both dust mite sensitization and impaired pulmonary function in later childhood. There may be, however, other exposures that may help protect against asthma or wheezing illness. These include maternal intake of probiotics during pregnancy, higher birth order, and exposure to dogs and cats during the first year of life.

A review of possible relevant mechanisms implicates immune-mediated processes and epigenetics. For example, multiple studies have shown that cytokine levels differ at birth among those children who may be more likely to develop allergy and wheeze. There also is evidence that the fetus can generate an independent immune response to proteins or allergens that the mother experiences in pregnancy. Epigenetic changes refer to those that influence gene expression without any change in the DNA sequence. They may influence gene expression differentially throughout a lifespan. In conclusion, prenatal and early postnatal exposures do impact risk for later asthma, but more cohort-driven mechanistic research must be done.

The Center for Childhood Asthma in the Urban Environment
Elizabeth Matsui, Johns Hopkins Hospital

Dr. Matsui, co-investigator for the Center for Childhood Asthma in the Urban Environment, provided results of some of the Center's studies. The Center conducted studies of indoor pollutants and asthma in Baltimore row homes. Preliminary data showed no differences between asthmatic children and controls and no differences in levels of other common allergens. Because mouse allergen levels were higher in these homes than in other cities, the researchers investigated whether the allergens were responsible for asthma morbidity among children with asthma who were also mouse sensitized; the results were striking. Across a multitude of asthma outcomes, there was a significant increase in asthma symptoms in children who were mouse sensitized and highly exposed. The findings of this study are an important reminder to conduct community or regional studies in addition to multicenter studies because local signals can be lost when combining data from different regions. The researchers examined indoor pollutants in children's bedrooms; although children with asthma had similar levels of exposure as control children, the causality of environmental exposure to asthma development cannot be ruled out because prevalence rates of asthma in this population were between 25 and 30 percent. In addition, the researchers have not conducted studies of the same asthmatic children in different environments. Surprisingly, indoor pollutant levels are much higher than outdoor levels, and the indoor exposure is likely to play a critical role in the development of asthma, which is compounded by the fact that children today spend more time indoors than outdoors. The researchers also looked at indoor particulate matter (PM) exposure in relation to poorer outcomes in children with asthma and found a strong signal for coarse PM. Coarse PM fraction in bedrooms increased risk in the number of days of symptoms and beta agonist use in children. There were some signals with fine PM also, but results were not as consistent as results with coarse PM.

Clinical Experience with the Environmental Management of Asthma and the NAEPP Expert Report 2007
James M. Seltzer, University of California at Irvine

Dr. Seltzer presented an overview of his experiences as an allergist/immunologist caring for children with asthma and as a PEHSU Director, who must respond to inquiries from families regarding symptoms and the role of environmental factors in allergy and asthma. As a clinician, he sees patients with environmentally induced illnesses, including asthma, and other allergic disorders. The role of environmental factors as precipitants of allergic disease is not always obvious, especially in children under 5 years of age or where allergens are only one of several types of exacerbating factors. This applies not only to the primary care doctor, but also to the allergist/immunologist who possesses particular expertise in determining the spectrum of allergic sensitivity for a given patient. Allergy testing, especially skin testing, can help identify potentially relevant allergens, whether or not they were suspected from the medical history. Environmental factors can easily be missed and should be confirmed or ruled out in each patient with the possibility of health problems that might be related to environmental exposures. As a PEHSU Director, Dr. Seltzer responds to inquiries from parents, schools, the media, and other entities or persons regarding environmental factors, and the questions typically are focused on high-profile exposures, such as mold and diesel, but not other common exacerbants, such as dust mite or cockroaches.

He discussed the significance of the assessment of environmental factors in each clinical case; the importance of taking a careful, extensive history; determining if exposures are relevant; and, if relevant, teaching the parent and child how to reduce exposure and to monitor future exposures and clinical responses to exposure reduction. Reducing factors contributing to asthma severity can be accomplished by environmental control measures for clinically relevant precipitants, such as reducing sources and reservoirs of allergens and airway irritants in the child's environment. Dr. Seltzer also discussed the hygiene hypothesis: early life exposures to certain allergens may provide protection from the development of asthma and other allergic disorders later in life. Although early life exposure appears to have more effect than exposure later, there are not enough data to recommend early exposure as a method to reduce future risk. Education is important. Patients and physicians can learn how environmental factors affect children's health, thereby improving recognition of these disorders as well as how to institute effective environmental control measures. Finally, he outlined the goals of asthma therapy. For control of asthma to be effective, it must be recognized, its nature defined, and the roles of all relevant environmental factors identified and addressed for any given child. With successful environmental control, pharmaceutical therapy and, if indicated, immunotherapy (desensitization), the need for clinician intervention ultimately can be minimized. Lastly, to be effective, asthma therapy must be practical, affordable, and convenient.

Discussion

A participant asked Dr. Matsui whether any composition studies have been done to identify PM. The Johns Hopkins Children's Center had examined the composition of ambient PM previously, but composition studies for indoor PM have yet to be performed. Animal particles, however, are much more readily airborne than insect particles. It will be difficult to measure cockroach PM, because these larger particles settle quickly and it is difficult to disrupt the dust to become airborne. The other session speakers contributed to the discussion in regard to outdoor air pollution, including pollen, mold, traffic emissions, and ozone, and all agreed that individual sensitivities and time of day need to be considered. Ozone levels generally are highest during middle to late afternoon, and some outdoor molds sporulate at different times of the day. Additionally, there is difficulty separating the effects of indoor pollutants from the effects of outdoor air pollutants. Often, allergen and irritant concentrations are higher indoors. The complexity of allergen and pollutant exposures, which occur in both indoor and outdoor environments, combined with individual differences in susceptibility to these exposures, makes it challenging to provide guidance regarding optimal environmental control measures to patients. In fact, recommendations in the new NAEPP guidelines are more general than specific for this very reason. It was mentioned that the guidelines are directed at the delivery of asthma care and what clinicians should do when interacting with and educating the patient. EPA regulations affect outdoor triggers but do not regulate indoor exposures, so patients who are advised to reduce particular indoor exposures are responsible for implementing the environmental control practices. For those who are not homeowners, appealing to landlords to make necessary modifications to the home or provide pest extermination is needed. Regarding outdoor exposure to pollutants, ORD is examining school sites and athletic fields near roadways to better understand this issue. A session speaker invited participants to become actively engaged in the process of updating the guidelines, because the guidelines are posted for public comment during development.

A participant asked Dr. Miller for clarification of her lab's work on inhaled allergen and diesel exposure on DNA methylation and immunoglobulin E (IgE) production in mice. The question was whether the exposures in her studies were mixed or single. Dr. Miller responded that the effects on DNA methylation and IgE production in mice were measured after combined exposures to the mold *Aspergillus* and diesel administered chronically by inhalation over 3 weeks.

A participant asked Dr. Seltzer whether there is a lower boundary for which to diagnose asthma in children and what the place of skin testing is in immunotherapy. Dr. Seltzer responded that the diagnosis

of asthma in a 1- or 2-year-old is problematic, because young children typically have recurring episodes of wheezing with viral infections. Children in families where other members have asthma or allergic disorders are at increased risk of developing asthma or recurring reactive airway disease. Although these and other risk factors can be identified, in a given child it is more a function of how often symptoms occur, what they are associated with, and how persistent they are that helps to make the diagnosis. Among 1- and 2-year-olds, although a wheezing child may have asthma, the clinician must be concerned about other diagnoses associated with recurring wheeze as well. Treatment usually involves a therapeutic trial of bronchodilator, with or without inhaled steroids delivered by nebulizer or a pediatric mask attached to a spacer, depending upon age and ability of the child to use a spacer. As far as skin testing, Dr. Seltzer has tested down to 6 months. Typically, there is less skin reactivity and less IgE in younger children, but testing can be performed at any time, even at birth.

SESSION IV: EARLY LIFE EXPOSURES TO METALS AND NEUROTOXIC OUTCOMES
Co-Chairs: Isaac Pessah, University of California at Davis, and Nigel Fields, U.S. EPA

Neurodevelopment, Autism, and Mercury: Biomarkers and Epidemiologic Approaches
Irva Hertz-Piciotto, University of California at Davis

Dr. Hertz-Piciotto discussed mercury and its relation to neurodevelopment and autism. The effects of mercury are complex, but it is known to cause developmental delays and deficits in the mental, muscular, visual/spatial, social, and sensory domains. Autism is a pervasive developmental disorder characterized by deficits in three domains: (1) social interaction, manifested in lack of eye contact, lack of response to name, failure to engage in joint attention, and so forth; (2) communications/language, including lack of language or odd use of language; and (3) repetitive behaviors or restricted interests. The current prevalence estimate of autism is about 1 case in 150 individuals and the ratio of males to females is 4:1. There is a strong genetic component to autism, but environment also may play a role. Autism is a multifactorial condition with a wide severity curve, yielding high-functioning individuals and individuals who cannot function independently. Historically, autism was thought to be a result of poor parenting. It now is generally accepted that it is a neuropathologic condition, but this legacy has led to a general mistrust of the medical community by parent and advocacy communities. Brain imaging studies have shown that facial recognition processing is one of the most affected areas and a hallmark of the condition. When looking at faces, areas of the brain that are used in typically developing individuals are much less activated in autistic individuals, and there is no one area of the brain that is affected by autism. Lesions from autopsies are very widespread; this suggests that the insults occur very early in development, most likely during gestation. The most replicated finding anatomically is the loss of Purkinje cells.

In the 1950s and 1970s, several high-profile mercury contamination episodes led to mass poisonings in Iraq and Minamata Bay. Children exposed *in utero* appeared to be the most vulnerable. Severe impairments, deficits, seizures, abnormal neuronal migration, and disorganized cerebral cortex were seen in some autopsies. Studies followed birth cohorts in communities with high fish consumption. More than 1,000 mother-child pairs in the Faroe Islands were used to relate development to prenatal exposure, which was measured through maternal hair, cord blood, and cord tissue levels. The results showed deficits in attention, language, memory, and visual/special domains in children at 7 years. Similar findings and motor deficits were evident at age 14. The Seychelles Islands study found no deficits, and it has been difficult to reconcile the conflicting findings. Project VIVA (Venue-Intensive Vaccines for Adults), which involved maternal hair mercury measurements, controlled for the benefits of fish consumption. Results clearly showed the benefits of fish consumption, and harm from mercury was measured in a dose-response fashion. Dental amalgams are a source of an inorganic form of mercury, which is broken down into the methylated form and travels more easily across the blood-brain barrier. A randomized study examining children who received mercury amalgams found no mental deficits, suggesting that

susceptibility to mercury neurodevelopmental toxicity may be greater when exposure occurs prenatally as compared with mid-childhood.

Studies regarding the link between mercury and autism are mixed and controversial. Several studies were conducted on thimerasol, a vaccine preservative introduced in the 1930s. Thimerasol breaks down into ethyl mercury and thiosalicylate. It was removed from many child vaccines in 2002 but remains in some vaccines (e.g., hepatitis B virus and influenza). Most studies examining the link between thimerasol and autism have been in the form of ecologic studies comparing before and after removal or introduction. Very few studies have individual data, and multiple factors related to better diagnosis make the data difficult to interpret. Vaccines, however, are not the only source of mercury. Home sources can include nasal sprays, contact lens solutions, ear wax removal products, damaged batteries and light bulbs, and skin lightening creams.

Dr. Hertz-Piciotto ended her discussion by presenting an overview of the Childhood Autism Risks from Genetics and the Environment (CHARGE) Study, which is examining the causes and contributing factors of childhood autism risk and the mechanisms of susceptibility, including those that are genomic, immunologic, and metabolic. Many possible mechanisms may affect neuronal maturation, regulatory genes, immune signaling, and endocrine processes. She discussed the catchment area, assessment measures, study design and laboratory methods, and some preliminary results. A multiple linear regression model was used to predict blood mercury. Preliminary findings showed that fish consumption is predictive of mercury, and the use of nasal spray or ear wax removers or amalgam fillings was associated with blood mercury level. There were no associations found with autism.

Future work will include multivariate analyses on baby hair locks, 483 newborn blood spots, and mothers' hair that may represent the prenatal period. Other subsets will be analyzed regarding the heterogeneity, metabolizing genes, and xenobiotics that may affect the immune system.

Genetic and Social Modifiers in Environmental Neuroepidemiology: The Role of Context in Chemical Exposure

Robert Wright, Harvard School of Public Health

Dr. Wright discussed the variance found in studies of chemical exposure and health outcomes and possible explanations for the different susceptibilities to certain neurotoxicants. A broad biological framework for the reasons children are more biologically susceptible was presented. Fundamentally, because the CNS is developing, there is ongoing activity (largely absent in adults) on generating cells, differentiating cells, and cell migration. Finally, those processes that determine synaptic architecture and the ability to develop acquired memory are dominant during early childhood. Environmental stimuli drive whether a given synapse is kept or regresses. This is a form of natural selection and mimics evolution. Synapses that serve an adaptive purpose are preferentially kept, and those that do not, regress. Environmental chemicals may interrupt these processes and send them down different developmental pathways. For example, at low doses, lead causes neurons to fire in a stochastic fashion, thereby mimicking inappropriate environmental stimuli and the natural process of natural selection for synapses. Over time, the resulting underlying synaptic architecture with prolonged exposure to toxic chemicals will be less efficient. Like chemicals, social factors can be either maladaptive or adaptive. Neurohormones such as cortisol are critical to synaptogenesis, and their metabolism changes in response to chronic stress. Chronic stress, which is a nonchemical toxicant, is known to impair memory and learning capacity. Because both chronic stress and lead share properties that can modify synaptogenesis, the joint or sequential presence of lead and stress can be interactive. If instead of being stressful, social factors are adaptive, animal studies demonstrate they will mitigate the effects of lead. On the other hand, if they are maladaptive (i.e., produce stress), they may increase its toxicity. There may be ways to treat lead toxicity beyond chelation. In animal studies, an enriched environment appears to mitigate the effects of lead

poisoning. Following lead poisoning, animals that are socialized perform better than those in isolation (stress environment). Self-esteem also may modify the effect of lead, as indicated by the results of one human study. Maternal self-esteem is not stress, but it may be considered a buffer to chronic stress. Mothers with higher self-esteem develop adaptive responses to chronic stress. Another pilot study in humans showed that teens exposed to prenatal tobacco smoke and high levels of exposure to violence as children (i.e., neurotoxicant and stressor) had worse performance on the Wisconsin Card Sorting Test than teens with high tobacco smoke exposure and low violence exposure.

Genes also regulate synaptic formation. The process of synaptogenesis and synaptic pruning is an interplay between genetics and the environment. At least three studies demonstrate that variants in the *apoE4* gene, which is critical to synaptogenesis, are associated with better cognitive performance. Further, results suggest that the *apoE4* gene variant might have a protective effect against lead. Blood manganese also may be a predictor of neurodevelopment, and there is some evidence that manganese is neurotoxic. Just as exposure does not occur in a social vacuum, it does not occur in a chemical vacuum. Some people exposed to lead also are exposed to other chemicals. Animal studies show that joint exposure is more neurotoxic than individual exposure to either lead or manganese, and human studies are being conducted to address this finding as well.

Ongoing work in Mexico City will examine a birth cohort, in terms of metal mixtures and neurodevelopment and also, with respect to stress as a modifier of lead poisoning, iron-deficiency anemia. The studies will measure prenatal and postnatal contributions, genetic susceptibility, mixtures of metals, and social modifiers and toxicity. The long-term goals are to identify those factors that increase or decrease metal toxicity, understand the biology of metal toxicity to prevent toxicity, and treat toxicity after it has occurred.

Criminal Behavior as a Late Outcome of Early Exposure to Environmental Lead
Kim Dietrich, University of Cincinnati

Data from previous cross-sectional and ecological studies suggest that there is an association between exposure to lead and antisocial behaviors, including delinquency and adult criminality, and data from the Cincinnati Lead Study show an association between prenatal and postnatal exposure and delinquent and criminal behavior. Lead exposure associated with a higher risk for engaging in criminal activity is not a new observation, but it is one that has resurfaced with some recent epidemiological studies. One 1996 study examined bone lead levels and the relationship of child scores on the Achenbach Child Behavior Checklist. Clinically significant high scores on delinquency, aggression, and attention problems were measured in those with high bone lead levels. An observational ecological study examined the correlation between homicide rates and air lead contamination levels in more than 3,000 counties in the United States and found a four-fold increase in homicide in counties with the highest rates of air lead concentrations. Another study reported a statistically significant relationship between trends in sales of leaded gasoline and violent crimes. Strong causal inferences cannot be made with ecological studies, but the results of these studies are very suggestive. Although there are limitations, these pioneering studies clearly suggest an association between environmental lead exposure in childhood and development of behavioral problems.

The Cincinnati Lead Study, funded by NIEHS since 1979, is a prospective longitudinal study that examines early and late effects of childhood lead exposure on growth, development, and neurobehavioral outcomes. There are many lead paint residues in the catchment area of this cohort study, and the researchers have a dense collection of blood lead determinations. Blood is collected prenatally and every 3 months through the first 6–7 years of life. From questionnaire data from study adolescents, there was a statistically significant relationship in terms of the number of total reported delinquent behaviors with respect to their blood lead levels. To determine relationships of early exposure to lead and adult

criminality, criminal arrest records from the State of Ohio were used. Prenatal and 6-year blood lead levels were significantly associated with total arrests, particularly for violent offenses. Lead increases antisocial behavior through the direct route; it affects brain systems that are important in regulating control. Gene-environment interactions also may play a role. It affects behavior through an indirect route as well. Early lead exposure is associated with high rates of school failure and reading disabilities, and children who perform poorly in school are more likely to engage in delinquent and criminal activities. Volumetric magnetic resonance imaging was used to examine the brains of study participants. When looking at the relationship between blood lead levels in these subjects, there was a significant association to gray matter loss in the frontal regions of the brain (i.e., those areas that are involved in attention, executive function, and regulation of social behaviors).

Discussion

A participant asked Dr. Dietrich about separate effects of blood lead at various ages to identify particular ages that are more important, higher late blood levels as an indicator of sustained exposure, and the temporal relation across the lifespan. Dr. Dietrich responded that the Cincinnati study did not address critical periods, but there are many intra-individual tracking data. Blood lead levels remained fairly consistent over the lifespan. When examining intra-individual blood lead levels in relation to IQ, measures of executive function, and criminality, the later the blood lead, the more robust the parameter estimate was in relationship to late outcomes. The higher late blood levels measured could be an accumulated effect, but genetic factors related to excretion or retention of lead in the blood may be involved.

A participant asked Dr. Hertz-Piciotto what advice she gives parents regarding consumption of fish. Dr. Hertz-Piciotto replied that communication is the key issue with respect to complicated messages. There is much variability across fish species, and not all fish have mercury. Several papers show that many fish species do not have high mercury, so it is best to emphasize consumption of low-mercury fish; consuming no fish is counterproductive because of the benefits of fish consumption, including during pregnancy.

A participant asked Dr. Hertz-Piciotto if her research collaborators have observed any co-morbidities between immune responses, mental disorders, and autism spectrum disorders. The participant asked for comment on the biological pathways by which environmental triggers may be causing some susceptibility to immunological responses and mental disorders or whether the environmental triggers are triggering immune responses that causes brain development to go awry, thus exhibiting the phenotype of autism spectrum disorders. Dr. Hertz-Piciotto replied that, in regard to co-morbidities, the research team is examining fatty acid screens in children in the CHARGE Study, and one of the findings is that certain fatty acids appear to be related to disorders that may be dysregulating. There may be a pathway where there is an accumulation of long-chain fatty acids that are not being metabolized to the shorter chain down the pathway. The team also is attempting to identify additional clinical signs of these disorders because they are not always present, indicating that there may be subclinical issues in a subset of the autism cases. One of the intriguing findings is of mothers of children with autism who make antibodies to fetal brain tissue. The CHARGE Study is being followed up by a prospective study called the MARBLES Study, which stands for Markers of Autism Risk in Babies—Learning Early Signs. Mothers of autistic children are being recruited during or before subsequent pregnancies. Regarding the question of biology versus environmental factors, all researchers would like to have insight on this issue.

A participant asked Dr. Wright about environmental treatment in humans, the current marker for stress in his cohort, and chemical water pollution and exposure assessment. Dr. Wright explained that he is not aware of any prospective human studies measuring whether the environment changes outcomes, but cross-sectional studies have been conducted that examine whether the social environment modifies

toxicity of lead or other neurotoxins. Because the brain is developing, there is no reason to think that an insult that occurs at age 2 necessarily has to be permanent. His study is utilizing a variety of questionnaires to assess stress that examine exposure to violence, negative life events, and perceived stress measured longitudinally. He also is collecting biological markers of stress, such as salivary cortisol. By collecting it multiple times over a random day, the diurnal rhythm of mothers during pregnancy and their children at age 2 can be measured. The NCS also is measuring salivary cortisol at various time points throughout the day in addition to collecting questionnaire data. Regarding water pollution, not all forms of lead are bioavailable today but may become bioavailable in the future; therefore, a critical issue in preparing long-term management plans at contaminated sites, particularly mining sites contaminated with the relatively inert lead sulfide, is to ensure that nonbioavailables remain so. As an example of what may develop, he cited the tragedy in Bangladesh in the 1980s. To counter the effects of a diarrhea epidemic, shallow wells were dug for cleaner drinking water. But the digging changed the reducing conditions in the soil so that the nonbioavailable form of arsenic in the soil changed to a bioavailable form, which was dispersed in the ground water and poisoned the population. Land and the environment may be stagnant, but human activity may change the bioavailability of chemicals.

OCTOBER 12, 2007

SESSION V: TRANSPORTATION, THE BUILT ENVIRONMENT, AND CHILDREN'S HEALTH
Moderator: Joanne Rodman, U.S. EPA

Development Patterns and Children's Health
Tim Torma, U.S. EPA

Mr. Torma presented background on development patterns, health, and the implications of the built environment. Contemporary community design has a tremendous impact on public health, particularly children's health, and the environment. There have been three macro trends during the last 50 years: (1) Employment and population growth heavily favored medium and large metropolitan regions versus nonmetropolitan areas. (2) Within metropolitan regions, most growth has occurred in low-density development at the fringe of urbanized areas. (3) There has been an emphasis on automobile travel at the expense of other modes. During the past 20 years, vehicle travel increased as a result of how and where populations are growing, not just because there are more people. Much has been known about this pattern and its impacts on the environment for a long time. The health impacts of these trends, however, have not been a focus of attention until recently.

The recent book *Urban Sprawl and Public Health* reveals that health outcomes are linked with land use and community design, including air pollution and related illnesses; a decline in physical activity; obesity and its attendant diseases; injuries related to auto dependence; threats to water quantity and quality; mental illnesses; and erosion of social capital. The authors cited the precautionary principle, "When an activity raises the cost of human health, precautionary measures should be taken even if some of the causes are not scientifically proven." Another message from this book is that urban planners are public health officials, whether they realize it or not. The public health community has been largely absent from and now needs to engage in the conversation on built environment and development patterns because how and where building occurs makes a difference.

Mr. Torma's presentation then focused on one particular aspect of the built environment—the size and location of schools. In 1969, 48 percent of children walked to school; in 2002, that percentage dropped to 16 percent. Today, there are far fewer schools than in the 1930s, but more students. Schools are now bigger, and these "mega-schools" are not accessible by foot. Many states have rules and policies that mandate or favor large schools; some local districts have even banned walking and biking access, citing

safety issues. Some argue that driving children to school protects them from predators, but the CDC performed a study to determine barriers to walking to school and learned that distance, not "stranger danger," was the main reason given by parents whose children did not walk to school. Many recently built residential subdivisions have no sidewalks and are built as pods that require driving to arterial roads to leave the neighborhood. There are multiple health implications as a result of the built environment in general, and unwalkable schools in particular. For public health professionals, school siting decisions are a logical place to start engaging on the built environment. Mr. Torma ended his presentation by showcasing The Safe Routes to School Program and the "Regulatory Blueprint for Healthy Community Design" handout.

Traffic, Trade, Air Pollution and Land Use Decisions
Andrea M. Hricko, University of Southern California

The Children's Environmental Health Center based at the University of Southern California has scientists who study air pollution. The Center's Community Outreach and Translation Core is responsible for translating science for the public, including policy-makers, and the Center's investigators testify frequently in front of local, state, and federal elected officials.. They also serve on public scientific committees and working groups at the local, state, and federal levels, with a focus on ensuring that the research is delivered to the scientific, transportation, and urban planning committees as it relates to traffic, trade, air pollution, and land use decisions. Studies by Center investigators show that children who live within 500 meters of a freeway have a greater risk of reduced lung function than children who live further away and that there is a greater probability of asthma in children who live close to busy roads. Local air pollution exposure has adverse effects on children's lung function, independent of air quality measures. Lung function at age 18 is 3–7 percent lower than expected for children living within 500 meters of a freeway. Asthma prevalence is greater than 15 percent for children living within 50 meters of a busy road their entire life, which is nearly double the prevalence for children living at least 200 meters away, according to Center studies. Real estate developers need to be informed of these statistics and should be encouraged to reconsider their development plans. School budget committees should be informed as well, but conflict can occur with parents who would prefer to have their children go to a school in their own neighborhood, even if it is situated close to a freeway, rather than have them be bused to another location. Some California schools still are being built close to freeways, despite state guidelines and laws; developers cite "overriding considerations" for not following these guidelines and laws. Another potential conflict includes economics; land is very valuable in certain areas, and the only affordable land may be in close proximity to freeways.

Ms. Hricko raised the following question: Should the Federal Highway Administration (FHWA) be advising state transportation agencies to consider the latest research findings in their freeway expansion decisions? Several years ago, EPA issued "hot spot rules" requiring mobile source air toxics analyses, but currently FHWA states that it cannot validate the proximity-to-traffic studies and is waiting for an upcoming Health Effects Institute evaluation.

Dr. Jonathan Samet, in a recent article in *Inhalation Toxicology*, suggests that: (1) control will require both reduced emissions and increased separation of people from emissions; (2) there is a need for further research to refine our understanding of the health consequences of traffic exposures (and as a basis for formulating mitigation policies); and (3) a "no-regrets" strategy should be instituted to reduce exposures while further evidence is obtained.

Ms. Hricko pointed out that the Los Angeles/Long Beach area is the epicenter for current international trade and health debates in the United States. The volume of containers coming through West Coast ports has increased dramatically since the 1970s (and U.S. ports have increased their international trade), and imports continue to grow. Los Angeles ports are the gateway for 40 percent of U.S. imported products

today, and imports through these two ports are expected to double or triple by 2030. California suffers the air and noise pollution and damage to infrastructure, while the rest of country benefits from inexpensive goods. The environmental impacts, however, also travel with the goods. Ships (with unregulated air emissions) bring millions of imported containers into California ports, which adds to regional pollution. Each container then becomes a truck on the freeway or is placed onto a train. Train and truck traffic creates local problems in communities throughout the country because rail yards often are located in immediate proximity to homes and schools, increasing the risk of health effects. Traffic, noise, and diesel pollution increase, and the sense of community is decreased. In California, Ms. Hricko pointed out, the proposed solution to the current congestion is to expand the infrastructure to accommodate three times as much cargo and trucks by 2030. California elected officials, government staff, and leaders in the transportation industry argue that expanding freeway infrastructure will reduce congestion and improve air quality. California bond money for infrastructure projects include budgets for bridges, rail lines, freeways, and possibly adding truck-only lanes to the I-710 Freeway. The governor's current high-priority projects are a new BNSF rail yard and an expanded Union Pacific rail yard located about 5 miles from the ports in residential areas. Community, public health, and environmental groups argue that it would be better to have rail yards at the ports so that containers are moved directly from ships to trains (and on to the rest of the country), rather than to have rail yards in local communities, where residents and school children have to breathe the diesel exhaust emanating from them.

Discussion

A participant asked about economic power as the driving consideration in the school development and siting. Ms. Hricko responded that there is significant literature that disputes the claim of expected savings of consolidated schooling. One study showed that costs are reduced in larger schools if costs are measured per student year, but smaller schools are less expensive if cost per student who graduates is measured; the issue is complicated. Often public policy dictates spending the money on a stadium in a prime area versus building a school there. Segregation is another issue. How is building bigger schools for integration addressed with well-intentioned public policy? Smaller neighborhoods and schools tend to segregate. In the long term, however, economic desegregation needs to be included in public policy.

A participant asked about hot zones and the options for building schools elsewhere when a full 40 percent of available land in Los Angeles may be adjacent to major roads and freeways. Ms. Hricko replied that there are other studies that examine school construction and configurations and that look at siting parking lots close to freeways, with the playgrounds and athletic fields farther away (to reduce exposure to pollutants). Air filtration and air quality management are being tested as other considerations.

A participant commented on the complexity of planning. Ms. Hricko responded that when scientists, physicians, and others in the public health community inject themselves into policy-making, a difference can be made. It would be a great model for participants to return to their communities and resolve to go to a zoning or planning meeting and offer health-based information in the planning process, said the discussant. He asked session speakers to speak more about how these complexities could be incorporated into practice. Mr. Torma explained that more reports and research are needed to provide evidence for take-home messages at these planning meetings, but he believes that attending these meetings with questions and concerns can be more effective than trying to provide all the answers. Merely mentioning health issues increases considerations from everyone involved in the planning process; the public health community needs to raise the questions. Another participant suggested developing a fact sheet of obstacles from the health care professional standpoint and including possible solutions to those obstacles. Participants can bring these fact sheets with them to the zoning meetings as a more effective contribution.

A participant commented about the fear factor in parents, with regard to children walking to school. "Stranger danger" needs to be factored into the equation, whether it is substantiated by the statistics or

not. Researchers must be proactive in obtaining and translating these data in a public forum when discussing school sitings.

One participant asked about cost considerations with building new schools versus updating old ones. Adaptive reuse is a great method to manage this issue, especially for buildings that were built in the 1920s and 1930s and stand for civic pride. Some of these schools are being turned into lofts instead of being demolished, but, if possible, the participant suggested, they should be kept as schools. There is a great amount of literature showing the relative costs of renovating versus replacement. It often is not cheaper to build new, but to bring the existing schools up to standards, depending on the age and condition of the schools. Private schools may be more amenable to some of these arguments because they operate under a different set of constraints and drivers.

A participant asked how lifestyle choices are considered when parents have a host of arguments against walking to school, including time. Mr. Torma agreed that time is an issue, but people need opportunities to engage their children; parents could be encouraged to walk their children to school and engage them in discussions along the way. It is about prioritizing and interacting with children in a manner that does not occur when driving them or spending time with them at night. A participant suggested that the global warming issue is beginning to encourage thinking about these issues.

A participant asked about replacing diesel engines in school buses and if that will change the proximity issue. A session speaker responded that there are attempts in many cities to replace diesel buses with cleaner fuel, although it may take some time to replace all of the diesel buses. The EPA Clean School Bus USA Web Site can be found at http://www.epa.gov/cleanschoolbus.

THE NATIONAL CHILDREN'S STUDY: ADJUNCT STUDIES

Marion J. Balsam, NIH

The NCS is an interagency, interactive study led by NICHD in partnership with CDC, EPA, and NIEHS. It was authorized by the Children's Health Act of 2000 to study the effect of the environment on child health and development. Environments to be studied include chemical, physical, biological, and psychosocial. Gene-environment interaction is an important aspect of the study. The sample will include 100,000 children from across the United States from before conception through age 21. The goal is to determine which environmental effects on children are harmful, harmless, or helpful. Another goal is to find preventable causes of health-related conditions and provide evidence-based data to guide children's health care, as well as health-related policy. Participants will be drawn from 105 sites across the country, and 40 Study Centers will perform the research. The priority is to determine environmental exposures (physical, chemical, biological, psychosocial) and their effects on specific outcomes. Priority outcome areas include: pregnancy outcomes, neurodevelopment and behavior, injury, asthma, obesity, physical development, and specific illnesses and disorders. Results from the core study are expected to spawn further research with different research questions.

Adjunct studies will draw upon a subset of the parent study participants and/or their biospecimens or environmental samples. These will be modular-focused studies, utilizing NCS infrastructure and samples. Anyone with a good idea can initiate adjunct studies. Specifically, it is expected that many adjunct studies will be initiated by government scientists or study center scientists. Independent researchers, research advocates, and industry can initiate adjunct studies as well. The focus of these studies can be about any topic, but there will need to be some mutual benefit to their leveraging the NCS. The adjunct studies will rely on outside funding, not on the core NCS funding source. Reviewers evaluating proposals for adjunct studies will rate such factors as scientific value to the NCS, public health importance, and proper fit with the NCS. Also considered will be the burden on participants regarding time or discomfort, the burden on the study infrastructure and logistics, human subject issues for any ethical or legal considerations,

appropriate institutional review board (IRB) review, and proof of funding. A brief electronic preliminary application is required. After the preliminary application is approved, a full application will be available for submission. The review process is aimed at facilitating the timely review of proposals. The NCS currently is expected to start in July 2008, which is the onset of a 1-year, Vanguard Center pilot year. The full national study will begin with enrollment 1 year later. Adjunct studies can begin with the full study. Proposals regarding preconception, delivery, and early infancy could be submitted soon. Opportunities will continue to arise for additional research by leveraging the NCS, and adjunct studies will broaden and enhance the NCS contribution to children's environmental health. More information can be found on the NCS Web site at http://www.nationalchildrensstudy.gov.

Discussion

A participant asked whether funding is required prior to applying for adjunct studies. Dr. Balsam replied that funding is not required, but the application asks about funding plans. After preliminary approval for adjunct studies pending IRB decisions and so forth, the studies can obtain funding.

A participant asked whether there will be an opportunity to develop gene expression analysis and arrays from the NCS. Dr. Balsam responded that the core protocol is very broad and will include specimen samples and questionnaires. The NCS will be obtaining, storing, and analyzing the specimens, and the data will be made publicly available. The research plan is available on the Web site now, so if others are planning to do similar studies, they may not want to repeat efforts. The protocol draft is not very specific about what gene expression analyses are planned, so if participants have specific questions, they can be submitted by e-mail to ncs@mail.nih.gov.

A participant asked about the funding status of the NCS. Dr. Balsam answered that the NCS is funded for Fiscal Year (FY) 2007 and anticipates funding for FY 2008. NCS is funded yearly.

A participant asked about the process for obtaining existing data and whether it will be similar to NHANES. Dr. Balsam replied that the policy and procedures dealing with data access currently are being developed.

A participant asked whether any of the people involved with the data warehousing for NHANES also are involved with the NCS. Dr. Balsam replied yes, the CDC is involved with sampling, information management, and laboratory and repository aspects.

A participant asked whether local sites have to wait for national data or whether access is available at the local level prior to full data. Dr. Balsam responded that data distribution currently is being developed. The NCS anticipates, however, that first access will be to government, followed by study centers, adjunct studies, and then public use. When communities can have access is part of the process being developed now.

SESSION VI: CHILDREN'S PROTECTION IN THE AFTERMATH OF A NATURAL DISASTER: TOOLS FOR RECOVERY AND COMMUNICATING RISKS

Chair: Debra Cherry, University of Texas Health Center at Tyler

Dr. Cherry opened the session with a brief overview of the topic: tools for recovery and communicating risks after hurricanes. The objectives of this panel were to describe the collaborative PEHSU response to Hurricanes Katrina and Rita, provide experience and feedback from a Gulf Coast pediatrician at ground zero, and describe the NIEHS Hurricane Response Portal. Hurricane Katrina was one of the most devastating natural calamities to affect the United States. More than 354,000 Gulf Coast homes were

destroyed; more than 200 sewage treatment plants and 140 oil and gas platforms were damaged; and multiple health risks increased as a result of rampant mold growth, mountains of debris, widespread demolition and reconstruction projects, and through exposure to toxicants in temporary housing. The Tyler, Texas, PEHSU was the closest Center to ground zero and was called to help with communication issues. The project involved multidisciplinary collaboration, and cleanup required the expertise of scientists, engineers, volunteers, health care workers, and safety training professionals.

The potential hazards included returning to home sites too soon, sludge, structural damage, and lack of respiratory protection. Joint documents and recommendations for dealing with environmental issues and returning children to previously flooded areas were created and distributed to officials and parents. The Center also answered calls from parents through a toll-free line.

Tales from Ground Zero: Hurricane Katrina and Pediatric Environmental Health in Coastal Mississippi
Scott Needle, Formerly of Bay St. Louis Pediatrics

Dr. Needle joined the workshop by telephone to share his experiences with the aftermath of Hurricane Katrina, including the logistical issues, the health effects, and the communication issues that he encountered, particularly as they related to the formaldehyde problem in Federal Emergency Management (FEMA) trailers.

He was in private practice in Bay St. Louis, Mississippi, when the hurricane made landfall. Between 50 and 90 percent of the local housing was damaged or destroyed, including his office and other public health spaces. Although the medical community was prepared for some of the expected problems, they did not anticipate the mental health issues that occurred including short-term memory problems, confusion, and disorganization. Trauma was anticipated but not chronic stress.

The Sierra Club found significantly elevated levels of formaldehyde in one FEMA trailer, which led to the finding that 29 of 30 trailers had elevated levels. Formaldehyde is a known respiratory irritant and is classified as a carcinogen; it was found in the particle board in the trailers. The manufacturers voluntarily had taken it out years before, but the boards were still circulating. There are no government levels regulating formaldehyde in travel trailers and no standard for levels of safety for children. Dr. Needle noted that many families reported recurring respiratory problems in their children when they had been in good health before staying in the trailers. FEMA explained that a small number of cases were being monitored, and no major problems were anticipated. No government resources were available through the summer of 2006 to analyze formaldehyde, but the Sierra Club still was finding elevated levels. In February 2007, the media investigated the manufacturer of the trailers and discovered respiratory problems with the factory workers and particle board sheets that were still wet with formaldehyde. In May 2007, the *CBS Evening News* ran a story of results of the 2-month investigation, which prompted the Department of Homeland Security to contact Dr. Needle to determine how best to study the issue. The next month, the House Committee on Oversight and Government Reforms announced that they would hold hearings and invited Dr. Needle to testify. FEMA workers testified that they had voiced formaldehyde concerns about the trailers as early as March 2006. FEMA finally announced last month that they are now taking steps to move people out of these trailers. But what about the families still living in these trailers? The fundamental question remains unanswered: Is the formaldehyde the cause of the health problems, and if not, what is? Researchers must work hard to find out. Almost every agency failed to take ownership and responsibility for public health, and the CDC cannot just launch an investigation. The providers on the ground are the ones providing public health the first few months following a natural disaster. These providers rely on the experts for advice and need government agencies to listen to their concerns. Will we be able to handle future problems that weren't anticipated?

NIEHS Environmental Health Sciences Data Resource Portal
Marie Lynn Miranda, Duke University

Dr. Miranda presented satellite imagery of the New Orleans area from pre- and post-Hurricane Katrina perspectives. These images showed the scale of persistent flooding in an expansive area to help gauge the potential environmental health effects. The group was tasked with setting up work for the entire Gulf area, not just New Orleans. The key health consequences questions that arose involved mold, respiratory health, contaminant transfer, solid waste management, and mental health, and the NIEHS chose to develop the Hurricane Response Web Portal to build and maintain an extensive data file and archive. This archive allows many different environmental health questions to be examined and provides a collaborative work space and working tools that allow people from all over the country to work together on a long-term living resource. Data from the Web portal can be accessed directly from the NIEHS Web Site. The portal is user friendly and provides maps and imagery, query tools, measurement tools, data manipulation tools, potential contamination sources, water quality information, and sediment information. There is free and open access to these data. She demonstrated examples of how to make specific queries and how to download data by geographic and other variables and provided navigation instruction. A customizable research environment and custom reports are available.

Discussion

A participant recommended a book called *One Dead in Attic* by Chris Rose for a more information about how New Orleans has been coping since Hurricane Katrina.

KEYNOTE ADDRESS: THE NATIONAL FORUM ON CHILDREN AND NATURE
Speaker: Lawrence A. Selzer, The Conservation Fund
Introduction and Discussant: Howard Frumkin, CDC

Mr. Selzer explained that he wanted to challenge researchers to broaden their investigations to include the health effects resulting from communing with nature. There is a growing body of evidence pointing to the benefits of nature, but more data are needed to effect positive change with respect to children's health and the environment. As the nation becomes more urban and the demographics continue to change, reconnecting children to nature will be less about bringing them to nature and more about bringing nature to them. Nature must be brought to children in a manner that makes sense to them. This requires a more strategic vision of reconnecting children and nature; it is a mission that cuts across sector, status, and geography. This is the challenge, and leadership is needed to succeed.

One in five American children is considered obese, and one in three with diabetes has the type II form; 25 years ago, doctors did not even have a name for it. Children in the United States now gain three to five times more weight during the summer than they do during the school year. There are classes in urban schools where as many as one-third of the boys are on Ritalin or similar medicines. Pediatricians do not see as many broken bones anymore, and one of the most common ailments among children eight to 18 today is repetitive motion disorder. Fifty percent of Hispanic boys in this country drop out of school by the eighth grade. Some states now project their future prison needs based on third grade reading scores. If this trend continues, the first generation since World War II will exist that will have a shorter life span than its parents. Sensationalist media coverage and fearful parents have scared children right out of the woods while promoting a litigious culture of fear that favors safe, regimented sports over imaginative play outdoors. This anxiety can feed on itself, and those who watch more television have more sense of the potential dangers and less engagement with their community. The result is the perception that the outside has become more dangerous and thus the freedom to explore and improvise is reduced dramatically. The radius beyond which children are not allowed to roam has shrunk by 89 percent during

the past 20 years. During the past 30 years, children of the digital age have become increasingly alienated from the natural world with disturbing implications for their physical fitness, their long-term mental and spiritual health, and the environment. Young people who grow up without spending time in nature are much less likely to be strong champions for the environment when they reach voting age, thereby jeopardizing the land legacy that the nation has spent the last 200 years setting aside.

Mr. Selzer provided an overview and history of The Conservation Fund, which has protected more than 6 million acres of America's outdoor areas during the past 21 years. Leadership and new ideas, resources, partners, research, and data are needed urgently. Reconnecting children with nature is the passion of our time. The National Forum on Children and Nature is a new initiative, a collaborative effort launched in June. The 2-year effort is to identify and implement signature projects across America that serve to reconnect children and nature. Individually and collectively they will be a most powerful form of advocacy for change, for a new direction in the products that are made, the services that are delivered in communities that are built, and the education that is provided. They will help to elevate this issue to the highest levels of society so it becomes a national priority. Reconnecting children with nature cannot be legislated or regulated; it must be done by changing the culture of the country and to do that we need to better understand the connection between children, nature, and health.

Two examples are being pursued through the Forum. The first is in the area of technology. The world is technological, so childrens' attraction to technology must be used to get them outdoors. One idea of the National Forum is to work with a new organization called the Serious Games Initiative, which was created by an independent group of game developers who view video games as an opportunity for social good and achieving social purpose. A national competition to make state-of-the-art technology that has to be played outdoors is being launched. The next example deals with the built environment, especially how the environments are built where Americans will live tomorrow.

The modern America of obesity, inactivity, depression, and loss of community has occurred because of legislation, subsidy, and planning. A subgroup of the National Forum consisting of some of the most progressive developers in the country has been formed. This group is focusing on understanding children and nature design elements, identifying best practices, and alternately arriving at a national certification standard for child-friendly developments. This is the kind of energy that the National Forum is channeling. The real value of the projects is the opportunity they provide to investigate what happens as a result. This chance to gather primary data that will help to influence policy and practice across the country must not be lost. Forum collaborators are building a solid component as part of each of these national projects. They will conduct research on what happens as a result and make these data available.

Beyond the allure of technology, beyond the isolating design of new development, beyond the fear of stranger danger, there is another fundamental issue that requires our immediate attention: the increasing lack of places to be outdoors and the lack of leadership at the federal level to address this issue in a meaningful way. America loses more than 3 million acres a year in development and sprawl. The current administration has proposed twice to permanently terminate the Land and Water Conservation Fund, the most powerful land protection program in this country. There also is a crisis in creativity. It is known that protecting watersheds is one of the methods by which to assure clean, safe drinking water, so protecting the sources of drinking water protects public health. It is known that air pollution contributes to cardiovascular disease, respiratory disease, and allergies. Therefore, protecting air quality and land protects public health.

Protecting natural landscapes is a powerful form of preventive medicine, but only 5 percent of the money spent on health care in the United States is allocated to preventing disease and promoting health and a healthy lifestyle. Nature needs to be viewed as the first prescription. People do not want less environmental protection; they want smarter protection that balances economic and environmental

objectives. It is this dynamic that is driving the tremendous force and support of the environment at the state and local levels. More than 30 billion dollars in just the last 5 years in state and local bond money were allocated by taxpayers to protect open spaces across the country, including natural areas and neighborhood parks. Recent election results show that a wide variety of Americans care about these issues. No one among us wants to be a member of the last generation to pass on to its children the joy of playing in nature.

Discussion

A participant asked for clarification about bringing nature to the children versus taking them to nature. Mr. Selzer responded that redefining what nature means (redesigning alleys to replace lost park land) is part of this, but he cited a National Geographic Society program that brings children to national parks. Children expressed fear of the dark, of quiet, and of nature. It was too foreign for them to continue interest in it. Children must be moved along a continuum to help them identify what represents nature in their own neighborhoods in a manner in which they can connect and continue with sustained investment. This improves school performance and increases the number of students who continue to secondary education; many of them have a lifelong interest in the natural world.

A participant asked about the issue of people who view nature as having a big backyard. Mr. Selzer explained that people tend to show a preference for a house and big yard as a sign of success, comfort, and quality of life. It is a cultural issue, but it has an ecological impact. It represents a loss of land and loss of migration and native species. The human health impacts of those kinds of sprawling developments have just begun to be understood. The impacts of changing those patterns of development must be considered and documented through research. For example, only 30 percent of people who live on a golf course play golf, but they all paid a higher premium to purchase the lots because they like the open green space. Developers should build housing developments on open land and charge the higher premium but they will not because it is an unfamiliar idea. Change must occur slowly, the success stories must be highlighted, and the results documented to effect cultural change.

A participant commented about the disconnect that she has seen in some of the nature programs; most of them failed or the children could describe the environment but could not see themselves in it. She asked for a description of a better way to design these programs. Mr. Selzer explained that what it means to experience nature must be redefined. Researchers need to come together and promote one curriculum on environmental education, because there are too many competing factions. Obesity rates are rising, but participation in structured sports is the highest it has even been; therefore, there is something about unstructured time and play outdoors that matters. It has to do with engaging with nature first hand. Environmental education must include being outside in a less structured way.

A participant described a recently convened a group of state and environmental directors that dealt with the issue of how to collaborate on smart growth and asked what can be done in the early stages. Mr. Selzer replied that all that can be achieved with legislation has been achieved, and now the power of the marketplace is needed to drive things forward. The developers must be encouraged to change.

A participant suggested that participants should consider running for local office to make changes. If researchers sit on local planning agencies or the school board, environmentalists and the local health community will help fund the campaign. Mr. Selzer added that a recent study showed that children who emerge as leaders in the gray playgrounds (blacktops) are the most physically mature. The children who emerge as leaders in a green playground are the most creative. Green space is not needed in an urban setting because sometimes it is not available; some schools put it on their roofs. He described a school of the future in downtown Manhattan. Regarding running for office, the only thing protecting the land is the will of the public officials; 20 years from now if the elected officials do not have a stake in the land, it is

in jeopardy, which is why we need to engage children today because it takes a lifetime to build a commitment like that.

A participant expressed a sense of personal frustration and lack of creativity and mentioned children who are afraid to go outside because of drive-by shootings. Mr. Selzer agreed that one of the central issues is safety. He described an initiative called America's Promise, started by Colin Powell. It is an umbrella organization designed to improve the quality of the lives of the 30 million children who are most at risk in the United States. One of the central directions is based on the concept of school as the center of community. Many inner city schools are barren and lacking in programs. Maybe, school can be the place where education takes place, not just in the classroom, and where children spend a lot more time. This will take time, budget, policy, and creativity; and schools as the center of community is the direction in which this program is headed.

Dr. Frumkin stated that now is the time to submit proposals through the National Forum on Children and Nature. Information can be found at http://www.conservationfund.org/children_nature.

CLOSING REMARKS
William H. Sanders III, U.S. EPA

Mr. Sanders thanked the presenters and expressed his appreciation for their quality talks. He specially thanked Mr. Fields and Dr. Frumkin, whose comments complemented the theme today of thinking in broader terms. The community is at a point of opportunity to think more broadly about CEH to demonstrate and measure the results. He thanked participants for engaging the speakers in each of the sessions and thanked the planning committee and coordination teams for their efforts in bringing about this workshop. Because this workshop was enlightening and a great opportunity to connect and discuss ideas, another workshop may be planed in the future. He anticipates great response to this workshop.

Mr. Sanders adjourned the meeting at 12:30 p.m.

2007 Children's Environmental Health Workshop: Discover, Treat, Prevent, Prepare

Hamilton Crowne Plaza
1001 14th Street, NW
Washington, DC

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Children's Environmental Health: Looking Backward, Looking Forward

2007 Children's Environmental Health Workshop
Discover, Treat, Prevent, Prepare
October 11, 2007

Howard Frumkin, M.D., Dr.P.H., Director
National Center for Environmental Health /
Agency for Toxic Substances and Disease Registry
Centers for Disease Control and Prevention

Looking Backward: Milestones

- 1993: NAS Report
- 1996: Food Quality Protection Act
- 1997: PEHSUs
- 1998: Children's Environmental Health Research Centers
- 1999:
- 2000: Children's Health Act (authorized Children's Health Study)

Looking Backward: Strengths

Research:

- Chemicals (Pb, Hg, PCBs, pesticides, ETS, air pollution, etc.)
- Diseases (asthma, autism, etc.)
- Methods (community-based participatory research, genetics)
- Vulnerable populations (farm families, inner city)

Looking Backward: Strengths

Education:

- Fellowship training
- Books and journals
- Web sites

Service

- Network of community resources in certain cities
- Technical tools (Healthy SEAT)

Measuring progress

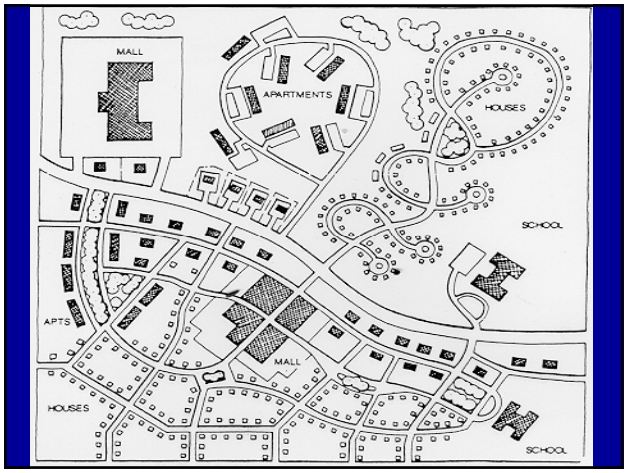
- Do children have healthier environments?
- Do we have a better understanding of how to protect children's health?
- Do health care providers address children's environmental health more effectively?
- Do parents understand how to provide safe, healthy environments for their children?
- Are policies adequately child-protective?

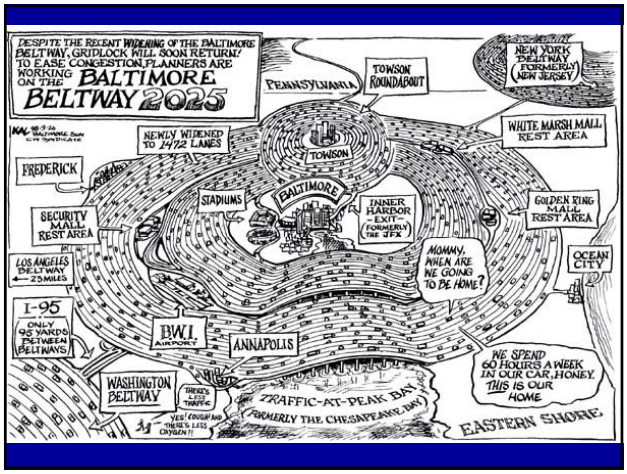
Changed circumstances

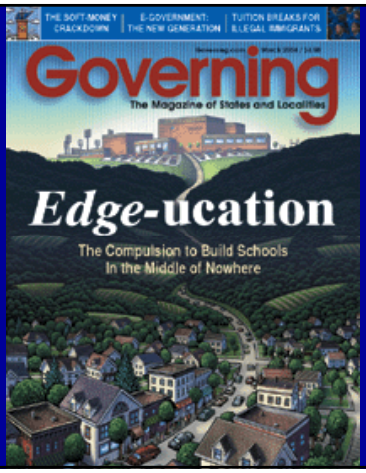
- Obesity epidemic
- Biomonitoring
- Genetic advances
- Poverty and uninsurance
- Political context

The next 10 years

- The built environment
- The outdoors
- Climate change
- Mental health
- Combining environmental and non-environmental factors
- Communication



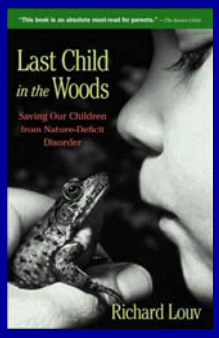




Marshall High School, Marshall, MN

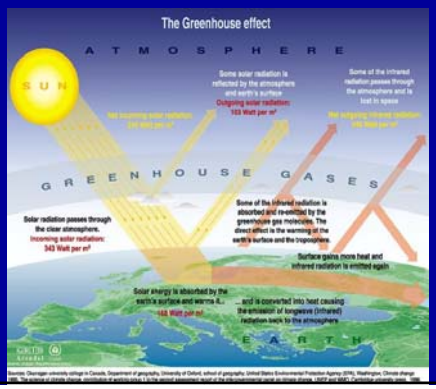
Hubbard Lake Elementary School, Hubbard Lake, Michigan.
"Outstanding in Its Field"

The outdoors



The outdoors

Climate change

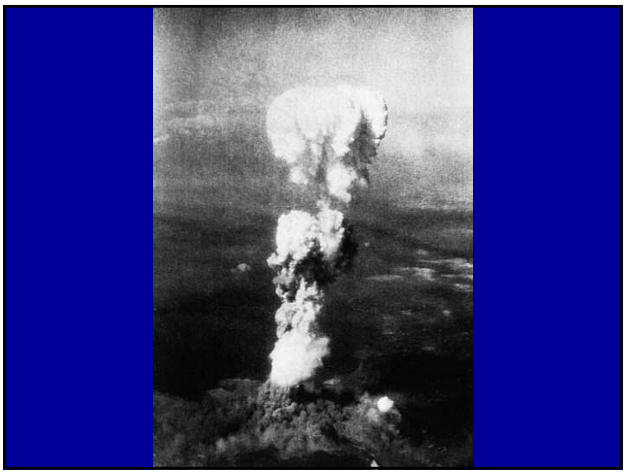


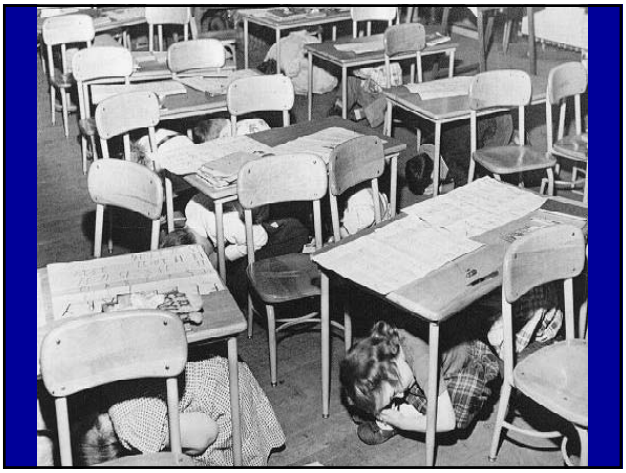
Potential Health Effects of Climate Change

Climate change:
- **Temperature rise**
- **Sea level rise**
- **Hydrologic extremes**

HEAT	Heat stress, cardiovascular failure
SEVERE WEATHER	Injuries, fatalities
AIR POLLUTION	Asthma, cardiovascular disease
ALLERGIES	Resp allergies, poison ivy
VECTOR-BORNE DISEASES	Malaria, dengue, hantavirus, encephalitis, Rift Valley fever
WATER-BORNE DISEASES	Cholera, cryptosporidiosis, campylobacter, leptospirosis
WATER AND FOOD SUPPLY	Malnutrition, diarrhea, harmful algal blooms
MENTAL HEALTH	Anxiety, post-traumatic stress, depression, despair
ENVIRONMENTAL REFUGEES	Forced migration, civil conflict

Adapted from J. Patz



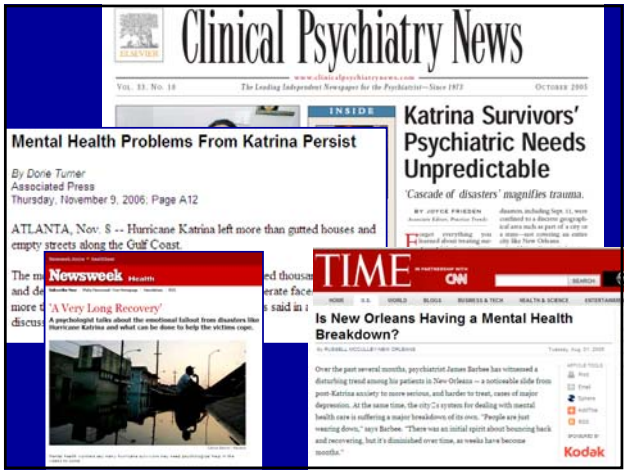



THE END OF THE WORLD IS NIGH
"Hurry up!"


REPENT! REUSE! RECYCLE! LEST YE BURN!
PRAISE THE GLOBE!
COX & FORKUM


BBC NEWS
Climate change is kids' top fear
How we're damaging the environment is more of a worry to you than getting a girl or boyfriend, says a survey.
The results showed three quarters of 11 to 14-year-olds worry about climate change, compared to 41% who are worried about going out with someone.
And it looks like you lot aren't just all talk - 63% turn off the lights when you leave a room, 82% of you recycle, and 75% say we should recycle more.
The survey quizzed 1,554 kids on their views on the
washingtonpost.com
Climate Change Scenarios Scare, and Motivate, Kids
By Darragh Johnson
Washington Post Staff Writer
Monday, April 16, 2007; Page A01
The boy has drawn, in his third-grade class, a global warming timeline that is his equivalent of the mushroom cloud.
"That's the Earth now," the 9-year-old says, pointing to a dark shape at the bottom. "And then," he says, tracing the progressively lighter stripes across the page, "it's just starting to fade away."


KOREN
"This past summer, I got deeply depressed about our planet—as if I didn't have enough problems of my own."


Clinical Psychiatry News
Mental Health Problems From Katrina Persist
By Dorie Turner
Associated Press
Thursday, November 9, 2006; Page A12
ATLANTA, Nov. 8 -- Hurricane Katrina left more than gutted houses and empty streets along the Gulf Coast.
Katrina Survivors' Psychiatric Needs Unpredictable
'Cascade of disasters' magnifies trauma.
Newsweek
'A Very Long Recovery'
TIME
Is New Orleans Having a Mental Health Breakdown?
Kodak

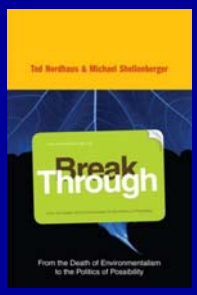
Edvard Munch does Climate Change

Despair

Anxiety

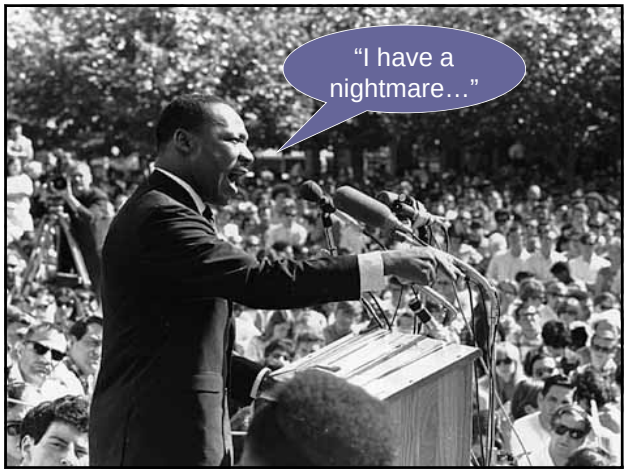
The Scream

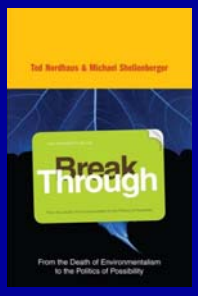
Nero playing while Rome burns
c.1536-9
Workshop of Giulio Romano (c.1499-1546)



"Think of the verbs associated with environmentalism and conservation: 'stop,' 'restrict,' 'reverse,' prevent,' 'regulate,' and 'constrain.' All of them direct our thinking to stopping the bad, not creating the good."

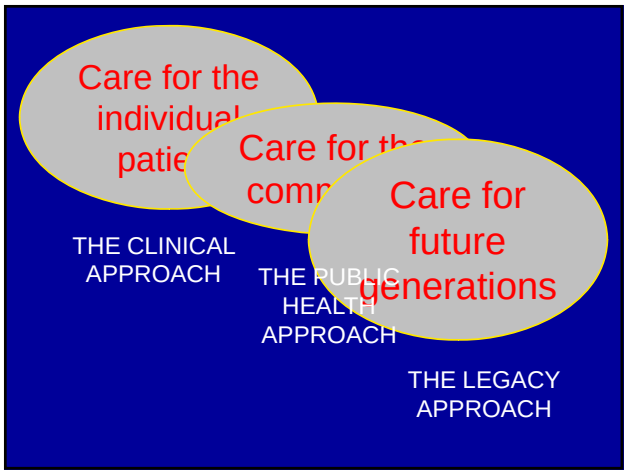
⇨ The need for positive, aspirational messages.





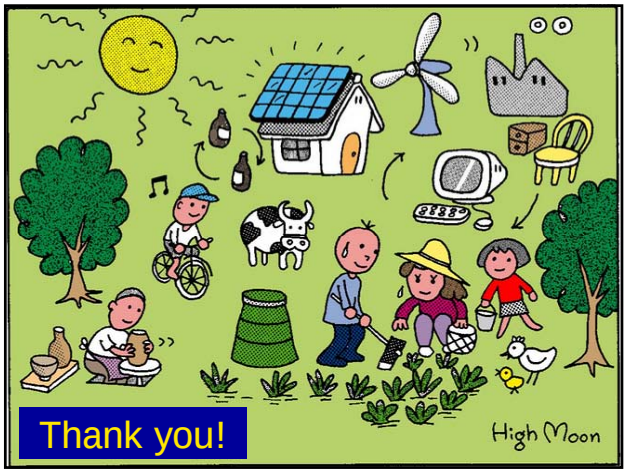
"The challenge of climate change is so massive, so global, and so complex that it can only be overcome if we look beyond the issue categories of the past and embrace a grand new vision for the future."

⇨ The need for bold, cross-cutting thinking.



Summary

- A decade of proud accomplishments
- A decade of emerging opportunities
  - The built environment
  - The outdoors
  - Climate change
  - Mental health
  - Combining environmental and non-environmental factors
  - Communication



Evolution of Biomarkers for Pesticides: Examples From the Agricultural Setting

Catherine Karr, MD, PhD
Director, Northwest PEHSU

Elaine Faustman, PhD
Director, Center for Child Environmental Health Risks Research

University of Washington, Seattle, WA

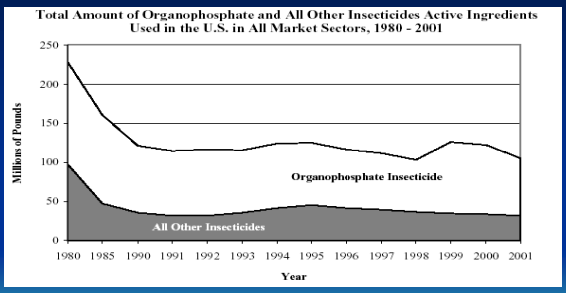
Focus: Organophosphate Pesticides

Reason # 1: Widespread exposure

Recent decreases in home/garden use (regulatory restrictions and phase outs based on child health concerns)

Continue to be used heavily in agriculture

70% of insecticide use in 2001 = OP



Kiely T et al. Pesticide industry sales and useage: 2000-2001 market estimates. U.S. EPA Office of Pesticide Programs. May 2004

Focus: Organophosphate Pesticides

Reason # 2: Acute Toxicity

OP = pesticide type most often implicated in symptomatic illness reported

Acute Poisoning Data

PESTICIDES MOST OFTEN IMPLICATED IN SYMPTOMATIC ILLNESSES, 1996

Rank	Pesticide or Pesticide Class	Child < 6 years	Adults 6-19 yrs.	Total*
1	Organophosphates	700	3274	4002
2	Pyrethrins and pyrethroids**	1100	2850	3950
3	Pine oil disinfectants	1336	903	2246
4	Hypochlorite disinfectants	808	1291	2109
5	Insect repellents	1081	997	2086
6	Phenol disinfectants	630	405	1040
7	Carbamate insecticides	202	817	1030
8	Organochlorine insecticides	229	454	685
9	Phenoxy herbicides	63	387	453
10	Anticoagulant rodenticides	176	33	209
	All Other Pesticides	954	3604	4623
	Total all pesticides/disinfectants	7279	15,015	22,433

* Totals include a small number of cases with unknown age.
** Rough estimate: includes some veterinary products not classified by chemical type.

Source: American Association of Poison Control Centers, Toxic Exposure Surveillance System, 1996 data.

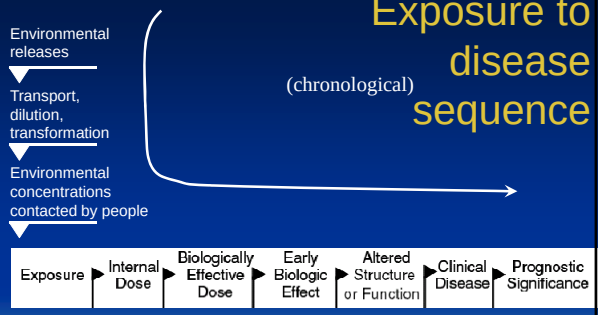
Focus: Organophosphate Pesticides

Reason # 3: Chronic exposure health implications

Focus of NIEHS/EPA children's environmental health centers

Growing evidence of neurodevelopmental effects with chronic, low level exposure (non-acute)

Exposure to disease sequence



urinary metabolites – cholinesterase inhibition
paraoxonase (PON1) status

NAS/NRC.Human Biomonitoring for Environmental Chemicals http://www.nap.edu/catalog/11700.html

Clinical Setting Questions

A parent….

I just read the CDC report and I have learned that my child may have pesticides in her body -- what does this mean? Do I need to have my daughter tested?

A colleague….

I am sensitive to drug X, could this affect my susceptibility to pesticides?

Public Health Sector Questions

A public health officer in a rural community…

Should our healthy family fact sheet include a recommendation for choosing organic foods?

Which populations are most vulnerable to potential adverse health outcomes from pesticide exposure?

A federal agency leader….

Should we have a national medical monitoring program for occupationally exposed agricultural workers?

Risk Assessment Questions

A policy maker asks….

Has the change in regulation of diazinon and chlorpyrifos reduced exposure in at risk populations?

Should regulatory decision making incorporate evaluation and protection of the most genetically vulnerable subset of the population?

Considerations for progress

Stage of validation/utility, limitations, knowledge gaps

↓

How to increase the clinical, public health and risk assessment relevancy?

Cholinesterase Testing: Pediatric Clinical Perspective

Catherine Karr MD PhD
University of Washington
Region X PEHSU

Key Issues

Unique clinical diagnostic tool for acute pesticide poisoning

Under recognition of OP poisoning in children
- Kids present differently
- Knowledge gap

Interpretation
- Inter-individual variability

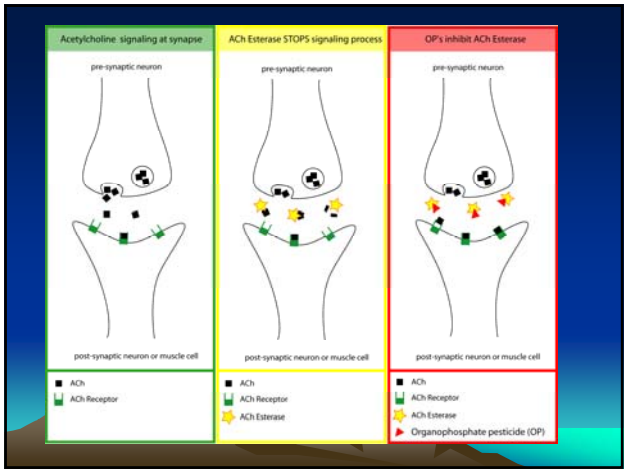
Acute vs chronic toxicity implications

Cholinesterase Test

Biomarker of biologically active dose

Measures inhibition of cholinesterase enzyme using a blood sample
- Plasma (pseudocholinesterase)
- RBC (acetylcholinesterase)

Surrogate for acetylcholinesterase in the nervous system



Cholinesterase Inhibitors Toxicity

Effect builds up over time and
the "Off Switch" gets stuck ON

Miosis
Diaphoresis
Salivation
Lacrimation
Urination
Defecation
Gastroenteric cramping
Emesis

Clinical Presentation in Children

More likely to have hypotonia & mental status changes such as lethargy and coma, seizures

eg. seizure occurrence based on case series:
- adults 2-3%
- children 22-25%

Less likely to have the classic hypersecretion, particularly at initial presentation

Often mistaken for viral illness (respiratory infection, gastroenteritis, meningitis)

Under recognition of OP poisoning in children

In one 1980s case series, the diagnosis was incorrect in 16 of 20 cases

In epidemic OP poisoning in midwest, southeast US, missing and delayed diagnosis for months to years

No index of suspicion = no diagnosis

Zwiener. Organophosphate and Carbamate Poisoning in Infants and Children. Pediatrics 1988;81;121-126
Rubin C. Assessment of human exposure and human health effects after indoor application of methyl parathion in Lorain County, Ohio, 1995-1996.Environ Health Perspect 2002;110(Suppl 6):1047–51.

Training Gap

Health care providers in NW agricultural setting caring for farmworker families (2005)

Any previous training on pesticides & health? 49%

Child specific info? 22%

Karr et al. Pacific Northwest Health Professionals Survey on Pesticides and Children. Journal of Agromedicine 2006;11:113.

NW PEHSU Web CME

Organophosphate Pesticides and Child Health: a primer for health care providers

http://depts.washington.edu/opchild/

Diagnostic Testing

If suspect OP exposure

- Red blood cell (acetylcholinesterase)
- Plasma (pseudocholinesterase)

Certain OPS may selectively inhibit either plasma or RBC acetylcholinesterase

Cholinesterase Activity Depression

Occurs w/in few minutes or hours

Effects on plasma enzyme generally persists for several days to a few weeks.

The RBC enzyme activity may take several days to reach its minimum and usually remains depressed longer, sometimes 1-3 months

Cholinesterase Activity Depression: Interpretation

Great variability in normal general population baseline limits usefulness of reference range

Need to interpret in relation to individual's own baseline – post exposure follow-up with same lab and method

20% increase in plasma OR 15% increase in RBC suggests clinically significant exposure occurred

Chronic Exposure Toxicity

Cholinesterase testing is limited to diagnosis of clinically significant acute poisoning via the cholinergic pathway

Neurodevelopmental toxicity may occur via alternative mechanisms

- Toxicological and epidemiological evidence

OP Pesticides & Developmental Toxicity: Cholinergic-Independent Mechanism

In vivo evidence (embryonic/neonatal rat models) and in vitro models (neuronal rat cell lines)

Dosage biologically plausible, below amount needed to effectively inhibit acetylcholinesterase

Effects seen throughout brain, including regions with little cholinergic innervation

- Cell loss & apoptosis seen immediately after exposure
- Neural deficits appear in adolescence & continue into adulthood
- Deficits in: brain cell numbers, neurite projections & synaptic communication

OP Pesticides & Developmental Toxicity: Cholinergic-Independent Mechanism

Several common signaling cascades shown to be effected that are used in many developmental pathways

- May help explain widespread & delayed-onset OP effects during development
- May explain observations in epidemiological cohort studies

Implications of Non-Cholinergic Organophosphate Toxicity

Child OP exposure toxicity may result from non-cholinergic endpoints

Clinical markers beyond cholinesterase testing……

Beyond cholinesterase testing

Development of clinical application of urinary marker monitoring?

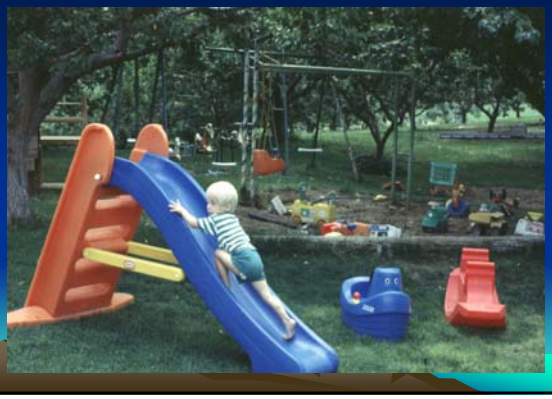
Confirm acute exposures?

Identify concerning chronic exposures?

Influence clinical decision-making?

- Preventive guidance
- Prognosis

Agricultural workplace/playground

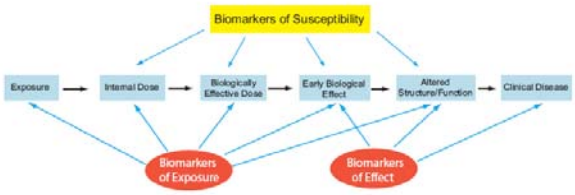


Biomarkers of Pesticide Exposure: Lessons for Children in Agricultural Communities

Elaine M. Faustman
Bill Griffith
NIEHS/EPA Center for Child Environmental Health Risks Research
Institute of Risk Analysis and Risk Communication
University of Washington

1

Biomarkers for Monitoring Exposure and Effect in Populations



2

Examples of Chemicals Applied to Washington State Crops, 2001

Chemical class	crop	Chemical	Pounds applied
Organophosphates	Apples	Azinphos-methyl	241,000
		Chlorpyrifos	234,000
		Phosmet	138,000
	Potatoes	Ethoprop	119,000
		Metamidophos	143,000
N-Me Carbamates	Apples	carbaryl	202,000
	Potatoes	Aldicarb	153,000
Dithiocarbamate	Apples	Mancozeb	82,000
	Potatoes	Mancozeb	343,000

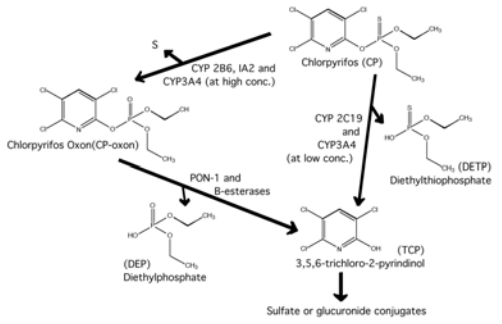
Source: "Agricultural Chemical Usage (PCU-BB)" National Agricultural Statistics Service, Agricultural Statistics Board, U.S. Department of Agriculture (http://jan.mannlib.cornell.edu/reports/nassr/other/pcubb Accessed 05/03)

3

Agricultural Pesticides: Contributions of Occupational Factors to Home Contamination

4

Metabolic Scheme for CP



Faustman et al. (2006)

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Metabolites of Organophosphate Pesticides

- Biomarkers of exposure
- Nonspecific Diakyl Phosphate (DAP) metabolites
  - Six DAP Metabolites
  - Each metabolite can be produced by multiple OPs
  - Divided into two groups
    - Dimethyl metabolites
      - DMP, DMTP, DMDTP
    - Diethyl metabolites
      - DEP, DETP, DEDTP
- Specific metabolites
  - Chlorpyrifos metabolites
    - TCP, DEP, DETP
  - Chlorpyrifos-methyl metabolites
    - TCP, DMP, DMTP

6

Metabolites of Organophosphate Pesticides

Selected OPs and DAP metabolites

Diethyl OPs			
chlorpyrifos		DEP	DETP
diazinon		DEP	DETP
disulfoton	DEDTP	DEP	DETP
ethion	DEDTP	DEP	DETP
parathion		DEP	DETP
Dimethyl OPs			
azinophos methyl	DMDTP	DMP	DMTP
chlorpyrifos methyl		DMP	DMTP
dichlorvos (DDVP)		DMP	
malathion	DMDTP	DMP	DMTP
methyl parathion		DMP	DMTP
naled		DMP	
phosmet	DMDTP	DMP	DMTP
trichlorfon		DMP	

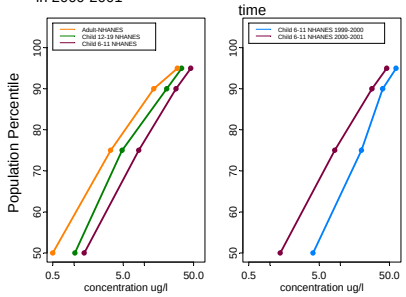
7

NHANES Data for DMTP in Urine

Random sample of US Population

Comparison across ages in 2000-2001

Comparison for children (6-11 years old) across time



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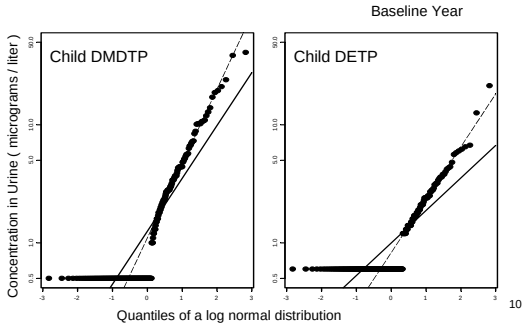
What do these values mean for my Children?

9

Many Values Are Below Limits of Detection



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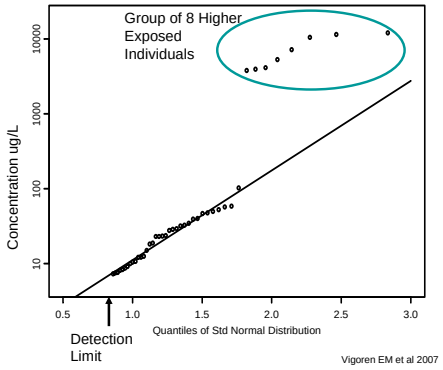
NHANES Compared to Farmworker Family Data for DMTP in Urine

11

DMP in Adult Urine: QQ Plots to Estimate Population Distribution

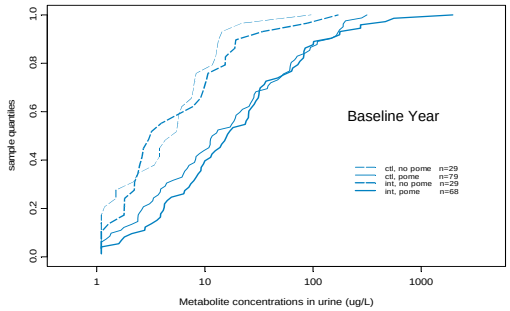


Vigoren EM et al 2007

12

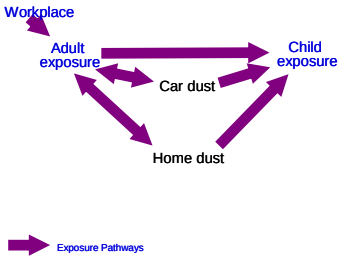
13

Distribution of Adult DMTP from year 1: Impact of Crop



14

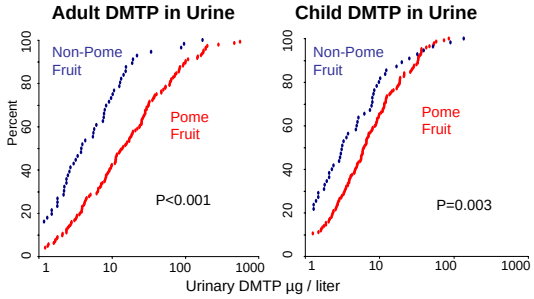
Assessing Children's Pesticide Exposure via the Take-home Pathway



Vigoren EM et al 2007

15

Urinary metabolites higher in adults who worked in pome fruit and their children



Coronado et al., Env. Hlth. Persp., 2004, 2006

16

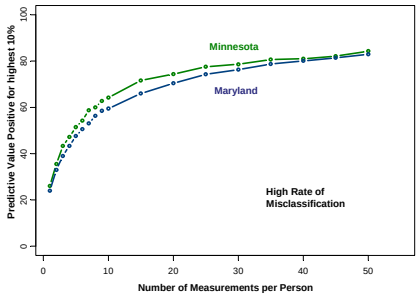
Two longitudinal studies of OP metabolites used to estimate within and between variability

- Multiple measurements in the same person across time permit estimation of both within and between person variability
  - Within and between person variability treated as a random effect and other variables such as age, gender ,residence, season treated as fixed effects
- TCP had a low percentage below limits of detection
- Measurements below limit of detection (LOD) were treated as being left censored in statistical analyses

17

Predictive Value Positive for Identifying Persons in the Upper 10% of the Population

The predictive value positive is the percent of the population assigned to a group that are correctly classified.



Based upon large within person variances it will require a large number of samples of urinary metabolites to correctly identify persons in a population who are more highly exposed to CP and CPM.

18

Sources of Uncertainty

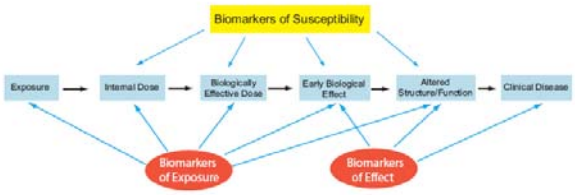
Stochasticity
- Characterization of Within and Between Person Variability

Parameter Uncertainty
- Year-to-Year Variability
- Observations below Limits of Detection (LOD)

Model Uncertainty
- Crop vs. Agricultural Job Task
- Identification of Highly Exposed Individuals

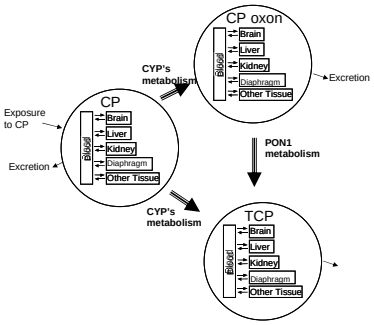
19

Biomarkers for Monitoring Exposure and Effect in Populations



20

Physiologic Based Toxicokinetic Models of CP Metabolism



21

Methodology Underlying Integrated Framework Tool

- Bayesian Based Mixed Effects Model
  - Correlational structure of a multivariate distribution used to estimate correlations between pesticide concentrations, metabolites, gene expression levels, and other variables
  - Markov chain Monte Carlo methods used for parameter estimation

22

OP Pesticide Exposures and Neurodevelopment in Children from Farmworker Families

Kim Harley, PhD
UC Berkeley
Center for Children's Environmental Health Research

Objectives

- To estimate sources, pathways and levels of ***in utero*** **and postnatal pesticide exposures of children living in an agricultural community.**
- **To determine the relationship of pesticide exposure and:**
  - **neurodevelopment**
  - **growth**
  - **respiratory disease**

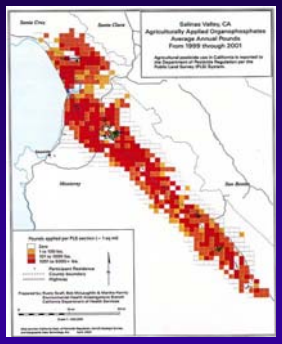
Center for the Health Assessment of Mothers and Children of Salinas

1998 - present

CHAMACOS
CENTER FOR THE HEALTH ASSESSMENT OF MOTHERS AND CHILDREN OF SALINAS

CHAMACOS Study Area

Pesticide Use in the Salinas Valley



500,000+ pounds of organophosphate pesticides used annually

Characteristics of CHAMACOS Mothers (N=601)

92%	Spanish-speaking
85%	born in Mexico; 54% ≤ 5 years in U.S.
96%	living within 200% of poverty
44%	6th grade education or less
44%	worked in agriculture during pregnancy
84%	other agricultural workers in home

CHAMACOS is a longitudinal birth cohort study

	1st Tri	2nd Tri	Delivery	6 M	1 Y	2 Y	3½ Y	5 Y	7 Y
• Maternal Questionnaire	✓	✓	✓	✓	✓	✓	✓	✓	✓
• Paternal Questionnaire			✓						
•Neurodevelopmental Assessment			✓	✓	✓	✓	✓	✓	✓
• Home inspection	✓			✓	✓	✓	✓	✓	
• Respiratory Function Tests								✓	✓
• School Performance									✓

CHAMACOS Biological Specimen Collection

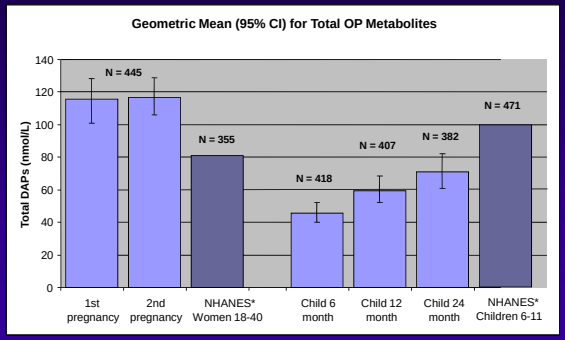
	1st Tri	2nd Tri	Delivery	6 M	1 Y	2 Y	3½ Y	5 Y	7 Y
• Maternal Urine	✓	✓	✓	✓					
• Paternal Urine			✓						
• Maternal Blood		✓	✓						
• Cord Blood			✓						
• Breast Milk			✓	✓					
• Child Urine				✓	✓	✓	✓	✓	
• Child Blood					✓	✓		✓	✓
• Child Saliva							✓	✓	

Pesticide Exposures

Organophosphate Pesticide Use in the Salinas Valley, 2001

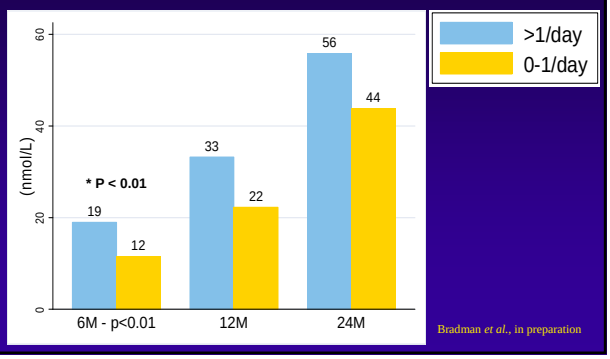
OP Pesticide	Pounds	Excreted in urine as
Malathion	96,520	Dimethyl (DM) phosphates ~220,000 lbs. (42%)
Oxydemeton-methyl	57,859	
Dimethoate	34,224	
Naled	17,045	
Methidathion	14,220	
Diazinon	133,537	Diethyl (DE) phosphates ~199,000 lbs. (38%)
Chlorpyrifos	54,945	
Disulfoton	10,216	
Acephate	71,725	Other ~104,000 lbs. (20%)
Bensulide	32,669	
Total	**~520,000**	

Prenatal and Child OP Metabolites in CHAMACOS and National Reference*



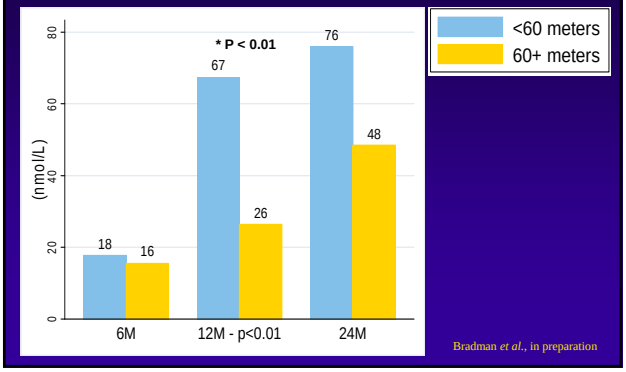
* National Health and Nutrition Examination Survey

Median DM Metabolite Levels by Fruit and Vegetable consumption



Bradman *et al.*, in preparation

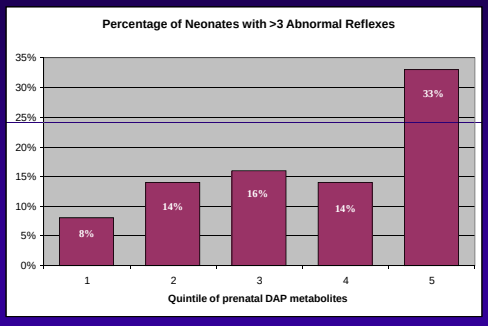
Median DM Metabolite Levels by Distance From Home to Ag Field



Bradman *et al.*, in preparation

Do these pesticide exposures affect children's neurodevelopment?

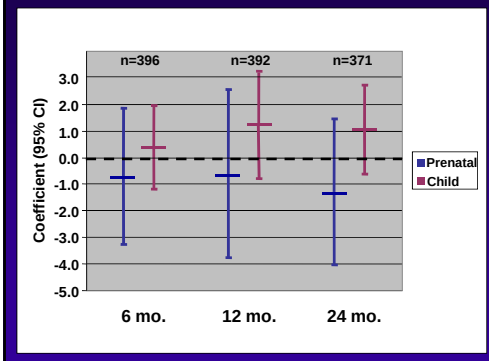
Newborns of Mothers with Higher Organophosphate Pesticide Exposures have More Abnormal Reflexes (n=184)



$X^2_{trend} = 6.7$
P-value = 0.01

Young *et al.*, 2005

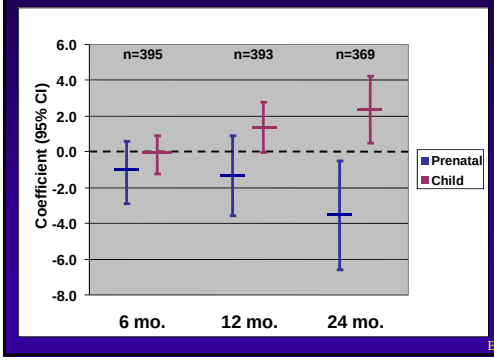
Total DAPs and Bayley Psychomotor at 6, 12, and 24 months (Adj.* ß±95%CI)



* All models adjusted for psychometrician, gender, age, parity, assessment location, breastfeeding duration, maternal PPVT, poverty status, and HOME score.

Eskenazi *et al.*, 2007

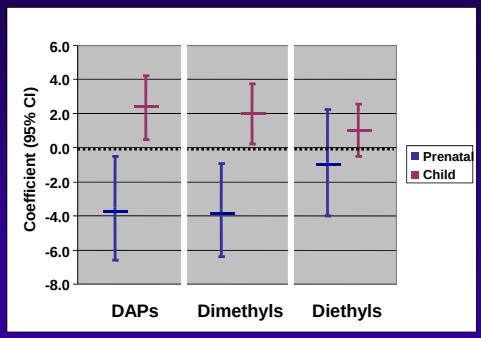
Total DAPs and Bayley Mental at 6, 12, and 24 months (Adj.* ß±95%CI)



* All models adjusted for psychometrician, gender, age, parity, assessment location, breastfeeding duration, maternal PPVT, poverty status, and HOME score.

Eskenazi *et al.*, 2007

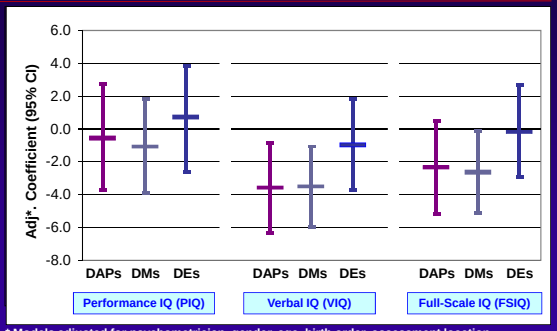
Total DAPs, DMs, and DEs and 24-month Bayley Mental (Adj.* ß±95%CI)



* All models adjusted for psychometrician, gender, age, parity, assessment location, breastfeeding duration, maternal PPVT, poverty status, and HOME score.

Eskenazi *et al.*, 2007

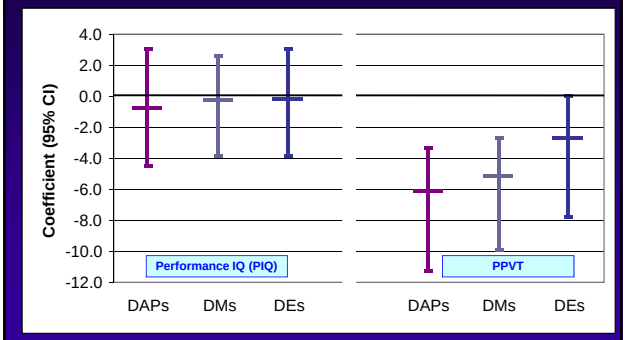
Preliminary Results: Prenatal OP Metabolites and 42-month WPPSI Scores (n=312)



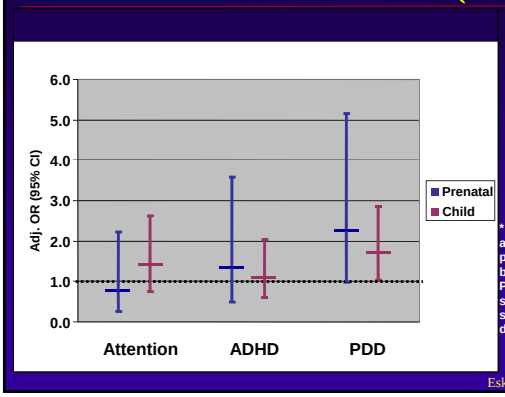
* Models adjusted for psychometrician, gender, age, birth order, assessment location, breastfeeding status at 12 months, maternal PPVT, poverty status, and preschool attendance.

Eskenazi *et al.*, in preparation

Preliminary Results: Prenatal OP Metabolites and 60-month WPPSI Scores (n=312)



Total DAPs and 24-month Child Behavior Checklist (Adj.* OR)



* All models adjusted for gender, parity, duration breastfed, maternal PPVT, poverty status, HOME score, and maternal depression.

Eskenazi *et al.*, 2007

Mary Wolff, Stephanie Engel, Gertrud Berkowitz
Mount Sinai School of Medicine

Virginia Rauh, Robin Wyatt, Frederica Perera
Columbia University

Brenda Eskenazi, Kim Harley, Asa Bradman, Amy Marks
University of California, Berkeley

Biomarkers of Prenatal OP Pesticide Exposures

	In Urine	In Blood
	Dialkyl Phosphates (DAPs)	**Chlorpyrifos (CPF)**
Berkeley	X	
Mt. Sinai	X	
Columbia		X

Early Childhood Neurodevelopmental Outcomes

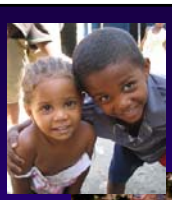
	Brazelton	Bayley				WPPSI	
	Neonatal	6M	1Y	2Y	3Y	3.5Y	5Y
Berkeley	X	X	X	X		X	X*
Mt. Sinai	X		X	X			
Columbia			X	X	X		X

* Verbal IQ assessed with PPVT

Early Childhood Neurobehavioral Outcomes

	Child Behavior Checklist (CBCL)		
	2Y	3Y	3.5Y
Berkeley	X		X
Mt. Sinai			
Columbia		X	

AGRICULTURAL CALIFORNIA

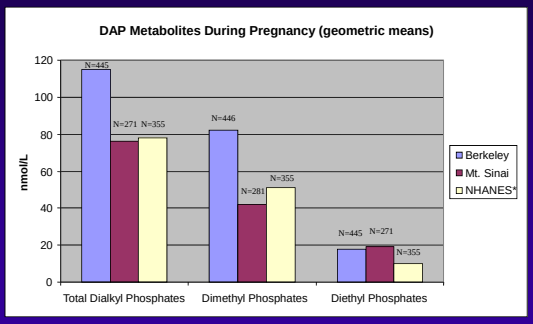


URBAN NEW YORK

Demographics of Study Populations

	Berkeley (%)	Mt. Sinai (%)	Columbia (%)
Race/Ethnicity			
Non-Hispanic White	1	20	--
African-American	--	27	35
Hispanic	Mexican 97	Mex, PR 51	Dominican 65
Other	2	1	--
Married	82	29	29
< High school	81	32	35

Comparison of Urinary Dialkyl Phosphate (DAP) Metabolite Levels



* NHANES data are for women aged 18-40

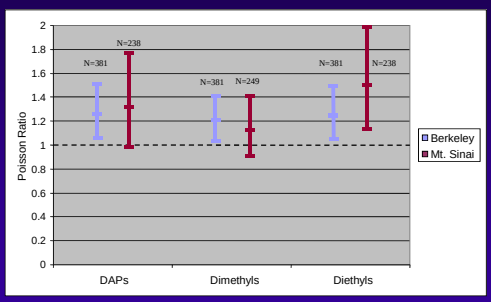
Associations with 7 Brazelton Clusters

	DAPs
Berkeley	6/7 No associations
Mt Sinai	6/7 No associations

EXCEPT….

Young *et al.* 2005; Engel *et al.* 2007

Association between DAPs and Brazelton reflexes in both cohorts



Young *et al.* 2005; Engel *et al.* 2007

Prenatal OPs and Bayley Psychomotor Development Index

	Berkeley (Log_{10}DAPs) Adj β	Mt. Sinai (Log_{10}DAPs) Adj β	Columbia (High v. Low CPF) Adj β
6 Months	-0.7	In prep	--
1 Year	-0.6		-3.3
2 Years	-1.3		1.2
3 Years	--		-6.5**

** p <0.05

Eskenazi *et al.* 2007; Engel *et al.* in preparation; Rauh *et al.* 2006

Prenatal OPs and Bayley Mental Development Index

	Berkeley (Log_{10}DAPs) Adj β	Mt. Sinai (Log_{10}DAPs) Adj β	Columbia (High v. Low CPF) Adj β
6 Months	-1.2	in prep	--
1 Year	-1.3		-0.3
2 Years	-3.5**		-1.5
3 Years	--		-3.3*

* p <0.1; ** p <0.05

Eskenazi *et al.* 2007; Engel *et al.* in preparation; Rauh *et al.* 2006

Prenatal OPs and Child Behavior Checklist

	Berkeley (Log_{10} DAPs) 2 Y Adj OR	Berkeley (Log_{10} DAPs) 3.5 Y Adj OR	Columbia (High v. Low CPF) 3 Y Adj OR
Attention Problems	0.8	in prep	11.3*
Attention Deficit/Hyperactivity	1.3		6.5*
Pervasive Developmental Disorder	2.3**		5.4*

* p <0.1, ** p <0.05

Eskenazi *et al.* 2007; Eskenazi *et al.* in preparation; Rauh *et al.* 2006

In summary…

- Three scientifically-rigorous, cohort studies
  - Different populations
  - Different exposure levels and sources
  - Exposure measured using biomarkers in urine (metabolites) and blood (parent compound)
- Despite these differences, some patterns emerge…

In summary…

- Prenatal OP exposure associated with:
  - Increased odds of abnormal reflexes in neonates
  - Poorer mental development in 2 and 3 year olds
  - Poorer verbal IQ in 3½ and 5 year olds
  - Increased odds of pervasive developmental disorder

Investigators

Exposure Studies
- Asa Bradman
- Tom McKone
- Dana Barr CDC
- Rosemary Castorina
- Martha Harnly, DHS
- Jim Leckie, Stanford
- Marcia Nishioka, Batelle
- Jackie Schwartz

Health Studies
- Brenda Eskenazi
- Ira Tager
- Kim Harley
- Laura Fenster, DHS
- Caroline Johnson
- Michael Lipsett, DHS
- Janet Macher, DHS

Mechanism Studies
- Nina Holland
- John Casida

Biostatistical Core
- Nick Jewell
- Alan Hubbard
- Amy Marks

Intervention and Community Outreach
- Abbey Alkon, UCSF
- Lisa Goldman
- Alicia Salvatore
- Jorge Hernandez Clinica

Clinica de Salud
- Jacki Sedgwick
- Max Cuevas

Natividad Medical Center
- Marc Tunzi

1998 CENTERS FOR EXCELLENCE: CHILDREN'S ENVIRONMENTAL HEALTH

With additional funding from:

California Wellness Foundation

www.chamacos.org

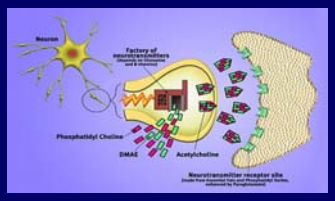
Cholinesterase Monitoring in Washington State

John Furman
Washington State Department of Labor & Industries

Thank you to Jonathan H. Siekmann, Ph.D

What Is Cholinesterase (ChE)?

- Enzyme
- Present in nerves, brain, and muscle
- Nervous system's "off" switch
- If ↓ ChE → ↑↑↑ acetylcholine → overstimulation & exhaustion of nervous system



Cholinesterase-inhibiting Pesticides

- Organophosphates
- N-methyl-carbamates
- Toxicity class I & II products
  - "DANGER" or "WARNING" on the label
    Class I LD 50 of < 50 mg oral or 100 dermal
    Class II LD 50 of >50 <500 oral or <1000 dermal

Pesticide-Related Illness

- Mild
  - tiredness, weakness, dizziness, nausea, blurred vision
- Moderate
  - headache, stomach cramps, sweating, drooling, vomiting, tearing, twitching
- Severe
  - urinating, diarrhea, muscle twitching, staggering gait, pinpoint pupils, seizures, hypotension, slow heartbeat, breathing difficulty, coma , death

Blood Cholinesterase: Convenient Biomarker

- Red Blood Cell (RBC) ChE
  - Sensitive to organophosphates
  - Measures longer-term exposures
  - Slow recovery
- Serum ChE
  - Sensitive to most ChE inhibiting pesticides
  - Measures recent exposures
  - Rapid recovery

Measure both for accurate picture of exposures

Considerations

- Normal individual ChE levels vary
  - Establish exposure-free baseline
  - Compare periodic samples to baseline
- Different analytical methods exist
  - Use same laboratory
  - Use same method
- "Depression" is a decrease in ChE activity in periodic sample vs. baseline

Why Monitor Cholinesterase?

- Detect overexposure to pesticides
- Increase hazard awareness
- Identify unsafe environments & fix problems
- Reduce risk of possible long-term adverse health effects
- Decrease take-home exposures

ChE Monitoring in Washington: History and Legal Authority

- 1993 – ChE monitoring recommended
- 2002 – Rios v Washington
- 2003 – WAC 296-307-148 adopted
- 2004 – 1st year of operation
- 2006 – Final SAC report
- 2007 – Move to commercial laboratory

Who is Tested in Washington?

Agricultural handlers of Class I and II

- Organophosphates
- N-methyl Carbamates

Exposure threshold:

2004	≥50 hours handling in 30 days
2005	≥30 hours handling in 30 days

Pesticide Handling

- **Agriculture pesticide handling***
  - Mixing, loading transferring applying
  - Disposing of pesticides or pesticide containers
  - Handling open containers of pesticides
  - Acting as a flagger
  - Cleaning, maintaining equipment that may contain pesticide residue
  - Assisting with application

**** See WPS for complete definition***

Handler Participation

- May decline participation
- Employer provided training
- Informed consent process with medical provider
- Signed declination statement
- Averaged ~12% annual declination rate

Required Actions

- **Work practice investigation**
  - ≥20% depression in either RBC or serum ChE
- **Exposure removal**
  - ≥30% depression in RBC ChE*

    or
  - ≥40% depression in serum ChE*

**Can return to handling when within 20% of baseline*

Experience

	2004	2005	2006	2007*
• # Employers	370	312	244	219
• # Baseline tests	2630	2239	1889	1859
• # Periodic tests	1048	994	692	494
• # Employees with periodic tests	580	612	471	362

** Preliminary numbers*

Experience

	2004	2005	2006	2007*
• Work practice investigations	97 (17%)	49 (8%)	50 (11%)	48 (13%)
• # Medical removals	22 (4%)	10 (2%)	7 (1%)	14 (4%)
Total	119 (21%)	59 (10%)	57 (12%)	62 (17%)

Work Site Violations

- Respiratory Protection
- Personal Protective Equipment
- Personal clothing as exposure source
- Decontamination
- Pesticide Handler Training

Effects

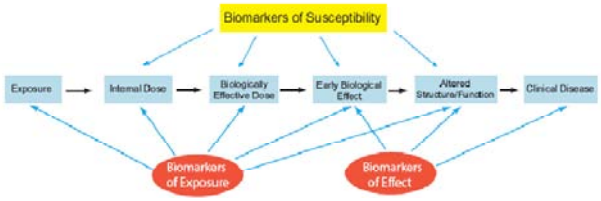
- Increased knowledge
- Increased hazard awareness
- Training integration
- Changes in pest management practices
- Improved medical services
- Increased stakeholder collaboration

Biomarkers of Pesticide Exposure: Lessons for Children in Agricultural Communities

Elaine M. Faustman
Bill Griffith
NIEHS/EPA Center for Child Environmental Health Risks Research
Institute of Risk Analysis and Risk Communication
University of Washington

Gustav Klimt, *Baby (Cradle)*, 1917/1918.
National Gallery of Art. From www.nga.gov

Biomarkers for Monitoring Exposure and Effect in Populations



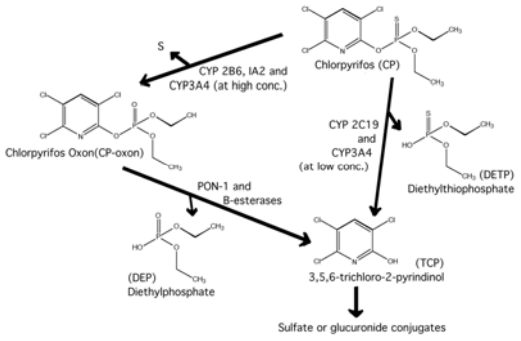
Examples of Chemicals Applied to Washington State Crops, 2001

Chemical class	crop	Chemical	Pounds applied
Organophosphates	Apples	Azinphos-methyl	241,000
		Chlorpyrifos	234,000
		Phosmet	138,000
	Potatoes	Ethoprop	119,000
		Metamidophos	143,000
N-Me Carbamates	Apples	carbaryl	202,000
	Potatoes	Aldicarb	153,000
Dithiocarbamate	Apples	Mancozeb	82,000
	Potatoes	Mancozeb	343,000

Source: "Agricultural Chemical Usage (PCU-BB)" National Agricultural Statistics Service, Agricultural Statistics Board, U.S. Department of Agriculture (http://jan.mannlib.cornell.edu/reports/nassr/other/pcubb Accessed 05/03)

Agricultural Pesticides: Contributions of Occupational Factors to Home Contamination

Metabolic Scheme for CP



Faustman et al. (2006)

Metabolites of Organophosphate Pesticides

- Biomarkers of exposure
- Nonspecific Diakyl Phosphate (DAP) metabolites
  - Six DAP Metabolites
  - Each metabolite can be produced by multiple OPs
  - Divided into two groups
    - Dimethyl metabolites
      - DMP, DMTP, DMDTP
    - Diethyl metabolites
      - DEP, DETP, DEDTP
- Specific metabolites
  - Chlorpyrifos metabolites
    - TCP, DEP, DETP
  - Chlorpyrifos-methyl metabolites
    - TCP, DMP, DMTP

Metabolites of Organophosphate Pesticides

Selected OPs and DAP metabolites

Diethyl OPs			
chlorpyrifos		DEP	DETP
diazinon		DEP	DETP
disulfoton	DEDTP	DEP	DETP
ethion	DEDTP	DEP	DETP
parathion		DEP	DETP
Dimethyl OPs			
azinophos methyl	DMDTP	DMP	DMTP
chlorpyrifos methyl		DMP	DMTP
dichlorvos (DDVP)		DMP	
malathion	DMDTP	DMP	DMTP
methyl parathion		DMP	DMTP
naled		DMP	
phosmet	DMDTP	DMP	DMTP
trichlorfon		DMP	

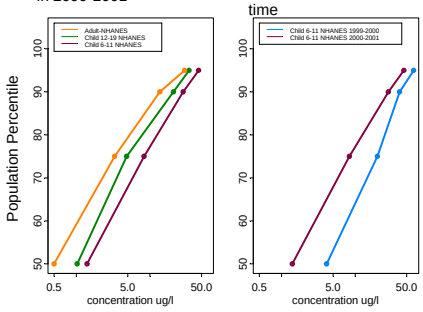
7

NHANES Data for DMTP in Urine

Random sample of US Population

Comparison across ages in 2000-2001

Comparison for children (6-11 years old) across time



8

What do these values mean for my Children?

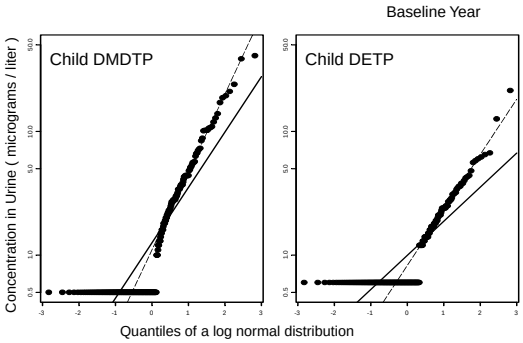
9

Samples Collected in Studies of Farmworker Families

- Types of samples collected from individuals and their children in 3 seasons
  - Urine analyzed for metabolites of OPs—collected 3 times in 1 week
  - Blood analyzed for parent OPs, metabolites of OPs, AChE in RBCs and plasma, genotypes and phenotypes of metabolizing enzymes—collected once
  - Buccal Cells analyzed for gene expression—collected 2 times in 1 week
- Dust is collected from homes and autos in thinning and non-spray seasons season and analyzed for parent OPs

10

Many Values Are Below Limits of Detection

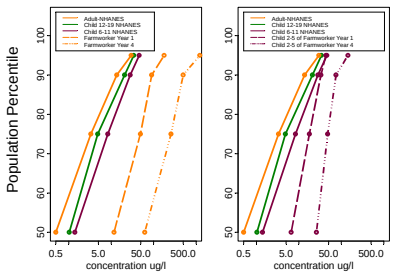


11

NHANES Compared to Farmworker Family Data for DMTP in Urine

Comparison to Adult Farmworkers

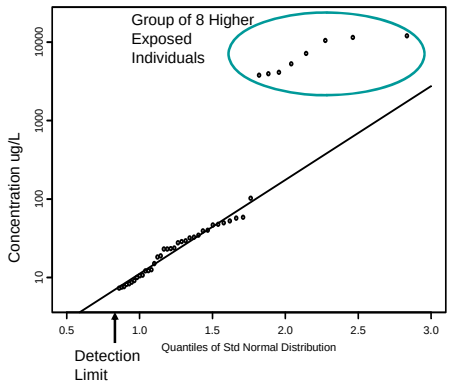
Comparison to Children of Farmworkers (2-5 years old)



Data for farmworkers and their children was collected in two different years

12

DMP in Adult Urine: QQ Plots to Estimate Population Distribution



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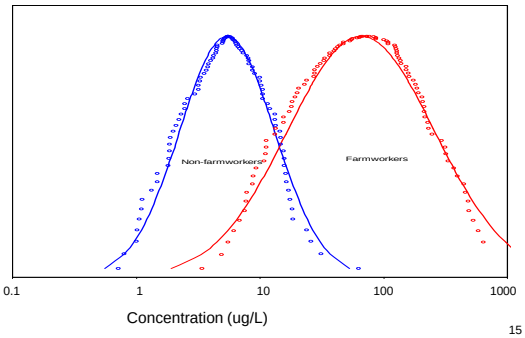
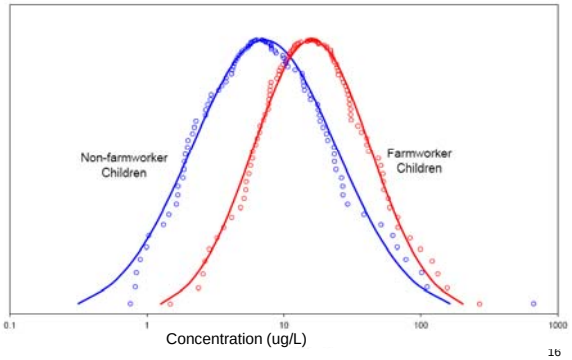
14

Distribution of Adult DMTP Metabolite Concentrations



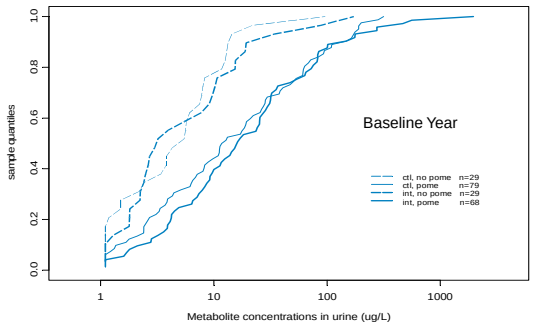
15

Distribution of Child Urinary DMTP Metabolite Concentrations



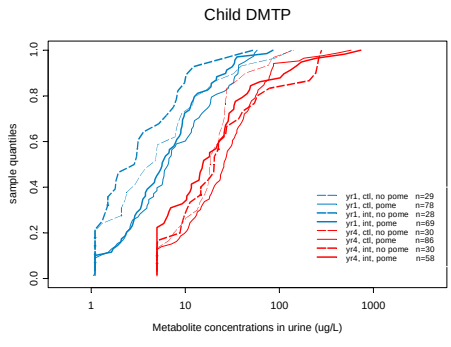
16

Distribution of Adult DMTP from year 1: Impact of Crop



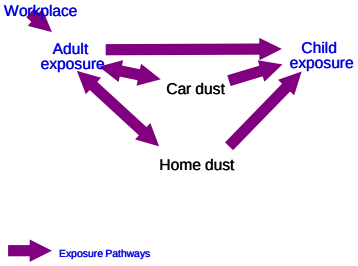
17

Distribution of Child DMTP from year 1 to year 4 of CHC study: Impacts of year to year variability



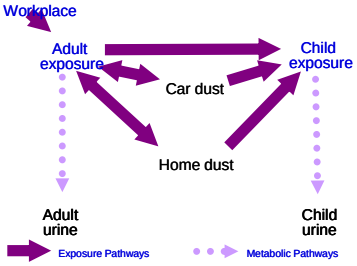
18

Assessing Children's Pesticide Exposure via the Take-home Pathway



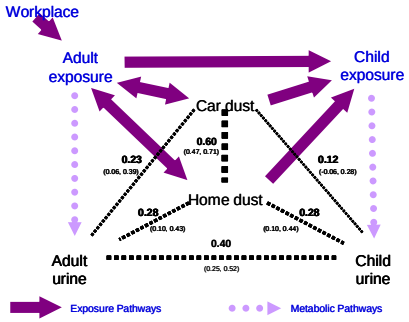
19

Assessing Children's Pesticide Exposure via the Take-home Pathway



20

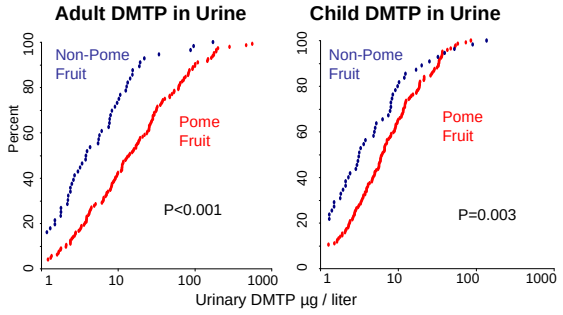
Azinphos-methyl Take-home Pathway



The dashed black lines that connect the samples illustrate the correlations between the sample concentrations. The lines are weighted according to the strengths of the correlations. The correlations are statistically significant if the 95% posterior probability intervals (in parentheses) do not include zero.

21

Urinary metabolites higher in adults who worked in pome fruit and their children



Coronado et al., Env. Hlth. Persp., 2004, 2006

22

Two longitudinal studies of OP metabolites used to estimate within and between variability

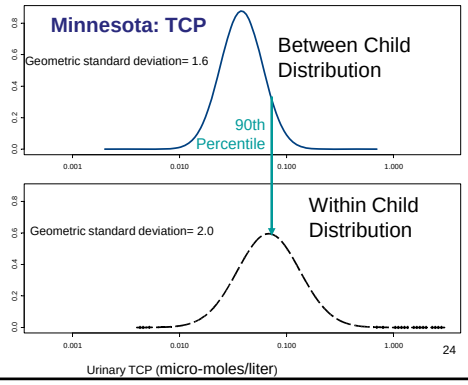
- Multiple measurements in the same person across time permit estimation of both within and between person variability
  - Within and between person variability treated as a random effect and other variables such as age, gender ,residence, season treated as fixed effects
- TCP had a low percentage below limits of detection
- Measurements below limit of detection (LOD) were treated as being left censored in statistical analyses

23

Within and Between Person Distributions for TCP

NHEXAS database

- Population based random sample collected at 3 times separated by 2 days
- 90 Children 3-14 yrs old and 263 samples
- Only 20 samples, 8%, below limit of detection
- Covariates of gender, age, residence were treated as fixed effects
- NHEXAS data Shared by John Quackenboss

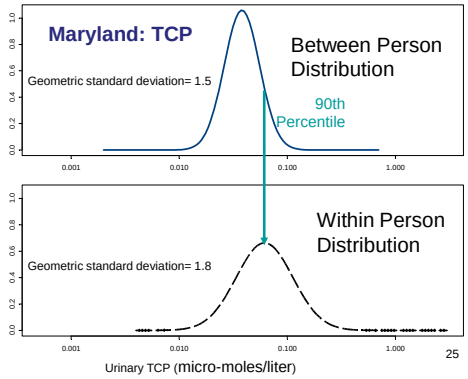


24

Within and Between Person Distributions for TCP

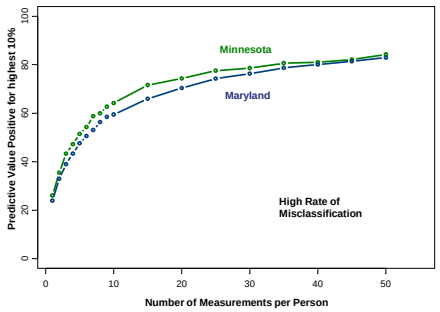
NHEXAS database

- Population based random sample collected over 1 year
- Up to 6 samples per person, samples separated by 2 months
- 79 individuals and 341 samples
- Only 14 samples, 4%, below limit of detection
- Covariates of gender, age, season were treated as fixed effects



Predictive Value Positive for Identifying Persons in the Upper 10% of the Population

The predictive value positive is the percent of the population assigned to a group that are correctly classified.



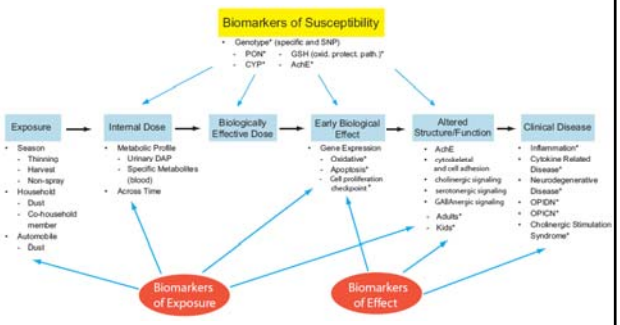
Based upon large within person variances it will require a large number of samples of urinary metabolites to correctly identify persons in a population who are more highly exposed to CP and CPM.

Sources of Uncertainty

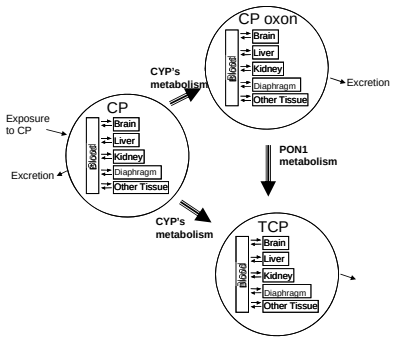
Stochasticity
- Characterization of Within and Between Person Variability

Parameter Uncertainty
- Year-to-Year Variability
- Observations below Limits of Detection (LOD)

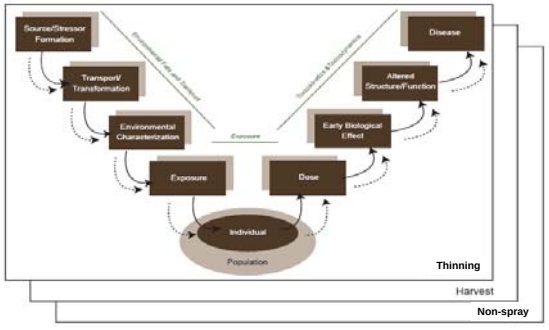
Model Uncertainty
- Crop vs. Agricultural Job Task
- Identification of Highly Exposed Individuals



Physiologic Based Toxicokinetic Models of CP Metabolism



Integrated Framework Tool



Methodology Underlying Integrated Framework Tool

- Bayesian Based Mixed Effects Model
  - Correlational structure of a multivariate distribution used to estimate correlations between pesticide concentrations, metabolites, gene expression levels, and other variables
  - Markov chain Monte Carlo methods used for parameter estimation

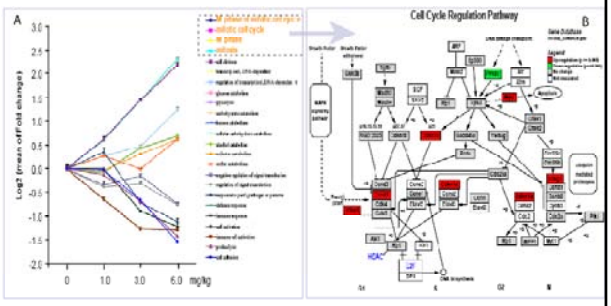
31

Hypotheses to be Tested

1. Knowing the genotype/phenotype for key genes that metabolize CP (biomarkers of susceptibility) will improve prediction of
   - Exposure response
   - At risk individuals in agricultural communities
2. Knowing polymporphisms of oxidant responsive pathways will allow us to:
   - Better evaluate the potential for genomic biomarkers of early response with OP metabolites of exposure.
   - Better predict relationship of biomarkers of effect (AChE) to respond in dose-response manner to the OP exposures in adults and children.
   - Better predict whether "omic" biomarkers of disease are correlated with OP exposure.

32

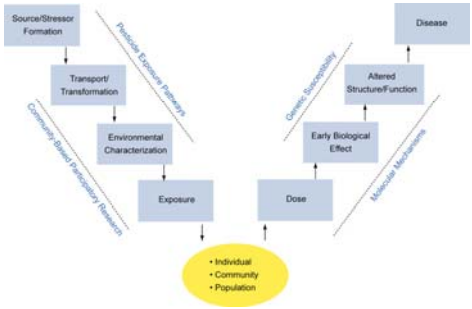
GO-Quant based quantitative pathway analysis



33

NIEHS/EPA Center for Child Environmental Health Risks Research

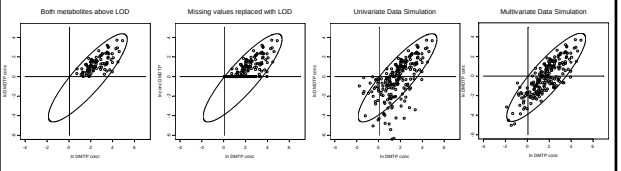
University of Washington



34

Using Markov Chain Monte Carlo Methods to Estimate Correlation Structure

Metabolites above LOD	Replace missing values by LOD	Univariate Data Simulation	Multivariate Data Simulation



35

Phthalates Exposure in Childhood: Is there Evidence of Harm?

Maida P. Galvez, MD, MPH
Region II PEHSU Director

Mount Sinai Children's Environmental Health Center

Phthalates

Phthalates

- Concerns exist about the potential for phthalates to act as endocrine disruptors, largely based on animal studies and a small but growing body of evidence in human studies.

Hormonal effects of phthalates

	Animal Studies	Human Studies
DEHP	↑gestational age	
DBP	↓ gestational age	√
BBP	↑body weight at lactation	
DBP, DEHP	↓ serum testosterone	√
BBP	↓ Anogenital distance in male infants	√
MBP	Decreases testicular function	√

Phthalates Legislation

- Several countries around the world, beginning with the European Union, have subsequently banned phthalates in children's products.

Phthalates in the Media

- Widespread media reports on the potential harms of toxic toys and other children's products containing phthalates have raised parental anxiety about the impact of environmental exposures on their children.

Primary care pediatricians

- Faced with clinical questions that are difficult to answer:
  - limited medical school training in children's environmental health
  - Especially limited knowledge of emerging exposures of concern such as phthalates
  - Conflicting messages in the media

What Parents Ask

- Where are phthalates found?
- Is this pacifier harmful to my child?
- How do I know if toys contain phthalates?
- Why was it banned?
- What health effects should I look for?
- Should I avoid phthalates if I am pregnant?
- What substitutes can I use for my child?

Goals for this Session

To describe:

- exposure levels in pregnant women, toddlers, and school aged children
- sources of exposure
- known and potential health outcomes

Is there Evidence of Harm?

Pregnant women in New York City
Dr. Robin Whyatt
Columbia University Center for Children's Environmental Health

6-24 month old infants from California, Minnesota, and Missouri
Dr. Sheela Sathyanarayana
University of Washington, Seattle, Northwest PEHSU

Pregnant women and 4-8 year old children in New York City
Dr. Mary Wolff
Mount Sinai Center for Children's Environmental Health

Phthalates Exposures are Widespread

	MEP	MBuPhth	MbZPhth	MECPP
NYC Pregnant Women (n=246)	232	37.5	17.5	-
NYC Pregnant women (n=382)	380	36	22	35
CA, MI, MO 2-24 mos (n=163)	65	19	15	4
NYC 6-8 yo girls (n=30)	100	50	22	111
NYC 6-8 yo boys (n=101)	152	68	48	123
NYC kids (n=35) 159 samples	166	56	38	139

Summary of Findings

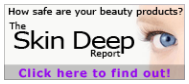
- Sources are varied
  - Products used
  - Indoor air
- Good biomarkers
- Health outcomes
  - Gestational Age
  - Anogenital Distance
  - BMI
  - Asthma

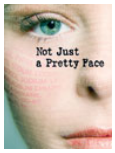
What's the evidence for Phthalates in Cosmetics?

- EWG report on phthalates in cosmetics
- Skin Deep Database

- Safe Cosmetics Fact Sheet
- 12 Ugly Truths Behind the Myth of Cosmetic Safety

- Campaign for Safe Cosmetics





Pocket Guide to Plastics for easy reference

Front of card | Back of card

Key areas for discussion include:

- What is the current evidence for adverse health outcomes?
- What are the research gaps?
- What health messages on phthalates can we share with families now?
- What policy issues remain unresolved?

Acknowledgements

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Kim Morland, PhD
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  - Children's Aid Society
  - East Harlem Pediatric/Child Health Subcommittee
  - Little Sisters of the Assumption
  - Mount Sinai Pediatrics Associates
  - Mount Sinai School Based Health
  - NYCDOHMH's East Harlem District Public Health Office
  - North General Hospital
  - Settlement Health
- **Susan Resnick at the NYCDOHMH**
- **Jodi Siskind, Jessica Kobil and Cherita Raines**

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Agency for Toxic Substances Disease Registry
- ATU Grant #300014

General Clinical Research Center
- NCRR Grant #MO1-RR-00071

Case Study on Phthalates

Phthalate exposures during pregnancy

Results from a birth cohort study of NYC inner-city mothers and newborns

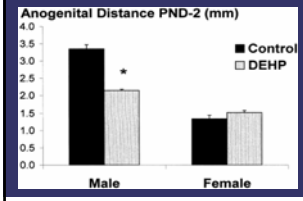
Robin M. Whyatt, DrPH
Professor Clinical Environmental Health Science
Columbia Center for Children's Environmental Health

Case Study on Phthalates

Why are we concerned about prenatal exposures?

Exposures are ubiquitous: 78 – 99% of U.S. population exposed.
A number are endocrine disruptors; including as antiandrogens.
Experimental and preliminary epidemiology evidence indicates

- A number are reproductive toxicants associated with:
- Malformations of developing male reproductive tract
- Increased intrauterine/postnatal death;
- Decreased fetal growth
- Modulation of gestational age (?)



(www.Nottoopretty.org)

Case Study on Phthalates

Specific aims of our research

Aim 1: Characterize phthalate exposures during pregnancy among NYC African American and Dominican women (n=350).

Aim 2: Examine effects of prenatal phthalate exposures on modulation of gene expression in placental tissue.

Aim 3: Examine effects of prenatal phthalate exposure on gestational age and fetal growth.

NIEHS RO1 ES013543 (Whyatt R., P.I.)

Case Study on Phthalates

Columbia Center for Children's Environmental Health

Pregnancy (N=725) . . . . . child age 9-11

Exposure Assessment | **Biomarkers of Exposure Effect/Susceptibility** | **Outcome**

Environmental Exposures	Biomarkers	Clinical Outcomes
Air Pollutants		
PAH, PM	PAH-DNA Adducts	Fetal Growth
ETS	Cotinine	Child Neurodevelopment
Allergens	Immune changes	Wheeze/Asthma
Metals	Lead, Mercury	
Pesticides	Pesticides	
Phthalate diesters	Phthalate monoesters	
Susceptibility Factors		

Funded by U.S. EPA and NIEHS

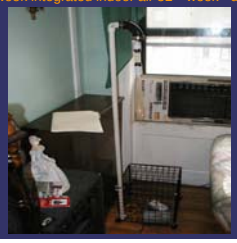
Case Study on Phthalates

Cohort

Number: 300 mother/newborn pairs from CCCEH cohort
Race/Ethnicity: African American and Dominican
Residence: Northern Manhattan and South Bronx
Exclusion: Smokers, Illicit Drug, HIV, Hypertension, Diabetes

48 hour personal air 3rd trimester

2 week integrated indoor air 32nd week - delivery



Case Study on Phthalates

Biologic Samples

- Maternal prenatal urine
- Maternal postnatal urine
- Newborn postnatal urine
- Meconium
- Placental tissue

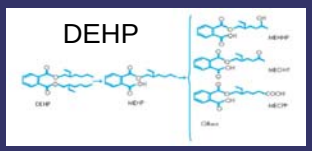
Medical record data: gestational age, gender, birth weight, length, head circumference, maternal height, pre-pregnancy weight and weight gain, medications

Case Study on Phthalates

Phthalate Diesters In Air	Monoester Metabolites In Urine
Di (2-ethylhexyl) phthalate (DEHP)	Mono(2-ethylhexyl) phthalate (MEHP) Mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) Mono(2-ethy-5-oxolhexyl) phthalate (MEOHP) Mono(2-ethy-5-carboxypentyl) phthalate (MECPP)
Di-n-butyl phthalate (DBP)	Mono-n-butyl phthalate (MBP)
Butylbenzyl phthalate (BBzP)	Monobenzyl phthalate (MBzP) Mono-n-butyl phthalate (MBP, minor metabolite)
Diethyl phthalate (DEP)	Monoethyl phthalate (MEP)

Once inside the body:
- Rapidly hydrolyzed to monoester & other oxidative metabolites
- Glucuronidated and excreted
- Half-life: 12 to 48 hours

DEHP



Case Study on Phthalates

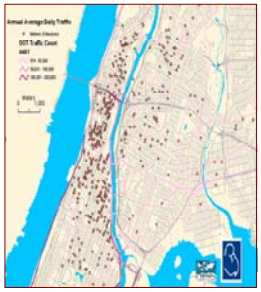
Placental gene expression

Pathways	Genes
Steroid synthesis and metabolism	peroxisome proliferator activated receptor (PPARγ) aromatase (CYP19) aryl hydrocarbon receptor (AhR) cholesterol side chain cleavage enzyme (P450scc) 17β-hydroxysteroid dehydrogenase (17β-HSD 1)
Xenobiotic metabolism	CYP1B1, AhR, CYP19
Oxidative stress	Epoxide hydrolase (EH)
Fatty acid transport	PPARγ, fatty acid transport protein (FATP)
Trophoblast differentiation	PPARγ, human chorionic gonadotropin (hCG)

Case Study on Phthalates

Demographics (n = 246)

Maternal age (years)	25.6 ± 4.6
Ethnicity	
Latina	74%
African American	26%
Marital Status	
Never married	62%
Education	
< High School	37%
Annual Household Income	
<$10,000	44%
Gestational age	39.2 ± 1.9



Case Study on Phthalates

Research Results

Aim 1: Characterize phthalate exposures during pregnancy among NYC African American and Dominican women.

Case Study on Phthalates

Phthalate levels in personal air samples and maternal urine samples during pregnancy

Air levels (µg/m3) (N=96)			Urine levels (ng/ml) (N=246)		
Diester	%>LOD	GM (95% CI)	Monoester	%>LOD	GM (95% CI)
DEHP	100%	0.18 (0.16, 0.21)	MEHP	85%	4.8 (4.0, 5.8)
			MEOHP	100%	18.2 (15.6, 21.3)
			MEHHP	100%	20.2 (17.2, 23.6)
DnBP	100%	0.45 (0.41, 0.51)	MnBP	100%	37.5 (33.3, 42.2)
BBzP	100%	0.05 (0.04, 0.06)	MBzP	100%	17.5 (14.8, 20.7)
DEP	100%	2.15 (1.92, 2.41)	MEP	100%	232 (199, 272)

- Correlations: BBzP to MBzP (r=0.51, p<0.0001); DEP to MEP (r=.22, p = 0.04)
- Urinary levels of MBP significantly higher than in US. women 18-40 years sampled in NHANES 2001-02
- Personal and indoor air levels similar and except for DEHP were highly correlated (r=0.51-67, p<0.01)

Adibi et al., submitted, 2007

Case Study on Phthalates

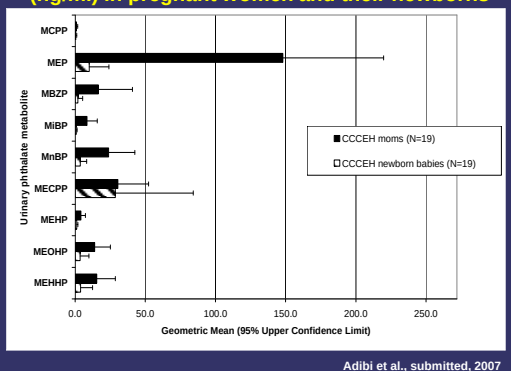
Intraclass correlation coefficients for phthalates in repeat indoor air samples (N=32 homes) and maternal urine samples (N=28) during pregnancy (2-4 samples per subject)

Indoor air		Maternal urine	
DEHP	0.48	MEHP	0.35
		MEOHP	0.34
		MEHHP	0.36
DnBP	0.59	MnBP	0.62
BBzP	0.83	MBzP	0.66
DEP	0.54	MEP	0.30

Adibi et al., submitted, 2007

Case Study on Phthalates

Urinary profile of phthalate metabolite concentrations (ng/ml) in pregnant women and their newborns



Adibi et al., submitted, 2007

Case Study on Phthalates

Research Results

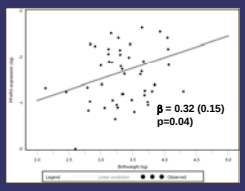
Aim 2: Examine effects of prenatal phthalate exposures on modulation of gene expression in placental tissue.

Case Study on Phthalates

Gene expression ⇒ Placental function ⇒ Clinical outcomes (n=55)

Gene	PPARγ	CYP19	Ahr	FATP
Median mRNA molecules/sample	3.0 X 10^3	2.0 X 10^4	4.4 X 10^2	8.6 X 10^2

(ln)PPARγ expression/cyclophilin ⇒ Birthweight



Regression model adjusted for sampling characteristics, maternal weight, health conditions in current pregnancy, previous pregnancy outcomes, and demographic factors

Adibi et al., in preparation

Case Study on Phthalates

Research Results

Aim 3: Examine effects of prenatal phthalate exposure on gestational age and fetal growth.

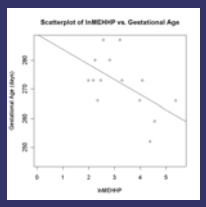
1. Latini et al.: cord blood MEHP inverse with gestational age (EHP, 2003)
2. Our pilot: gestatiional age inverse with maternal oxidative metabolites

Gestational Age

(ln)MEOHP -5.3 days, p=0.01

(ln)MEHHP -5.4 days, p<0.01

3. Two recent epidemiologic study show positive associations between maternal prenatal urinary levels and gestational age.



Case Study on Phthalates

Conclusions

- **Phthalate exposures are widespread among NYC African Americans and Dominicans during pregnancy**
- **Phthalates are detected in 85%-100% of indoor air, personal air and maternal urine samples**
- **Indoor air levels appear stable over time and are significantly correlated with personal air levels in most cases.**
- **A significant correlation between air and urine levels was seen for two phthalates**
- **DEHP exposures may be modulating gestational age**

Case Study on Phthalates

Acknowlegements

Co-Investigators

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Study participants

Infant Phthalate Exposures and Potential Developmental Impacts

Study For Future Families:

Cohort of Mother/Baby Pairs from Missouri, California, and Minnesota

Shanna Swan PhD – Primary Investigator

Sheela Sathyanarayana MD MPH
Acting Assistant Professor
University of Washington
Department of Pediatrics

Research Questions

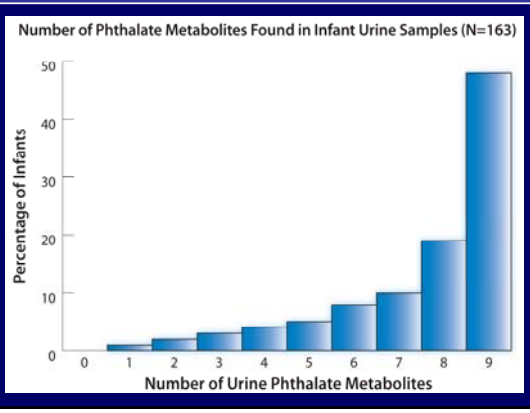
- Is Infant Personal Care Product Use Associated with Urine Phthalate Concentrations?
- Is Maternal Phthalate Exposure Associated with Developmental Outcomes in Infants?

Demographic Characteristics

Cohort: 163 Infants

Sex	
Females	52%
Males	48%
Geographic	
Minnesota	48%
California	26%
Missouri	26%
Ages (mo)	
2-8	25%
9-16	50%
17 – 24	25%
Race	
White	80%
Hispanic/Latino	11%
Asian	5%
African American	3%
Native American	1%
Socio-Economic Status	
Health Insurance	91%
No Health Insurance	9%

Results



Results

Distribution of Phthalates (mcg/L)

Phthalate (N = 163)	% > LOD	Geometric Mean
Monoethyl (MEP)	98	64.5
Monobutyl (MBP)	99	19.3
Monomethyl (MMP)	66	1.8
Mono-3-carboxypropyl (MCPP)	83	4.0
Monobenzyl (MBZP)	94	14.9
Monoisobutyl (MiBP)	85	3.5
Mono-2-ethyl-5-oxohexyl (MEOHP)	94	11.4
Mono-2-ethylhexyl (MEHP)	76	2.9
Mono-2-ethyl-5-hydroxyhexyl (MEHHP)	93	13.7

LOD = Limit of Detection
** These levels are similar or lower to those of age 6-11 children in NHANES

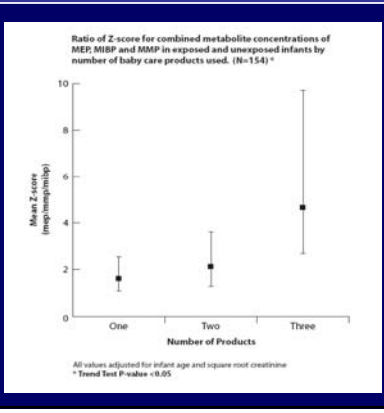
Results

Ratio of Z-Score Combined Phthalate Metabolite Concentration (mep/mmp/mibp) by Age in Exposed and Unexposed Infants

	Product Type	Mean Z-score Subgroup N % <= 8 months 42 (26)	Mean Z-score Subgroup N % > 8 months 112 (74)	Mean Z-score Subgroup N % All Infants 154 (100)
Strong/ Significant	Baby Powder	**2.7* (1.3, 5.9)**	**2.0* (1.02, 4.0)**	**2.1* (1.3, 3.6)**
	Baby Lotion	**5.6* (1.7, 18.3)**	1.5 (0.8, 2.6)	**2.1* (1.3, 3.4)**
	Baby Shampoo	2.1 (0.6, 7.4)	1.4 (0.4, 4.3)	**1.6* (1.03, 2.4)**
Weak/Not Significant	Desitin/Diaper Cream	1.4 (0.5, 3.9)	0.7 (0.6, 1.6)	1.1 (0.7, 1.7)
	Baby Wipes	2.1 (0.4, 11.1)	1.4 (0.4, 4.3)	1.4 (0.5, 3.6)

All values adjusted for infant age, and square root creatinine, nine infants had missing creatinine values are were not included in analysis
*p-value <0.05

Results



Conclusions

- Phthalate exposure is widespread and distribution varied in infants
- Reported infant exposure to lotion, powder, and shampoo significantly increased urinary concentrations of MEP, MMP, and MiBP and associations are strongest in younger infants
- Dermally applied baby products significantly contribute to infant phthalate body burden

Research Question

- Is Maternal Phthalate Exposure Associated with Developmental Outcomes in Infants?

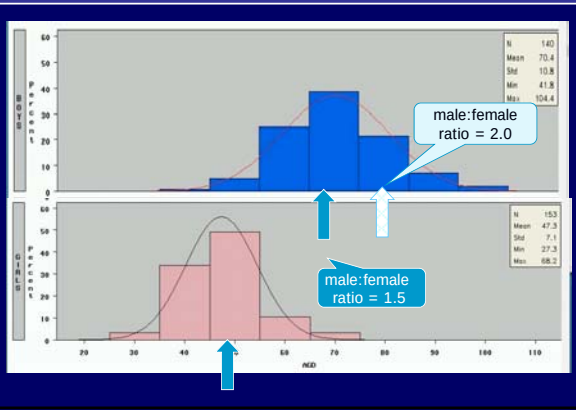
Anogenital Distance

- Significance – marker of masculinization in animals

  - length ratio 2:1 for Males : Females in rats

  - shortened AGD associated with genital tract abnormalities

AGD by Sex



Analysis of Male Anogenital Distance

- AGD increases with both age and weight
- These are strongly correlated (R^2 = 0.88, p<0.0001)
- We used standard growth curves to adjust for body size (CDC, 2000)
- Weight percentile (WT%) calculated for each boy at each visit
- Expected AGD modeled for male infants:
  - Using all visits (mixed model)
  - WT% and age were the only significant predictors
  - Residual AGD = Observed – Expected → categorized into short, intermediate, and longer

Results of Regression Analysis*:

Significant (p-value)
- MBP (0.048)
- MEP (0.005)
- DEHP metabolites
  - MEHP (0.017)
  - MEOHP (0.001)
  - MEHHP (0.002)

Borderline
- MMP (0.053)
- MiBP (0.097)

Not Significant
- MBzP (0.826)
- MCPP (0.591)

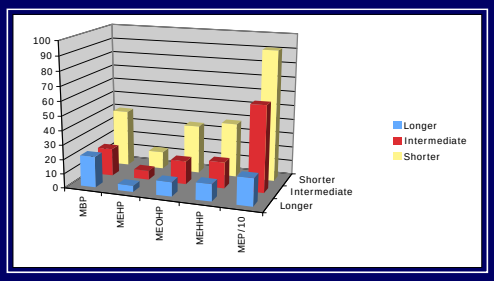
* Mixed model including 106 boys and 165 visits

Odds Ratio (95% CI) for Shorter AGD

Exposure	Medium : Low *	High : Low *
MBP	5.7 (1.2, 27.3)	9.2 (1.8, 46.2)
MEHP	1.7 (0.5, 5.2)	3.2 (0.9, 11.5)
MEOHP	10.2 (1.3, 82.5)	29.1 (3.4, 245.6)
MEHHP	4.8 (1.0, 22.9)	13.0 (2.6, 66.4)
MEP	4.6 (1.0, 21.6)	7.9 (1.5, 41.3)

*Low < 25th %, High >=75th%, Medium, other

Mean Phthalate Concentration by AGD Category



AGD Category

Phthalate Score	Shorter	Longer	P-value*
Low	0	11	Referent
Medium	16	14	0.0014
High	13	1	< 0.0000

* Fisher's Exact Test

Clinical Implications

In Rodents
- At birth: Shorter AGD, impaired testicular descent, hypospadias
- Later: Low sperm count, rarely testicular tumors

Our Study of Humans Suggests
- At birth: Shorter AGD (some, but most NS, decrease in testicular descent, smaller penile volume)

Future studies needed to determine clinical correlates in humans

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THE MOUNT SINAI CENTER FOR CHILDREN'S ENVIRONMENTAL HEALTH & DISEASE PREVENTION RESEARCH 1998-2009

Inner City Toxicants, Child Growth and Development

Endocrine-disrupting Chemicals in the Urban Built-Environment

Funded by NIEHS, EPA, NCI, ATSDR

COMMUNITY PARTNERS: Little Sisters, Boriken Neighborhood Health, Settlement Health, Children's Aid Society, Mount Sinai and North General Pediatric Clinics

MOUNT SINAI CHILDREN'S ENVIRONMENTAL HEALTH & DISEASE PREVENTION RESEARCH CENTER - RECENT PHTHALATE RESEARCH

EXPOSURES	.3 childhood and one maternal cohort
	.consistency of levels over time in children
	.relationships with reported product-use
MATERNAL BMI	.relationships to phthalate biomarkers
BIRTH SIZE	.relationships to prenatal phthalate biomarkers
4-7 year-old BMI	.relationships to prenatal phthalate biomarkers

HORMONALLY ACTIVE EXPOSURE BIOMARKERS in NYC RESIDENTS

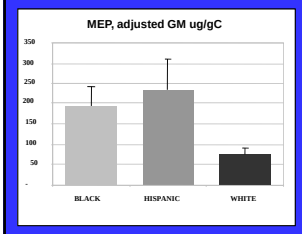
Urinary phthalate metabolites in 3 populations

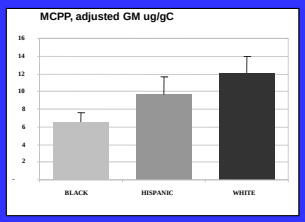
	MEPhth ug/L	MBuPhth ug/L	MBzPhth ug/L	MECPP ug/L
382 Maternal (prenatal) 1998-2002	380*	36	22	35
30 girls 6-8 yo 2004	100	50	22	111
101 boys 6-8 yo 2004-7	152	68	48	123
159/35 kids 2004-5	166	56	38	139

*Higher than NHANES females

October 2007

Adjusted Geometric Means of 2 Phthalate Urine Biomarkers by Race/ethnicity among 90 girls from 3 BCERC sites (EHP, January 2007)





Patterns of phthalate metabolites by race vary for different agents

October 2007

Predictive Ability of the Product Use Questionnaire

Relationships of urine biomarkers with responses from a 32-item questionnaire about products used in past 7 days

- *BPA: - with use of drink containers (p= **, wrong direction)
- *BPA: no correlation with "foods that come in cans"
- *BP3: + with use of sunscreen (p<.001)
- *MEHHP, MEOHP: + with nail polish use (p<.1)
- *MBP, MECPP + with hair gel (p<.1)
- *MBP, MEHP + with shampoo (p<.1)
- *MBP, MBZp + with conditioner (p<.1)

October 2007

Phthalate, Phenol, Phytoestrogen Temporality Data (NYC kids)

Baseline | 8-10 wks | 12-14 wks | 23-29 wks

ICC for Urinary biomarkers (4+ specimens over 6 months) ug/gC

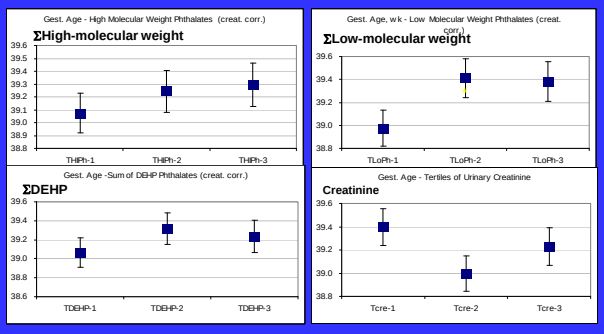
Phthalates ug/gC:	0.21 (DEHPs)	0.35 (MBP)	0.62 (MBZP)
Phytoestrogens:	0.17 (Dai)	0.33 (Gen)	0.42 (Enterolactone)
Phenols:	0.35 (BPA)	0.4 (TRCS, 25DCP)	0.46 – BP3

ICC: 0.2-<0.4 = 'fair' 0.4-0.75= 'fair-good '

ICCs Based on 159 samples from 35 children over 6 months
S. Teitelbaum, in press

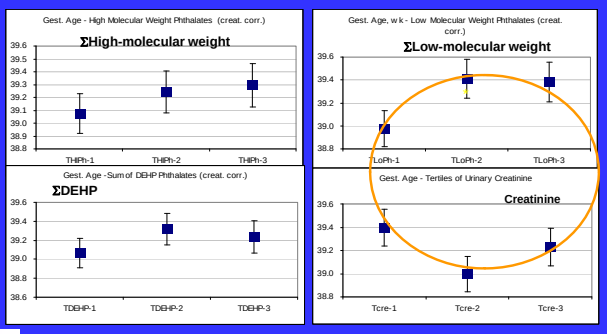
October 2007

Gestational age, Adjusted means, by Tertiles of prenatal maternal urinary phthalate biomarkers. Children's Environmental Health Study, 1998-2002.



For Low-MWP, 2nd-3rd tert LSMn=39.4 wk vs 39.0 for 1st; p=0.036 for the 2nd vs 1st and p= 0.054 for 3rd vs 1st intertertile differences; p=0.066 for the tertiles as a class variable) Adjusted for race, infant sex, gestational age, ln-creatinine; restricted to samples with creatinine >20 mg/dL. R_s with creat = .49 (Hi) .42 (DEHP .39 (Lo)

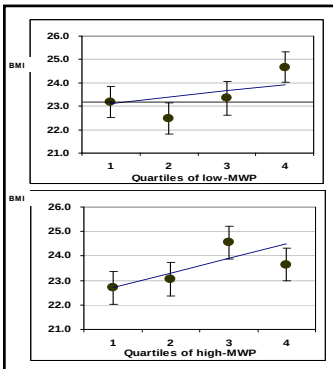
Gestational age, Adjusted means, by Tertiles of prenatal maternal urinary phthalate biomarkers. Children's Environmental Health Study, 1998-2002.



Adjusted for race, infant sex, gestational age, ln-creatinine; restricted to samples with creatinine >20 mg/dL. Rs with creat = .49 (Hi) .42 (DEHP .39 (Lo)

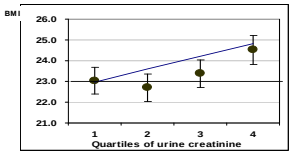
October 2007

Maternal pre-pregnancy BMI (kg/m²) predicted from phthalate and creatinine biomarkers Children's Environmental Health Study, 1998-2002.



P for quartiles of Low-MWP-creatinine corrected = 0.005. Line beta = 0.23 ± 0.17 units of BMI/ln-Low-MWP, p=0.17

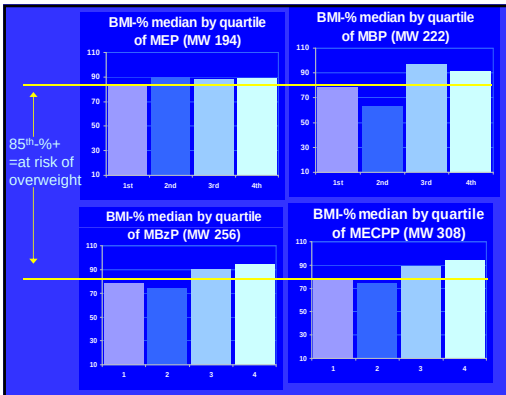
P for quartiles of High -MWP-creatinine corrected = 0.017. Line beta = 0.22 ± 0.30 units of BMI/ln- High -MWP, p=0.30



P for quartiles of creatinine = 0.024.
Line beta= 1.02 ± 0.33 units of BMI/ln- creatinine, p=0.002

Adjusted BMI means ± se by quartiles of biomarkers , regression line from the ln-metabolites. Adjusted for smoking, age, age-squared, race, ln-creatinine, restricted to women with BMI < 50 kg/m² and samples with creatinine ≥ 20 mg/dL; n=352 for phthalates and 367 for creatinine. ΣDEPH metabolites are the molar sum of MECPP, MEHHP, mEOHP, MEHP; low-MWP= sum of MMP, MEP, MBP, MIBP; high-MWP = sum of DEHP group + MBZP, MCPP.

October 2007



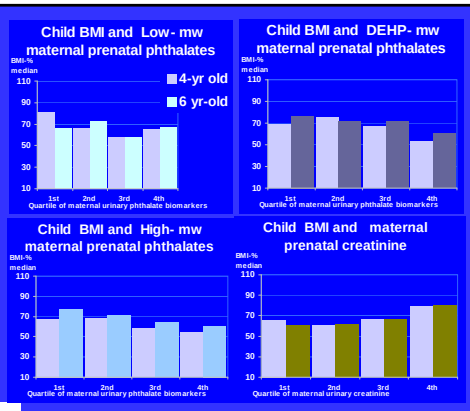
Boys' age/sex-specific BMI-%-ile (kg/m²) by Phthalate Biomarker Quartiles

tmpbmiph.xls

Consistent with 2 studies on NHANES data

October 2007

Associations of prenatal phthalate metabolites with childhood body size



(No positive associations with phthalates)

MOUNT SINAI CHILDREN'S ENVIRONMENTAL HEALTH & DISEASE PREVENTION RESEARCH CENTER – RECENT PHTHALATE RESEARCH

EXPOSURES	.MEP higher in mothers, DEHP in kids, others are similar
	.Biomarkers are ok as indicator of exposure
	.recent product-use does not predict well the biomarker levels
MATERNAL BMI	.weak association, possibly confounded by creatinine
BIRTH SIZE	.weak effect for longer gestational age with higher low-mw-phthalate biomarkers, possibly confounded
4-7 year-old BMI	.6-8 yo have association with high-mw- phthalate biomarkers (not yet adjusted for covariates)
	.4 & 6 yo have inverse association with prenatal maternal urinary levels of high-mw- phthalate biomarkers (not yet adjusted for covariates)

The Mount Sinai Center for Children's Environmental Health & Disease Prevention Research 1998-2009

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COMMUNITY PARTNERS: Little Sisters, Boriken Neighborhood Health, Settlement Health, Children's Aid Society, Mount Sinai and North General Pediatric Clinics

Improving Asthma Outcomes:

2007 NAEPP Guidelines focus attention on education and environmental interventions

David Rowson, Director
Center for Asthma and Schools
US EPA Indoor Environments Division

Overview

- Overview of the 2007 NAEPP Guidelines for the Diagnosis and Management of Asthma
- Highlight Guidelines recommendations for patient education and control of environmental factors
- Introduce EPA Initiative to accelerate adoption of best practices

National Guidelines for the Diagnosis and Management of Asthma

www.nhlbi.nih.gov/guidelines/asthma/index.htm

National Guidelines for the Diagnosis and Management of Asthma

- New focus on monitoring asthma control as the goal for asthma therapy and distinguishing between classifying asthma severity and monitoring asthma control.
- New focus on impairment and risk as the two key domains of severity and control, and multiple measures for assessment.
- Modifications in the stepwise approach to Managing Asthma Long Term.
- New emphasis on multifaceted approaches to patient education and control of environmental factors and comorbid conditions that affect asthma.
- Modifications to treatment strategies for managing asthma exacerbations.

Guidelines Framework: 4 Essential Components of Asthma Care

- Assess and Monitor Asthma Severity and Control
- Education for a Partnership in Asthma Care
- Control of Environmental Factors and Comorbid Conditions
- Medications

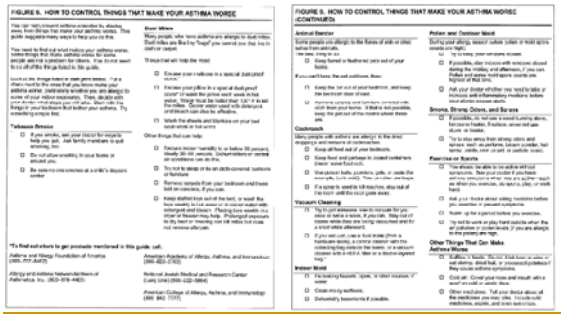
Educating patients, families, and providers

Education for a Partnership in Asthma Care:

Self-management education is essential, should be integrated into all aspects of asthma care, and requires repetition and reinforcement.

- Patient education
  - Many potential sites/points of care outside office setting
  - Written asthma action plan emphasizes both daily management and worsening asthma
  - Attention to cultural, ethnic factors and health literacy
- Provider education
  - systems-based interventions and
  - effective clinician education programs

Multi-faceted approach to control environmental factors



Multi-faceted approach to control environmental factors

- Reducing exposures to inhalant indoor allergens and irritants improves asthma control
  - Determine exposures and sensitivities—use skin testing or in vitro testing for persistent asthma
  - Consider allergen immunotherapy for persistent asthma and clear, consistent exposure/response
- Multi-faceted approach is most effective
  - Tobacco Smoke
  - Dust Mites
  - Animal Dander
  - Cockroach
  - Indoor Mold
  - Pollen and Outdoor Mold
  - Smoke, Strong Odors, Sprays, Formaldehyde, VOCs
  - Vacuum Cleaning
  - Exercise or Sports

Asthma in the US

- 20 M, including 6.3M kids
  - 2M ER visits
  - 14M missed school days
- Some National indicators leveling off, but at all-time highs
  - Prevalence, ER visits, hospitalizations
- Important disparities in morbidity and mortality continue
  - Children and the elderly
  - African Americans, Native Americans, Hispanics
- $16.1 B in annual costs
  - direct health care costs, e.g. physician services -$11.6 B
  - indirect costs, e.g. school/work absence, mortality -$4.5 B

Healthy People 2010: How are we doing?

Healthy People 2010 Objective	2010 Target	Midcourse Status
With prescribed inhalers who receive instruction on how to use them properly	98.8%	96%
Medication regimens that prevent the need for more than one canister of short-acting inhaled beta agonists per month for relief of symptoms	92%	80%
Follow-up medical care for long-term management of asthma after any hospitalization due to asthma	87%	76%
Education about recognizing early signs and symptoms of asthma episodes and how to respond appropriately, including instruction on peak flow monitoring for those who use daily therapy	71%	68%
Written asthma management plan from their HC provider	38%	35%
Assistance with assessing and reducing exposure to environmental risk factors in their home, school, and work environments	50%	49%
Formal patient education, including information about community and self-help resources as an essential part of the management of their condition	30%	12.4%

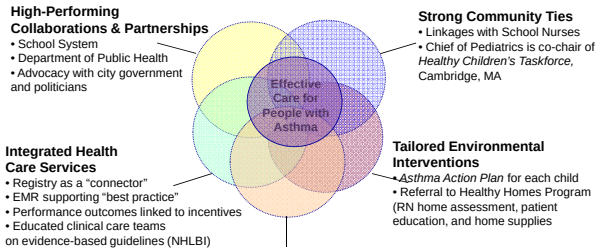
Driving Improvements in Asthma Care through Increased Patient Education/Control of Triggers

- Health Care Provider outcomes
  - Increasing numbers of patients receiving
    - written asthma management plans
    - education
    - assistance with trigger avoidance
- Patients/Caregivers
  - ~30% taking essential environmental control actions
- Health Plan Results
  - Widespread promotion of guidelines to providers
  - Increased support for education/environmental interventions
  - Business case is becoming more evident

Accelerating progress through Community-based asthma care

- Asthma Health Outcomes Project
  - Identified program elements linked to health outcomes
- *Change Package* of Successful Strategies
  - Compendium of field tested actions
- Network of programs driving toward best practices and outcomes
  - www.asthmacommunitynetwork.org

Cambridge Health Alliance



High-Performing Collaborations & Partnerships
- School System
- Department of Public Health
- Advocacy with city government and politicians

Strong Community Ties
- Linkages with School Nurses
- Chief of Pediatrics is co-chair of *Healthy Children's Taskforce,* Cambridge, MA

Integrated Health Care Services
- Registry as a "connector"
- EMR supporting "best practice"
- Performance outcomes linked to incentives
- Educated clinical care teams on evidence-based guidelines (NHLBI)

Tailored Environmental Interventions
- *Asthma Action Plan* for each child
- Referral to Healthy Homes Program (RN home assessment, patient education, and home supplies

Committed Program Champions
- Providers, nurses, and staff at practice sites
- CEO and Senior Leaders
- Chief of Pediatrics and Family Medicine
- Ambulatory Administration
- Performance Improvement Department
- IT Department

Communities in Action Network

Objective	HP 2010 Target	*Best in Class* Results
Reduce ED Visits	30% – 50% (15-80 per 10,000)	50% – 75%
Reduce Hospitalizations	38% – 45% (8-25 per 10,000)	50% – 80%
Increase Symptom-Free Days	>10 per 14 days	10.4 days in a row
Patients receiving Education	30%	100%
Patients receiving Assistance to Assess/Reduce Triggers	50%	100%

Communities in Action Network

Mobilizing 1000 Communities to deliver quality asthma care

Looking Ahead

- Educate clinicians and others in health care community to follow new NAEPP Guidelines
- Clinicians collaborate with community resources to deliver comprehensive care addressing all 4 components of asthma care
- Your programs are leaders in understanding effective care
- Join the Communities in Action Network
  www.asthmacommunitynetwork.org
- Join us May 1-2 at the 3rd National Asthma Forum
  www.epaasthmaforum.com

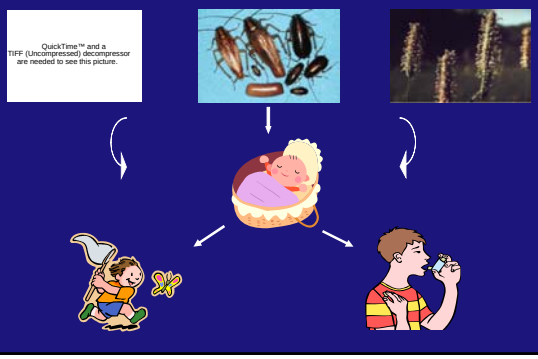
Prenatal and early postnatal exposures and asthma risk- How???

Rachel L. Miller M.D., FAAAAI
Assistant Professor of Clinical Medicine and Public Health
Columbia Center for Children's Environmental Health (CCCEH)
Columbia University
Children's Environmental Health Workshop: Discover, Treat, Prevent, Prepare
Oct 11, 2007

Asthma is a complex disease

- Mediated by
  - genetic predisposition
  - environmental exposures
  - host factors eg obesity, psychosocial
  - infections

Prenatal and early postnatal exposures modify asthma risk



How???

- What does the literature tell us so far?
- How is CCCEH cohort study* addressing this question?

Exposure Assessment	Biomarkers of Exposure/ Effect/Susceptibility	Outcomes
• Monitoring • Questionnaire • GIS	• PAH metabolites • PAH-DNA adducts • Cotinine • Pesticides • IgE, Cytokines • T cell proliferation • Gene expression • Genetic polymorphisms • Lead, mercury • Chromosomal aberrations	• Asthma • Allergic sensitization • Obesity • Growth & neurobehavioral development • Cancer risk

*Pregnancy through childhood: Repeat measures on women and children

Epidemiological support: Prenatal exposure to ETS

- ETS is associated with
  - impaired respiratory function
  - transient wheeze,asthma, and/or respiratory infections in infants, young children, and adolescents

Magnusson L, et. al. *Clin Exp Allergy* 2005;35:1550-1556
Alati R et. al. *Epidemiology* 2006;17:138-144

Additional prenatal exposures

- Increase asthma risk?
  - Low maternal intake of vitamin E, zinc
  - Use of antibiotics
  - Respiratory infections during pregnancy
  - Ambient air pollution eg PAHs
- Decrease asthma risk?
  - Probiotics
  - Multiple pregnancies

Devereux G et. al. *Am J Respir Crit Care Med* 2006;174:499-507.
Jedrychowski W. et. al. *Int J Occup Med Environ Health* 2006;19:70-76.
Kukkonen K et. al. *J Allergy Clin Immunol* 2007;119:192-198.
Hughes et. al. *Clin Exp Allergy*; 1999;29 (10): 1378-81

Epidemiological support: Early postnatal exposures

- Dust mite allergen during infancy
  - determinant for later childhood asthma
- Dog, cat allergen
  - associated with protection from later childhood wheeze
- Combustion-related pollutants
  - associated with later childhood sensitization to dust mite
  - reduction in FEV_1

Sporik R et. al. *N Engl J Med* 1990;323:502-507
Remes et. al. *J of Allergy and Clinical Immunol* 2001;108:509-515
Ponsonby et. al. *Clin Exp Allergy* 2001;31:1544-1552

Prenatal PAH, postnatal ETS and respiratory score (CCCEH)

	Analysis for Main Effects			Analysis for Interactions		
	Exposure	B	P value	Exposure	B	P value
12 months (n=263)	Intercept	1.04		Intercept	0.73	
	Pre ETS	-0.02	0.90	Pre ETS	-0.01	0.92
	PAH	0.01	0.72	PAH	0.09	**0.018**
	ETS	0.15	0.29	ETS	-0.23	0.27
				PAH x ETS	**0.11**	**0.014**
24 months (n=169)	Intercept	0.68		Intercept	0.30	
	Pre ETS	-0.07	0.67	Pre ETS	-0.08	0.65
	PAH	0.03	0.28	PAH	0.13	**0.002**
	ETS	-0.09	0.60	ETS	-0.63	**0.011**
				PAH x ETS	**0.15**	**0.003**

Miller, R.L., et. al., *Chest* 2004, 136: 1071-78.

Potential mechanisms?

- Immune
- Epigenetic

Immune-mediated mechanisms

- Altered cytokine regulation
- Generation of antigen-specific T cell immune responses

Altered cytokine regulation

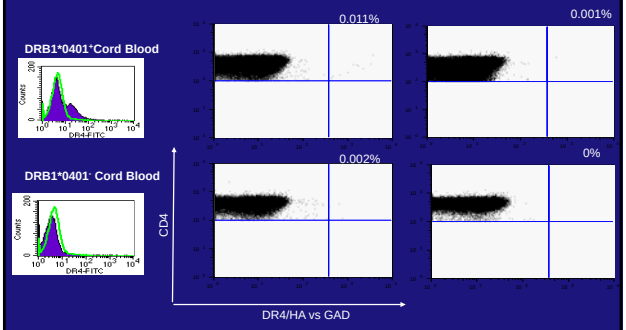
Description of Study		Methods and Measures			Major Findings
Source	Study Population	Age,Sample	Cytokines	Antigens	
Contreras JP et al. Boston, MA J Allergy Clin Immunol, 2003	112 children with parental history of asthma or allergy Birth to age 2 yrs	Age 2 years: PBMCs	IFN-γ TNF-α IL-10 IL-13	Bla g 1 (cockroach) Der f 1 (HDM) Fel d 1(cat)	Children w/ atopic disease, repeated wheeze had **lower IFN-γ levels** in response to HDM and cockroach allergen.
Prescott SL et al. Perth, Australia Allergy, 2003	60 children Birth to age 6 yrs All born by elective C-section	Birth: CBMCs Age 6, 12, 18, 24 mos: PBMCs	IFN-γ IL-4, IL-5 IL-6 IL-9 IL-10 IL-13	HDM Ovalbumin Fel d 1 PHA Tetanus toxoid	Children w/ family history of allergy had **lower IFN-γ resp** to PHA stimulation of CBMCs Children with atopy at 6 yrs had 1) incr in **IL-5 mRNA** in response to HDM age 2 yr 2) **incr IL-13** resp to HDM at 1 yr.
Neaville WA et al. Madison, WI J Allergy Clin Immunol, 2003	285 Children Birth to age 1 yr Parent w/ allergies, asthma	Birth: CMBCs Age 1 yr: PBMCs	IFN-γ IL-5 IL-10 IL-13	PHA	**Lower IL-10** production in response to PHA-stimulated CBMCs risk factor for egg sensitization at age 1
Kondo N et al. Gifu, Japan CEA,1998	21 children Birth to age 6 yrs Full term, vag birth	Birth: CBMCs	IFN-γ IL-2	Ovalbumin BSA	Children with allergy by age 6 yrs had **lower IFN-γ** in response to ovalbumin or BSA

Modified from Chung, E.K., R. L. Miller, M. T. Wilson, S. J. McGeady, J. F. Culhane. *Arch. Dis. in Child. Fetal Neonatal Ed.* 92: 68-73, 2007

Cord blood proliferation in response to indoor antigens (CCCEH)

Miller et al *Am. J. Respir. Crit. Care Med*, 2001, 164 (6), 995

Influenza-specific T cells identified in cord blood following prenatal vaccination of mother



Rastogi, D., C. Wang, X Mao, C. Lendor, P. B. Rothman, R. L. Miller. *Journal of Clinical Investigation*, 2007, 117 (6):1637-46

Epigenetic-mediated mechanisms

- Heritable changes* in gene expression that occur in the absence of alterations in DNA sequences

* at least between cells

Epigenetic regulation

- DNA methylation
  - covalent addition of a methyl group to cytosines in CpG dinucleotides
- Chromatin packaging of DNA via post-translational modifications of histones
  - egs. acetylation,methylation,phosphorylation
- Believed to occur predominantly prenatally and shortly after birth
- May influence gene expression differentially throughout lifespan

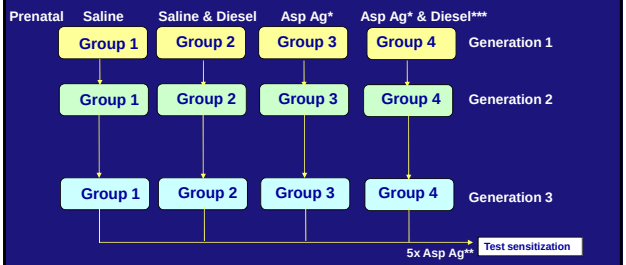
Eg: T helper cell differentiation

- Proallergic IL-4 production and Th2 differentiation
  - demethylation of sites at the prox promoter and conserved intronic regulatory element (CIRE) in 1st intron of the IL-4 gene
  - hypermethylation of sites in the counterregulatory IFNγ promoter
- Th1 differentiation
  - methylation of a highly conserved DNaseI-hypersensitive region at the 3' end of the IL-4 locus

Lee DU et. al. *Immunity* 2002;16:649-660.
Agarwal S,et al. *Immunity* 1998;9:765-775.
Tykocinski LO, et. al. *J Biol Chem* 2005;280:28177-28185.
Jones B et. al. *The EMBO Journal* 2006;25:2443-2452

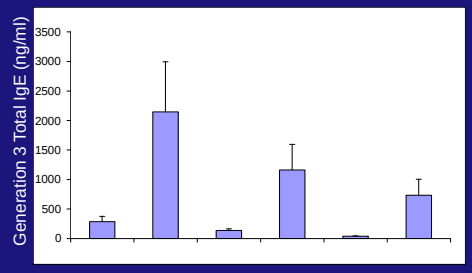
CCCEH work-in-progress

Multigenerational effects of exposure to mold *aspergillus*, diesel



*5 x 1.25 mg Asp Ag prior to mating; 2x during pregnancy
**5 x 125µg Asp Ag
***last week of pregnancy 6 hr/day

Grandparental exposure to mold protected against development of IgE



In vivo study of methylation of IL4 gene in asthma-like mouse models

Saline | Asp Ag | Diesel | Asp Ag & Diesel

Group 1 | Group 2 | Group 3 | Group 4

saline or Asp Ag (62.5 µg/dose) X 5
diesel 6 hr/day x 3 weeks

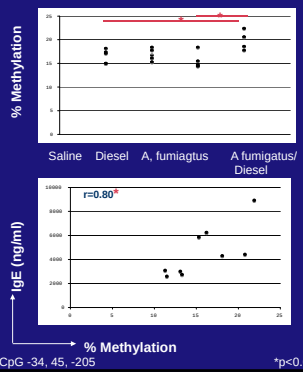
→ IgE

Collect CD4+ cells

Isolate genomic DNA

Bisulfite conversion
PCR amplification
Pyrosequence of IL4, IFNγ gene:
Quantify methylation level

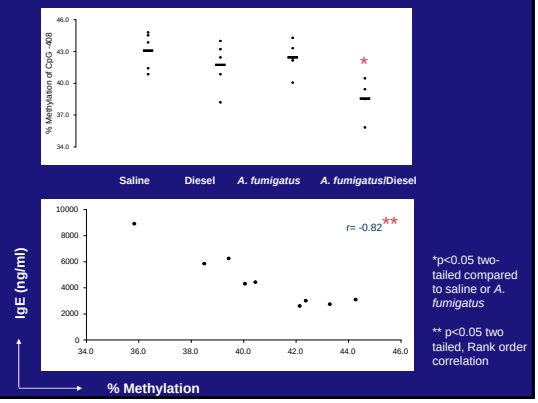
In vivo A. fumigatus and DEP exposure are associated with increased methylation of IFNγ promoter at CpG-53 site and increased IgE



Significant correlations also with CpG -34, 45, -205

*p<0.05 two tailed t test

In vivo A. fumigatus and DEP assoc with hypomethylation of IL-4 at CpG^{-408} and decreased IgE



*p<0.05 two-tailed compared to saline or *A. fumigatus*

** p<0.05 two tailed, Rank order correlation

Prenatal exposure to airborne PAHs and alterations in DNA methylation

Bench ⟶ Bedside and beyond

Question: Does prenatal PAH exposure affect asthma risk via epigenetic mechanisms, such as CpG methylation?

F.P. Perera, D. T.Tang, J. Herbstman, S. C.Edwards, R. Whyatt, P. Kinney, R.L. Miller (CCCEH) in collaboration with Drs. Shuk0mei Ho and W.Tang of the University of Cincinnati

Methylation profiling using methylation sensitive restriction fingerprinting

- Study population/samples: CCCEH cord blood
- PAH exposure
  - high prenatal PAH exposure: highest quartile prenatal air PAHs/high PAH-DNA adducts
  - low exposure: lowest quartile PAHs/low PAH-DNA adducts

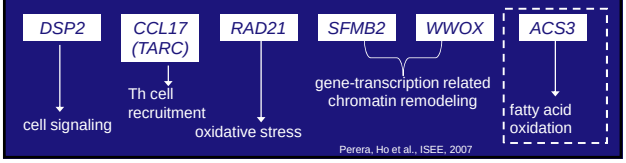
Pilot study (n=60): Identification of candidate genes

50+ clones were chosen for sequencing and *in silico* analysis

34 candidate clones were identified

7 clones contained 5' CpG islands

6 were homologous (>90%) to known genes expressed in lung or lymphoid tissue



Perera, Ho et al., ISEE, 2007

Differential ACS3 methylation status confirmed by MSPCR

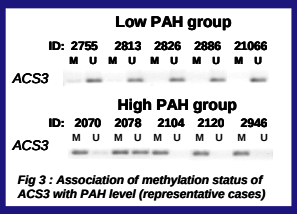


Fig 3 : Association of methylation status of ACS3 with PAH level (representative cases)

ACS3 unmethylated in low PAH group

ACS3 methylated in high PAH group

•Trend suggesting that methylated ACS3 is associated with parental report of childhood asthma at age 5 (OR: 3.76, 95% CI: 1.04, 13.65)

Perera, Ho et al., ISEE, 2007

Conclusion

- Prenatal and early postnatal exposures impact risk for later asthma
- Both immune-mediated and epigenetically-regulated mechanisms likely contribute
- Much more cohort-driven mechanistic research needed to assess:
  - dose of specific exposures
  - time periods of increased susceptibility
  - interactions btw genetics and epigenetics

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  R01 ES013163
  P30 ES009089
  R21ES013063
  R01ES015495
  ES00260
  P50ES015905
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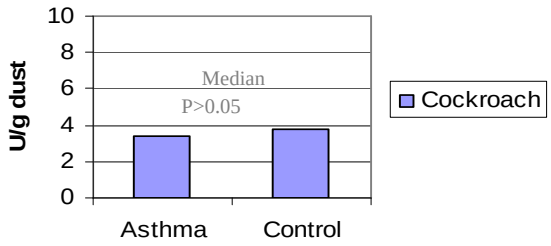
  RD-832141; RD-83209601

The Center for Childhood Asthma in the Urban Environment

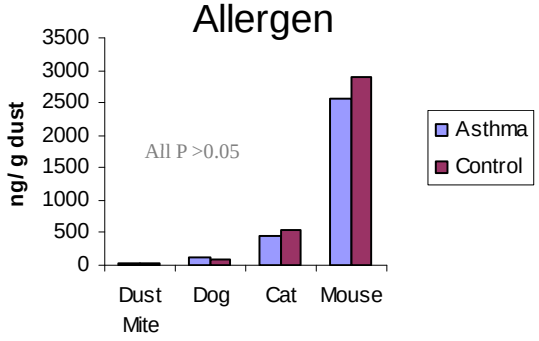
Elizabeth Matsui, MD MHS
Patrick Breysse, PhD, Director
Gregory Diette, MD MHS, Deputy Director
Johns Hopkins University

Bedroom Cockroach Allergen



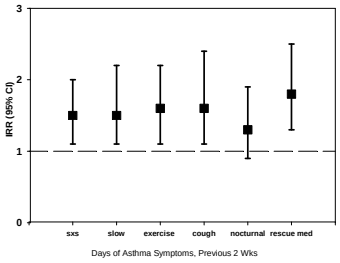
Diette G et al, Env Health Perspective, In Press

Bedroom Settled Dust Allergen



Diette G et al, Env Health Perspective, In Press

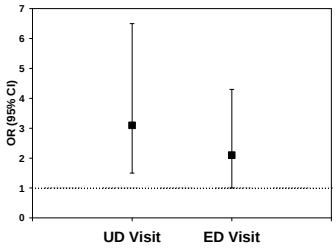
Recent Asthma Symptoms & Rescue Medication use



* adjusted for age, sex, atopy, cockroach sensitization and exposure, public health insurance, and study visit

Matsui E et al, Ann Allergy Asthma Immunol. 2006 Oct;97(4):514-20.

Asthma-related Health Care Use

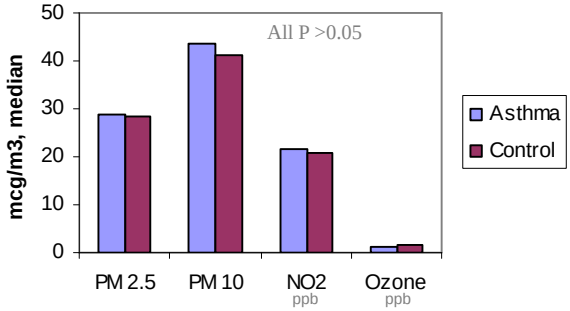


- Hospitalization Adjusted OR: 69.9 (5.8-838.9)
- 9/10 hospitalizations occurred among sensitized/high exposure group

* adjusted for age, sex, atopy, cockroach sensitization and exposure, public health insurance, and study visit

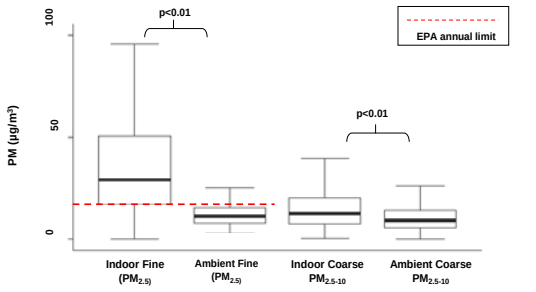
Bedroom Air Pollutants

Diette G et al, Env Health Perspective, In Press



Distribution of Indoor PM in Children's Bedrooms

Figure 2. Distribution of Indoor and Ambient Fine and Coarse PM
Boxplots display indoor and ambient fine and coarse PM. Indoor PM concentrations were significantly higher than ambient. The red dashed line demonstrates the EPA annual limit for ambient $PM_{2.5}$. Over 75% of homes had indoor PM concentrations that exceeded this limit.



Extreme outliers not shown

Indoor PM Exposure and Asthma Morbidity

Outcomes	Coarse PM (per 10 µg/m3)		Fine PM (per 10 µg/m3)	
	IRR	P-value	IRR	P-value
Cough/wheeze/ chest tightness	1.06	0.03	1.02	0.21
Slow/stop activities	1.13	<0.01	1.01	0.47
Limited speech from wheeze	1.14	<0.01	1.04	0.19
Nocturnal Symptoms	1.10	<0.01	1.02	0.20
Symptoms with running	1.03	0.33	1.05	<0.01
Beta agonist use	1.10	<0.01	1.03	0.05

*Adjusted for age, gender, race, socioeconomic status

Presented ATS 2007

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  - Timothy Buckley
- Staff
  - Study Staff
  - Laboratory Staff
  - Exposure Assessment Core
  - Data Management Core
- Community Advisory Board
  - Adrian Mosley (chair)

Clinical Experience with the Environmental Management of Asthma & NAEPP Expert Report 2007

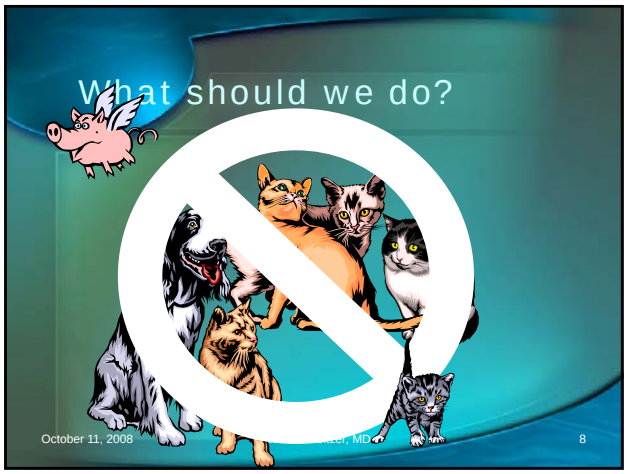
James M Seltzer, MD
Clinical Professor of Medicine
University of California, Irvine
School of Medicine
Co-Director
Pediatric Environmental Health Specialty Unit, UCI
US EPA Region IX

The Three Questions

- What is my experience as an allergist/immunologist caring for children with asthma as this disease relates to environmental factors?
- What is my experience as a PEHSU director responding to inquiries from children with asthma, their parents, and other involved entities/persons regarding environmental factors?
- What is the significance of the new asthma guidelines for the clinician in his office?
  - Primary care
  - Specialist

The 4 essential components of asthma care

1. Assessment and monitoring
   - Relevant or potentially relevant environmental exposures
   - Compliance with exposure reduction
   - Response to exposure reduction
   - Monitoring of future exposures
2. Controlling factors contributing to asthma severity
   - Environmental factor exposure reduction and minimization (or possibly, **exposure enhancement)** – "environmental control measures"
   - Co-morbid conditions



The 4 essential components of asthma care

3. Pharmacologic **and immunologic** treatment – stepped care
   - Anti-inflammatory "controller" medications still the mainstay for asthma control
   - Specific immunotherapy can reduce the risk of future asthma development
4. Patient **and physician** education
   - Asthma mechanisms, including effect of environmental exacerbants
     - Medication use
     - **Relevant** environmental control measures
   - Written action plan

FAMILY Allergy & Asthma

Goals of asthma therapy

- Effective asthma control – define it
- Minimal therapeutic regimen, e.g., number of medications for asthma and other allergic disease
- Minimize need for health care professional intervention, e.g., doctor's office, E.D., hospital
- Affordable
- Convenient
- Practical, i.e., doable


TUCKING YOU IN USED TO BE ONE OF THE THINGS I LOOKED FORWARD TO.
DUST AND DIRT FIGHT ALLERGIES
HOW ABOUT A LIVE BUNNY?
TOLES
UNIVERSAL PRESS SYND.
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Neurodevelopment, Autism, and Mercury: Biomarkers and Epidemiologic Approaches

University of California Davis,
M.I.N.D. Institute

Outline

- Outcomes
- Literature on:
  - Hg & Neurodevelopment
  - Hg & Autism: vaccines
  - Hg & Autism: non-vaccine sources
- UC Davis CCEH: *The CHARGE Study*
  - Goals, methods & results for Blood Hg
- Discussion & Next steps

Outcomes

- Developmental delay or deficits
- Mental or Cognitive:
  - Language
  - Memory
  - Spatial
  - Executive function
- Neuromuscular
- Sensory deficits
- Social: autism

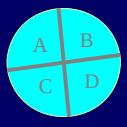
What is Autism?

Pervasive developmental disorder defined as characterized by three behavioral domains:

- Deficits in social interaction
- Communication: Language impairment/delay or unusual speech patterns
- Repetitive behaviors and/or restricted interests

Facts about Autism

- Male:female ratio is 4
- Current reliable prevalence estimates: 1 in 150 (=60-70 per 10,000)
- Strong genetic component
  - 60-90% concordance: monozygotic twins
- Multifactorial
- Wide variation in severity, trajectory
- Historically attributed to 'bad parenting'
- Now known to have a neurobiologic basis: aberrant brain development



Neural Substrate of Autism

- Anatomical, electrophysiologic, MRI
- fMRI: esp face processing
- Highly diffuse throughout the brain:
  - Cerebellum
  - Hippocampus
  - Amygdala
  - Cerebral cortex

$\Rightarrow$ early insult

- Purkinje cell loss

Mercury and Neurodevelopment

Mercury: food contamination episodes

- 1953-1961 Minimata, Japan, chronic
- 1970's Iraq
  - *in utero* exposure ~ mental retardation, physical impairments, seizures
  - autopsies showed abnormal neuronal migration, disorganized cerebral cortex

Mercury and Neurodevelopment

Chronic Hg intake via fish consumption - (lower levels)

- Faroe Islands (n~900) Grandjean et al 1997, Debes 2006

prenatal exposure: maternal hair, cord blood, cord tissue

  - at 7 years: deficits in language, attention, memory, visuospatial domains
  - at 14 years: deficits in motor, attention, verbal

- Seychelles Islands Davidson et al 2005
  - at 5.5 years: no deficits in language, visual-motor integration, various cognitive domains
- Project Viva (n=135) Oken et al 2006

maternal hair mercury

  - at 6 months : deficit in visual recognition memory
  - able to separate beneficial effects of fish consumption from harmful effects of mercury

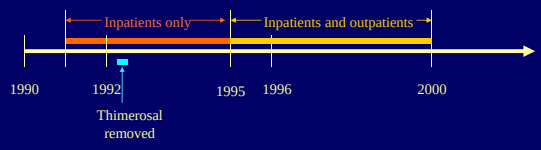
RCT of dental amalgams in school-aged: no effect

Mercury and Autism: Vaccines

- Controversy: thimerasol as preservative breaks down to ethyl Hg and thiosalicylate
- Polarization "Autism: a novel form of mercury poisoning" (Bernard et al)
- Removed from most childhood vaccines in 2001/02
- Numerous ecologic studies using before/after comparisons
- Few studies with individual-level data: Verstraeten et al of CDC…Vaccine Safety Datalink Rh- and thimerasol-containing rhogam
- Clarify: issue of MMR is unrelated

Epidemiologic Considerations

Hviid et al 2003



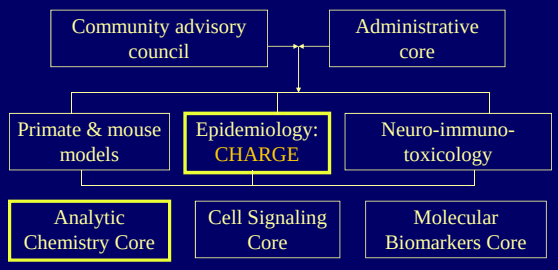
Sources of Hg:

- Combustion of fossil fuels
- Consumption of seafood or ocean or freshwater fish
- Erosion of dental amalgams
- Occupational exposure from mining
- Direct contact from damaged mercury thermometers, blood pressure cuffs, barometers, incandescent lights, or batteries.
- Dermal absorption from skin-lightening cremes
- Use of nasal sprays, ear wax removal products, contact lens solutions
- Vaccines

Studies of (nonvaccine) Hg & Autism

- Palmer et al (2006): TRS emissions inventory, Hg only & autism rates by school district
  - Special education availability - confounder
- Windham et al (2006): HAP model for multiple ambient pollutants
  - Used model-based estimated exposure for a different year (1996) than the births (1994)
- Both reported associations with autism
- Both were ecological
- *Think about timing!!*

UC Davis Center for Children's Environmental Health (CCEH)



Hg in the *CHARGE** Study

**CHildhood Autism Risk from Genetics and the Environment*

Goals of the CHARGE Study

To identify causes and contributing factors for childhood autism:

- Genetic susceptibility factors
- Environmental exposures
- Interplay of the two

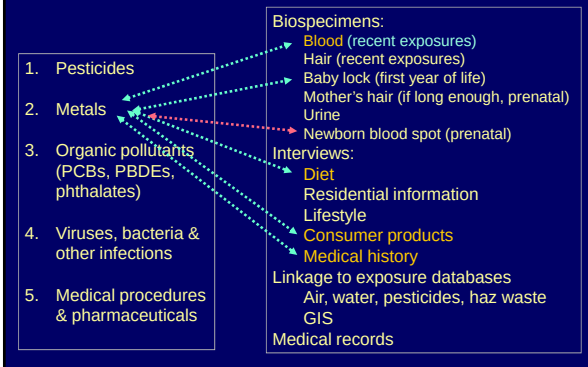
To determine mechanisms of susceptibility for childhood autism

- Immunologic
- Genetic/Genomic
- Metabolic/metabolomic

Mechanisms for Xenobiotics

- Direct action on neural tissue during:
  - Differentiation
  - Migration
  - Dendritic branching/pruning
  - Synaptogenesis
- Effects on genes that regulate CNS development: neuroligin 4
- Perturbation of immune signaling/inflammation via neurotransmitters &/or cytokines
- Endocrine disruption: sex steroids/thyroid hormones

Environmental Exposures



METHODS

The CHARGE Study Design

Case-control design…three groups:

- Children with autism
- Children with developmental delay
- Children drawn using probability sampling from the general population of births

Eligibility Criteria in the CHARGE Study

Children :

- 24-60 months of age
- born in California
- parents speak English and/or Spanish
- child living with at least one biologic parent
- residing in catchment area

CHARGE Study Recruitment Protocol:

Autism or Developmental Delay

- Recruited from Department of Developmental Services (DDS)

Population-based Controls

- State birth files, frequency matched to autism group by age, gender & Regional Center

The CHARGE Study Clinical Protocol

Confirmation of diagnosis:

- ADI and ADOS (autism cases only)
- Social Communication Questionnaire (all others)

Assessment of cognitive development (all children)

- Mullens Scales of Early Learning
- Vineland Adaptive Behavior Scales
- medical exam

Parent forms

Medical records obtained

The CHARGE Study Clinical Protocol

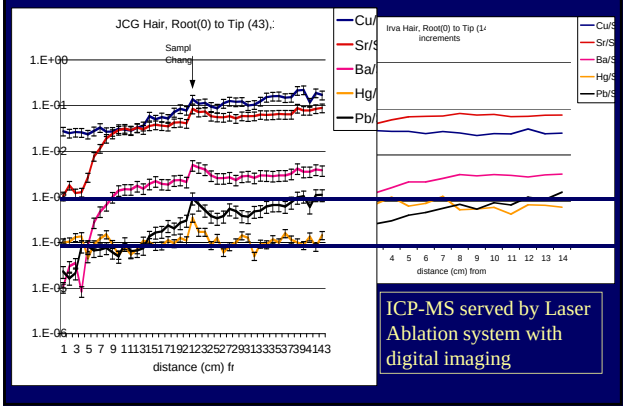
- Parents interviewed:
  - Family History Interview
  - Exposures, events, activities covering prenatal, early childhood periods
- Specimens:
  - blood
  - urine
  - hair

  …from index child, parents & siblings
- newborn blood spots from CDPH GDB

Measurement of Blood Hg

- Blood collected by venipuncture into metal-free tubes
- Analyzed for metals using ICP-MS: Inductively Coupled Plasma Mass Spectrometry
- Detection limit: 1 pg/ml in blood
- Blood samples thawed, diluted in .005% solution of metal-free surfactant into sterilized double de-ionized H_2O with nitric acid.
- QC: cleaning exterior & interior; calibration every 10th sample
- In every batch of 30-40, NY state proficiency standards at low, medium and high levels

Hair Hg measurement - time course



ICP-MS served by Laser Ablation system with digital imaging

Statistical Analysis

- Duplicate entry into online system
- Immediate flag of discrepancies
- Histograms, log transformation of Hg

Prediction model for blood Hg concentration:

- Multiple linear regression adjusting for recent:
  - Fish consumption
  - Dental amalgams
  - Use of nasal sprays, ear drops

Also excluded children who had been chelated, and adjusted for differential participation by SES

RESULTS

Participation:

70% among Autism group

50% among General Population controls

Blood specimens analyzed for Hg:

271 AU (on ADOS or ADI)

61 DD

144 GP

Confirmation of diagnoses:

63% meet criteria for AD on both ADOS+ADI

98% meet criteria for AD or ASD on at least one

Log Hg and Covariates by Case Status

	Autism/ASD (N=271)			GP Typical (N=144)			Delayed (N=61)		
	Mean	STD	%>0	Mean	STD	%>0	Mean	STD	%>0
Log Hg	-1.71	1.54		-1.25	1.38		-1.68	1.54	
Servings tuna	0.11	0.31	16%	0.44	0.69	42%	0.39	0.62	42%
Servings ocean fish	0.29	0.50	37%	0.53	0.75	55%	0.39	0.59	44%
Servings freshwater fish	0.06	0.28	7%	0.20	0.51	19%	0.18	0.48	17%
Frequency nasal spray or ear wax removal	0.39	0.94	19%	0.22	0.63	13%	0.51	1.14	22%
Number amalgams x Chew or grind teeth	0.10	0.59	4%	0.18	0.87	5%	0.52	1.80	10%
Thimerosal dose*	0.005	0.082	1.2%	0.103	0.699	3.6%	0.005	0.032	2.2%

* assumes 7 day half-life, calculation based on vaccines in previous 90 days

Prediction of log(Blood Hg)*

	Beta	P-value
Autism or ASD	-0.01	0.95
Ate tuna (1+ servings/wk)	0.56	0.001
Ate ocean fish (")	0.68	<0.0001
Ate freshwater fish (")	0.57	0.01
Hg amalgams x chew/grind teeth	0.15	0.004
Nasal spray or ear wax removal	0.52	0.02

* Multivariate analysis to adjust for confounding
Subjects weighted to adjust for differential participation by SES

Baby Locks (first haircut)

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

DISCUSSION

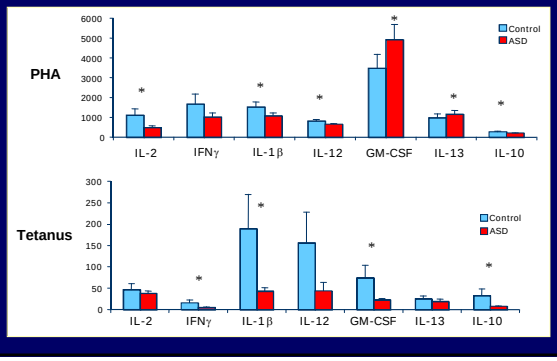
Discussion

- *Timing:* Current concentrations of blood metals in children 2-5 years of age unlikely to represent causal factors:
possibly concommitant, or downstream of ASD,
- Some authors suggested abnormal metabolism or faulty excretion of metals in children with autism
- Chelation
- Statistical analyses validate use of questionnaire data about recent exposures to predict current blood Hg level

Future Work on Metals

- Earlier time windows for causal factors:
  - Analyses of baby locks (first haircuts) currently underway
  - Newborn blood spots
  - Maternal hair (if long enough)
- Evaluate subsets: early onset/regressive
- Gene x environment interaction: GSTM1, GSTT1
- Develop a pharmacokinetic model of life-course Hg profiles (need funding!)
- Analysis of other metals: Pb, Cd, As, Mn

Altered Immune Responses in Children with Autism Spectrum Disorder



Be in *CHARGE !*

http://beincharge.ucdavis.edu/

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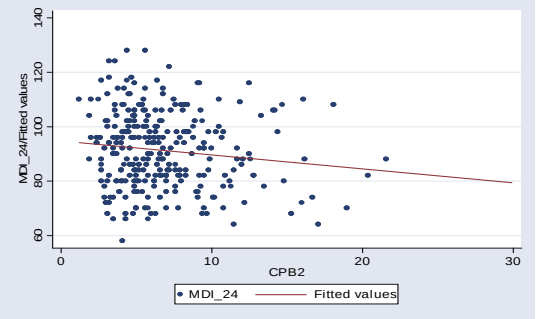
- Cure Autism Now
- NIEHS 1R01 ES015359

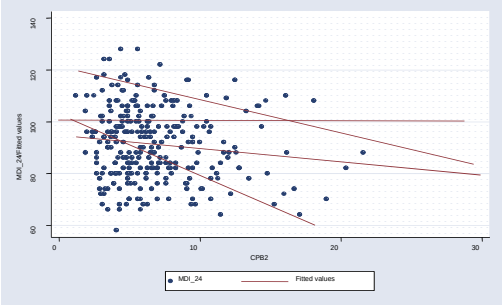
Comparison of CHARGE Subjects to the Target Population

	CHARGE AU (n=341)	AU Pool (n=876)	CHARGE DD (n=54)	DD Pool (n=299)	CHARGE GP (n=101)	GP Pool (n=1240)
	%	%	%	%	%	%
Male sex of child	88.0	83.3	66.7	63.9	83.2	79.4
Parents' Race: White	81.4	66.9	72.2	68.4	78.0	72.2
Black	2.4	5.3	11.1	10.1	6.0	7.6
Asian	5.9	14.2	0.0	6.1	2.0	10.2
Other	0.0	0.2	3.7	1.0	1.0	0.7
Mixed	10.3	13.4	13.0	14.5	13.0	9.3
One or Both Parents Hispanic	33.8	27.5	42.6	34.7	40.6	50.3
Non-Singletons	6.2	5.8	0	5.0	3.0	1.6
Primiparous	42.8	39.0	38.9	37.1	40.6	37.3
Mother's age ≥35 Years (at Birth of Child)	25.5	23.3	18.5	23.6	28.7	16.0
MotherÕs Eduation <12 yrs	6.8	9.6	14.8	21.1	12.1	29.8
16 Years or More	41.8	32.9	27.8	22.8	41.4	23.1
Mother born: Inside USA	72.4	69.1	68.5	73.2	70.3	54.5
Mexico	10.3	9.3	25.9	14.7	14.9	24.1
Outside USA or Mexico	17.3	21.7	5.6	12.0	14.9	21.4
Payment Method for Delivery						
Public	17.3	21.1	37.0	40.3	19.8	42.1
Private	81.2	77.5	63.0	57.4	80.2	56.0
Other	1.5	1.4	0.0	2.4	0.0	1.9

"Genetic and Social Modifiers in Environmental Neuroepidemiology: The Role of Context in Chemical Exposure"

Robert Wright MD MPH
Department of Pediatrics,
Children's Hospital, Boston,
Department of Environmental Health
HSPH



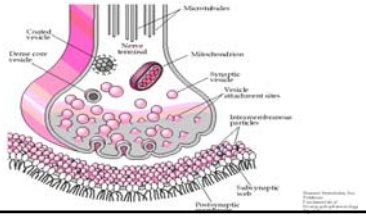


Biological Vulnerability

- Construction of the central nervous system (CNS) begins in utero,
- Continues throughout childhood and involves the production of 100 billion nerve cells and 1 trillion glial cells.
- Cell migrate, differentiate, and form synapses

Synapses

- Transmits signals between neurons
  - Environmental stimuli will cause neurons to fire
  - Neuronal/synaptic firing is a signaling process to mold the synaptic architecture of the brain



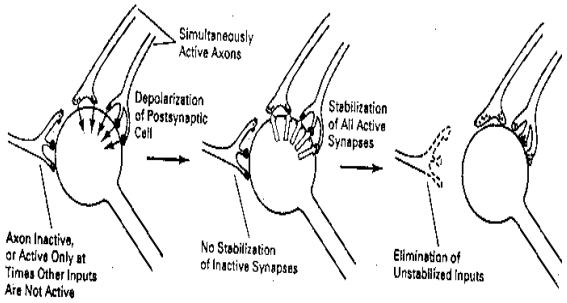
How does the Brain Build this Network?

- Some of it is stochastic
  - Synapses are made by the billions, and in some respects randomly, between neurons.
  - We make a net gain in synapses from fetal life till about age 2 years
  - Then the number of synapses in our brain starts to decrease
    - Why?

Synaptic Networks

- Environmental Stimuli cause nerves to fire:
- When they fire neurotransmitters are released into synaptic junctions
  - This releases growth factors- signals that this is an important neuronal connection (i.e. it gets used)
- In other words there is a “natural selection” process
  - Functional synapses release growth factors
  - Nonfunctional synapses do not release the growth factors

Hebb Synapses



So how do Environmental Chemicals affect Development?

- At “low” doses (blood lead around 5-10 ug/dL)
  - Lead will interact with Protein Kinase C
    - Stimulate neurotransmitter release
    - Neurons fire in the absence of an appropriate environmental stimuli
  - Lead mimics calcium
    - Calcium is critical to nerve signal transmission
    - Calcium enters neurons during depolarization
    - Lead blocks calcium channels

Lead and the Brain

- Net effect
  - Lead stimulates nerves to fire in a more stochastic fashion
  - Lead also inhibits neurotransmission (both appropriate neurotransmission and inappropriate neurotransmission)
- Changes the underlying synaptic architecture, making it less efficient

Plasticity

- The brain’s capacity to diminish the effects of toxic insults through structural/functional changes
  - This occurs through the same processes as synaptic selection
  - In other words plasticity allows for new connections to be made which improve function following an insult
- Maladaptive vs adaptive plasticity

Neurodevelopment and Social Environment

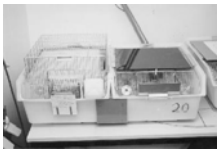
- **Chronic Stress known to impair memory and learning capacity**

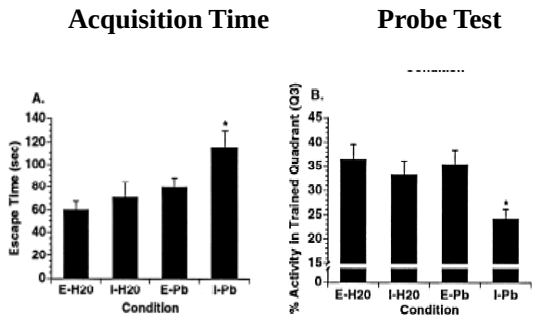
Non-chemical Toxicants- Psychological Stress

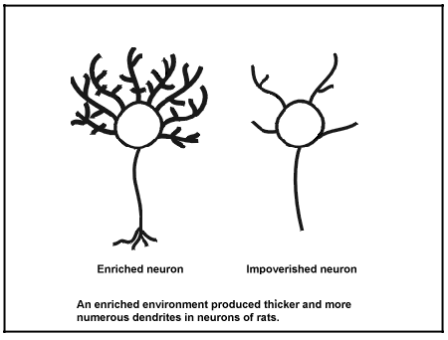
- Psychological stress - activates HPA axis Increases cortisol
- Hippocampus - highest density of glucocorticoid receptors
  - modulate neuro and synaptogenesis
  - acutely, stress enhances memory formation,
  - chronic stress appears to inhibit it

Social Environment and Pb

- Guilarte et al
- Lead poisoned animals during lactation
- Randomized to 2 groups
  - Animals raised in social isolation
  - Animals raised in groups with social stimulation
    - Tested on memory in Water maze







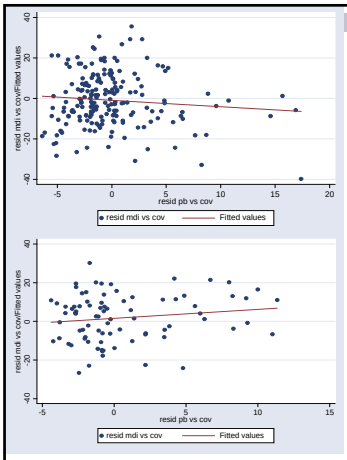
Can Reducing Stress be a Treatment?

- Mexico City
- Coopersmith self-esteem administered to mothers when child 24 months of age
- Cross-sectional analysis
- Covariates
  - Blood Pb, mom's IQ, mom's education, child's sex,

Main Effect of Maternal Self-Esteem

mdi24	Coef.	P>|t|	[95% CI]	
Blood Pb	-.11	0.569	-.50	.276
autoes	***.46***	***0.006***	***.12***	***.78***

Adjusted for Maternal IQ, education, Infant Sex,

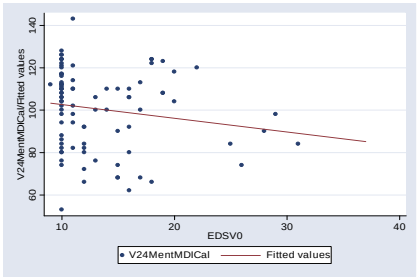


Blood Pb and MDI

Self esteem Quartile 1,2,3

Self esteem Quartile 4

Maternal Depression scale at delivery vs 24 month MDI



Another Pilot Study: Maternal Child Lung Study

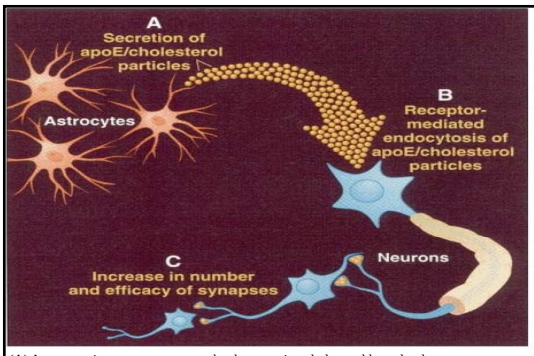
- Pregnancy cohort recruited from 1986-1992
- Study of in utero/environmental tobacco smoke exposure and respiratory outcomes
- Women enrolled before 20th EGA week
- Children followed after birth
- Measured ETV (violence) and WCST as pilot

Effect of Cotinine in Predicting Errors on WCST: Stratified by Median Violence Exposure

	Cotinine Beta (Low violence)	Cotinine Beta (High violence)
% Errors	2.9 (p=0.6)	9.8 (p=0.07)
# Perseverative Responses	1.7 (p=0.7)	11.1 (p=0.007)
%Perseverative Responses	2.0(p=0.7)	10.7 (p=0.007)
# Perseverative Errors	0.8 (p=0.9)	10.7 (p=0.01)
% Perseverative Errors	1.4 (p=0.8)	9.9 (p=0.02)

How Does Genetics play into this?

- Genetics regulates synapse formation
  - Pruning
  - Maintenance
    - Growth factors
    - Protection from oxidative xenobiotics
    - Nutrition



(A) Astrocytes increase synapse number by secreting cholesterol bound to large lipoprotein particles containing apolipoprotein E (apoE).
(B) These particles are internalized by neurons, leading to increased cholesterol within neuronal membranes. It is possible that apoE also activates yet to-be-identified signaling pathways within the neurons.
(C) These changes stimulate an increase in the number and efficacy of synapses.
From: Barres: Science, Volume 294(5545).November 9, 2001.1296-1297

APOE and Neurodegeneration

- E4 allele associated with 2-5 fold increased risk of AD if heterozygote
  - 5-17 fold increased risk if homozygote

APOE and Neurodevelopment

- Study of lead exposure and infant development in Mexico.
- Infants enrolled at birth, cord lead levels measured, Mothers receive calcium supplements in RCT.
- Bayley Infant Development scales performed at 24 months of age.

APOE and Neurodevelopment

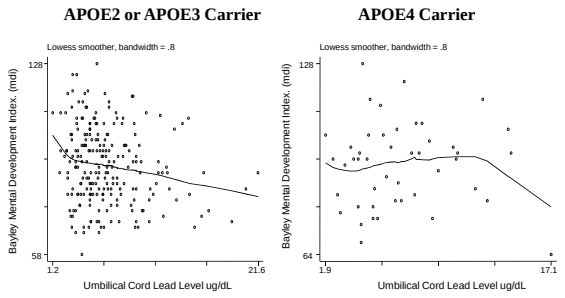
Multivariate Analysis	Beta
#APOE4	4.3(95% CI: 0.03 – 8.5)

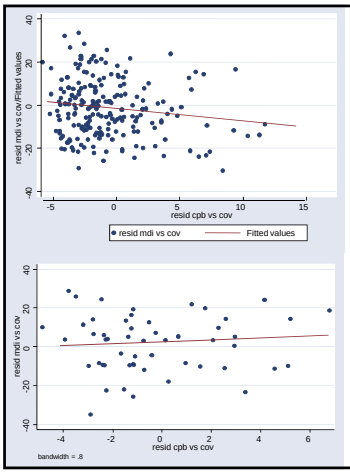
Study Group- subjects E4/E3. E4/E4

Referent group- subjects E3/E3, E3/E2, E2/E2

OR adjusted for the maternal IQ, Sex, gestational age, dietary calcium, umbilical cord blood lead level and Maternal years of Education.

Figure 1: Smoothed Plots of MDI Score vs Umbilical Cord Lead Levels





C2 Genotype as Modifier of Cord Pb Effect

Transferrin C2 Wildtype

Transferrin C2 Carrier

Metal Mixtures

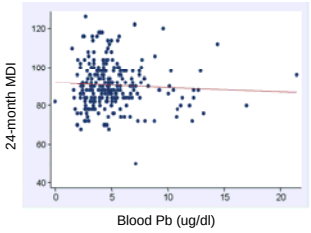
- Just as exposure does not occur uniformly against a given social context.
- Exposure to Neurotoxicants is mixed.
  - Pb
  - Mn
- Both have evidence of neurotoxicity.

Mexico City

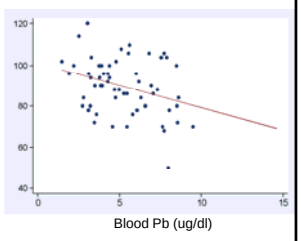
- Blood Mn measured on 300 infants at 1 year of age from archived samples.
- Blood Pb measured at 12, 18 and 24 months
- Bayley MDI at 12, 18 and 24 months.

Blood Pb and 24-month MDI Association Varies by Blood Mn Level

Lowest 4 Quintiles of Blood Mn



Highest Quintile of Blood Mn



Interaction beta: -1.5, p=0.04 (N=290)

Manganese-Lead Interaction

Highest Quintile of Blood Mn x Blood Pb

	Adjusted beta*	p
12-month MDI	-0.66	0.28
18-month MDI	-1.4	0.02
24-month MDI	-1.5	0.04
Repeated Measures	-0.9	0.04

*Adjusted for 12-month blood Pb level, infant sex, maternal IQ, maternal education

Mexico Birth cohort

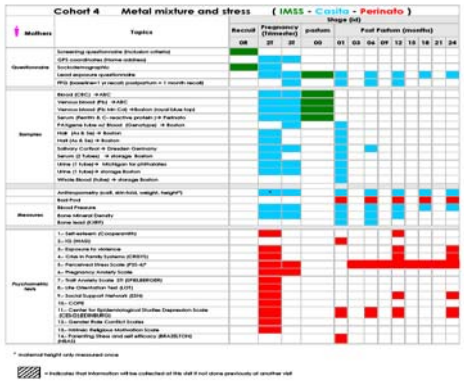
- The work just reviewed led to the establishment of a new birth cohort in Mexico City.
- 1) R01 ES014930 Metal Mixtures and Neurodevelopment
- 2) R01 ES013744 Stress, Lead, Iron Deficiency and Neurodevelopment.

Mexico City Birth Cohort

- Designed to study
  - Prenatal vs post-natal contributions to development
  - Genetic susceptibility
  - Metal mixtures
  - Social modifiers of toxicity

Mexico City Cohort

- Long term goals
  - Identify factors that increase/decrease metal toxicity
  - Understand the biology of metal neurotoxicity
  - Prevent toxicity
  - Treat toxicity after it has occurred



Tar Creek Superfund Site

The *MATCH* Study

(Metals **A**ssessment **T**argeting **C**ommunity **H**ealth**)**

"Ga-Du-Gi"- Working Together

Thanks

Element
Adrienne Ettinger
Mara Tellez-Rojo
Hector Lamadrid
David Bellinger
Rosalind Wright
Howard Hu
Lourdes Schnaas
Adriana Mercado

Tar Creek
Mary Happy
Mark Osborn
Rebecca Jim
Earl Hatley

Criminal Behavior as a Late Outcome of Early Exposure to Environmental Lead

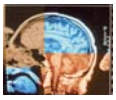
Cincinnati Lead Study

Kim N. Dietrich, Ph.D.

Environmental Factors in Criminal Disposition

- Parental dysfunction
- Community violence
- Poverty
- Media
- Lead
- Nutrition
- Alcohol
- Illicit Drugs

Biological Factors in Criminal Disposition



- Functional Anatomical Characteristics of Brain
- Neurotransmitter Metabolism
- Autonomic Function
- Traumatic Brain Injury (Frontal Lobes)
- Genetic endowment (Functional Polymorphisms)

Criminal Behavior as an Outcome of Childhood Lead Poisoning

Lead Exposure and Juvenile Delinquency: Earlier Observations

1943: Byers and Lord reported a high prevalence of behavior problems among survivors of lead encephalopathy. "…violent aggressive behavioral difficulties such as attacking teachers with knives and scissors."

Byers & Lord, *Am J Dis Child. 1943*

Dr. Randolph Byers

Bone Lead Levels and Percentage of Children Scoring in the Clinical Range for Aggression, Delinquency, and Attention on the Achenbach Child Behavior Check List

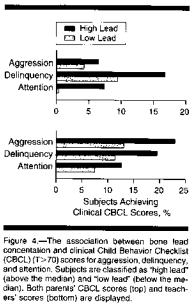


Figure 4.—The association between bone lead concentration and clinical Child Behavior Checklist (CBCL) (T>70) scores for aggression, delinquency, and attention. Subjects are classified as "high lead" (above the median) and "low lead" (below the median). Both parents' CBCL scores (top) and teachers' scores (bottom) are displayed.

Needleman, et al., JAMA, 1996.

Bone Lead Levels (ppm) in Adjudicated Delinquents: A Case Control Study*

	Cases		Controls		*P value*
	n	Mean (SD)	*n*	Mean (SD)	
All Subjects	195	11.0 (32.7)	150	1.5 (32.1)	0.007
African-American	158	9.0 (33.6)	51	-1.4 (31.9)	0.05
White	36	20.0 (27.5)	95	3.5 (32.6)	0.008

*Needleman, et al. 2002, Neurotoxicol Teratol.

Other Observations: Ecological Studies

- Stretesky and Lynch (2001) reported positive correlations between homicide rates and air lead contamination levels for 3111 counties in the US. Even after adjustment for 15 confounding variables, a four-fold increase in homicides in the counties with the highest air lead concentrations compared to counties with the lowest air lead concentrations was found.

  Stetesky & Lynch, *Arch Pediatr Adolesc Med., 2001*

- Nevin (2000) reported a statistically significant relationship between trends in sales of leaded gasoline and violent crime after adjustment for such variables as unemployment rates and percent of population in the age range where there is a higher risk for criminal behavior.

  Nevin, *Environ Res.,* 2000

Limitations of Earlier Studies

- These studies suggest that exposure to environmental lead during childhood is associated with the development of behavioral problems, delinquency and criminality.
- Questions remain, however, because the majority of these studies were cross-sectional, relied on indirect measures of lead exposure or did not follow the children into adulthood to examine the relationship of lead exposure with persistent criminality.

The Cincinnati Lead Study of Juvenile Delinquency and Adult Criminality

Cincinnati Lead Study catchment area

The Cincinnati Lead Study

- A prospective, longitudinal study initiated in 1979 that is examining the early and late effects of childhood lead exposure on growth and development with a particular emphasis on neurobehavioral outcomes.
- The Cincinnati Lead Study has collected data on exposure (blood lead concentrations), neurobehavior, child health, and sociodemographic variables on a quarterly to yearly basis since its inception.

Blood Lead Concentrations in the Cincinnati Lead Study

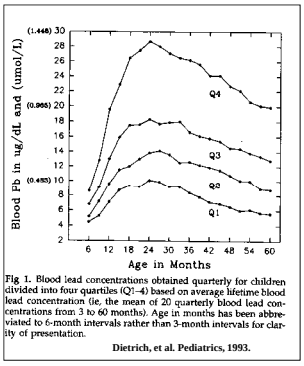
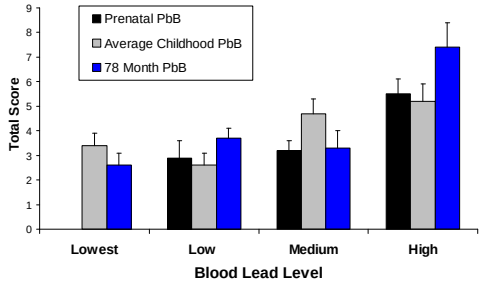


Fig. 1. Blood lead concentrations obtained quarterly for children divided into four quartiles (Q1–4) based on average lifetime blood lead concentration (ie, the mean of 20 quarterly blood lead concentrations from 3 to 60 months). Age in months has been abbreviated to 6-month intervals rather than 3-month intervals for clarity of presentation.

Dietrich, et al. Pediatrics, 1993.

Association of Blood Lead Levels and Self-Reported Delinquency in 16 Year-Old Adolescents in the Cincinnati Lead Study



Dietrich, et al. 2001, Neurotoxicol Teratol.

Cincinnati Lead Study Cohort as Adults (N = 250)

Characteristic	No. (%) / Mean (SD)
Subject Characteristics	
Male	125 (50.0%)
African-American	225 (90.0%)
Age at study date (years)	**22.5 (1.5)**
Marijuana use	29 (11.6%)
Blood lead (μg/dL)*	
Prenatal blood lead**	8.3 (3.8)
Average childhood blood lead	13.4 (6.1)
6-year blood lead	8.3 (4.8)

Cincinnati Lead Study Cohort as Adults (N = 250)

Maternal Characteristics	No. (%) / Mean (SD)
Age at delivery (years)	22.5 (4.2)
Maternal IQ (points)	75.3 (9.3)
High School graduate	132 (52.8%)
HOME Inventory at age 3 (points)	32.3 (6.6)
Socioeconomic status (Hollingshead score)	18.0 (4.8)
History of arrest (yes)	111 (44.4%)
Marital Status	
Married	39 (15.6%)
Single	155 (62.0%)
Other	56 (22.4%)
Smoked during pregnancy	129 (51.6%)
Number of children in home	3.0 (1.4)
Public assistance	190 (76%)

Table: Relationship of Prenatal, Early Childhood Average and Six-Year Blood Lead Concentrations with Arrests Rates in Young Adults (N = 250)

		Adjusted Estimates*	
Blood Lead Variable	Median (5^{th}-95^{th} percentile) μg/dL§	Attributable Risk (95%CI) per year	Rate ratio for 5 μg/dL increase in blood lead (95% CI)
Prenatal	7.8 (2.9-16.0)	0.48 (0.29-0.79)	1.40 (1.07-1.85)
Early Childhood Average	12.3 (6.0-26.3)	0.13 (0.03-0.33)	1.07 (0.88-1.29)
Six-Year	6.8 (3.4-18.3)	0.39 (0.21-0.68)	1.27 (1.03-1.57)

*Adjusted for maternal IQ, sex, socioeconomic status (SES) using the Hollingshead Score, and primary caregiver education level.

§Convert to umol/L ([ug/dL] x 0.04826)

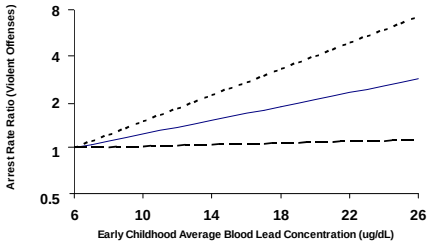
Table: Relationship of Prenatal, Early Childhood Average and Six-Year Blood Lead Concentrations with Violent Arrests Rates in Young Adults (N = 250)

		Adjusted Estimates*	
Blood Lead Variable	Median (5^{th}-95^{th} percentile) μg/dL§	Attributable Risk (95% CI) per year	Rate ratio for 5 μg/dL increase in blood lead (95% CI)
Prenatal	7.8 (2.9-16.0)	.055 (.026-.118)	1.34 (0.88-2.03)
Early Childhood Average	12.3 (6.0-26.3)	.077 (.039-.156)	1.30 (1.03-1.64)
Six-Year	6.8 (3.4-18.3)	.087 (.049-.152)	1.48 (1.15-1.89)

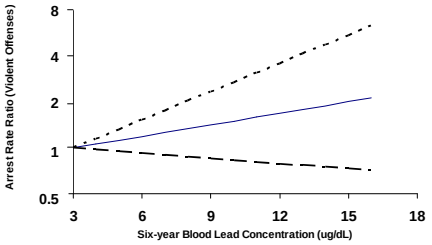
*Adjusted for maternal IQ, sex, socioeconomic status (SES) using the Hollingshead Score, and primary caregiver education level.

§Convert to umol/L ([ug/dL] x 0.04826)

Blood Lead Concentrations and Arrests for Violent Offenses in the Cincinnati Lead Study



Blood Lead Concentrations and Arrests for Violent Offenses in the Cincinnati Lead Study



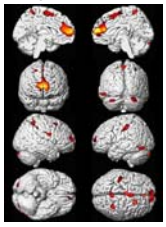
Mechanisms: How Does Lead Increase Antisocial Behavior?

- Direct route: Lead affects brain systems that regulate social-emotional functioning, including neurotransmitter metabolism and function, and neural growth, survival and differentiation in critical areas such as prefrontal cortex. Gene-environment interactions may also play a role.
- Indirect route: Early lead exposure is associated with higher rates of school failure and reading disabilities. Students who do poorly in school are more likely to engage in delinquent and criminal activities.

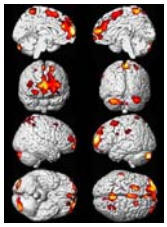
Biological Underpinnings: Imaging Studies of the Cincinnati Lead Study Cohort

Mechanism: Lead Associated Gray Matter Loss in Brain*

Average Childhood PbB



Six-Year PbB



*The effects of lead on gray matter loss were most severe in the frontal regions of the brain which are involved in attention, executive functions, and regulation of social behaviors.

Summary

- Data from previous cross-sectional and ecological studies suggest an association between exposure to lead and antisocial behaviors including delinquency and adult criminality.
- Data from the Cincinnati Lead Study indicate an association between prenatal and early postnatal exposure to lead and delinquent and criminal behaviors.
- Neuroimaging studies of the Cincinnati Lead Study cohort indicate lead-associated losses in gray matter of the cerebral cortex in areas of the brain that regulate attention, executive functions, judgment and social behaviors.

Questions and Discussion

Development Patterns and Children's Health

Tim Torma
EPA Smart Growth Program
October 12, 2007

A brief look at development patterns and health with a focus on school siting.

Growth Patterns Influence Community Goals

- Public health
- Economic development
- Efficient use of tax dollars
- Open space and farmland preservation
- Traffic congestion
- Air and water quality
- Revitalization of downtowns & existing neighborhoods
- Community character
- Quality of life

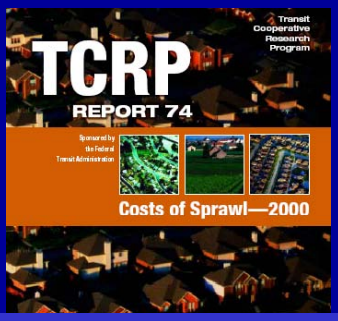
Three distinct growth trends over the last 50 years

1. Employment and population growth heavily favored medium and large metropolitan regions over nonmetropolitan areas.
2. Within metropolitan regions, most growth occurred in low-density development at the fringe of urbanized areas.
3. Emphasis on automobile travel at the expense of other modes.

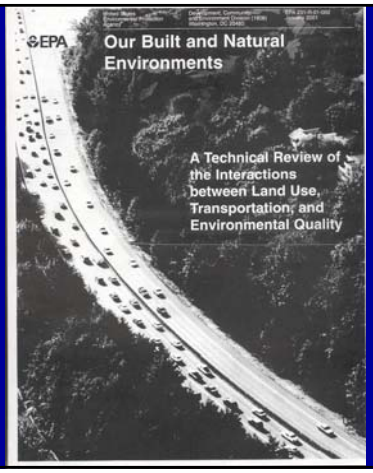
We've known about this pattern and it's impacts on the environment for a long time.

It has been studied – a lot.

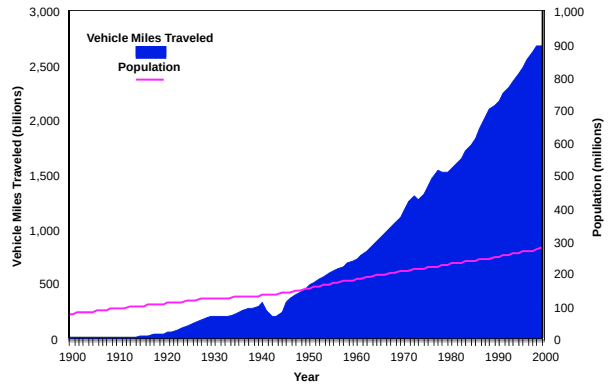
"The results of the study . . . show a surprising consistency: 'planning' to some extent, but higher densities to a much greater extent, result in lower economic costs, environmental costs, natural resource consumption, and some personal costs for a given number of dwelling units."

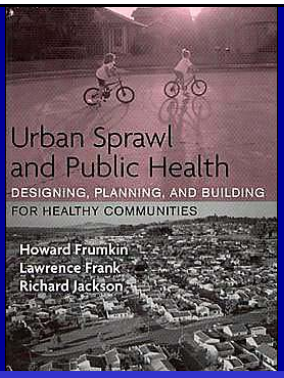


"More-compact development patterns produce savings that are both profound and measurable."



Trends in Vehicle Miles Traveled

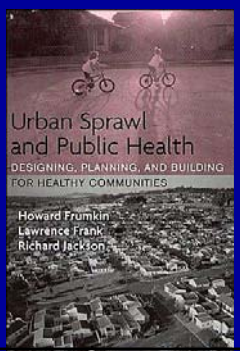




"We are only now realizing that the way we have built ... over the last half century has been extremely costly...to human health and well-being."

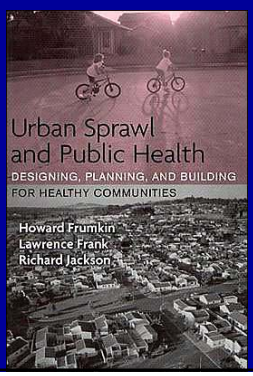
Health Outcomes Linked with Land Use and Community Design

- Air pollution and related illnesses.
- The decline in physical activity.
- Obesity and its attendant diseases.
- Injuries related to auto dependence.
- Threats to water quantity and quality.
- Mental illnesses.
- Erosion of social capital.



Health Outcomes Linked with Land Use and Community Design

- The authors issue a call for rebuilding American communities using smart growth strategies such as:
  - mixing land uses,
  - decreasing automobile dependence by providing more transportation choices,
  - increasing density balanced by preservation of open spaces.



Let's turn the focus to schools – how and where we've been building them.

The Demand for Facilities

- Over half of our school facilities are at least 40 years old.
- Nationwide, the student population is growing and will continue to do so until at least 2013.
- We spend over $40 billion per year on school construction

We're going to continue to see a lot of this type of activity.

During this time of great investments in school building…

- 1969: 48% of all children walked or biked to school
- 2002: 14% of kids walk or bike to school
- This is an extraordinary shift.
- It's almost as if we planned it that way.

Hmmm…Why can't Johnny walk to school?

- "National No Child Shall Bike or Walk to School Campaign"
- Top 11 strategies for implementing the campaign.

Strategy #1: Bigger Schools

www.governing.com/articles/3schools.htm

Strategy #1: Bigger Schools

- 1930 = 262,000 Schools
- 2002 = 91,000 Schools
- Student population over the same time: up from 28 million to 53.5 million
- Largest U.S. high school in 2003-04: 5,299 students (CA).

Dorman High School in Spartanburg, SC

Strategy #2: Mandate Minimum Acreage for School Sites

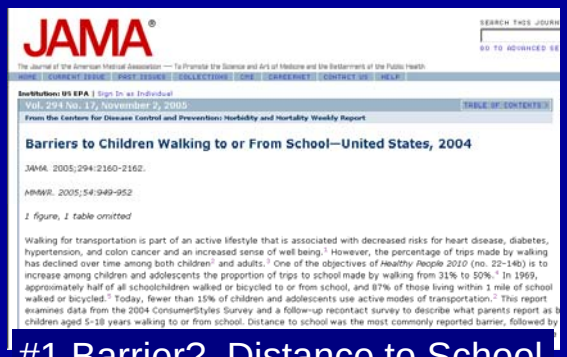
27 states have **mandatory** minimum acreage requirements.

Strategy #3: Locate Schools Far From the Students they Serve

Side benefits = demand for new:

- Roads
- Sewer lines
- Utilities
- Other infrastructure and services

Strategy #3: Locate Schools Far From the Students they Serve

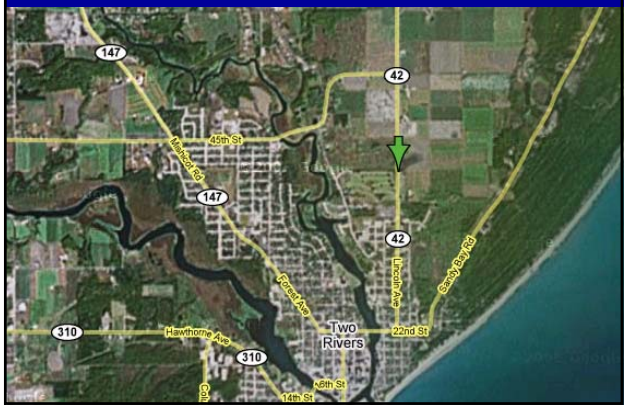


#1 Barrier? Distance to School

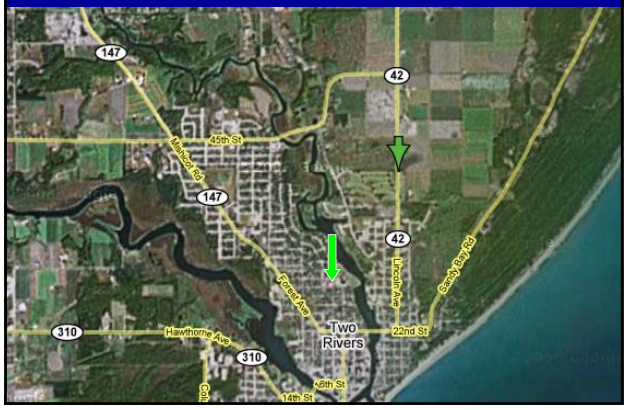
Strategy #4: Neglect or Demolish Existing Neighborhood Schools

Strategy #4: Neglect or Demolish Existing Neighborhood Schools

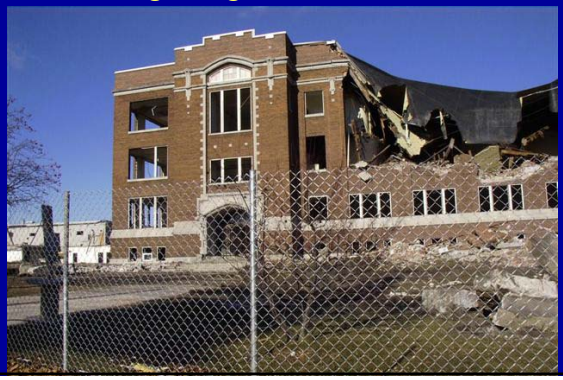
Location of New School



Location of Old School



Strategy #4: Neglect or Demolish Existing Neighborhood Schools



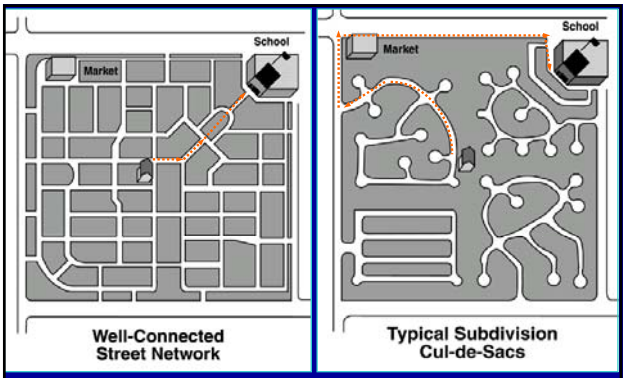
Strategy #5: Locate Schools On Unwalkable Roads

Strategy #5: Locate Schools On Unwalkable Roads

- A pedestrian hit at 40 mph has an 85% chance of being killed.
- At 20 mph the fatality rate is only 5%

(FHWA, Pedestrian Facilities Users Guide, 2002)

Strategy #6: Decrease "Pedestrian Route Directness" Around Schools



Strategy #7: Do Not Provide Sidewalks or Crosswalks

Strategy #7: Do Not Provide Sidewalks or Crosswalks

PHOTO BY STEVE RINGMAN / THE SEATTLE TIMES

Strategy #8: Creative Approaches to the Sidewalk Problem

Image courtesy of National Center for Biking and Walking

Strategy #8: Creative Approaches to the Sidewalk Problem

Image courtesy of National Center for Biking and Walking

Strategy #8: Creative Approaches to the Sidewalk Problem

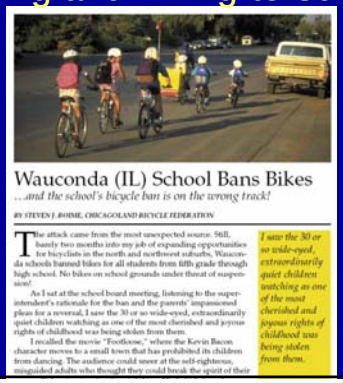
Strategy #8: Creative Approaches to the Sidewalk Problem

Richard Drudl

Strategy #8: Creative Approaches to the Sidewalk Problem

Photo: Michael Tobis
University of Chicago

Strategy #9: Simply Prohibit Walking and Biking to School



Wauconda (IL) School Bans Bikes

...and the school's bicycle ban is on the wrong track!

BY STEVEN J. BOIME, CHICAGOLAND BICYCLE FEDERATION

The attack came from the most unexpected source. Still, barely two months into my job of expanding opportunities for bicyclists in the north and northwest suburbs, Wauconda schools banned bikes for all students from fifth grade through high school. No bikes on school grounds under threat of suspension!

As I sat at the school board meeting, listening to the superintendent's rationale for the ban and the parents' impassioned pleas for a reversal, I saw the 30 or so wide-eyed, extraordinarily quiet children watching as one of the most cherished and joyous rights of childhood was being stolen from them.

I recalled the movie "Footloose," where the Kevin Bacon character moves to a small town that has prohibited its children from dancing. The audience could sneer at the self-righteous, misguided adults who thought they could break the spirit of their

I saw the 30 or so wide-eyed, extraordinarily quiet children watching as one of the most cherished and joyous rights of childhood was being stolen from them.

Strategy #10: Base School Siting Decisions on Desire for Massive Athletic Facilities

- Two recent studies in MI both found that desire for large athletic facilities was a significant factor leading to mega-schools on large sites.

Strategy #10: Base School Siting Decisions on Desire for Massive Athletic Facilities

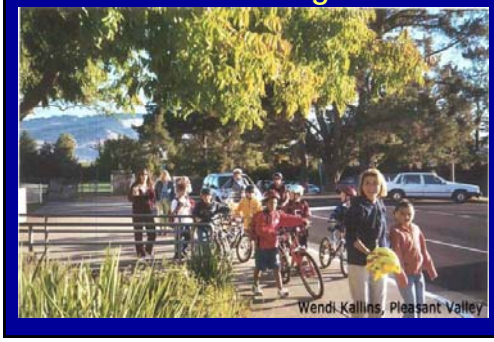
University Of Michigan Expands Michigan Stadium To Seat Everyone In Michigan

The Onion

Strategy #11: Show Children Innovative Alternatives to Walking

- Thanks, intellectual credit and apologies to Dr. Howard Frumkin of CDC for inspiring the preceding series of slides.

Trouble Brewing – No Walk Campaign Threatened by Insurgents



Voters say no to 'mega-campus'

Challengers overwhelm incumbents to win seats on Pottstown School Board

By Evan Brandt
ebrandt@pottsmerc.com

POTTSTOWN – Voters swept from office Tuesday the incumbent school board team that had advocated closing the borough's five elementary schools.

Instead, voted chose by a roughly 460-1 margin the team that championed saving those schools.

Unofficial results tabulated at Republican campaign headquarters showed a whopping 78 percent of the voters favoring the challengers – Dennis Wousnock, Julie Wilson, Michele Pargeon, Rick Huss and Nat White.

They handily defeated the team of one-term incumbents led by Barry Robertson, James Snock, Philip Thees, Borita Barnhill and Cathy Skirko.

Both teams "cross-filed" for both the Republican and the Democratic line on the November ballot.

The challengers' overwhelming majority on both ballot lines makes the November election a foregone conclusion.

"I got tired, I understand that," Robertson said from his home after the results had become obvious.

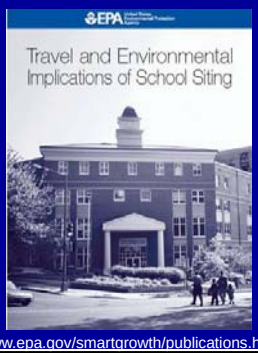
"Of all the elections I've been in, this is the most exciting," said Huss, a former school board member who "came out of retirement because the issue meant so much to me" to run for a fourth time.

"It was exciting because the people spoke," Huss said.

What they spoke about was the rejection of the

EPA has verified the effectiveness of many of these strategies

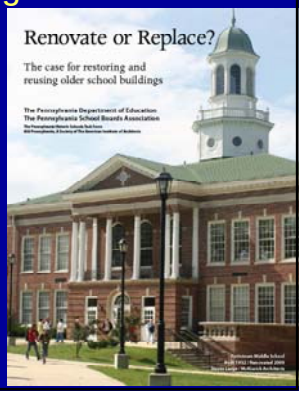
- School location and design DO affect the environment
- Schools built close to students, in walkable neighborhoods
  - Can reduce traffic
  - Yield increase in walking and biking
  - Reduce emissions



www.epa.gov/smartgrowth/publications.htm

Public Health Officials and School Siting

- Trend towards big schools on the edge of towns has multiple health considerations
- Health departments are already engaged in the "Safe Routes to School" movement
- Next: engage on school siting
- Health departments can influence these conversations



http://icma.org/main/ld.asp?ldid=19338&hsid=1&tpid=31

Expert tests walking routes

Urban designer Dan Burden will speak today at a workshop at The Forum at 9 a.m.

08/31/06
By Chris Fincher
Respond to this story
Email this story to a friend

... ...Parents and city officials walked in the tiny footsteps of children Wednesday to determine if their commute to school is as safe as it could be.

About 20 people, including parents and neighbors, joined in the field trip around Elm Street Elementary School led by Dan Burden, an urban designer from Florida who specializes in walkable communities.

Other walks took place around parks and school districts in Cave Spring,

Dan Burden leads a group doing a walkability

"Burden will be a featured speaker at a workshop **hosted by the district health administration** today at The Forum."

The pedestrian/ bicyclist is an indicator species for a healthy, livable, place.

www.pedbikeimages.org / DanBurden

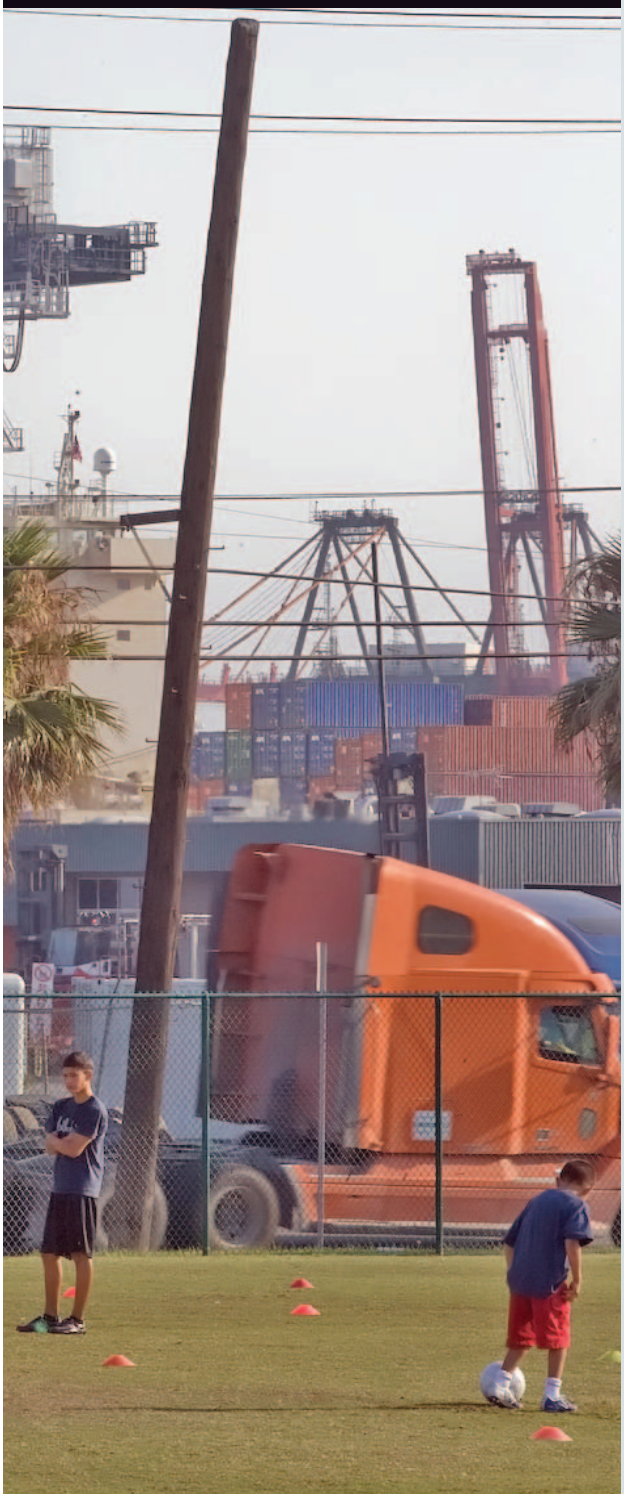
Web: www.epa.gov/smartgrowth

For more information…

– My Contact information:
– Tim Torma
– torma.tim@epa.gov
– 202-566-2864

– www.epa.gov/smartgrowth/schools

Global Trade Comes Home
Community Impacts of Goods Movement



California Department of Transportation, District 7

For many U.S. residents, 2007 was a year of heightened awareness of some of the problems of global trade. Extensive recalls of melamine-tainted pet food in the spring followed by even larger toy recalls in the summer and fall raised consumer concerns about how the United States can ensure the safety of products shipped in from overseas. The *Salt Lake Tribune* and the *Wall Street Journal* detailed injuries and illnesses threatening the health of Chinese workers making products for export to the United States. And on 15 December 2007, a *New York Times* feature detailed the practice of farming fish in toxic Chinese waters for export to the United States and other countries.

While these news stories demonstrate some of the pitfalls of globalization, much less attention has focused on air pollution and other community-level impacts in the United States, as toys, electronics, food, and other imports travel through ports, then to trucks, trains, warehouses, and stores in a complex system called "goods movement." Along the route, residents are exposed to diesel exhaust and other vehicle emissions, noise from truck-congested roads, bright lights from round-the-clock operations, and other potential health threats.

Transportation experts refer to these impacts simply as "externalities" of transport, but to community residents they can directly harm the quality of daily life. As ports and goods movement activity expands throughout the United States, a major challenge is how to make its health and community impacts a more central part of policy discussions.

Economic Benefits, Community Costs

Economic development advocates call the side-by-side ports of Los Angeles and Long Beach Southern California's "economic engine." Combined, they handle the most containers of any U.S. port. With more than 40% of all imports for the entire United States coming through the Los Angeles/Long Beach port complex, according to the U.S. Department of Transportation, the ports are critical to the national economy. A March 2007 national economic impact study by the twin ports reported that imports coming

Children play soccer next to the TraPac terminal at the Port of Los Angeles, Wilmington, California.

through the complex generated jobs, income, and tax revenue in every state of the nation.

While recognizing the economic importance of international trade, the U.S. Environmental Protection Agency (EPA) has called the movement of freight a "public health concern at the national, regional and community level." In a 22 August 2007 *Federal Register* announcement of a meeting of its National Environmental Justice Advisory Council (NEJAC), the EPA also described mounting evidence that local communities adjacent to ports and heavily trafficked goods movement corridors are the most significantly impacted by the goods movement system.

The ports of Los Angeles/Long Beach combined contribute more than 20% of Southern California's diesel particulate pollution and are the single largest source of pollution in Southern California, according to the South Coast Air Quality Management District (AQMD), the region's air quality regulatory agency. The California Air Resources Board (CARB), in its 2006 *Emission Reduction Plan for Ports and Goods Movement*, calculated that in California alone there are 2,400 premature heart-related deaths related to port and goods movement pollution, 62,000 cases of asthma symptoms, and more than 1 million respiratory-related school absences every year. Nationwide, reports James Corbett of the University of Delaware and colleagues in the 15 December 2007 issue of *Environmental Science & Technology*, an estimated 60,000 lives are lost prematurely every year due to ship emissions, which are virtually unregulated.

Recent research findings about living close to traffic emissions add to concerns. A study by investigators at the University of Southern California (USC), published 17 February 2007 in *The Lancet*, showed that children living near freeway traffic had substantial deficits in lung function development between the ages of 10 and 18 years, compared with children living farther away. "Since lung development is nearly complete by age eighteen," says lead author W. James Gauderman, "an individual with a deficit at this time will probably continue to have less than healthy lung function for the remainder of his or her life."

Other studies published in the February 2003 and September 2005 issues of *EHP* linked traffic exposure to increased risk for low birth weight and premature birth. A new study published 6 December 2007 in the *New England Journal of Medicine* showed that adults with asthma who spent just 2 hours walking on a street with heavy diesel traffic suffered acute transient effects on their lung function along with an increase in biomarkers that indicate lung and airway inflammation. In addition, research by the EPA-funded Southern California Particle Center at the University of California, Los Angeles, published in the April 2003 issue of *EHP*, demonstrated that ultrafine particles from incomplete combustion of engine fuels and lubricating oils can bypass the body's defense mechanisms, gain entry to cells and tissues, and alter or disrupt normal cellular function.

Regulation to Date

In 2005, CARB issued guidelines that recommend avoiding construction of new schools and homes within a mile of a railyard or 500 feet of a busy highway. A few years earlier, California legislators, citing health effects research findings, passed SB 352, a law prohibiting building new schools within 500 feet of a busy road or freeway. But the 2003 law permits several loopholes, such as allowing a school district to show that it is able to mitigate traffic emissions so that pupils and staff will suffer no significant health risk. The law also requires that a school district verify that any railyard within a quarter mile of a new school will not present a public health threat. Some school districts, in the scramble to build new facilities, are continuing to site new schools near freeways and rail operations.

Conversely, railyards and freeways also continue to be proposed in close proximity to schools and homes, such as a proposed truck expressway to speed trucks away from the Southern California ports, which would pass within 100 feet of homes and 700 feet of a local school. The draft environmental impact statement (EIS) for the project, issued in August 2007 by the California Department of Transportation (Caltrans) acknowledges the scientific research: "Some recent studies have reported that proximity to roadways is related to adverse health outcomes—particularly respiratory problems." But the EIS goes on to say that using these studies to determine if there will be adverse impacts from the truck expressway project is premature.

According to Ron Kosinski, deputy district director for the Caltrans district covering Los Angeles County, the Federal Highway Administration (FHWA) is delaying any policy decisions related to health effects from proximity to traffic until the conclusion of a review of all the studies by the Health Effects Institute—a report that is not expected for several years. FHWA spokesman Doug Hecox says, "[The agency is] not suggesting that nothing should be done. But there are no conclusive studies right now drawing a direct relationship between the number of trucks on a road and the percent of impairment of an affected child."

Environmental, community, and public health groups have long pressured Los Angeles and Long Beach port authorities to take action on port pollution. In 2006, an historic agreement called the Clean Air Action Plan (CAAP) was signed, vowing that the ports would reduce air pollution by 45% within the next 5 years. However, some community and environmental groups are concerned that the deadlines set in the CAAP are slipping.

Port of Los Angeles executive director Geraldine Knatz responds that the CAAP "is a five-year process that requires major investment in construction and new equipment, and in the interim, cargo movement through our ports continues." Knatz also points to a new program to reduce port-related truck emissions by 80% by 2012—a $2 billion initiative that she says "cannot simply happen overnight." In December 2007, both ports adopted container fees to fund the replacement of 17,000 polluting big-rig trucks with new models that meet tighter EPA diesel emission standards.

At the state level, CARB issued new rules in December 2007 that would require ships to plug in to electricity rather than using diesel auxiliary engines when docked in the harbor and that would require stricter emissions standards for trucks frequenting ports and railyards. The South Coast AQMD has long championed stricter controls on ports and rail operations to protect public health, as well as environmental justice considerations. In 2006 the agency issued rules to reduce pollution from idling locomotives in railyards, but railroad companies sued to block them. In 2007 a Los Angeles–based U.S. District Court judge struck down the agency's rules, arguing that it lacked authority to adopt them; the agency is appealing the decision.

According to the South Coast AQMD, emissions from ships are also underregulated, with no significant international or federal emission control regulations. In 2004, the EPA announced plans to put in place new standards for ships and locomotives. On 15 January 2008, the Greenwire news service reported these standards were under review at the White House Office of Management and Budget, which must approve them before the EPA can sign off on them.

Increased Trade Expected

The health and environmental justice impacts of port, rail, and trucking pollution are not limited to California. In South Carolina, for example, environmental groups and homeowners are troubled by anticipated impacts of a proposed terminal expansion at the old Charleston Navy Base, which the South Carolina Coastal Conservation League says will triple the container volume through Charleston and generate thousands more truck trips a day through a low-income black neighborhood. "An access road and off-ramp will go right through our Rosemont community as trucks leave the port terminal for the

nearby interstate highway," New Rosemont Neighborhood Association president Nancy Button told participants of a recent community–academic conference on port health impacts held in Los Angeles.

According to *The Journal of Commerce Online* (*JoC*), a news magazine covering international trade and goods movement, many U.S. ports are expanding in hopes of capitalizing on rising international trade volumes. Historically, says maritime industry economist Bill Ralph, as quoted in the 16 January 2008 *JoC*, international container trade in the United States has an annual growth of about 7%. In 2006, U.S. containerized imports grew by 11%. But in 2007, says Ralph, they increased by only 3%, due to a slowdown in the housing and auto markets. Economist Walter Kemmsies, quoted 2 days earlier in the *JoC*, predicts that U.S. container trade will return to its normal 7% annual growth within the next 2 years and continue to grow steadily—even faster if the United States enters into more free trade agreements.

The EPA Office of Environmental Justice (OEJ) has taken note of the growth trends and the rising environmental health concerns about port and goods movement expansion. In August 2007, acting OEJ director Charles Lee appointed a new working group to study the impacts of ports and goods movement through an "environmental justice lens," with a report expected in June 2008. Land use decision making will be 1 element in the report, along with community participation, regulatory mechanisms, innovative technologies, and more.

Projected increases in foreign trade, along with many states' planned expansion of highways, rail facilities, and ports to handle Asian imports, cause concern about increased air pollution if regulations to reduce emissions do not keep pace with trade growth. In the 22 August 2007 *Federal Register*, the EPA noted that the anticipated increase in trade will have air quality impacts, and the agency threw out a challenge to the ports and companies involved in goods movement: "It is becoming increasingly important that these entities operate sustainably, i.e., economically viable, environmentally and socially responsible, safe and secure."

Community Response

As this global goods movement system expands, communities across North America are now recognizing that they are facing similar circumstances and common conflicts. And they are banding together, in small and large coalitions, to address the impacts.

In the 1990s, just a few groups such as the Sierra Club, the Environmental Health Coalition, the Center for Community Action and Environmental Justice, and homeowners near the ports were focused on the effects of the global supply chain. But 2001 turned out to be a watershed year. That year, the Natural Resources Defense Council, the Coalition for Clean Air, Communities for a Better Environment, and 2 harbor-based homeowner's associations filed a lawsuit challenging the Port of Los Angeles's environmental review of planned construction for a major shipping terminal. Two years later they won a $50 million landmark settlement from the city requiring environmental mitigations, such as the "plug in" rule issued by CARB in December. A new era had begun—one that started to shift public attention from the role of international trade simply as the region's major economic engine to the potential perils of uncontrolled goods movement expansion.

That same year, the NIEHS-funded Southern California Environmental Health Sciences Center, based at USC, held a town meeting to share its research findings with community groups, residents, workers, and policy makers. In turn, scientists heard the emerging concerns of residents about diesel emissions near the ports, railyards, and warehouses. Research findings on the health impacts of air pollution soon began to find their way into policy debates on goods movement and port expansion.

Over the next 5 years, multiple partnerships started to come together to specifically address issues of ports and goods movement in California. Among the collaborative efforts active today are the Ditching Dirty Diesel Collaborative based in Oakland, aimed at developing a regional strategy to reduce diesel emissions; the Trade, Health & Environment (THE) Impact Project, a community–academic collaborative aimed at elevating community voices in the goods movement policy debate and using science-based information to inform public policy; the Port Work Group of Green LA, which aims to ensure that the Port of Los Angeles becomes truly green, with the support of the city's mayor; and a broad-based coalition aimed at improving wages and working conditions (including less-polluting vehicles) for port truck drivers.

Elsewhere, residents in a neighborhood near the Port of Seattle have been counting big-rig trucks parked overnight in their community in an effort to keep port-related pollution, safety hazards, and blight out of their neighborhoods. In Arizona, a school superintendent has asked officials not to enact zoning changes that would allow construction of a major intermodal facility (a railyard at which cargo is transferred between trucks and trains) across the street from a local elementary school. And on Long Island, residents are asking the state of New York to reconsider its plans to build an intermodal facility near residential communities and a wildlife preserve.

Tools for Action

Many groups impacted by ports and goods movement came together in late 2007 at Moving Forward, the first North American community-oriented gathering on this topic, which was organized by THE Impact Project and cosponsored by private groups along with NIEHS- and EPA-funded centers.

Participants shared information on current health research related to goods movement, community concerns about health impacts, future goods movement expansion projects (such as plans to deepen the harbor at the Port of Savannah, Georgia, to handle larger ships carrying twice as many containers), and community efforts to effect change. Presenters described tools for action, such as methods for mapping goods movement activities in communities; understanding who the key goods movement stakeholders and decision makers are; ways to incorporate credible, current scientific research findings into educational and policy efforts; and new methods for developing health impact assessments.

Eric Kirkendall from Kansas was struck by the commonalities at the conference. Back home, he had formed the Johnson County Intermodal Coalition in response to proposals to build an intermodal railyard near the small town of Gardner and surround his 4-acre homestead on 3 sides with 12-acre warehouses. Kirkendall says, "We sometimes feel alone in Kansas. But by the end of the conference I understood that we are not alone. We have much to share with, and learn from, other groups with similar challenges, as well as from scientists and policy makers."

Some attendees thought more attention should be focused on American consumer habits, a point echoed by Rev. Peter Laarman, executive director of Progressive Christians Uniting. He urges a closer look at the hidden costs of imports. "Americans think of themselves as consumers rather than as citizens," he says. "We don't care, for example, if Chinese workers toil in factories with no safety regulations, or if residents in communities near our ports have to breathe dirtier air. What we care about is 'How much do I have to pay for an iPod?' and 'Where can I buy this doll for under ten dollars?'"

By their very nature, the ports and goods movement debates faced by community groups throughout North America can help to inform future discussions about consumerism and globalization. As far as health effects go, however, research findings and community experience are strongly suggesting that global trade, while an apparent boon to our economy, will continue to pose a serious threat to our population's environmental health unless protective and collective action is taken, and soon.

Andrea Hricko

THE NATIONAL CHILDREN'S STUDY

MARION J. BALSAM M.D.

Research Partnerships Program Director

National Children's Study

National Institute of Child Health and Human Development/NIH/DHHS

THE NATIONAL CHILDREN'S STUDY: ADJUNCT STUDIES

2007 Children's Environmental Health Workshop: EPA

October 12, 2007

US Department of Health and Human Services

US Environmental Protection Agency

The National Children's Study

- Authorized in 'The Children's Health Act of 2000': study effects of the environment on child health and development
- Environment broadly defined: chemical, biological, physical, psychosocial-cultural
- Gene-environment interaction and gene expression
- Largest/longest such study ever conducted in the U.S.
- Longitudinal study of 100,000 children, from before birth (even before conception) through age 21
- Representative sample of children across the U.S.
- Power to study important but uncommon outcomes
- National resource for future research

Aims of the Study

- Identify environmental effects on children:
  - harmful, harmless, and helpful
  - in the context of gene-environment interaction

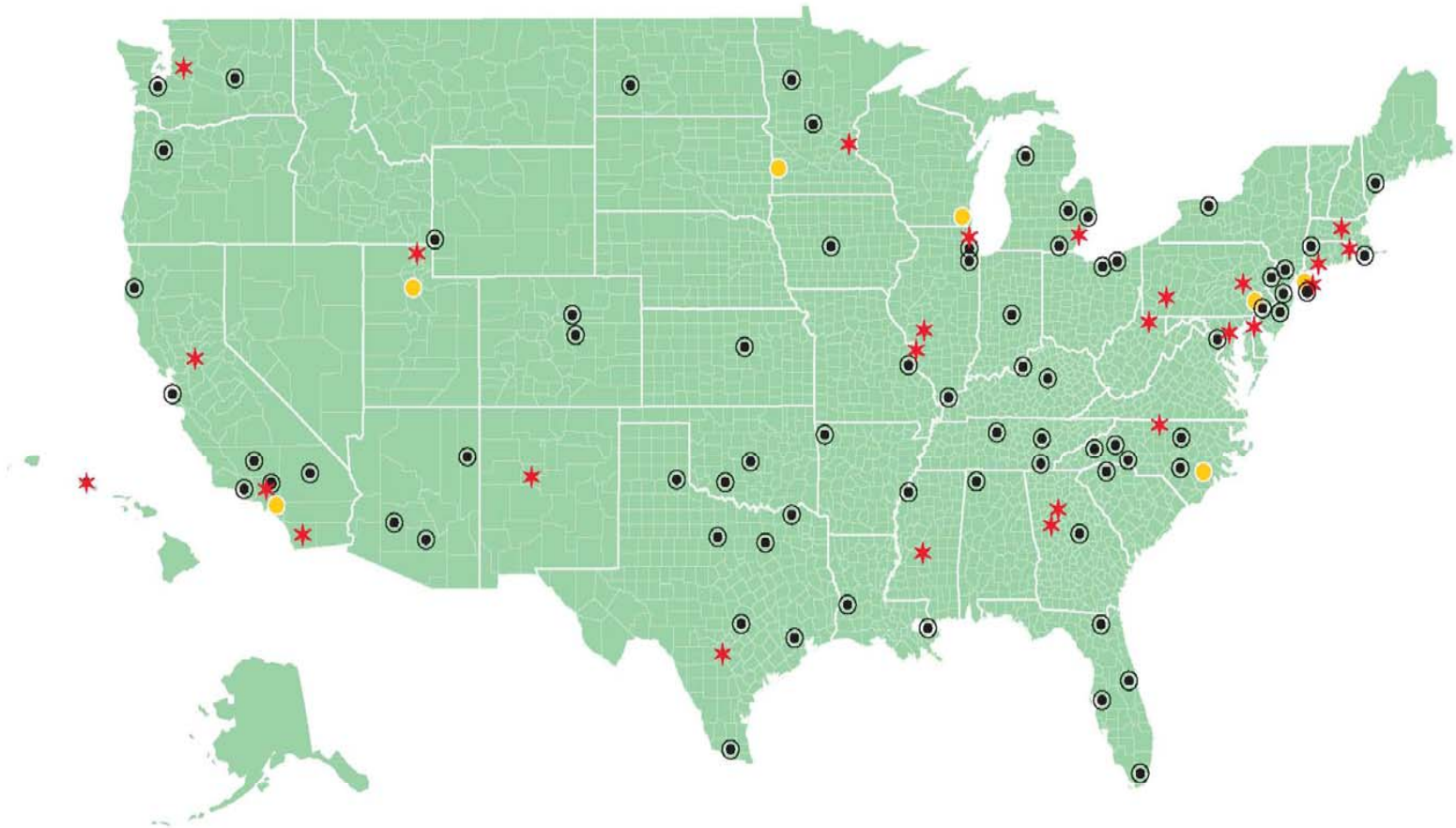
- Identify preventable causes of important health-related conditions in children

- Provide evidence-based data to guide decisions regarding children's healthcare and health policy

Organizational Structure

- Program Office (PO) at NICHD – NCS Director, scientists, administrative staff
- Interagency Coordinating Committee – NICHD, CDC, EPA, NIEHS
- Chartered Advisory Committee
- Federal Consortium: key government agency reps
- Steering Committee – Study Center PIs, federal scientists and community representatives
- Coordinating Center – Data management/coordination
- Study Centers – 7 Vanguard Centers & 22 new Centers
- Study Assembly - 4500 interested scientists & others

National Children's Study Locations



Map Legend

- 2007 Locations
- Vanguard Locations
- 2008-2010 Locations

THE NATIONAL CHILDREN'S STUDY
HEALTH GROWTH ENVIRONMENT

October 2007

Priority Exposures and Outcomes

Priority Exposures	Examples
Physical Environment	Housing quality, neighborhood
Chemical Exposures	Pesticides, phthalates, heavy metals
Biologic Environment	Infectious agents, endotoxins, diet
Genetics	Interaction between environmental factors and genes
Psychosocial-cultural Milieu	Families, SES, institutions, social networks

Priority Health Outcomes	Examples
Pregnancy Outcomes	Preterm, Birth defects
Neurodevelopment & Behavior	Autism, schizophrenia, learning disabilities
Injury	Head trauma, Injuries requiring hospitalizations
Asthma	Asthma incidence and exacerbation
Obesity & Physical Development	Obesity, Diabetes, altered puberty

Leveraging the National Children's Study

The Research Plan or Protocol…

The potential links between exposure & outcome measures…

The ongoing research findings as the Study progresses…

will spark ideas for further research leveraging the core study ->adjunct study proposals

Adjunct Studies: Key Characteristics

- **Involve a subset of the NCS cohort**
- **Modular, focused studies utilizing NCS infrastructure: participants, and/or bio-specimens, and/or environmental samples.**
- **Initiated by: government scientists, Study Center scientists, independent investigators, research advocates, industry…**

Adjunct Studies: Key Characteristics (cont'd)

- **Focus**
  - **a unique research interest/capability**

    or

  - **a specific public health or community concern**
- **Utilize, complement, leverage the core protocol for mutual benefit**
- **'Outside' (not core-NCS) funding**

Key Review Factors For NCS Quality and Integrity

- **Scientific merit**
- **Public health importance: potential contribution to health care or policy**
- **‘Fit’ with the NCS (priority exposure or outcome, sampling, tools, timing…)**
- **Appropriate use of bio-specimens and environmental samples**

Key Review Factors (cont'd)

- **Burden on participants (time, discomfort…)**
- **Burden on the Study infrastructure (logistics…)**
- **Human Subjects issues: ethical & legal considerations**
- **Peer review, IRB review, funding**

Application:
Review and Approval Process

- **Brief electronic Preliminary Application**
- **The Full Application is provided after NCS approval of the Preliminary Application**
- **Iterative process to facilitate timely review of proposals: Program Office, ICC, Steering Committee, Sample Oversight Group…**

‘Outside’ Funding (not ‘core-NCS’ $$$)

- **‘Partnerships’ with government agencies (e.g. intramural scientists and funding; RFAs to extramural scientists…)**
- **Government grants (e.g. R-01…)**
- **Public-private partnerships: industry, foundations, academia, research advocacy groups, etc.**

Timing (as of 10-07)

- **July 2008 to July 2009: VC pilot year**
- **July 2009: Enrollment begins at Vanguard and new Study Centers for the ‘full Study’**
- **Adjunct Study proposals for pre-conception, pregnancy, delivery, newborn and early infancy periods could be submitted soon to commence ~July ‘09**

In summary: Opportunities for scientists in government and academia

- **Opportunities will continuously arise for additional research by leveraging the NCS**
- **Opportunities exist for public-public (other government agencies) and public-private partnerships**
- **Adjunct studies will broaden and enhance the NCS contribution to children's environmental health**
- **On the NCS website:**
  - **'Adjunct Study Overview'**
  - **Application for adjunct study proposals**

Marion J. Balsam M.D.

Research Partnerships Program Director

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www.NationalChildrensStudy.gov
ncs@mail.nih.gov

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NCSAdjunctStudies@mail.nih.gov

Tools for Recovery and Communicating Risks After Hurricane Katrina

Objectives of Today's Panel

- Describe the collaborative PEHSU response to Hurricanes Katrina and Rita (Debra Cherry, MD)
- Experience and feedback from a Gulf Coast pediatrician at Ground Zero (Scott Needle, MD)
- New tool: The NIEHS Hurricane Response Portal (Marie Lynn Miranda, PhD)
- Discussion

Disaster Strikes: Aug 29, 2005

- Over 354,000 Gulf Coast homes destroyed
- Over 200 sewage treatment plants and 140 oil and gas platforms damaged
- Rampant mold growth
- Mountains of debris
- Widespread demolition/reconstruction projects
- Residents in temporary housing

Tyler: The closest PEHSU

Tyler, TX to New Orleans:

424 miles

In Katrina's Wake…

- "This is the mother of all multidisciplinary problems" – John McLachlan, Tulane/Xavier Research Scientist*
- "The public health community must articulate key health issues, keep the message simple and focused, and develop effective strategies to provide targeted timely results" – Kellogg Schwab, Johns Hopkins Bloomberg School of Public Health*
- *Lessons Learned, In Katrina's Wake, EHP 114 (1): Jan 2006, pg A39

The Hazards

DORRY CARONNA, 10, carries her sister Lizzy, 2, over the mud-covered floor as the girls visit their home in New Orleans yesterday. The home was flooded nearly a month ago.

CHILDREN: RETURNING TOO SOON

MOLD, DEBRIS, SLUDGE, MUD

Joint Documents and Recommendations

- NYC, Atlanta, and Tyler PEHSUs
  - Clinician recommendations for return of children to previously flooded and/or hurricane impacted areas
- EPA: Siobhan McNally (Boston PSR), Martha Berger, Michael Shannon
  - Tip Sheets for Parents – Mold, sludge
  - Environmental Questionnaire for Clinicians
- More Recently - Poor indoor air quality in FEMA trailers
  - Formaldehyde fact sheet

Sample Call: Sludge, Sep 2005

A mother of three children, ages 8, 4, and 3 months, called about moving back to her home that had standing water for 3 weeks and sludge contaminants from an oil refinery spill. The refinery offered to remove the soil from her yard and sludge from her home.

Photo: Clip art from Power Point

Sample Call: Formaldehyde, July 2007

A mother called SWCPEH regarding her 6 y/o daughter with a nasal polyp and nosebleeds several times per month. She and her daughter have been living in a FEMA trailer in the New Orleans area since Katrina (almost 2 years as of July). The girl has no known allergies, and the problems started in the last year. Mom wants to know if this could be related to formaldehyde.

"My home"; www.fematrailersong.com

Summary: SWCPEH/PEHSU Network Hurricane Response

- Prepared guidelines for returning children to previously flooded areas
- Prepared fact sheets and questionnaires in conjunction with EPA, PSR
- Answered calls from concerned parents

NIEHS Environmental Health Sciences Data Resource Portal

Marie Lynn Miranda, Ph.D.

12 October 2007

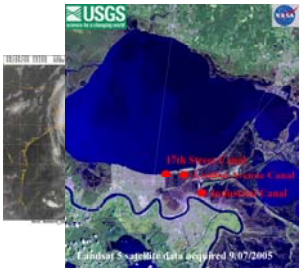
Children's Environmental Health Initiative

A research, education, and outreach program committed to fostering environments where all children can prosper.

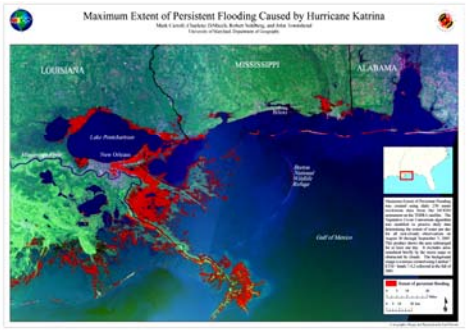
New Orleans: Before and After Hurricane Katrina

Before

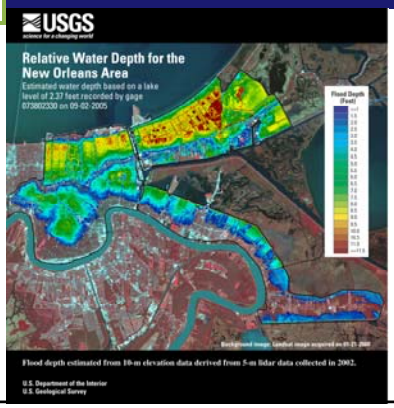
After



Regional Overview



Extent of Flooding



Industrial Canal Levee Breach

Lower 9th Ward Pre Katrina

Lower 9th Ward September 1st, 2005

Lower 9th Ward December 14th, 2005

Key Health Consequence Questions

- Mold and respiratory health
- Contaminant transport
- Solid waste management
- Mental health

NIEHS Response: Web Portal

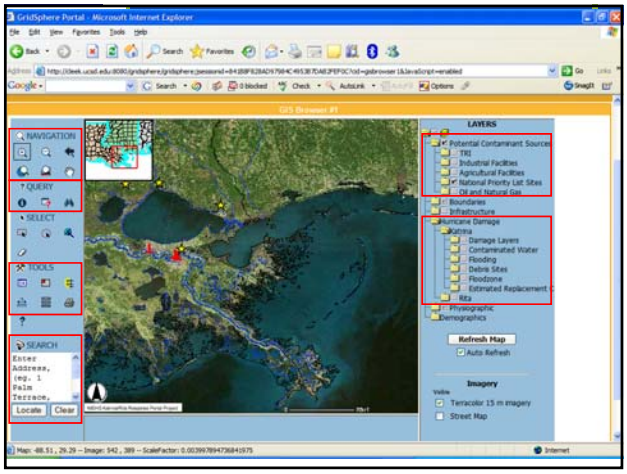
- Build and maintain extensive data archive designed to investigate environmental health consequences of the hurricanes
- Provide a collaborative workspace for analysis of georeferenced data
- Provide a Gulf Coast resource to support environmental health research more broadly

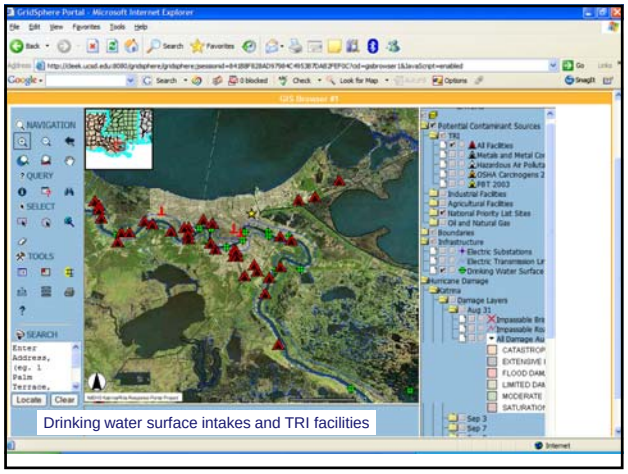
Collaborative Team

- NIEHS
- Columbia University (CIESIN)
- University of Kentucky
- Research Triangle Institute
- San Diego State University
- University of California, San Diego
- Duke University

NIEHS Hurricane Response Web Portal

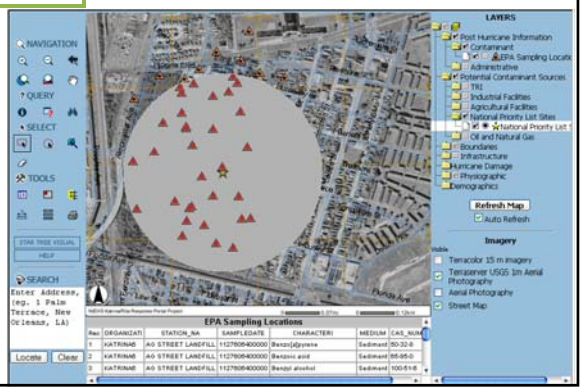
http://www.niehs.nih.gov



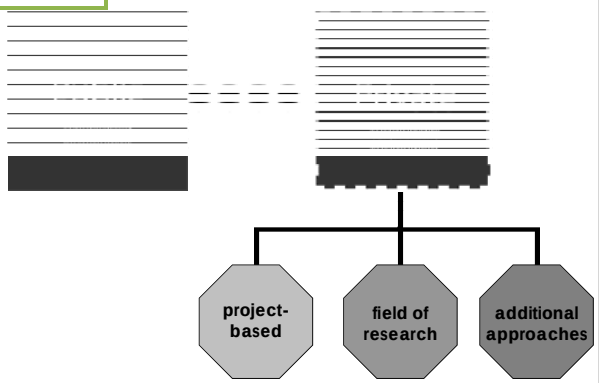


Drinking water surface intakes and TRI facilities

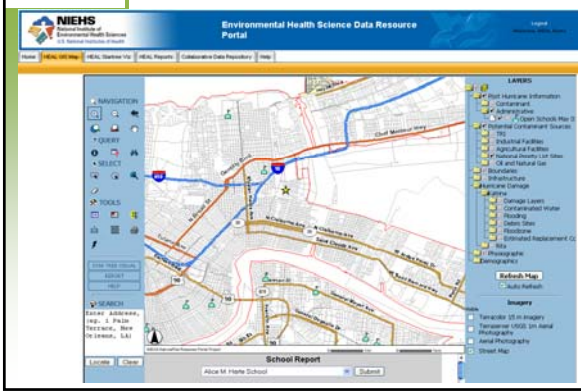
Analysis Tools



Models for Customizing Research Environments



Project Based Research Environment



Custom Reports

Defining the Geographic Scope

- Louisiana
- Mississippi
- Alabama
- Texas
- Florida
- United States

Acknowledgements

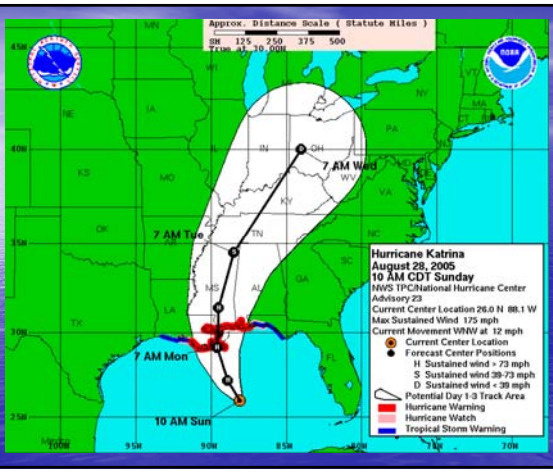
Children's Protection in the Aftermath of a Natural Disaster: Tools for Recovery and Communicating Risks

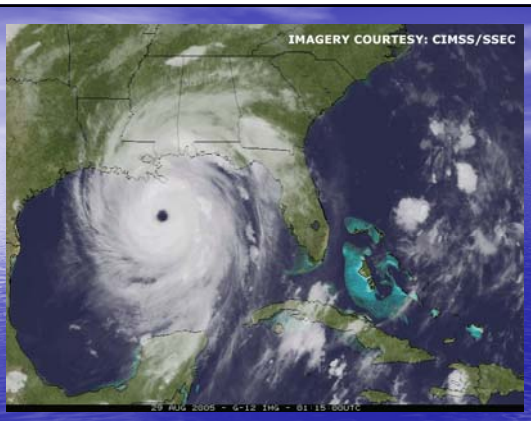
Tales from Ground Zero:

Hurricane Katrina and Pediatric Environmental Health in Coastal Mississippi

Scott Needle, MD, FAAP

October 12, 2007





Bay St. Louis Pediatrics, back office (Bay St. Louis, MS)

Hancock Medical Center ER

Photograph courtesy of David Bailey, copyright 2005

Pediatric office trailer in front of Hancock Medical Center

Interior, pediatric office trailer, Bay St. Louis, MS

Risks after Katrina: knowns, surprises, and in-betweens

- Debris
- Mold
- Gastrointestinal illness
- "Katrina Cough"
- "Katrina Brain"
- Psychological trauma and the honeymoon period

Formaldehyde and FEMA Trailers

A Case Study

Lessons Learned

- Blurring the line b/t "public" and "private"
- Shortage of resources in disaster area
- Communication is the priority
- Keep eyes and ears open
- Flexibility and ingenuity