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EPA/NIEHS/CDC Centers for Children's Environmental Health and Disease Prevention Research Progress Review Workshop

November 5-7, 2000
University of California, Berkeley
Clark-Kerr Center

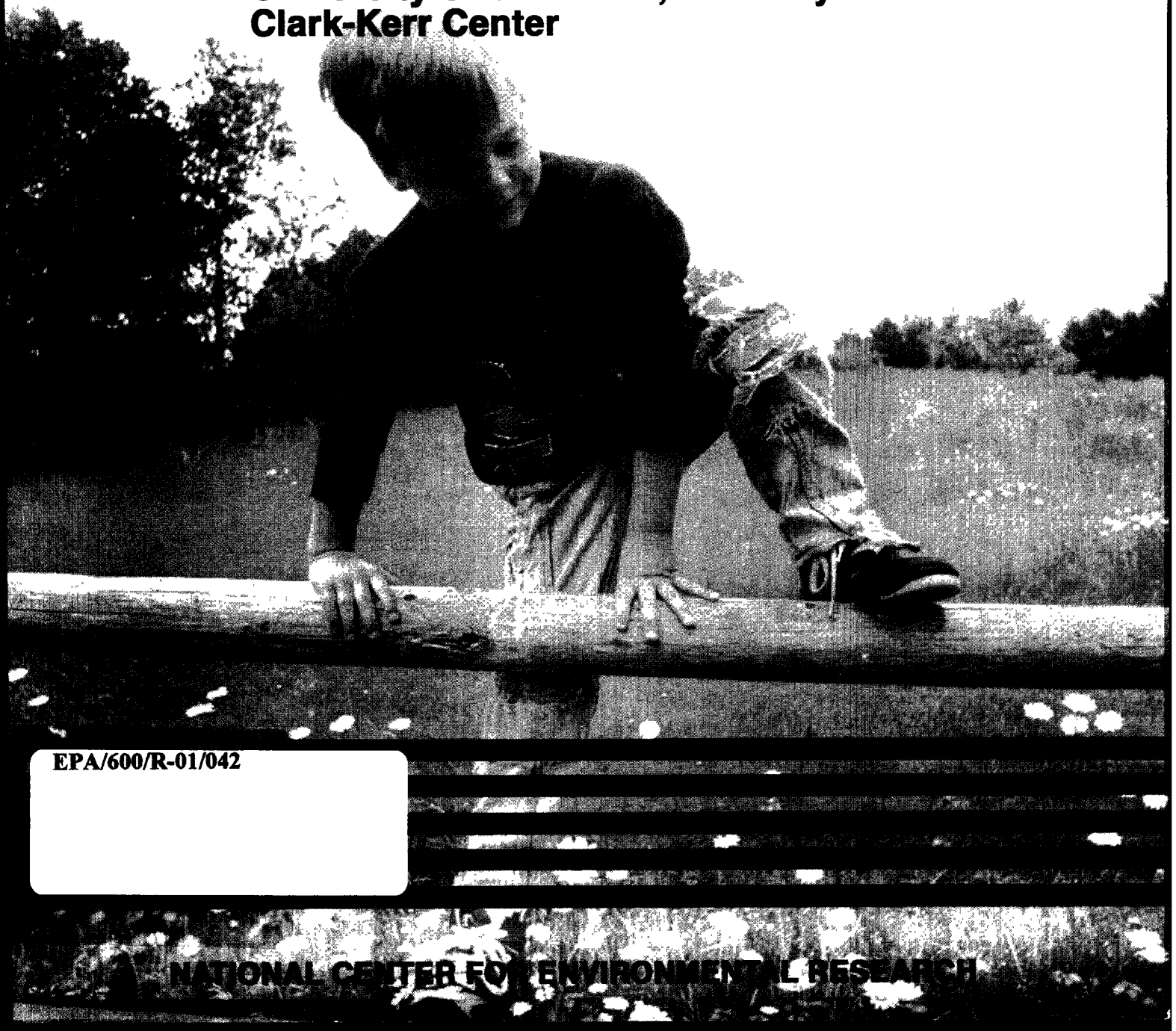

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Table of Contents

Introduction vii

University of Southern California

Overview and Description of the Southern California Children s Environmental Health Center: Respiratory Disease and Prevention 3
H. Gong, Jr., J. Peters, R. McConnell, D. Diaz-Sanchez, F. Gilliland, C. Jones, A. Hricko

Environmental Tobacco Smoke Alters the *In Vivo* Allergic Response in the Human Upper Airway 5
David Diaz-Sanchez

Determinants of Childhood Lung Susceptibility to Air Pollution 6
Frank Gilliland

Columbia University

Overview and Description of the Columbia Center for Children s Environmental Health 9
Frederica Perera

Pesticide Exposure During Pregnancy Among Minority Women Residing in Northern Manhattan and the South Bronx 12
R.M. Whyatt, D.E. Camann, D.B. Barr, P.L. Kinney, A. Reyes, J. Ramirez, J. Dietrich, D. Diaz, F.P. Perera

Indoor and Outdoor Environmental Exposures In Minority Children of Northern Manhattan and the South Bronx 13
P.L. Kinney, M. Aggarwal, G. Chew, R.M. Whyatt, F.P. Perera

Mount Sinai School of Medicine

Overview and Description of the Mount Sinai Center for Children s Environmental Health and Disease Prevention: Inner-City Toxicants and Neurodevelopmental Impairment 17
Mary S. Wolff

Kinetic PCR on Pooled DNA: A High-Throughput, High-Efficiency Alternative in Genetic Epidemiologic Studies 18
J. Chen, R. Higuchi, S. Germer, J.G. Wetmur

University of Washington

Overview and Description of the Center for Child Environmental Health Risks Research 21
Elaine M. Faustman

Effects of Human Paraoxanase (*PON1*) Single Nucleotide Polymorphisms on Susceptibility to Specific Organophosphate Insecticides 22
Clement E. Furlong, Wan-Fen Li, Lucio G. Costa, Victoria H. Brophy, Rebecca J. Richter, Diana M. Shih, Aaron Tward, Aldon J. Lusis

Table of Contents (continued)

Preliminary Baseline Results From the Randomized Community Trial To Assess the Efficacy of a Community-Wide Program To Reduce Children s Exposure to Pesticides 23
Beti Thompson, Gloria Coronado, Cam Solomon, John Kissel

Summer Project for Minority High School Student Interns: Effects of Home Parties on Farmworkers 25
R. Godina, G. Martinez, I. Islas , G.D. Coronado, B. Thompson

University of California, Berkeley

Overview and Description of the Center for the Health Assessment of the Mothers and Children of Salinas (CHAMACOS): A Community/University Partnership 29
Brenda Eskanazi

Preliminary Approaches To Assessing Organophosphate Pesticide Exposure and Potential Health Risks to Pregnant Women Living in the Salinas Valley, California 30
Brenda Eskanazi

CHAMACOS Laboratory Core: Challenges of Biological Sample Collection and Processing 32
Nina Holland

Johns Hopkins University

Overview and Description of the Johns Hopkins University Center for Childhood Asthma in the Urban Environment 35
Peyton Eggleston

Ambient Urban Particulate-Induced Airway Hyperresponsiveness and Inflammation in Mice 38
D. Walters, P.N. Breysse, M. Wills-Karp

Air Pollution and Allergen Exposure Among Asthmatic Children in Inner-City Baltimore 39
T.J. Buckley, P.N. Breysse, C. Beck, A. Escamillia, P.A. Eggleston

University of Iowa

Overview and Description of the Children s Environmental Airway Disease Center 43
Gary W. Hunninghake

A Multicomponent Intervention Study of Asthma in Children From Rural Communities 45
E. Chrischilles, J. Merchant, A. Kuehl, R. Ahrens, S. Reynolds, L. Burmeister, P. Pomrehn, P. Thorne

Lipopolysaccharide Responsiveness and the Development of Subchronic Grain Dust-Induced Airway Injury 46
C.L.S. George, H. Jin, C.L. Wohlford-Lenane, J.N. Kline, D.A. Schwartz

IL-10 Reduces Grain Dust-Induced Airway Inflammation and Airway Hyperreactivity 47
T.J. Quinn, S. Taylor, C.L. Wohlford-Lenane, D.A. Schwartz

Table of Contents (continued)

TLR4 Mutation Is Associated With Endotoxin Hyporesponsiveness in Humans 48
N.C. Arbour, E. Lorenz, B.C. Schutte, J. Zabner, J.N. Kline, M. Jones, K. Frees, J.L. Watt, D.A. Schwartz

Bronchial Hyperreactivity Is Associated With Enhanced Grain Dust-Induced Airflow Obstruction 49
J.N. Kline, P.J. Jagielo, J.L. Watt, D.A. Schwartz

TNF-Alpha and IL-1Beta Are Not Essential to the Inflammatory Response in LPS-Induced Airway Disease 50
J.G. Moreland, R.M. Fuhrman, C.L. Wohlford-Lenane, T.J. Quinn, E. Benda, J.A. Pruessner, D.A. Schwartz

Endotoxin Responsiveness and Subchronic Grain Dust-Induced Airway Disease 51
C.L.S. George, H. Jin, C.L. Wohlford-Lenane, M.E. O Neill, J.C. Phipps, P.O Shaughnessy, J.N. Kline, P.S. Thorne, D.A. Schwartz

Mechanisms That Initiate, Promote, and Resolve Grain Dust-Induced Inflammation 52
Kevin Leidal, William Nauseef, Gerene Denning

Activation of ERK Kinase Activity by Respiratory Syncytial Virus in A549 Cells Is Linked to the Production of Interleukin 8 53
W. Chen, M.M. Monick, A.B. Carter, G.W. Hunninghake

Effects of Ragweed and Th-2 Cytokines on the Secretion of IL-8 by Human Airway Epithelial Cells 54
W. Chen, G.W. Hunninghake

Respiratory Syncytial Virus Infection Results in Activation of Multiple Protein Kinase C Isoforms Leading to Activation of Mitogen-Activated Kinase 55
M.M. Monick, J.M. Staber, G.W. Hunninghake

Endotoxin Augments Viral Replication and the Inflammatory Response in Respiratory Syncytial Virus-Infected Epithelium 56
A.B. Carter, M.R. Donohue, K.L. Knudtson, G. Gudmundsson, M.M. Monick, G.W. Hunninghake

University of Michigan

Overview and Description of the Michigan Center for the Environment and Children s Health 59
Barbara Israel

Use of a Screening Questionnaire To Estimate Prevalence of Diagnosed and Undiagnosed Asthma Among Minority Children in Detroit 61
T.G. Robins, E.A. Parker, B.A. Israel, R.W. Brown, T.C. Lewis, CAAA Steering Committee

Detroit School Children With Symptoms of Persistent Asthma Are Sensitized to Both Indoor and Outdoor Allergens 62
T.C. Lewis, T.G. Robins, E.A. Parker, R.W. Brown, W.R. Solomon, T.R. Trestyn, B.A. Israel, CAAA Steering Committee

Evaluation of Murine Model of Asthma Induced by Exposure to House Dust Extract Containing High Levels of Cockroach 63
Jiyoun Kim, Andrew C. Merry, Jean A. Nemzek, Daniel G. Remick

Table of Contents (continued)

Measurements of Indoor, Outdoor, and Personal Exposure to Particulate Matter Among Asthmatic Children in Detroit, Michigan 64
Fuyuen Y. Yip, J. Timothy Dvonch, Thomas G. Robins, Edith Parker, Masako Morishita, Gerald J. Keeler

Field Comparison of $PM_{2.5}$ TEOM and $PM_{2.5}$ Manual Filter-Based Measurement Methods in Urban Atmospheres 65
J. Timothy Dvonch, Frank J. Marsik, Gerald J. Keeler, Thomas G. Robins, Fuyuen Yip, Masako Morishita

Index of Authors 67

Appendix A: Agenda 69

Appendix B: Report From Pesticide Breakout Session and List of Breakout Session Participants 73

Appendix C: List of Participants 77

Introduction

Nearly 3 years ago, the United States Environmental Protection Agency* (EPA) in partnership with the National Institute for Environmental Health Sciences (NIEHS) and the Centers for Disease Control and Prevention (CDC) created the first federally funded research program devoted exclusively to children s environmental health and disease prevention. The spirit of partnering nurtured by these three agencies has rippled into every aspect of this extramural grant program. These center grants were awarded to eight university/community partnerships that intricately and wisely merge the expertise and resources of community-based organizations with those of competitive research institutions. The Centers are proving the concept that basic and applied research is made more meaningful when the public has input and access to scientists, and vice versa. Because information exchange between researchers and local citizens was a requirement for grant award, public outreach and participation are a cornerstone of this program. In total, the Centers are conducting a wide breadth of research targeting the etiology and risk factors for respiratory ailments, such as asthma and developmental effects from environmental toxins in the urban and rural areas.

The Centers for Children s Environmental Health and Disease Prevention Research Annual Meeting offers the Center investigators an opportunity to present their findings to date, discuss advances in research and practice, and share their insights with other scientists, federal and state officials, policymakers, community-based organizations, and others interested in pediatric environmental health. The 1998 meeting in Research Triangle Park, NC, and the 1999 meeting in Atlanta, GA, were successful in engaging the university and community investigators in forward-thinking discussions about children s vulnerability and susceptibility to toxins and the challenges of conducting clinical and household interventions in communities fraught with environmental justice concerns.

However, to address these critical issues in a more focused setting, it was decided that in 2000, two separate meetings would commence to allow investigators ample time to share and discuss their findings and chart future directions. Thus, in October 2000, the community-based intervention/prevention research components of the eight Centers met in Seattle, WA, with other like researchers, federal partners, and nonprofit organizations. For more information regarding the October meeting and the published proceedings, please contact Fred Tyson via e-mail at tyson2@niehs.nih.gov or call (919) 541-0176.

This proceedings booklet documents the meeting in November 2000 in Berkeley, CA. The meeting brought together the basic scientists, exposure teams, biostatisticians, and clinicians of the eight Centers for 2 days of presentations, dialogue, focused group discussions, and a field visit in the Salinas Valley. The researchers presented preliminary results, highlighted their published data, and advanced new hypotheses in childhood susceptibility and analytical methodologies. These studies are of critical importance to EPA s Office of Research and Development, as they have the potential to strengthen the scientific basis for risk assessment and culturally appropriate risk management practices while addressing uncertainties in the supporting science. For more information about the 2000 Centers for Children s Environmental Health and Disease Prevention Research Annual Meeting, please contact program administrators Nigel Fields via e-mail at fields.nigel@epa.gov or Gwen Collman at collman@niehs.nih.gov.

*The mission of EPA is to protect public health as well as safeguard and improve the natural environment. Achievement of this mission requires the application of sound science to the assessment of enviromental problems and to the evaluation of possible solutions. The National Center for Environmental Research at EPA is committed to providing the best products in high-priority areas of scientific research through significant support for long-term research.

University of Southern California
Los Angeles, CA

Overview and Description of the Southern California Children s Environmental Health Center: Respiratory Disease and Prevention

H. Gong, Jr., J. Peters, R. McConnell, D. Diaz-Sanchez, F. Gilliland, C. Jones, and A. Hricko
University of Southern California and University of California at Los Angeles, Los Angeles, CA

The Southern California Children s Environmental Health Center (CEHC) involves multi-institutional and multidisciplinary participation in an administrative core and three related projects with the common goal of examining how host susceptibility and environmental exposure determine children s respiratory disease. The following describes the key cores and their progress to date:

- *The Administrative Core supervises and coordinates the Center s research and outreach efforts in children s environmental health issues*. Highlights include:
  - Funds will be committed for a new faculty member (new scientist) specializing in children s environmental health.
  - A Web site is currently under development.
  - Research and educational interactions with the NIEHS-supported Southern California Environmental Health Sciences Center (SCEHSC) continue to grow.
  - The Community Outreach and Education Program has facilitated numerous collaborations with community-based and public health organizations in Southern California.
- *Dr. Gilliland is evaluating the effect of outdoor air pollution on the susceptibililty to respiratory disease in a large cohort of school children, and the potential protective effects of dietary intake and genetic polymorphisms involved in lung defenses.* Highlights include:
  - Buccal cell collections (n = 419) have continued for DNA assays. One challenge has been children who have moved or refused participation.
  - During Year 2, more than 2,100 food frequency questionnaires were collected. Two papers on nutrients and lung function are being prepared.
  - A Taqman was purchased to increase the throughput of DNA assays for genotyping target enzymes.
- *Dr. Diaz-Sanchez is evaluating the effect of environmental tobacco smoke (ETS) on allergic responses in children with smokers in the home and in chronic animal models.* Highlights include:
  - Preliminary studies show that ETS and ragweed nasal challenge potentiate local ragweed-specific IgE and IgG4 as compared to ragweed challenge alone.
  - ETS synergizes with allergen to produce both Th2 interleukins (IL-4, IL-5, IL-13) and eosinophil influx in the nose.
  - Animal models (challenged with ovalbumin) were developed with BALB/c and CB57/Black/6 mice for chronic ETS exposures. This allows longitudinal immunologic evaluation according to genetic background and age.

➢ *Drs. McConnell and Jones are evaluating the efficacy of a community-based health education intervention to control indoor allergen exposure and to reduce the severity of asthma in the homes of children who are allergic to cockroach or house dust mite allergen.* Highlights include:

- A new set of health education materials on reducing exposure to indoor allergens was developed for use in training inner city families in the study.
- Community-based educators (supported by several community partners) are being trained for the intervention group.
- The CEHC provided staff support for subject recruitment, protocol development, and data analysis for a pilot study of professionally cleaned homes of children allergic to cockroaches. This experience and pilot data will assist the current project.

In addition to regular meetings, the projects investigators collaborated by using certain assays (e.g., genotyping, IgE levels), as well as with the SCEHSC s Facility Cores (e.g., DNA storage, biostatistics, ETS generation).

Environmental Tobacco Smoke Alters the *In Vivo* Allergic Response in the Human Upper Airway

David Diaz-Sanchez
University of Southern California, Los Angeles, CA

We have focused on experiments to determine how environmental tobacco smoke (ETS) interacts with allergen and demonstrated our hypothesis that acute challenge with ETS will exacerbate allergen-induced nasal allergic responses. We recruited 10 volunteers with a positive skin test to short ragweed and a history of allergic rhinitis. The antigen used in our challenge studies, short ragweed, is not present in the Los Angeles area. Subjects were challenged by spraying the nose with a symptom active dose of allergen. After a space of at least 4 weeks, the subjects were recalled and challenged with their active dose of allergen following ETS exposure. We have used our previously established human ETS exposure model performed in collaboration with Dr. Gong at the Los Amigos Research and Education Institute. In this model, subjects are exposed to the side-stream smoke of five Kentucky Reference cigarettes in a 2-hour period. Production of antibody of the Immunoglobulin E class (IgE) is the hallmark of allergy. Ragweed-specific IgE levels measured in nasal lavages performed 4 days after exposure to ragweed plus ETS were significantly higher than following challenge with ragweed alone (mean = 58.4 U/mL vs. 2.2 U/mL, $p<0.001$ paired t-test). Similarly, ragweed-specific IgG4 levels were enhanced by ETS exposure (mean = 26.7 U/mL vs. 5.6 U/mL). ETS also potentiated levels of total IgE and IgG4. Histamine levels were measured in nasal lavages performed before and 10 minutes following allergen challenge. As expected, in these ragweed allergic subjects, challenge with ragweed caused a significant rise in histamine levels from baseline levels (3.8 nM vs. 0.6 nM, $p<0.01$). However, this increased more than fourfold to 16.1 nM when subjects were exposed with ETS immediately before allergen. When the above experiments were repeated, but instead of ETS, exposure was to Carbon Black, elemental carbon essentially devoid of chemicals, no increase in histamine levels was apparent. Similarly, ETS synergised with allergen produced a local Th2 cytokine milieu. This cytokine response is characteristic of an enhanced allergic response and is critical to allergic inflammation.

We also have successfully established an animal model of chronic exposure to ETS mice. In our model, mice receiving the protein ovalbumin (OVA) alone did not produce either OVA-specific allergic antibody at any time. In contrast, animals receiving both ETS and OVA had significantly elevated levels of both total and OVA-specific allergic antibodies 12 days after the initial exposure. The levels of these antibodies were significantly higher in young rather than adult mice.

These results demonstrate that ETS can synergize with allergen to exacerbate the allergic response in both human and murine models. They demonstrate for the first time in humans a direct causal effect of ETS on the allergic response. In addition, the murine model suggests that the effects of ETS also are relevant and, indeed, may be of greater importance in the young.

Determinants of Childhood Lung Susceptibility to Air Pollution

Frank Gilliland
University of Southern California, Los Angeles, CA

In the last year, efforts have focused on examining the effects of diet on children s lung health. An emerging body of evidence supports an adverse effect of low antioxidant vitamin intake on adult lung function. The respiratory health effects of low antioxidant vitamin during childhood have yet to be fully defined. To investigate the effects of dietary intake of three antioxidant vitamins, vitamins A, E, and C, on children s lung function, we examined cross-sectional dietary data and pulmonary function tests from 2,566 participants in the Children s Health Study. At followup visits during the 1998-1999 school year, each student completed a health update questionnaire, a validated food frequency questionnaire (FFQ), and spirometric lung function testing. To assess the effects of vitamins A, E, and C on lung function, regression splines that account for the nonlinear relationship between pulmonary function, height, and age in children were used. Low vitamin C intake was associated with deficits in measures of airway flow that were larger in girls (FEV_1 -3.3% [95% CI -6.0, -0.5], FEF_{25-75}-5.5% [95% CI -10.5, -0.3]) than boys (FEV_1 -2.3% [95% CI -4.8, 0.3], FEF_{25-75} -2.4%, [95% CI -7.4, 2.8]). Children with low vitamin E intake had lower FEF_{25-75} (boys -8.9 [95% CI -14.2, -3.3], girls, -2.5% [95% CI -8.3,3.7]). Low vitamin A intake also was associated with FEV_1 only among boys with asthma (-6.3% [-12.4,0.3]).

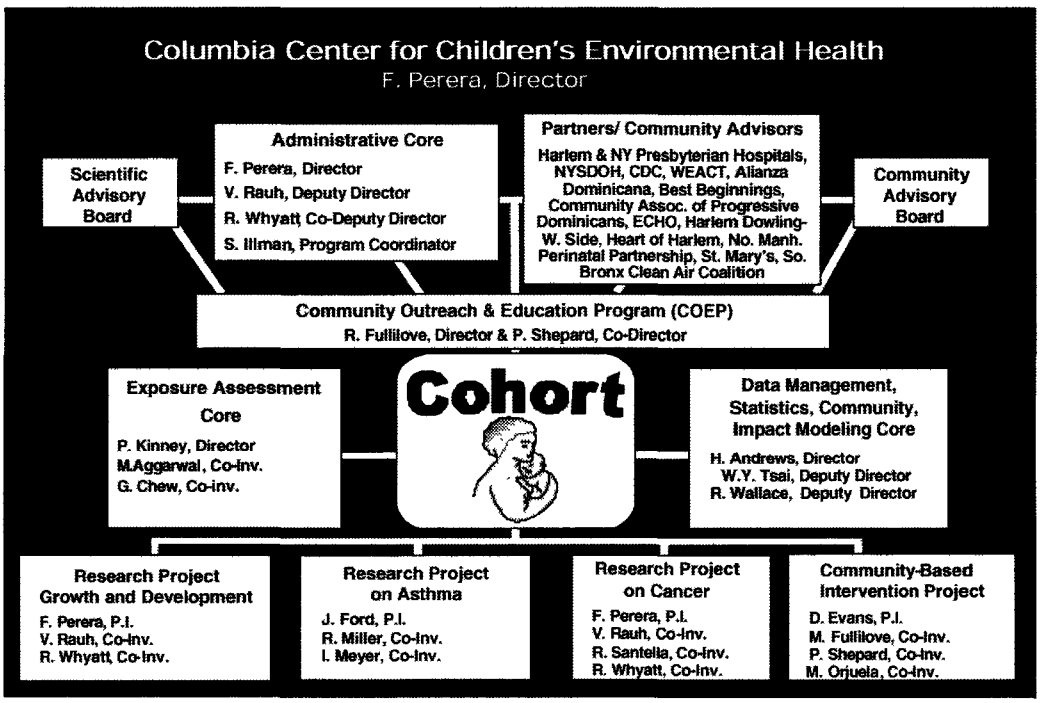
We also investigated the effects of dietary magnesium (Mg) on children s lung function. Girls with low Mg intake had lower FEF_{25-75} (-4.8%, 95% CI -9.8, 0.4) and FEF_{75} (-8.3%, 95% CI -14.8, -1.4) than girls with a higher intake; and the reductions were larger in girls with asthma (FEF_{25-75} [-16.2%, 95% CI -22.7, -9.1] and FEF_{75} [-24.9%, 95% CI -32.8, -16.1]) than in girls without asthma (FEF_{25-75} [-2.0%, 95% CI -7.4, 3.8] and FEF_{75} [-4.1%, 95% CI -11.3, 3.7]). Boys with low Mg intake showed deficits in FEV_1 (-2.7%, 95% CI -5.4, 0.1) and FVC (-2.8%, 95% CI -5.4, -0.2) compared to boys with higher intake. In summary, children with low antioxidant vitamin intake had lower lung function. The effects of low Mg intake did not vary substantially in boys with and without asthma. Because children s magnesium intake is generally inadequate, small individual deficits in lung function associated with low Mg intake may be important on a population level, especially among girls with asthma.

Columbia University
New York, NY

Overview and Description of the Columbia Center for Children s Environmental Health

Frederica Perera
Columbia University, New York, NY

The long-term objective of the Columbia Center for Children s Environmental Health (CCCEH) is to prevent developmental damage, asthma, and cancer risk in African-American and Latino infants and children living in Northern Manhattan and the South Bronx, as well as children elsewhere. These communities are disproportionately exposed to various environmental neurotoxic, asthmagenic, and carcinogenic pollutants; and they have disproportionately high rates of low birth weight, other developmental disorders, and childhood asthma. The main hypotheses of the Center are: (1) prenatal and/or postnatal environmental exposures to airborne particulate matter (PM), including diesel exhaust particulate (DEP), polycyclic aromatic hydrocarbons (PAH), environmental tobacco smoke (ETS), pesticides, and home allergens, increase the risk of developmental impairment and/or asthma and cancer in these disadvantaged communities, controlling for known physical (e.g., PCBs and lead) and psychosocial risk factors; (2) inadequate nutrition and family and community stressors exacerbate the impact of these environmental toxicants; and (3) community and individual-level interventions to reduce these toxic exposures and improve nutritional status can reduce the risk of disease. The structure of the CCCEH is shown in the Figure below.



The research team is investigating these hypotheses in a molecular epidemiologic prospective cohort study of 600 pregnant women, following the infants and their mothers for 2 years postnatally. Questionnaire, monitoring, biomarker, and clinical data are collected. A multilevel analysis is examining relationships between environmental and susceptibility factors and adverse health outcomes at the individual and community levels. An intervention research project is testing whether a community campaign, Healthy Home Healthy Child, can be effective in heightening awareness about environmental risks and measures individuals can take to protect their children. An individual/household intervention will test whether reduction in levels of

allergens and nutritional supplementation can reduce the risk of asthma among infants at high risk. Through its Community Outreach and Education Program, the CCCEH is working in partnership with the community in all phases of the etiologic research, as well as in communicating the research results and their implications for policy.

Enrollment: As of September 12, 2000, 498 women had been enrolled, 357 of whom had undergone prenatal monitoring. A total of 334 babies had been delivered, of whom 27 had reached their second birthday. The ethnic distribution was 43 percent African American and 57 percent Latina.

Summary of Preliminary Findings: (1) Monitoring and biomarkers show variable, widespread, and in some cases, high exposure during pregnancy to PAH, pesticides, ETS, and allergens (Kinney, Chew, Whyatt, Perera et al.); (2) *In utero* allergic sensitization to multiple indoor allergens is common (Miller et al.); (3) There is a high prevalence of respiratory problems (Meyer, Ford et al.) and developmental disorders (Rauh et al.) by age 1; (4) Community-level analyses of NYC show geographic concordance for high rates of childhood asthma hospitalization, low birth weight, and social/economic stressors (Wallace et al.; Rauh and Andrews); and (5) A survey of 556 women showed awareness of environmental health threats to be high, but practical knowledge about preventing harmful exposures was low (Evans, Fullilove, Shepard et al.).

Personal Monitoring: Personal exposure monitoring (48-hour) to determine the pregnant woman s inhalation exposure to pollutants showed that all 157 samples initially tested had detectable levels of one or more carcinogenic PAH. Total PAH exposures averaged 3.94 ng/m^3 and varied significantly among the women, with a range of 0.02 44.81 ng/m^{-3} (Kinney et al., in preparation).

Analysis of Pesticides: Analysis of pesticides in personal air samples from an initial subset (72) of the pregnant women showed detectable concentrations of at least three neurotoxic pesticides (chlorpyrifos, diazinon, and propoxur) that are widely used to control cockroaches and other pests in urban homes (Whyatt et al., in preparation). The concentrations were similar to those reported in Jacksonville, Florida, an area with high household pesticide use (Whitmore et al., 1994).

Home Monitoring/Exposure Assessment: Eighty-five percent of the homes had detectable concentrations of cockroach allergen, with 46 percent above 8 mg/g; 70 percent had detectable mouse allergen, with 30 percent above 8 mg/g (Chew, Aggarwal, and Kinney). These concentrations are comparable to those seen in a major national study (NCICAS) and show that exposure to these allergens is prevalent, in some cases ranging up to levels associated with health effects.

Immune Changes: Immune biomarkers have been analyzed in the initial subset of mothers and newborns, including total IgE levels, allergen-specific IgE levels, mitogen or allergen-induced lymphocyte proliferation, and cytokines. In the first group of babies enrolled, there was a high prevalence of *in utero* allergic sensitization as evidenced by the lymphocyte proliferation assay (>50% to cockroach allergen) (Miller et al, submitted). In many cases, cord blood allergen-induced proliferation occurred in the absence of maternal blood allergen-induced proliferation.

Respiratory Health: Preliminary analysis of data on the initial 158 infants whose mothers were interviewed shows a higher rate of health care utilization for respiratory complaints in the study population (Meyer et al., manuscript in preparation) compared to both New York City and the entire United States. The 3-month prevalence of breathing symptoms at ages 3, 6, 9, and 12 months were 46 percent, 54 percent, 50 percent, and 43 percent with correspondingly high rates of Emergency Room (20%, 22%, 17%, and 9%, respectively) and doctor s office visits for these symptoms (37%, 39%, 28%, and 20%, respectively). Ten percent of the infants had a physician-diagnosed asthma by the age of 12 months.

Fetal Growth and Child Developmental Assessments: Measures of fetal growth and gestational age (abstracted from medical records) showed that 9 percent were low birth weight. The ethnic difference in birth

weight is explained by the larger proportion of African American preterm infants (p=.02). Cognitive and motor developmental testing at infant age 6 months (Denver II Developmental Test) showed that 14.9 percent of infants scored in the at-risk range. Twelve-month Bayley scores show that 15.9 percent of infants scored in the delayed range for cognitive development, and 25.8 percent in the delayed range for motor development (Rauh et al.).

Community Participation, Outreach, and Education: The CCCEH has an active working relationship with local community organizations. Specifically, the Center has worked closely with West Harlem Environmental Action (WEACT) on many projects, including the development of materials for an environmental health education campaign and the organization of a large community conference in March 2000, which engaged more than 500 health care providers, scientific researchers, grassroots and community organization representatives, environmentalists, and local and national policymakers in a discussion about children s health and the urban environment. The Center has formed a Community Advisory Board (CAB) comprised of representatives from nine different organizations working in Washington Heights, Harlem, and the South Bronx in the areas of health, education, environment, and community development. The advice of the CAB is sought on issues such as how the Center can better meet the needs of the communities in which it works, the development and distribution of educational materials, and the effective communication of research results to the study subjects and the community.

Pesticide Exposure During Pregnancy Among Minority Women Residing in Northern Manhattan and the South Bronx

R.M. Whyatt [1], D.E. Camann [2], D.B. Barr [3], P.L. Kinney [1], A. Reyes [1], J. Ramirez [1], J. Dietrich [1], D. Diaz [1], and F.P. Perera [1]

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Residential pesticide use is widespread in the United States, with the nonpersistent pesticides (NPP) (organophosphates, carbamates, and pyrethroids) generally used for insect control. However, little data are available specific to pesticide use among minority populations. As part of the prospective cohort study being conducted by the Columbia Center for Children s Environmental Health, we have gathered questionnaire data on pesticide use during pregnancy from 131 African American and Dominican women residing in Washington Heights, Harlem, and the South Bronx. Additionally, 72 of the women underwent personal ambient air monitoring for 48 hours during the third trimester to determine NPP exposure levels. Of the women questioned, 34 percent report that their homes were sprayed by an exterminator during the pregnancy, with 47 percent of those saying the spraying was done once per month. One-third of the women also report use of can sprays. Ninety percent of the pesticide use was for cockroach control. Of the women monitored, all (100%) were simultaneously exposed to two organophosphates, diazinon (range in air concentrations 2.0-6,000 ng/m^3) and chlorpyrifos (range 0.7-193 ng/m^3), and to the carbamate, propoxur (range 3.8-1,380 ng/m^3. These results are of concern in light of experimental evidence linking prenatal organophosphate exposure to adverse neurocognitive development. We recently have begun to validate the measurements of NPP in meconium as a biomarker of cumulative prenatal exposure to facilitate evaluation of the effects of this exposure on newborns in the cohort. Pilot results on 20 meconium samples found that two organophosphate metabolites, diethyltphosphate and diethylhiophosphate, which are common to both chlorpyrifos and diazinon, were detected in 95 percent and 100 percent of the samples, with a range of 0.8-3.2 mg/g and 2.0-5.6 mg/g, respectively.

Indoor and Outdoor Environmental Exposures in Minority Children of Northern Manhattan and the South Bronx

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African-American and Latino residents of New York City experience some of the highest rates of asthma morbidity and mortality in the United States. Children and individuals with preexisting respiratory diseases may be especially sensitive to the effects of airborne particles and other toxic air pollutants. As a part of the Children s Environmental Health Center, exposure to indoor allergens (cockroaches, dust mites, and mice) and air pollutants ($PM_{2.5}$, NO_x, PAHs, and diesel exhaust particles) is assessed in mothers and newborns. During the 32nd week of pregnancy, each participant s home is visited to collect dust samples from the woman s bed and kitchen. At this time point, women also carry a portable personal exposure monitor for 48 hours to determine their inhalation exposure to polycyclic aromatic hydrocarbons (PAHs). The home is revisited when the child turns 12 months of age, when four separate dust samples are collected from the mother s bed, the child s bed, the floor surrounding the child s bed, and the kitchen. Also, a 25 percent sub-sample of homes undergo air pollution monitoring within and immediately outside the home at the 12-month time point. Air monitors are placed in subjects homes for a 2-week period to collect $PM_{2.5}$, NO_x, elemental carbon, and indoor airborne allergens. At each of these homes, traffic also is counted for two 15-minute periods on the street segment nearest to the apartment. Traffic counts are segregated as diesel buses, diesel trucks, and cars. Currently, 159 samples of PAH have been analyzed and all were found to have detectable levels of one or more carcinogenic PAHs. Total PAH exposures for these 159 women averaged 3.94 ng/m^3 and ranged from 0.02-44.81 ng/m^3. Results for allergen analysis from prenatal dust samples are shown in Table 1.

Table 1. Prenatal samples.

	Mother s Bed Samples			Kitchen Samples		
Allergen	**n**	**% > 2 µg/g***	**Max Conc.**	**n**	**% > 2 µg/g***	**Max Conc.**
Cockroach (Bla g 1)	80	31%	46 U/g	72	58%	781 U/g
Cockroach (Bla g 2)	117	27%	148 U/g	108	63%	798 U/g
Mouse Urinary Protein	96	17%	20 µg/g	89	17%	1478 µg/g

* Cockroach allergens are expressed in U/g.

Mount Sinai School of Medicine
New York, NY

Overview and Description of the Mount Sinai Center for Children s Environmental Health and Disease Prevention: Inner-City Toxicants and Neurodevelopmental Impairment

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Children in America s cities are at risk of exposure to multiple known and potential developmental toxicants pesticides, polychlorinated biphenyls (PCBs), and lead. The goal of the Mount Sinai Center for Children s Environmental Health and Disease Prevention will be to identify, elucidate, and prevent developmental deficits that result from exposures to environmental toxicants in the inner city.

Project 1, Barbara Brenner, Principal Investigator (PI), is a community-based prevention program being undertaken in East Harlem, New York City, in partnership with Boriken Health Center. At Boriken, we are recruiting expectant mothers and implementing an intervention to reduce exposures to pesticides and other developmental toxicants in their homes. A nonintervention comparison group consists of expectant mothers in similar housing enrolled in Project 2 and at Settlement Health, a nearby community health center. Pesticide levels and roach infestation levels are being assessed in both groups. In Years 3 and 4, IPM will be generalized to housing and schools throughout East Harlem, using community intervention strategies.

Project 2, Trudy Berkowitz, PI, is a prospective epidemiologic study of an ethnically diverse birth cohort of infants born at Mount Sinai. More than 400 mothers have been recruited so far, with more than 100 births. The ultimate aim is to assess whether *in utero* exposures to pesticides and other toxicants are associated with developmental delays in children in New York City.

Project 3, Jim Wetmur, PI, is studying polymorphisms in the enzymes that activate and detoxify organophosphates and other pesticides in the population of mothers and infants enrolled in Project 2.

Project 4, Tom Matte, PI, is a retrospective study of African-American men enrolled in the Collaborative Perinatal Project. PCBs have been measured in 154 maternal sera to assess whether *in utero* exposures to PCBs are associated with disordered neuropsychological function in adolescent or adult life.

Project 5, supports Dr. Andrea Gore as a newly recruited Center scientist. She is examining the mechanisms by which environmental toxicants affect neuroendocrine development. Experiments in a female rat model will characterize interactions between toxicants and hypothalamic GnRH neurosecretory neurons, key regulators of reproductive development. Using a neuronal cell line, effects of chlorpyrifos, PCBs, and methoxychlor have been assessed *in vitro* and found to alter GnRH expression in GT1 cells.

The Center contains Facilities Cores in Exposure Assessment and Biostatistics/Data Management as well as an Administration Core.

Kinetic PCR on Pooled DNA: A High-Throughput, High-Efficiency Alternative in Genetic Epidemiologic Studies

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The ideal technology for screening SNPs requires high-throughput with minimal cost per sample, minimal usage of valuable DNA resources, and maximal flexibility for introduction of new polymorphisms. Array hybridization that relies on the difference between hybridization of matched and mismatched products to allele-specific oligonucleotides on the array is powerful, although not foolproof for detecting heterozygosity. Other competing methods such as Taqman and molecular beacons probes require fluorescent labeling of probes, which increases the expense. We will describe a new technology, kinetic allele-specific PCR with DNA pooling, developed at Roche Molecular Systems (S. Germer, M.J. Holland, and R. Higuchi. High-throughput SNP allele-frequency determination in pooled DNA samples by kinetic PCR. *Genome Res* 2000; 10:258-266), which satisfies all of these criteria and offers a powerful new tool for detecting meaningful polymorphic differences in candidate gene association studies and genome-wide linkage disequilibrium scans.

We will present data from two blinded tests of the technology. We had three individuals prepare pooled DNA samples from (A) 252 individuals and (B) 271 individuals separated into three ethnic groups. We had previously determined their PON1 Q191R genotypes by PCR-RFLP. These 12 pooled DNA samples were genotyped by our collaborative investigators at Roche Molecular Systems using kinetic allele-specific PCR. For test A, with 3 pools and a total of 12 PCR measurements, the allele frequency was 0.449–0.010, compared to 0.448 determined by PCR-RFLP. For test B, with 9 pools and a total of 36 PCR measurements, the allele frequencies for Caucasians (n=56), Latinas (n=127), and African-Americans (n=86) were 0.266–0.011, 0.386–0.011, and 0.617–0.010, respectively, compared to 0.267, 0.409, and 0.610 determined by PCR-RFLP. These results demonstrate a powerful new technology for determining frequencies of SNPs in an epidemiological study.

University of Washington
Seattle, WA

Overview and Description of the Center for Child Environmental Health Risks Research

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University of Washington, Seattle, WA

In 1998, the U.S. Environmental Protection Agency awarded grants to create eight centers across the Nation to examine children s environmental health. The Center for Child Environmental Health Risks Research, part of the Department of Environmental Health at the University of Washington, is one of these centers. Our research aims to understand the mechanisms defining children s susceptibility to pesticides, and the implications of this susceptibility to development and learning.

Researchers at the Center for Child Environmental Health Risks Research represent multiple disciplines and several different institutions. Our work spans the continuum of environmental health research from the cellular level to community-wide intervention projects. Our research takes place in the laboratory, and in the field.

Laboratory-based researchers are working to identify the cellular, biochemical, and molecular mechanisms of developmental neurotoxicity of pesticides. The emphasis of these studies is to assess the potential for functional impacts on neurodevelopment. Researchers also will evaluate the impact of genetic variations on how people metabolize pesticides, particularly organophosphate pesticides.

Field-based researchers are working to identify the critical pathways of pesticide exposure for children. Our Center includes a partnership with communities in the Yakima Valley, a key Washington State agricultural area. Researchers are working to develop culturally appropriate interventions to reduce occupational take-home exposure. The goal is to ultimately reduce exposure of farmworker families to pesticides.

To learn more about the Genetic and Cellular, Behavioral, Exposure Assessment, and Community Intervention and Communication projects at the Center for Child Environmental Health Risks Research, please contact Tiffany Potter-Chiles at 206-616-9133.

Effects of Human Paraoxanase (*PON1*) Single Nucleotide Polymorphisms on Susceptibility to Specific Organophosphate Insecticides

Clement E. Furlong [1], Wan-Fen Li [1], Lucio G. Costa [1,2], Victoria H. Brophy [1], Rebecca J. Richter [1], Diana M. Shih [3], Aaron Tward [3], and Aldon J. Lusis [3]

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Paraoxonase (*PON1*) is tightly associated with HDL particles and appears to be involved in the metabolism of oxidized lipids; however, its role in the metabolism of organophosphate insecticides has been investigated much more extensively. Human *PON1* exhibits a substrate dependent polymorphism determined by the R192Q polymorphism. The $PON1_{R192}$ isoform hydrolyzes paraoxon at a tenfold higher catalytic efficiency than does the $PON1_{Q192}$ polymorphism; however, it is much less efficient at hydrolyzing sarin. A second polymorphism, M55L, also present in human populations, has been associated with lower serum *PON1* levels; however, this association may be due to linkage with inefficient promoter polymorphisms.

For many years, it has been assumed that individuals homozygous for the $PON1_{R192}$ isoform would be much more resistant to paraoxon/parathion exposures than individuals with the $PON1_{Q192}$ polymorphism. Development of the *PON1* knockout mouse model has allowed us to examine directly this assumption. Surprisingly, *PON1* knockout mice, which are devoid of both plasma and liver *PON1*, were not more sensitive to paraoxon than wild type mice. They were, however, very sensitive to both diazoxon and chlorpyrifos oxon. Injection of the knockout mice with either human $PON1_{192}$ isoform allowed for the testing of the efficacy of each in the detoxication of paraoxon, diazoxon, and chlorpyrifos oxon under physiological conditions. Both $PON1_{192}$ isoforms afforded equivalent protection against diazoxon exposure, while the $PON1_{R192}$ isoform provided better protection against chlorpyrifos oxon exposure. Neither $PON1_{192}$ isoform provided protection against paraoxon exposure, nor did expression of a high level of human $PON1_{R192}$ in a transgenic mouse line. *In vitro* catalytic efficiency of *PON1* for specific substrate hydrolysis was closely correlated with the protection against exposure to specific OPs afforded by injection into knockout mice of each $PON1_{192}$ isoform. The relatively low efficiency of paraoxon hydrolysis by *PON1* explains the lack of increased sensitivity to paraoxon observed in the *PON1* knockout mice. Exposure of the knockout mice to the parent compounds, diazinon and chlorpyrifos, indicates that *PON1* provides protection mainly against the oxon forms of these OPs, which can be significant in actual exposures. These findings also raise the important point that safety testing of diazinon and chlorpyrifos should include oxon levels comparable to those experienced in actual exposures. Previous testing has been done with very pure compounds.

Plotting the rates of diazoxon hydrolysis versus paraoxon hydrolysis for human population samples provides an accurate inference of $PON1_{192}$ genotype as well as the level of *PON1* expressed in each individual, which can vary by as much as fifteenfold among individuals. Polymorphisms in the *PON1* promoter region are responsible for a large part of the observed variability in serum *PON1* levels among individuals. Newborns have very low *PON1* levels, which increase to their respective adult levels at about 1 year of age. Thus, three factors appear to govern an individual s sensitivity to diazoxon and chlorpyrifos oxon: age, position 192 genotype, and the level of serum *PON1*.

Preliminary Baseline Results From the Randomized Community Trial To Assess the Efficacy of a Community-Wide Program To Reduce Children s Exposure to Pesticides

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Introduction

For Healthy Kids! is a community-based, randomized trial taking place in the Lower Yakima Valley of Washington State. After baseline data collection that included an in-person interview, urine collection from a farmworker and a child aged 2 to 6 in the same household, a dust sample from the referent household, and a dust sample from a vehicle used by a farmworker in the referent household, 24 communities were randomized to an intervention or control condition.

A Community Advisory Board, made up of representatives from all of the constituents interested in pesticide use or control, is extremely active in the project. The Board was formed prior to the baseline assessment and was able to contribute to questionnaire development. The Board selected the local Project Coordinator and staff. The Board reviews data and progress, makes recommendations, and suggests strategies for intervention components. The Board also has opened many doors to other gatekeepers in the community.

Methods

Using randomly selected census blocks and randomly selected households within blocks, an in-person survey was conducted with agricultural workers in 20 communities and 8 labor camps in the Yakima Valley of Washington State. The survey included questions about job tasks, pesticide exposure, workplace characteristics, and home practices. A total of 571 respondents completed the interviews.

Results

Baseline Results: Response Rates. Responses were received from 571 farmworkers, constituting 89.6 percent of the sample drawn or 93.1 percent of known eligibles. Of farmworkers with an eligible child in the household (N=231), 92.2 percent participated in the urine collection part of the trial; 91.3 percent of the children participated. Of eligible households, 96.3 percent participated in the house dust collection and of those who had vehicles, 97.2 percent participated in the vehicle dust collection.

Baseline Results: Interview. The farmworkers were overwhelmingly Hispanic (88%), had low education levels (74% of Hispanics had an 8th grade education or less), the vast majority of respondents lived in the Valley year-round (95%), and respondents tended to be male (76%).

Respondents were asked about the job tasks they had performed in the past 3 months and perceived exposure to pesticides during those job tasks. Of four job tasks harvesting, weeding, thinning, and pruning 56.7 percent of farmworkers reported being exposed while thinning. For all tasks combined, 50 percent of farmworkers reported exposure to pesticides.

Applicators and mixer/loaders were more likely to use personal protective equipment while performing their job tasks than farmworkers who reentered the fields before the approved interval. Among nonapplicator farmworkers, less than 50 percent reported wearing protective boots (42%), gloves (40%), or protective lenses (23%) when working in a pesticide-exposed area.

There was considerable variation in decontamination facilities at workplaces. Most had bathrooms, and 90 percent had drinking water available. About 78 percent of workplaces had water for washing hands; however, only 64 percent provided soap or towels. Showers onsite were reported in 25 percent of workplaces. Only 40 percent of workplaces had eyewash stations onsite.

Farmworker home practices to prevent pesticide transmission to their children and the home environment varied by practice. The vast majority removed hats (88%) when entering the home. Eighty-three percent reported washing work clothes separately from the rest of the family s laundry. Fewer farmworkers reported removing their boots before coming into the home (57%), changing out of work clothes soon after entering the home (52%), and washing work clothes after one wearing (58%). About 49 percent reported bathing or showering within 1 hour after coming from their work, and only 50 percent reported that they never held their children while wearing their dirty work clothes after coming in from the field.

Baseline Results: Urine Data. The overwhelming majority of adults in the study (N=213) were Hispanic (97%). The total family income for 90 percent of respondents was $25,000 or less per year. Dimethyl compounds were the only compounds found in measurable quantity in both the adult and child urine. Among workers who reported harvesting, 60.5 percent had detectable urinary metabolites of pesticides (0.1 mg/L or greater) compared to 47.4 percent of those who did not harvest. The difference was not detectable among weeders, but was significant among pruners and thinners.

In comparing the relationship between adult urinary metabolite concentrations and child concentrations, there is a direct relationship between the amount of adult metabolite concentrations and those of children in the household. Sixty-seven percent of children in households with farmworkers in the highest quartile of metabolite concentrations also had detectable concentrations. Conversely, among adults in the lowest quartile of concentrations, only 28.9 percent of children had a detectable level of urinary metabolites.

An examination of the child-based urinary metabolite concentration (creatine-based) dose estimates, assuming the samples are the result of guthion (azinphosmethyl) exposure, indicates that 23 percent of the children exceed the RfD (for volume-based, the percentage is 40%). If the samples are the result of exposure to phosmet, then only 1.5 percent (creatine-based) or 2.6 percent (volume-based) of children exceed the RfD. The highest estimated child dose was 31 times (creatine-based) or 137 times (volume-based) higher than the azinphosmethyl RfD.

Baseline Results: Dust Data. House dust samples were assessed for six different chemicals (diazinon, malathion, chlorpyrifos, methyl-parathion, phosmet, and azinphosmethyl). Azinphosmethyl was detected in the greatest proportion of households (63.8%). The median concentration of azinphosmethyl was 0.53 mg/g. Less than one-half of the households had detectable levels of the other chemical types. The median concentration of azinphosmethyl in vehicles was 0.85 mg/g.

There were few differences in median child urinary metabolite concentrations in homes with detectable dust residues compared with those without detectable dust residues. Similarly, there were few differences in child urinary metabolites and vehicle dust; however, in households where vehicle dust contained measurable levels of methylparathion, phosmet, or azinphosmethyl, the median levels of child urinary metabolites of pesticide were consistently higher than in households without detectable levels of those compounds in vehicle dust.

Conclusion

The baseline data indicate that there is reason to be concerned about pesticide exposure in the Lower Yakima Valley. The intervention study as conducted in a randomized community trial should provide insights about the value of community-wide intervention on this issue.

Summer Project for Minority High School Student Interns: Effects of Home Parties on Farmworkers

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Background

Agricultural workers and their children are thought to experience high levels of exposure to pesticides. Little is known about the effectiveness of strategies to change agricultural workers practices and beliefs related to pesticides. In a large randomized, community trial, a variety of community events are being used to make farmworkers aware of things that can be done to reduce the amount of pesticides taken home from their workplaces. By reducing this take-home pathway, it is thought that children in the homes are less likely to be exposed to pesticides. One intervention strategy used in this project is home parties, where family members and neighbors gather in a farmworker s home and participate in an interventionist-led discussion about pesticides and prevention techniques.

Purpose

The purpose of this student project was to conduct a process evaluation of the efficacy of the home parties. This was done by characterizing the beliefs and home practices of agricultural workers who attended in-home pesticide education sessions (home parties) and comparing these with baseline community survey findings.

Methods

Telephone interviews were conducted among a random sample of 150 home party attendees from two communities in the Lower Yakima Valley. A number of telephones were disconnected, and some individuals were unable to be reached, leaving 92 known eligible agricultural workers.

Results

Ninety-eight percent of known eligible attendees responded to the survey. The educational and income distribution of the sample matched those of the baseline survey. Home party attendees were more familiar with the factual information of pesticide exposure than those in the baseline survey. They reported engaging in more pesticide protective home practices compared to community baseline survey respondents. Attendees reported having learned important key messages, including general pesticide information, washing work clothing separately from family clothing, and removing shoes before entering the home.

Conclusion

Home parties appear to be an efficacious way to present messages regarding pesticides to agricultural workers. This study compared attendees to baseline respondents and, therefore, has methodological limitations. Future research should evaluate home parties using control groups for comparison.

*Minority High School Student Interns

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Overview and Description of the Center for the Health Assessment of the Mothers and Children of Salinas (CHAMACOS): A Community/University Partnership

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In the last few years, several studies have demonstrated pesticide contamination in the homes of young children living in both agricultural and suburban areas. However, to date, only a few studies have been conducted to assess the extent of children s exposure to pesticides and no studies have examined whether low-level chronic exposure can lead to adverse health consequences. Our goal is to investigate *in utero* and postnatal pesticide and allergen exposures and their potential health effects on young children living in the Salinas Valley, an agricultural community in Monterey County, California. Ultimately, we aim to translate research findings into sustainable strategies to reduce environmental exposures to children, and thus reduce the incidence of potentially environmentally related childhood disease. Our Center also will generate information critical for implementation of the Food Quality Protection Act, which requires that pesticide tolerance levels in food take into account the special vulnerabilities of children.

Our specific aims are to:

- Estimate sources, pathways, and levels of *in utero* and postnatal pesticide exposures of children living in an agricultural community by measuring biological and environmental samples.

- Determine whether exposure to pesticides is associated with poorer neurodevelopmental functioning and behavioral problems, delayed growth, and increased respiratory symptoms and disease.

- Determine whether exposure to environmental allergens and respiratory irritants is associated with increased respiratory symptoms and disease. We will determine whether pesticide exposure modifies the relationship of allergen exposure and respiratory outcomes.

- Evaluate the impact of Healthy Homes interventions on the reduction of pesticide exposure to farmworker children.

Enrollment ended in October 2000, after a full year of recruitment through community clinics. We have succeeded in enrolling the targeted number of pregnant women (n=550) by the expected date. Overall, we have been able to meet our goals and are developing a repository of samples that we will be able to utilize for future studies (e.g., endocrine-disrupting pesticides). As of October 5, 2000, we have collected and processed approximately 1,100 urine, 650 maternal and cord blood samples, and 118 breast milk samples. Preliminary pesticide urinary metabolite data are available for 93 women. We also have completed 395 prenatal home inspections and successfully collected 790 mini-burkard for airborne pollen and mold, 1,106 dust samples for allergen testing, and 395 dust samples for pesticide analysis. A total of 202 babies have been born; Brazelton assessments have been completed on 136. To date, we have been able to locate more than 90 percent of these women when their child reached 6 months. More than 80 percent have participated at 6 months, and we have been able to collect urine samples from all children participating in the 6 months neurobehavioral assessments (17 children to date). Currently, we are entering the data from prenatal questionnaires and home inspections, and we are working with collaborators at the California Department of Health Services to begin utilizing the *1999 Pesticide Use Reports*, which recently became available. Statistical analyses of prenatal and delivery data will begin later this fall as data entry progresses and the CDC provides additional testing results. We also have maintained close contacts with our community partners and advisory board. Pending notification of funding from the California Endowment Foundation, we will plan and implement a community-based education and intervention program to reduce environmental exposures to children.

Preliminary Approaches To Assessing Organophosphate Pesticide Exposure and Potential Health Risks to Pregnant Women Living in the Salinas Valley, California

Brenda Eskanazi
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Unique in the Nation, California requires reporting of all agricultural pesticide use. Pesticide use reporting (PUR) data indicate widespread use of organophosphate pesticides in California agriculture. In the Salinas Valley, which is intensively farmed for vegetables and fruit, approximately 500,000 pounds are used annually, raising concerns about exposures to farmworkers, other members of the community, and their families. Organophosphate (OP) metabolite data are available for 93 of approximately 550 pregnant women participating in the Center for the Health Assessment of the Mothers and Children of Salinas study. These urine samples were collected between October 1999 and January 2000, when fewer agricultural pesticides are used compared to the spring and summer. The Centers for Disease Control and Prevention (CDC) tested the samples for six dialkylphosphate metabolites: dimethylphosphate (DMP); dimethyldithiophosphate (DMDTP); dimethylthiophosphate (DMTP); diethylphosphate (DEP); diethyldithiophosphate (DEDTP); and diethylthiophosphate (DETP). These metabolites derive from approximately 40 OP compounds, falling into the general categories of dimethoxy and diethoxy organophosphate pesticides.

Median concentrations for the three dimethyl metabolites were 27 percent to 240 percent higher than the median reference range reported by the CDC for the National Health and Nutrition Examination Survey III (NHANES III) (D. Barr, personal communication) DMP: 2.3 vs. 1.8 mg/L; DMTP: 16.5 vs. 4.8 mg/L; and DMDTP: 1.4 vs. 0.55 mg/L. Median concentrations for the three diethyl metabolites, however, were lower than or very similar to the reference values DEP: 1.0 vs. 4.5 μg/L; DETP: 1.1 vs. 1.2 μg/L; and DEDTP: 0.09 vs. Not detected above LOD.

We estimated women s OP pesticide doses from urinary OP metabolite concentrations using a deterministic steady-state model described by Fenske et al.[1] Preliminary dose estimates were calculated assuming that diethyl urinary metabolites were attributable to either chlorpyrifos or diazinon, and that dimethyl metabolites were attributable to malathion or oxydemeton-methyl. These compounds are four of the most heavily used OP compounds in the Salinas Valley (see Table 1).

Table 1. Preliminary risk assessment of organophosphate exposures to study participants, n=93 (assumes all exposure due to single parent compound[1]).

Pesticide	1999 Use (pounds)[2]	Proportion of Women Exceeding Reference Dose (%)
Chlorpyrifos	59,000	19
Diazinon	104,000	2
Malathion	67,000	0
Oxydemeton-methyl	69,000	56

[1] Fenske RA, Kissel JC, Lu C, Kalman D, Simcox NJ, Allen E, Keifer MC. Biologically based pesticide dose estimates for children in an agricultural community. *Environ Health Perspect* 2000;108(6):515-520.
[2] Monterey County. Source: California Department of Pesticide Regulation PUR system.

These findings suggest the possibility that a significant proportion of pregnant women participating in the study experience exposures that exceed EPA chronic dietary reference doses, which may not account for the special sensitivity of the fetus. Our exposure calculations may be an underestimate because pesticide use and potential exposures are higher during the growing season. Additional risk evaluations will be completed when data for all participants are available from the CDC. We also are developing modeling approaches to estimate fetal exposures and risk. Finally, we are exploring the possibility of metabolite-specific chemical analyses to quantitatively attribute risk to specific OP compounds. Planned statistical analyses will investigate determinants of pesticide metabolite levels in urine, such as nearby pesticide use (PUR data) and occupational status.

CHAMACOS Laboratory Core: Challenges of Biological Sample Collection and Processing

Nina Holland
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Children differ from adults in size, types and extent of exposures, diet, and potential long-term health effects of environmental exposure. To learn more about differences between adults and children, and to predict potential adverse effects, new molecular and cytogenetic methods need to be developed and employed to identify biological markers or biomarkers. Biological measurements, such as changes in the structure of chromosomes, DNA polymorphisms, cellular characteristics, activities of enzymes, and levels of pesticides or other chemicals in blood or other body, can be used as biomarkers. The main advantage of biomarker studies is the ability to detect effects long before clinical manifestation of disease, thus allowing for intervention and prevention. A far smaller population is needed to obtain an informative conclusive study. Mechanistic information can be acquired, including factors that affect interindividual variability; in other words, biomarkers may help us to understand not only why children are different from adults but also how children differ from one another in response to diet, environmental pollution, or infectious diseases. The main focus of our study is to establish potential effects of pesticide exposure, by obtaining comprehensive epidemiological information and environmental and biological samples from pregnant women and their children during early development.

Specific aims of the Laboratory Core of the CHAMACOS project include development of standard operating procedures for sample collection and processing, optimization of sample banking, database management, and implementing quality control and quality assurance (QA/QC) procedures. An additional aim of the Laboratory Core is to obtain consent in a manner that would allow future use of these specimens. Collection, processing, and storage of samples is coordinated between the Natividad Hospital field office in Salinas, the Children s Hospital of Oakland Research Institute in Oakland, and the School of Public Health at the University of California at Berkeley. Samples are sent for analysis to the Centers for Disease Control and Prevention and other collaborators.

As of October 5, 2000, we have collected and processed approximately 1,100 urine, 650 maternal and cord blood, and 118 breast milk samples; 790 mini-Burkard slides for airborne pollen and mold analysis; 1,106 dust samples for allergen and endotoxin testing; and 395 dust samples for pesticide analysis. Each individual blood sample processing results in at least 18 different aliquots, including serum, clot, plasma, buffy coat, red blood cells, blood smears, and stabilized samples for folate and cholinesterase analysis. Urine and breast milk are aliquoted for assessment of organophosphate pesticide exposure, as well as other potential environmental pollutants. Dust is being processed for allergen and endotoxin analysis, and for potential pesticide measurement. The total number of expected samples will reach approximately 60,000, to be completed within the next year.

Quality Assurance/Quality Control (QA/QC) procedures have been developed and maintained for storage, processing, and analysis of various specimens. For example, blank and spiked samples and internal control replicates were created for both urine and dust samples. All samples are barcoded, and all further analyses are performed blindly. Currently, provisions have already been made for the analysis of a number of biomarkers of exposure and susceptibility.

The main goal for the future is to develop and implement a comprehensive plan for the most effective and informative use of the valuable biological and environmental samples collected from this unique population of agricultural workers and their children exposed to pesticides. To accomplish this important task, discussions with prospective collaborators from other Children s Environmental Health Centers and other organizations are underway. It will require the acquisition of significant additional resources through extramural funding.

Johns Hopkins University
Baltimore, MD

Overview and Description of the Johns Hopkins University Center for Childhood Asthma in the Urban Environment

Peyton Eggleston
Johns Hopkins University, Baltimore, MD

The long-term goal of the Center for Childhood Asthma in the Urban Environment is to understand how exposures to environmental pollutants and allergens may relate to airway inflammation and respiratory morbidity in children with asthma living in the inner city of Baltimore, and to develop effective strategies to reduce morbidity by changing these exposures.

The immediate goal of these studies is twofold: (1) test currently available recommendations for modifying environmental pollutant and indoor allergen exposures, and (2) develop data that will allow us to create new strategies that may combine other interventions or target them at genetically susceptible hosts. Within the Center, the research projects will function in an integrated way, directed toward a single goal and holding frequent conferences to discuss our progress and to increase our understanding of relevant scientific progress in each component s field. At the same time, we will provide this information to the Baltimore community and involve them in an ongoing dialog to evaluate our progress and plan our intervention efforts. Finally, we will have involved a large number of families in scientific studies of asthma and will have developed relationships that will allow trials of these newly developed interventions to be conducted efficiently. Our ultimate goal remains to develop the scientific understanding that will allow us to recommend effective intervention strategies.

To accomplish these goals, we have created a multidisciplinary program that includes both basic and applied research programs in combination with a community-based prevention research project.

Genetic Mechanisms of Susceptibility to Inhaled Pollutants. Steven R. Kleeberger, Ph.D., Principal Investigator (PI). This research project is designed to examine the genetic basis for susceptibility to an inflammatory response in airways to reactive oxidant species generated as a result of exposure to ozone (O_3). Using O_3-susceptible C57BL/6J (B6) and O_3-resistant C3H/HeJ (C3) mouse strains, this project is generating high-resolution linkage maps of the regions of mouse chromosomes 17 and 11 carrying O_3 susceptibility quantitative trait loci (QTL). Candidate genes in the two QTLs have been identified, and we currently are searching for sequence polymorphisms in two genes, tumor necrosis factor alpha (TNF-α) and heat shock protein 70 (Hsp-70), located in the chromosome 17 QTL. Using BXH recombinant inbred (BXH RI) strains of mice, a strong susceptibility QTL was identified on chromosome 4, and minor QTLs were identified on chromosomes 3 and 11. Within the chromosome 4 QTL, we identified toll-like receptor 4 (*Tlr4*) as a strong candidate gene. Significantly greater injury in wild type C3H/HeOuJ mice compared to the *Tlr4* mutant C3H/HeJ strain, strongly supported a role for *Tlr4* in responsivity to O_3. A manuscript that reports our findings has been published (*Am J Respir Cell Mol Biol* 2000;22:620-627). In the coming year, we will continue to pursue our objectives to understand the role(s) of susceptibility genes in pulmonary responses to O_3.

Mechanisms of Particulate-Induced Allergic Asthma. Marsha Wills-Karp, Ph.D., PI. The objective of this project is to examine the mechanisms by which ambient particulate matter (PM) may exacerbate allergic airways disease, or play a role in the induction of an asthma-like phenotype in a murine model. Our studies show that a single exposure to ambient PM (0.5 mg) collected in inner city Baltimore induces sustained airway hyperresponsiveness (AHR), and pulmonary inflammation (i.e., eosinophilia and neutrophilia). Conversely, these responses are not observed when animals are exposed to a reference source of fly ash. Interestingly, this phenotype is observed in all murine strains studied to date, although to varying degrees, suggesting that genetic susceptibility to develop allergic airway responses is not required. Additionally, in an ongoing study, our results indicate that repeated exposure to low doses of PM (5 μg) may have a cumulative effect in the development of AHR accompanied by mild, but persistent eosinophilia. Studies are underway to investigate the role of different cell types such as eosinophils and macrophages in PM-induced airway responses. One of our most interesting findings is that PM-induced AHR appears to be dependent on the complement component (C3). Studies are underway to define the exact mechanisms by which comple-

ment activation mediates AHR. Taken together, these results indicate that exposure to low levels of ambient PM alone is sufficient to induce an allergic phenotype and may provide an explanation for the increased incidence in asthma in inner city environments. Some of these results were published in abstract form at the 1999 and 2000 American Thoracic Society (ATS) meetings, and future findings will be presented at the 2001 ATS meeting. A manuscript on the kinetics of airway responses to ambient PM has been submitted to the *American Journal of Respiratory Cell and Molecular Biology*. Additional manuscripts reporting the strain distribution pattern of PM responsiveness, the role of eosinophils in PM-induced AHR, and the role of complement in these responses are in preparation. Dr. Wills-Karp has accepted a position at the University of Cincinnati, and she hopes to continue as PI of this component. Pending institutional, EPA, and National Institute of Environmental Health Sciences approval, this Center is enthusiastic about accepting her continued involvement under a subcontract as she has been very productive and is willing to continue the goals of the Center at the University of Cincinnati.

The Relationship of Airborne Pollutants and Allergens to Asthma Morbidity. Gregory Diette M.D., M.S., PI. This community-based epidemiologic research will compare ambient and indoor exposures to a variety of pollutants and allergens in the home and ambient environment to children s morbidity from asthma. A case-control study will be conducted among children 6 to 12 years old with 150 prevalent cases of asthma from several East Baltimore schools and neighborhood controls. Participants will be evaluated with a questionnaire regarding demographics, environmental exposures, psychosocial stressors, and health. A home visit will be conducted to assess the home exposure to pollutants and allergens. During a clinic visit, the child will be evaluated with allergen skin tests, spirometry, and serum cotinine and RAST tests. Recruitment and evaluation procedures for this study are identical to those in the intervention study, and have thus been fully established at this point. The Principal Investigator for this study, Dr. Jounni Jaakkola, left the University on March 1, 2000, to take a position at the University of Gothenburg, Sweden. Dr. Eggleston assumed administrative direction of the study until a new Principal Investigator, Greg Diette M.D., M.S., could be recruited to head the epidemiologic study. We are enthusiastic with this choice in that he has already had experience conducting epidemiologic and intervention research in East Baltimore, has a joint appointment in the Departments of Medicine and Epidemiology, and is willing to carry the original study into the field.

A Randomized, Controlled Trial of Home Exposure Control in Asthma. Peyton A. Eggleston, M.D., PI. This community-based prevention research project will conduct a randomized, controlled trial of the effectiveness of current intervention methods to reduce hazardous exposures and their adverse health effects. It will test a global intervention that is composed of several components that have proved already to be effective in middle-class homes. The major outcome of this trial will not be changes in health status, but will be environmental exposure, and it will examine the feasibility of modifying inner-city home environments with currently recommended procedures. Data on the child s health status also will be collected, but it is anticipated that future studies with interventions that already have been proved effective will be necessary to provide adequate power to test a health outcome. During Year 2 of the Centers funding, we have established recruiting, evaluation, and intervention procedures. Recruiting has begun with the presentation of an asthma self-management curriculum in five schools: Tench Tilghman, Dr. Bernard Harris, Collington Square, Dr. Raynor Brown, and Thomas G. Hayes elementary schools. The curriculum has been presented to 61 children in 49 families by the educator and her assistant. The families were visited a second time and 35 had an eligible child and were interested in participating in the intervention project. Twenty eight (28) of these families have been consented and 24 have been fully evaluated and randomized into the trial. This is an extraordinarily high rate of recruiting success and is a tribute not only to the educators but also to the study interviewer and to the study coordinator. During the coming year, recruitment should be even more rapid as we expand the asthma curriculum from three to five elementary schools. The treatment group will receive an allergen-proof mattress and pillow encasings for the child s bed, a room air cleaner for the child s room, pest control services if needed, smoking cessation support, and environmental avoidance education. The intervention is being conducted by a community health educator, Mayme Grant, and Karen Callahan, B.S.N., M.S., and has been well received by nine families. All families will receive two home visits at 6 and 12 months, a telephone interview at 3, 6, 9, and 12 months, and a final clinic evaluation.

The project for the newly recruited young investigator is entitled Evaluation of Indirect PM_{10} Exposure Assessment in a Cross-Sectional Epidemiological Study of Asthma Exacerbation in Urban Children. Timothy J. Buckley, Ph.D., PI. This project compares the exposure assessment in children as gathered from home area samples with that measured by diary and continuous personal monitoring over a 3-day period. To date, 29 children and their homes have been successfully monitored for allergens, PM, nitrogen dioxide, and ozone. Urinary samples have been collected to assess ETS exposure by cotinine analysis. Questionnaires have been developed and administered to acquire information about time activity patterns and housing characteristics. All measures are within the range of previous environmental studies. Results of this study have been presented at PM 2000: Particulate Matter and Health: The Scientific Basis for Regulatory Decision Making in Charleston, SC. Preliminary results show median PM_{10} levels of 53, 32, and 22 mg/m^3 for the personal, indoor, and outdoor measurements, respectively. On average, the personal PM_{10} levels were 24 percent and 134 percent higher than indoors and outdoors, respectively. Median indoor levels of NO_2 and O_3 were 10.2 (n=5) and 5.6 (n=7) ppb, respectively. Dust allergen concentrations varied by location (bedroom, TV room, kitchen) from below detection to 51,000 ng/g of MUP measured in one home s kitchen.

With the completion of Dr. Buckley s Newly Recruited Young Investigator Project, we have selected two young investigators for the position, starting in November 2000. Sekhar Reddy, Ph.D., will conduct a project entitled Molecular Basis of TLR4 Receptor Regulation by Endotoxin and Ozone. Alison Geyh, Ph.D., will begin a project entitled Assessing Early Childhood Exposures to Transition Metals Associated With Particulate Matter.

The two community-based applied research projects will be supported by an experienced Data Management Core Facility directed by Sukon Kanchanaraksa, Ph.D., and by an Exposure Assessment Core Facility directed by Patrick Breysse, Ph.D. Dr. Kanchanaraksa has established the study forms on an automated screening format and has recruited staff who are contributing to interim data analysis in the center and in several other asthma-related projects. Dr. Breysse has established the laboratory procedures to allow three homes to be evaluated weekly.

The Community Advisory Committee met monthly to review the protocol regarding feasibility and appropriateness in the East Baltimore community, review study protocols and progress reports, provide a forum to discuss community-based issues concerning the conduct of the trial, and provide liaison to translate study findings to the community. Members of the Committee have been chosen from the school system, community-based research and service organizations, churches, and from families of asthmatic children. The Committee has met monthly during the past year and has been invaluable in designing the protocol and the implementation plan.

Ambient Urban Particulate-Induced Airway Hyperresponsiveness and Inflammation in Mice

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Airborne particulate matter (PM) is hypothesized to play a role in increases in asthma prevalence, although a causal relationship has yet to be established. To investigate the effects of real-world PM exposure on airway reactivity and bronchoalveolar lavage (BAL) cellularity, we exposed naive A/J mice 6 7 weeks of age to a single dose (0.5 mg/mouse) of PM collected in urban Baltimore (AUB) or to coal fly ash. We found that AUB exposure induced increases in airway responsiveness (AHR) and BAL cellularity, whereas coal fly ash (CFA) exposure did not elicit significant changes in either of these parameters. We further examined AUB-induced temporal changes in AHR, BAL cells, and lung cytokine levels over a 2-week period. AUB-induced AHR was sustained over 7 days and returned to control levels at 14 days. The increase in AHR was preceded by dramatic increases in BAL granulocytes, particularly eosinophils. The decline in AHR from peak values was associated with significant increases in macrophages. A Th2 cytokine pattern (IL-5, IL-13, eotaxin) was observed early on with a shift toward a Th1 pattern (IFN-g), as AHR and granulocytes returned to normal levels. Finally, in a leaching experiment, we found that the active component(s) of AUB are not water-soluble, but remain particle-bound. We conclude that ambient PM can induce asthma-like parameters in naive mice suggesting that PM exposure may contribute to increases in asthma prevalence.

Air Pollution and Allergen Exposure Among Asthmatic Children in Inner-City Baltimore

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The number of asthmatics has more than doubled from 1980 to 1994. It is estimated that 7 percent of children under 18 years old suffer from asthma. Populations in the inner-city environment are most severely affected. Air pollution and allergens in the indoor environment are believed to play a prominent etiologic role, although few studies have been conducted characterizing exposure in this susceptible population. The goal of this study is to demonstrate the feasibility of assessing allergen and air pollution exposure among inner-city asthmatic children and to evaluate the effectiveness of a strategy based on time-weighted indoor and outdoor monitoring to estimate actual exposure. We also examine the contribution of air pollution of ambient origin on indoor and personal exposures.

Methods: Monitoring was conducted from April 1999 through August 2000, on a convenient sample of 29 children with reported physician-diagnosed asthma. All were Baltimore City residents and ranged in age from 6 to 12 years. PM_{10} and/or $PM_{2.5}$ were collected indoors, outdoors, and on the child (personal) using MSP impactors (St. Paul, MN) over a 3-day sampling period. Indoor and personal ozone and NO_2 were sampled passively using Palmes tubes. A single urine sample was collected on the third day of monitoring for analysis of cotinine as an indicator of exposure to environmental tobacco smoke. Indoor allergens, including dust mite *Der p I*, cockroach *Bla g I*, cat *Fel d I*, and mouse urine protein *MUP*, were sampled in the settled dust by vacuum in three indoor home locations (bedroom, kitchen, and child s bedroom) and analyzed by immuno-chemical assay. Each child was asked to maintain a 24-hour time activity diary for each of the 3 days of sampling, a home inspection was conducted, and a household questionnaire was administered.

Results: Preliminary results show median PM_{10} levels of 56, 39, and 22 g/m^3 for the personal, indoor, and outdoor measurements. On average, the personal PM_{10} levels were 24 percent and 134 percent higher than indoors and outdoors, respectively. As has been observed in the general population, children s personal exposures were poorly predicted from the outdoor central site monitoring (R^2=0.01). On average, the children reported that they spent 86 percent of their time indoors (home, school, and other). Median indoor levels of NO_2 and O_3 were 14 and 5.6 ppb, respectively. Dust allergen concentrations varied by location (bedroom, TV room, kitchen) from below detection to 51,000 ng/g of MUP measured in one home s kitchen.

Conclusions: PM concentrations and their relationships between personal, indoor, and outdoor locations have been measured for a population subgroup believed to be susceptible to PM morbidity and mortality. These concentrations and relationships are within the range of what has been observed in previous studies of the general population. Allergens in house dust have been measured at concentrations shown to result in sensitization and exacerbation of disease. Therefore, the current study establishes procedures and provides preliminary data by which to assess exposure to test for synergistic effects of air pollution and common in-door allergens in a susceptible urban population.

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Overview and Description of the Children s Environmental Airway Disease Center

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The theme of the Center is to investigate the etiology and pathogenesis of airway disease in children from rural communities. We chose this theme for the Center for the following reasons: (1) asthma is the most common chronic illness in children; (2) the rural setting introduces unique environmental exposures that are known to play a role in the development of airway disease; (3) environmental models of asthma provide an ideal opportunity to investigate fundamental issues in childhood asthma such as the biological origin and persistence of airway disease; and (4) this theme builds on existing scientific expertise and ensures a highly interactive program. Because grain dust and endotoxin are common in the rural setting and both are associated with acute and chronic forms of airway disease, we have used these very relevant environmental exposures to further focus the projects in the Center. The end result is a highly integrated and focused program that has the potential to make a number of novel, related observations. In aggregate, the coupled scientific findings from the Center will substantially enhance our understanding of airway disease in children. The primary hypothesis unifying this research program is that understanding the etiology and pathogenesis of airway disease in children from rural communities will provide the scientific rationale to develop primary, secondary, and tertiary preventive programs that reduce the morbidity and mortality of childhood asthma in the rural setting.

The project-specific hypotheses within the Center are:

- Project 1: Environmental intervention is an essential component of an asthma intervention program that must be coordinated with other improvements in health care to reduce the prevalence and severity of asthma among children from rural communities.

- Project 2: Many of the biologic features of acute and reversible airway inflammation are fundamental to the development of chronic grain dust-induced airway disease.

- Project 3: Mechanisms that initiate, promote, and resolve grain dust-induced inflammation may be distinct from those mechanisms involved in LPS-induced airway inflammation.

- Project 4: Respiratory syncytial virus infection upregulates the response of airway epithelium to LPS.

During Year 2 of the Children s Environmental Airway Disease Center at the University of Iowa, substantial progress has taken place. The four funded projects at the Center have made excellent progress and have met all of their goals for the first year. In this regard, a number of publications have either been submitted, accepted, or published. The investigators also have received a substantial number of invitations to present their results at national and international meetings. Finally, the overall structure and necessary interactions within the Center have been formalized to ensure the continued success of the program. Further evidence of the health of the program is that the Center has provided some financial support for exciting new programs that were not described in the original application but that will interface closely with existing projects and provide new directions for research. In Year 1, we were able to provide support for Dr. Klekamp, a promising Assistant Professor in Pediatrics, to pursue studies on the role of adhesion molecules in airway inflammation. She has found that ICAM-1 and the B integrins are essential to neutrophil recruitment. In Year 2, we provided support for Dr. Carter, who is a promising new investigator in the Department of Medicine. He has found that endotoxin increases the replication of viruses in airway epithelia. Drs. Hunninghake, Nauseef, and Schwartz are evaluating the role of toll-4 in lipopolysaccharide signaling.

Thus, the Children s Environmental Airway Disease Center at Iowa strengthens our research efforts related to environmental airway disease. The program is energetic, imaginative, cohesive, and productive. In the following paragraphs, the highlights of the accomplishments of various components of the program are described. More detailed progress reports can be found in the individual projects.

Project 1: Multicomponent Interventions Study of Asthma in Children From Rural Communities: The Rural Health Study.

The most significant achievement during the past year has been the development of a specific protocol for the multicomponent intervention and for the assessment of its effect. To date, no protocol is available for a community-based intervention encompassing both environmental and medical issues related to asthma care in a rural environment, particularly with a focus on individualized family counseling related to barriers for asthma care. The most important aspect of the study is that we have a 90 percent response rate.

Project 2: A Model To Study the Development of Persistent Environmental Airway Disease.

These investigators have found that subacute exposure to grain dust caused chronic airway lesions that are associated with airway hyperreactivity and airway remodeling. Moreover, the development of chronic grain dust-induced airway disease appears to be mediated by endotoxin, because mice genetically hyporesponsive to endotoxin do not develop chronic grain dust-induced airway disease.

Project 3: Mechanisms That Initiate, Promote, and Resolve Grain Dust-Induced Inflammation.

Studies related to the pathophysiology of asthma commonly involve either *in vivo* human and animal systems or *in vitro* systems with single cell types. Although both of these approaches provide crucially important insights, it is often difficult to bridge the knowledge that the two systems provide. We are developing co-culture systems that will allow us to explore the complex interactions between airway cells that are the basis for the inflammatory response to grain dust. We have found that the response to grain dust is very cell specific.

Project 4: Role of RSV Infection and Endotoxin in Airway Inflammation.

RSV upregulates the p45 ERK kinase and then is related to IL-8 production by airway epithelium. These investigators also observed that TH-1 and Th-2 cytokines regulate IL-8 release by airway epithelium. Importantly, we found that environmental exposures may increase replication of viruses in the airways.

A Multicomponent Intervention Study of Asthma in Children From Rural Communities

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The complex interrelationship of allergens and nonspecific airway stimuli may amplify the effects of individual airway stimuli as well as weaken single-agent exposure reduction interventions. Factors such as physician awareness of patient symptom control, patient self-management, early response to upper respiratory infections, parent modification of smoking, and modification of cleaning behaviors may all influence a child s asthma-related quality-of-life. A multicomponent intervention approach appears warranted. This community-based intervention study will take place in two counties in Iowa. The goal is to test the effect of the multicomponent intervention by comparing asthma health outcomes and change in environmental exposures between an intervention county and a demographically similar, noncontiguous comparison county. A target total of 300 children, ages 6 14 years, and their families will be enrolled in three, 1-year waves. Children will be identified through the schools and mailed a 3-page asthma screening questionnaire. The screening questionnaire will be used to classify children as having no asthma, intermittent asthma, or persistent asthma. Severity of persistent asthma also will be assessed via the screener. Measures include annual spirometry and the following measures at baseline and 1 year: in-home administered questionnaires; home inspection environmental checklist; and environmental measures. Questionnaire-based measures include asthma symptom control and severity, quality-of-life, barriers to asthma care, self-management behaviors, adequacy and understanding of asthma care plans, environmental control issues, and health care utilization. Environmental measurements will include quantitative assessments of endotoxin and antigen levels via dust sampling; CO, CO_2, relative humidity, and temperature via instantaneous air sampling; and NO_2 and environmental tobacco smoke via passive dosimeter. The intervention includes family-level, health provider-level, school-level, and community-level components. The individualized family-level intervention addresses medication management and environmental control issues and is delivered by the study asthma counselor in quarterly in-person sessions and monthly interval telephone followups. Feedback is provided from the counselor to the family s regular asthma physician.

Lipopolysaccharide Responsiveness and the Development of Subchronic Grain Dust-Induced Airway Injury

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Endotoxin is one of the principal components of grain dust that causes acute reversible airflow obstruction and airway inflammation. To determine if endotoxin responsiveness influences the development of chronic grain dust-induced airway disease, physiologic and airway inflammation/remodeling parameters were evaluated following an 8-week exposure to corn dust extract (CDE) and again following a 4-week recovery period, in one strain of mice sensitive to (C3H/HeBFeJ) and one resistant to endotoxin (C3H/HeJ). Following the CDE exposure, both strains of mice had equal airway hyperreactivity to a methacholine challenge; however, airway hyperreactivity persisted only in the C3H/HeBFeJ mice after the recovery period. Only the C3H/ HeBFeJ mice showed significant inflammation of the lower airway following the 8-week exposure to CDE. Following the recovery period, this inflammatory response completely resolved. Lung stereologic measurements indicate that an 8-week exposure to CDE results in persistent expansion of the airway submucosal cross-sectional area only in the C3H/HeBFeJ mice. Collagen type III and an influx of cells into the subepithelial area participate in the expansion of the submucosa. Our findings demonstrate that subchronic inhalation of grain dust extract results in the development of chronic airway disease only in mice sensitive to endotoxin, but not in mice that are genetically hyporesponsive to endotoxin, suggesting that endotoxin is important in the development of chronic airway disease.

IL-10 Reduces Grain Dust-Induced Airway Inflammation and Airway Hyperreactivity

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To determine if interleukin-10 (IL-10) could alter the development of grain dust-induced airway disease, we pretreated mice with either saline or IL-10 intravenously, exposed the mice to an inhalation challenge with corn dust extract (CDE), and measured inflammation and the development of airway hyperreactivity. Pre-treatment with IL-10, in comparison to saline, reduced the concentration and percentage of polymorphonuclear cells in the lavage fluid 30 minutes after the inhalation challenge with CDE ($p < 0.05$). In comparison to saline-treated mice, IL-10 did not significantly alter the degree of airway hyperreactivity 30 minutes after the exposure to CDE. IL-10-treated mice lavaged 18 hours after challenge with CDE also exhibited a lower percentage of polymorphonuclear cells in the lavage fluid ($p < 0.05$) and had significantly less airway hyperreactivity than did mice pretreated with the saline placebo ($p < 0.05$). These findings indicate that exogenous IL-10 is effective in reducing airway inflammation and airway hyperreactivity due to the inhalation of CDE.

Publications:

Quinn TJ, Taylor S, Wohlford-Lenane CL, and Schwartz DA. IL-10 reduces grain dust-induced airway inflammation and airway hyperreactivity. *J Appl Physiol* 2000;88:173-179.

TLR4 Mutation Is Associated With Endotoxin Hyporesponsiveness in Humans

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There is much variability between individuals in the response to inhaled toxins, but it is not known why certain people develop disease when challenged with environmental agents and others remain healthy. To address this, we investigated whether encoding the toll-like receptor-4 (TLR4), which has been shown to affect lipopolysaccharide (LPS) responsiveness in mice, underlies the variability in airway responsiveness to inhaled LPS in humans. In this study, we show that common, cosegregating missense mutations (Asp299Gly and Thr399Ile) affecting the extracellular domain of the TLR4 receptor are associated with a blunted response to inhaled LPS in humans. Transfection of THP-1 cells demonstrates that the Asp299Gly mutation (but not the Thr399Ile mutation) interrupts TLR4-mediated LPS signalling. Moreover, the wild-type allele of TLR4 rescues the LPS hyporesponsive phenotype in either primary airway epithelial cells or alveolar macrophages obtained from individuals with the TLR4 mutations. Our findings provide the first genetic evidence that common mutations in TLR4 are associated with differences in LPS responsiveness in humans, and demonstrate that gene-sequence changes can alter the ability of the host to respond to environmental stress.

Publications:

Arbour NC, Lorenz E, Schutte BC, Zabner J, Kline JN, Jones M, Frees K, Watt JL, and Schwartz DA. TLR4 mutation is associated with endotoxin hyporesponsiveness in humans. *Nat Genet* 2000;25:187-191.

Bronchial Hyperreactivity Is Associated With Enhanced Grain Dust-Induced Airflow Obstruction

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Bronchial hyperreactivity (BHR) is associated with the presence of airway inflammation in asthma and is seen in individuals occupationally exposed to grain dust. To better understand the relationship between BHR and pulmonary inflammation after grain dust exposure, we conducted an inhalation challenge to corn dust extract (CDE) on seven subjects with BHR, [a 20% or greater decrease in forced expiratory volume in 1 second (FEV(1)) compared with diluent FEV(1) with a cumulative dose of histamine ≤ 47.3 breath units] and compared their physiological and inflammatory responses with those of seven matched control subjects. BHR subjects were exposed to nebulized CDE (target dose of 0.16 mμg/kg endotoxin) as tolerated; matched controls received equal amounts of CDE. Subjects with BHR complained of chest tightness and dyspnea within 2 hours after inhalation of CDE significantly more frequently than controls. Similarly, subjects with BHR developed significantly greater percent declines in FEV(1) at time points up to 4 hours after exposure to CDE. Significant increases in total cells, neutrophils, tumor necrosis factor-alpha, interleukin-6, and interleukin-8 were detected in bronchoalveolar lavage fluid 4 hours after inhalation of CDE in all subjects, but no differences were detected between the control and BHR groups. These results suggest that, although subjects with BHR develop a more precipitous decline in FEV(1) after exposure to CDE, the inflammatory response to CDE is similar in subjects with and without BHR.

Publications:

Kline JN, Jagielo PJ, Watt JL, and Schwartz DA. Bronchial hyperreactivity is associated with enhanced grain dust-induced airflow obstruction. *J Appl Physiol* 2000;89:1172-1178.

TNF-Alpha and IL-1Beta Are Not Essential to the Inflammatory Response in LPS-Induced Airway Disease

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To determine the role of TNF-α and IL-1β in the lower respiratory tract inflammatory response following inhalation of LPS, we conducted inhalation exposure studies in mice lacking expression of TNF-α and/or IL-1 receptor 1; and in mice with functional blockade of these cytokines using adenoviral vector delivery of soluble receptors to one or both cytokines. Alterations in airway physiology were assessed by pulmonary function testing, prior to and immediately following 4-hour LPS exposure, and the cellular inflammatory response was measured by whole lung lavage and assessment of inflammatory cytokine protein and mRNA expression. Airway resistance following LPS exposure was similarly increased in all groups of mice without evidence that blockade of either or both cytokines was protective from this response. Additionally, all groups of mice demonstrated significant increases in lung lavage cellularity with a complete shift in the population of cells to a predominantly neutrophilic infiltrate as well as elevation of inflammatory cytokine protein and mRNA levels. There were no significant differences between the groups in measures of lung inflammation. These results indicate that TNF-α and IL-1β do not appear to have an essential role in mediating the physiologic or inflammatory response to inhaled LPS.

Publications:

Moreland JG, Fuhrman RM, Wohlford-Lenane CL, Quinn TJ, Benda E, Pruessner JA, and Schwartz DA. TNF-Alpha and IL-1Beta are not essential to the inflammatory response in LPS-induced airway disease. *Am J Physiol Lung Cell Mol Biol* 2001;280(1):L173-180.

Endotoxin Responsiveness and Subchronic Grain Dust-Induced Airway Disease

C.L.S. George, H. Jin, C.L. Wohlford-Lenane, M.E. O Neill, J.C. Phipps, P. O Shaughnessy, J.N. Kline, P.S. Thorne, and D.A. Schwartz
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Subchronic exposure to corn dust extract (CDE) in a murine model causes airway inflammation and bronchial hyperreactivity similar to that seen in humans with recurrent occupational exposure to grain dust. Lipo-polysaccharide (LPS) is one of the principle components of grain dust, which causes acute reversible airflow obstruction and airway inflammation. To determine if LPS responsiveness influences the development of chronic grain dust-induced airway disease, physiologic parameters and indicators of airway inflammation/ remodeling were evaluated following an 8-week exposure to CDE in a strain of mice sensitive to LPS (C3H/BFeJ) and one resistant to LPS (C3H/HeJ). Airway hyperreactivity, measured by response of enhanced pause pressure (Penh) to methacholine, was assessed at baseline, after 8 weeks of CDE exposure, and after a 4-week recovery period. Following the 8-week CDE exposure, the C3H/BFeJ mice had a significantly greater increase in their Penh values compared to the C3H/HeJ mice. This increase persisted through the 4-week recovery period. The C3H/BFeJ mice, but not the C3H/HeJ mice, showed a significant increase in the number of total cells, the percentage of neutrophils, and the concentration of TNF-α, IL-6, and MIP-2 in the lavage fluid after the 8-week exposure to CDE; however, after the recovery period, the concentration of cells and cytokines in the lavage fluid returned to preexposure values in both strains of mice. Morphometric measures indicate that an 8-week exposure to CDE results in expansion of the airway submucosa with minimal change in the airway epithelia in the C3H/BFeJ mice, but not the C3H/HeJ mice. Our results demonstrate that subchronic inhalation of grain dust extract results in the development of chronic airway disease in mice sensitive to endotoxin but not in mice that are genetically hyporesponsive to endotoxin; suggesting that endotoxin is one of the principle components of grain dust causing the development of chronic airway disease.

Publications:

George CLS, Jin H, Wohlford-Lenane CL, O Neill ME, Phipps JC, O Shaughnessy P, Kline JN, Thorne PS, and Schwartz DA. Endotoxin responsiveness and subchronic grain dust-induced airway disease. *Am J Physiol Lung Cell Mol Biol* 2001;280(2):L203-213.

Mechanisms That Initiate, Promote, and Resolve Grain Dust-Induced Inflammation

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The hallmark of the bronchial hyperreactivity observed in children with asthma is airway inflammation. In contrast to eosinophil-mediated asthma, responses stimulated by grain dust are predominately neutrophilic, suggesting that grain dust elicits pro-inflammatory signals largely geared toward stimulating infiltration of neutrophils. Our studies use primary human airway cells and cell lines to identify early steps in this neutrophilic inflammatory response.

Hypothesis: Exposure of alveolar macrophages to grain dust results in the release of macrophage-specific cytokines. We found that: (a) grain dust stimulates an increase in the release of the cytokines TNF-α, IL-8, ENA-78, and Rantes in a dose-dependent manner; (b) the effect is maximal at ~ 0.4-2 mg/mL of grain dust (2-14 μg/mL of associated LPS); and (c) conversely, higher concentrations of grain dust (10 mg/mL) inhibit release of all four cytokines relative to maximal levels. These data support the hypothesis that factors present in grain dust stimulate cytokine release by human alveolar macrophages.

Hypothesis: LPS contributes to the effects of grain dust on release of cytokines by human alveolar macrophages. In our studies, although both purified LPS and grain dust increase release of TNF-α by human alveolar macrophages, we have observed striking differences in the characteristics of these effects. First, the dose response curves for LPS and grain dust (with comparable LPS concentrations) are different. Namely, at low concentrations LPS is the more potent agonist, while at higher concentrations grain dust elicits a greater response. Next, the effects of LPS but not of grain dust are enhanced by the addition of LPS-binding protein (LBP). Also, the effects of LPS, but less so of grain dust, are inhibited by the endotoxin inhibitors polymyxin B and bacterial permeability-increasing protein (BPI). Finally, we observed no correlation between TNF-α release and LPS concentrations using multiple grain dust preparations. These data lead to two alternative hypotheses: (1) the effects of grain dust on TNF-α release are independent of LPS; and (2) LPS bound to endotoxin has different biological activity and interacts differently with host proteins and surface receptors when compared to purified LPS.

Hypothesis: Grain dust activates human neutrophils and this activation is due, at least in part, to LPS. Preliminary studies measuring chemiluminescence demonstrate differences in the dose response curves between LPS and grain dust and differences in the effect of LBP. These data further suggest the two alternative hypotheses stated above. Additional studies currently are underway to characterize further the inflammatory effects of grain dust using human airway cells. A thorough understanding of these early inflammatory events will provide essential insight for developing interventions to prevent and/or treat grain dust-mediated airway disease.

Activation of ERK Kinase Activity by Respiratory Syncytial Virus in A549 Cells Is Linked to the Production of Interleukin 8

W. Chen, M.M. Monick, A.B. Carter, and G.W. Hunninghake
University of Iowa, Iowa City, IA

Respiratory syncytial virus is a major cause of viral bronchiolitis and pneumonia in children. The airway inflammation that results from the viral infection is associated with a marked increase in interleukin 8 and neutrophils in the infected sites of the lung. In this study, the relationship between release of interleukin 8, infection of A549 cells (a human lung epithelial carcinoma cell line) by respiratory syncytial virus, and activation of mitogen-activated protein kinases was investigated. Infection of A549 cells by the virus caused an increase in the activity of ERK2 by about tenfold compared with the noninfected cells. The increase in the activity of ERK2 during the viral infection was an immediate event and occurred prior to the viral replication process. PD98059, a synthetic chemical inhibitor that blocks the activation of MEK1, inhibited the increase in the activity of ERK2 by infection of respiratory syncytial virus by about 50 percent at 10 mM. Pre-treatment of A549 cells with PD98059 before the viral infection also inhibited the increase in the production of interleukin 8 by 50 percent. This treatment had little effect on the virus-induced increase in interleukin 8 mRNA. The viral infection had no effect on the activities of p38 and JNK. These observations suggest that activation of ERK2 by respiratory syncytial virus infection may be one of the mechanisms that result in the increase of the production of interleukin 8.

Publications:

Chen W, Monick MM, Carter AB, and Hunninghake GW. Activation of ERK2 by respiratory syncytial virus in A549 cells is linked to the production of interleukin 8. *Exp Lung Res* 2000;26(1):13-26.

Effects of Ragweed and Th-2 Cytokines on the Secretion of IL-8 by Human Airway Epithelial Cells

W. Chen and G.W. Hunninghake
University of Iowa, Iowa City, IA

Ragweed-induced asthma is a very common pulmonary disease. An important part of asthma is a large increase in inflammatory cells, including neutrophils and eosinophils, in ragweed-sensitized subjects. In this study, we determined whether ragweed treatment could induce the release of interleukin-8 (IL-8) by human airway epithelial cells. We found that ragweed induces a substantial increase of the secretion of IL-8 from A549 cells in a dose- and time-dependent manner. Th-2 cytokines, IL-4, and IL-13 partially inhibited the ragweed-induced secretion of IL-8. Our results suggest that airway epithelial cells may be one of the cell sources that provide IL-8 during ragweed-induced asthma. The results also indicate that IL-4 and IL-13 may exert inhibitory effects on IL-8 secretion by airway epithelium.

Publications:

Chen W and Hunninghake GW. Effects of ragweed and Th-2 cytokines on the secretion of IL-8 by human airway epithelial cells. *Exp Lung Res* 2000;26:229-239.

Respiratory Syncytial Virus Infection Results in Activation of Multiple Protein Kinase C Isoforms Leading to Activation of Mitogen-Activated Kinase

M.M. Monick, J.M. Staber, and G.W. Hunninghake
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Respiratory syncytial virus (RSV) is an important respiratory pathogen that preferentially infects epithelial cells in the airway and causes a local inflammatory response. Very little is known about the second messenger pathways involved in this response. To characterize some of the acute response pathways involved in RSV infection, we utilized cultured human epithelial cells (A549) and optimal tissue culture infective $(TCID)^{50}$ doses of RSV. We have previously shown that RSV-induced IL-8 release is linked to activation of the ERK MAP kinase pathway. In this study, we evaluated the upstream events involved in ERK activation by RSV. RSV activated ERK at two time points, an early time point consistent with viral binding and a later, sustained activation consistent with viral replication. We next evaluated the role of PKC isoforms in RSV-induced ERK kinase activity. We found that A549 cells contain the Ca^{++} dependent isoforms a and b1, and the Ca^{++} independent isoforms d, e, h, m, q, and z. Western analysis showed that RSV caused no change in the amounts of these isoforms. However, kinase activity assays demonstrated activation of z at the early time point and sustained activation of b1, d, e, and m later in the infection. A cell-permeable peptide inhibitor specific for the z isoform decreased early ERK kinase activation by RSV. Downregulation of the other PKC isoforms with PMA blocked the late sustained activation of ERK by RSV. These studies suggest that RSV activates multiple PKC isoforms, resulting in the downstream activation of ERK kinase.

Publications:

Monick MM, Staber JM, Thomas K, and Hunninghake GW. Respiratory syncytial virus infection results in activation of multiple protein kinase C isoforms leading to activation of mitogen-activated protein kinase. *J Immunol* 2001;166(4):2681-2687.

Endotoxin Augments Viral Replication and the Inflammatory Response in Respiratory Syncytial Virus-Infected Epithelium

A.B. Carter, M.R. Donohue, K.L. Knudtson, G. Gudmundsson, M.M. Monick, and G.W. Hunninghake
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Respiratory syncytial virus (RSV) is an important cause of lower respiratory tract illness in young children, and RSV infection often results in increased airway reactivity. Airway reactivity in asthma also is increased following exposure to endotoxin (LPS), and viral respiratory tract infections are increased in children exposed to indoor and outdoor pollutants. Due to the fact that many environmental agents contain LPS, we inquired if LPS enhanced viral replication. We found that LPS significantly increased the amount of virus in infected cells when compared to RSV-infected cells alone. To determine if this increase in viral replication was associated with more inflammation, we used IL-8 gene expression as a marker of epithelial inflammation. As expected, we found that RSV alone increased IL-8 gene expression in epithelium, while LPS alone had no significant effect. We also found that RSV-infected epithelium exposed to LPS had about a twofold increase in IL-8 mRNA accumulation and IL-8 protein release. These data show that LPS increases viral replication and inflammation in infected epithelium.

Publications:

Carter AB, Donohue MR, Knudtson KL, Gudmundsson G, Monick MM, and Hunninghake GW. Endotoxin augments viral replication and the inflammatory response in respiratory syncytial virus-infected epithelium. *J Clin Invest* 2000 (submitted).

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Overview and Description of the Michigan Center for the Environment and Children s Health

Barbara Israel
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The Michigan Center for the Environment and Children s Health (MCECH pronounced M-Check) is one of eight Centers of Excellence for Children s Environmental Health funded by the National Institute of Environmental Health Sciences (NIEHS) and the U.S. Environmental Protection Agency (EPA) for 5 years, beginning in the fall of 1998. The overall goal of MCECH is to investigate the environmental, pathophysiological and clinical mechanisms of childhood asthma, which will translate into risk assessment and comprehensive community and household level interventions aimed at increasing knowledge and behaviors to reduce asthma-related environmental threats to individuals and neighborhoods.

MCECH grew out of the priorities set by the Detroit Community-Academic Urban Research Center (URC), funded by the Centers for Disease Control and Prevention (CDC). Since 1995, the URC has conducted community-based research to identify ways to improve health in selected communities in the southwest and east sides of Detroit. Representatives of community-based organizations, public health agencies, health care organizations and academia are involved in every major phase of the research from defining the health problems to collecting data and disseminating results, to evaluating plans of action to address issues identified. One such plan of action was the creation of MCECH.

Based at the University of Michigan Schools of Public Health and Medicine, MCECH involves partners working in the southwest and east sides of Detroit, including Latino Family Services, Community Health and Social Services (CHASS), Warren-Conner Development Coalition, Butzel Family Center, Detroiters Working for Environmental Justice, Friends of Parkside, United Community Housing Coalition, Kettering-Butzel Health Initiative, Henry Ford Health System, the Detroit Health Department, and the CDC.

MCECH conducts its research in ways that are consistent with the Community-Based Public Health Research Principles developed initially by the Detroit-Genesee County Community-Based Public Health Consortium, and subsequently modified for and adopted by the Detroit URC. These principles include an emphasis on the local relevance of public health problems and an examination of the social, economic, and cultural conditions that influence health status and the ways in which these affect lifestyle, behavior, and community decisionmaking. Thus, MCECH s projects involve a collaborative, empowering process that builds upon the local knowledge of community members, relies on community resources, and contributes to community capacity-building and community control of efforts aimed at understanding and changing the environment to promote and improve community and family health.

There are three projects of MCECH two of which are being implemented in the southwest and east sides of Detroit, and one of which will be based at the University of Michigan School of Medicine. The three projects are engaged in coordinated interdisciplinary research aimed at:

- Increasing knowledge and behavior to reduce environmental hazards in households and neighborhoods, thereby improving asthma-related health status, through a community-based household and neighborhood level intervention;

- Examining the effects of daily and seasonal fluctuations in indoor and outdoor ambient air quality on pulmonary function and severity of asthma symptoms; and

- Determining the effects of allergen-induced local, excessive production of chemokines on redox status and innervation of the bronchial tree.

Current MCECH projects are:

Community Action Against Asthma (CAAA): This project consists of two closely integrated components: (1) a community-based intervention to reduce environmental triggers for asthma among children, and (2) a study of the role of indoor and outdoor air contaminant exposures in childhood asthma aggravation. A primary aim of the household and neighborhood level community-based intervention research project is to reduce exposure of children to environmental contaminants within their homes and neighborhoods that trigger asthma, thereby improving asthma-related health status and reducing asthma-related medical care utilization. Children ages 6-10 years with moderate to severe asthma will be identified through a screening questionnaire mailed to families. Families will be asked to enroll in a household intervention in which outreach workers will visit each household 12 times in 2 years. Outreach workers will work with the family to reduce indoor household exposure factors identified as exacerbating asthma such as cockroach mites, cat dander, environmental tobacco smoke, and mold. Each household will be supplied with education materials and other resources to reduce indoor asthma triggers such as vacuum cleaners, bedding covers, cleaning kits, and mats. Community organizers also will work with neighborhood groups on asthma awareness and reduction of environmental threats to children s respiratory health.

The key hypothesis of the exposure study is that ambient air contaminants such as particulate matter and ozone will worsen the health status of asthmatic children by increasing the adverse effects of common indoor air contaminants, especially indoor allergens. The same families enrolled in the intervention also will participate in this component. Levels of outdoor air contaminants as well as indoor air contaminants in schools and homes will be measured. Indoor measures will include common allergens in dust. The health status of the children with asthma will be assessed through the use of daily symptom diaries and portable devices to measure breathing function.

Chemokines in the Pathogenesis of Asthma: Recent studies have identified that many asthmatic attacks, particularly for inner-city children, are triggered by exposure to cockroaches. It is not exposure to the entire cockroach, but only small fragments or residue, called allergens that are responsible for the allergic response. In response to such allergens, the body releases chemicals or mediators, which cause inflammation and thus an asthmatic episode. Targeted therapy has the potential to improve the treatment of asthma by identifying those mediators directly responsible for asthma. This research project will test the hypothesis that asthma-like pulmonary injury is mediated by the local production of mediators, which are called chemokines. Chemokines are small molecular weight proteins, which induce the movement and recruitment of inflammatory cells. The chemokines are powerful mediators with long-lasting and potent biological activities. The first specific aim of this project is to determine the acute and chronic pulmonary inflammation that develops after direct injection of the chemokines into the lung. The second aim is to develop a mouse model of asthma-like pulmonary inflammation in response to cockroach allergens. The third aim is to investigate the signals responsible for inducing the cells to make the chemokines. Finally, the last specific aim is to rigorously test the central hypothesis that chemokines are important in causing asthma.

The three projects of the MCECH will provide the following benefits to the Detroit communities involved as well as to the asthma research community:

- Identification of previously undiagnosed asthmatic children
- Provision of household materials, such as vacuum cleaners and clean bedding, aimed at reducing asthma triggers
- Education on potential asthma triggers and methods for reducing those triggers
- Assistance to families for negotiation with landlords regarding environmental factors in the home associated with asthma
- Referrals to families with asthma for available and affordable medical care
- The collection of detailed multiple daily measures of ambient and indoor air contaminants
- Identification of the underlying mechanisms of asthma and potential targets for further intervention.

Use of a Screening Questionnaire To Estimate Prevalence of Diagnosed and Undiagnosed Asthma Among Minority Children in Detroit

T.G. Robins, E.A. Parker, B.A. Israel, R.W. Brown, T.C. Lewis, and the CAAA Steering Committee
University of Michigan, Ann Arbor, MI, and community partners, Detroit, MI

A screening questionnaire designed to identify asthmatic children ages 6 to 11 years was developed, pilot tested, and mailed (n=7,498) or hand-delivered (n=2,182) to households in two geographic areas of Detroit with predominantly African-American and Hispanic populations as part of Community Action Against Asthma (CAAA). CAAA, a project of the Michigan Center for the Environment and Children s Health, is a randomized staggered-entry cohort study of a household-level and community-level intervention to reduce exposure to environmental triggers of childhood asthma. Among the 3,226 returned questionnaires, 1,671 (51.8%) were consistent with probable or known asthma of any severity and 425 (13.2%) with probable or known moderate to severe asthma based on National Asthma Education and Prevention Program diagnostic guidelines. Calculated minimum population-based estimates of prevalence for any asthma (17.3%) and moderate to severe asthma (4.4%) substantially exceed national averages. Among those with known or probable moderate to severe asthma, more than 30 percent had not been diagnosed by a physician, more than one-half were not taking daily asthma medication, and approximately one-quarter had not taken any physician-prescribed asthma medication in the past 12 months. Our data suggest that well-constructed screening surveys conducted with community support can identify large numbers of children with undiagnosed and/or undertreated moderate to severe asthma. These children are likely to particularly benefit from interventions to improve their asthma disease status.

Detroit School Children With Symptoms of Persistent Asthma Are Sensitized to Both Indoor and Outdoor Allergens

T.C. Lewis, T.G. Robins, E.A. Parker, R.W. Brown, W.R. Solomon, T.R. Trestyn, B.A. Israel, and the CAAA Steering Committee

University of Michigan, Ann Arbor, MI, and community partners, Detroit, MI

Environmental factors can be significant triggers of asthma. Community Action Against Asthma (CAAA) is a randomized staggered-cohort study of a household-level and community-level intervention to reduce exposure to environmental triggers of childhood asthma among African-Americans and Hispanics in Detroit. As part of this effort, we sought to describe the pattern of allergen sensitization in this population. We hypothesized that sensitization to indoor allergens would be more prevalent than sensitization to outdoor allergens in this inner-city cohort. Children ages 6-11 years with symptoms consistent with persistent asthma were identified via a screening questionnaire distributed to parents of elementary school students. After obtaining informed consent, baseline atopic status was assessed by skin prick test with a panel including indoor allergens (cockroach, dust mite, cat, dog, mouse, rat), outdoor allergens (ragweed, mixed grasses, *Alternaria*), and negative and positive controls. Wheals were scored on a scale of 0-4, with 2 or greater interpreted as a positive reaction. Of 510 children who met entrance criteria, to date 242 have successfully undergone skin testing. A total of 185 (76%) responded to at least one allergen; 120 (50%) responded to three or more allergens. Atopy to dust mite and mixed grasses were most common, followed by cat and ragweed. The proportion of children with positive response to each allergen is shown:

Indoor allergens:

Mite	Cat	Roach	Rat	Dog	Mouse
49%	38%	33%	17%	16%	13%

Outdoor allergens:

Grass	Ragweed	*Alternaria*
47%	38%	36%

These allergen sensitivity patterns have implications for exposure reduction strategies.

Evaluation of Murine Model of Asthma Induced by Exposure to House Dust Extract Containing High Levels of Cockroach

Jiyoun Kim, Andrew C. Merry, Jean A. Nemzek, and Daniel G. Remick
University of Michigan, Ann Arbor, MI

Asthma represents a serious health problem, particularly for inner city children. Recent studies have identified that many asthmatic attacks are triggered by exposure to indoor allergens including cockroach allergens. However, the mediators within the lung dictating the progression of disease have still not been fully defined. This study tested the hypothesis that asthma-like pulmonary injury may be induced by house dust containing high levels of cockroach allergens. Households (n=10) with asthmatic children were identified, and the house dust was collected and tested for cockroach allergens. The sample, which tested highest for cockroach allergens (Bla g1=65.8U/mL), was used for subsequent studies. BALB/c mice were immunized with serially diluted aqueous house dust extract and received two additional pulmonary challenges. Control mice received sterile PBS only. The inflammatory cells in bronchioalveolar lavage and peripheral blood and myloperoxidase activity in the lung were analyzed. Eosinophil counts and myloperoxidase activity were significantly increased in a dose-dependent manner by exposure to the house dust. A kinetics study was then performed using dilutions of the house dust extract with mice sacrificed every 12 hours after second pulmonary challenge. The inflammatory response reached the peak at 48 hours. In peripheral blood, there were no meaningful changes in the number of lymphocytes and red blood cells while the number of PMN was augmented in all three immunized groups. Thus, these mice were successfully sensitized and manifested asthma-like responses after house-dust extract challenge containing high levels of cockroach allergens. This murine model may be used for studying the mechanisms of indoor house dust-mediated asthma.

Measurements of Indoor, Outdoor, and Personal Exposure to Particulate Matter Among Asthmatic Children in Detroit, Michigan

Fuyuen Y. Yip, J. Timothy Dvonch, Thomas G. Robins, Edith Parker, Masako Morishita, and Gerald J. Keeler
University of Michigan, Ann Arbor, MI

The prevalence of childhood asthma in Detroit is particularly high, reflecting trends found elsewhere among urban populations. Reasons for this higher prevalence in urban populations are likely to include both socio-economic and environmental risk factors. In a number of studies, particulate matter (PM), generally limited to measurements in ambient air, has been associated with increases in childhood asthma prevalence and severity. As part of Community Action Against Asthma (CAAA), a multiyear community-based initiative for which data collection began in October, outdoor, indoor, and personal exposures to PM are characterized to assess their impact on childhood asthma.

To study the effects of PM exposure and the potential role of PM in the aggravation of childhood asthma, continuous $PM_{2.5}$ is characterized throughout the study period at two community monitoring sites using a TEOM. At the same sites, daily filters of $PM_{2.5}$ and PM_{10} are collected for 2 weeks each season over 2 years. During each seasonal assessment, $PM_{2.5}$ and PM_{10} samples also are being collected in the homes of 20 asthmatic children. Additionally, personal monitoring for PM_{10} is conducted for each child. This data provides a basis for assessment of indoor, outdoor, and personal levels of PM exposure; thereby contributing to a better understanding of the role PM may play on the exacerbation of childhood asthma.

Field Comparison of $PM_{2.5}$ TEOM and $PM_{2.5}$ Manual Filter-Based Measurement Methods in Urban Atmospheres

J. Timothy Dvonch, Frank J. Marsik, Gerald J. Keeler, Thomas G. Robins, Fuyuen Yip, and Masako Morishita
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As part of a community-based project, the effects of air pollutants and the role they play in exacerbating childhood asthma are being assessed in Detroit, MI. One specific aim of the project is to identify sources of air pollutants through chemical characterization of particulate matter (PM), particularly $PM_{2.5}$ and PM_{10}, to which the children are exposed. In addition to daily filter collection during seasonal intensive measurement campaigns (each 2 weeks in duration) at three ambient monitoring locations, continuous measurement of $PM_{2.5}$ is made at each location with a TEOM. Because the uncertainties in physical characterization of PM may vary between monitoring sites and between measurement techniques on a seasonal basis (due to large variations in ambient conditions), a direct field comparison of measurement techniques is needed in the airshed of interest.

For the first intensive measurement period in autumn 1999 (October 26,1999 November 8, 1999), daily $PM_{2.5}$ levels at the three sites ranged from 2-48 $\mu g/m^3$, with mean values ranging from 17-21 $\mu g/m^3$ across the three sites. A comparison of $PM_{2.5}$ TEOM measurements and $PM_{2.5}$ manual filter-based measurements was conducted at each monitoring site during this period. The $PM_{2.5}$ TEOM (with sharp cut cyclone, SCC) at the southwest Detroit site reported relatively lower values than those determined with the manual collection technique using a classical cyclone, with a regression slope of 0.88 (N=13). This relationship also was observed at the east Detroit site, as the regression slope was 0.77 (N=13). A comparison at the Ann Arbor monitoring site resulted in a regression slope of 1.02 (N=11). In contrast to the two Detroit TEOMs, the Ann Arbor TEOM utilizes a classical cyclone inlet instead of an SCC. Also in contrast to the two Detroit sites, the measurements from the Ann Arbor TEOM were not statistically different from those of the manual filter method, as they both utilized a classical cyclone inlet. The differences observed between the TEOM and manual method at the two Detroit sites is likely due to the sharper particle size cut incorporated by the SCC.

Further intercomparative sampling periods, by season through 2000 and 2001, in addition to chemical characterization of the PM will lend additional insight into the performance of these various PM measurement methods in an urban environment. In addition, these data will allow investigations into the sources of PM in the Detroit airshed regarding PM exposure assessment and the role of air pollutants in exacerbation of childhood asthma.

Index of Authors

Arbour, N.C., 48
Buckley, T.J., 39
Carter, A.B., 56
Chen, J., 18
Chen, W., 53, 54
Chrischilles, E., 45
Diaz-Sanchez, D., 5
Dvonch, J.T., 65
Eggleston, P., 35
Eskanazi, B., 29, 30
Faustman, E.M., 21
Furlong, C.E., 22
George, C.L.S., 46, 51
Gilliland, F., 6
Godina, R., 25
Gong, H., 3
Holland, N., 32
Hunninghake, G.W., 43
Israel, B., 59
Kim, J., 63
Kinney, P.L., 13
Kline, J.N., 49
Leidal, K., 52
Lewis, T.C., 62
Monick, M.M., 55
Moreland, J.G., 50
Perera, F., 9
Quinn T.J., 47
Robins, T.G., 61
Thompson, B., 23
Walters, D., 38
Whyatt, R.M., 12
Wolff, M.S., 17
Yip, F.Y., 64

APPENDIX A

Agenda

EPA/NIEHS/CDC Centers for Children's Environmental Health and Disease Prevention Research Annual Meeting

November 5-7, 2000
University of California–Berkeley
Clark–Kerr Center

Sunday, November 5 ***Evening Session***

4:00 p.m. **Registration and Poster Set-Up**

5:00 p.m. **Welcome and Introduction of Speaker**
Brenda Eskanazi, Ph.D.
Director, Center for the Health Assessment of the Mothers and Children of Salinas (CHAMACOS), University of California–Berkeley

Invited Speaker: "Socioeconomic Status and the Health Gradient: Mechanisms of Influence"
Nancy Adler, Ph.D.
Vice Chair of Psychiatry, *University of California–San Francisco*

5:45 p.m. **Open Discussion:** Opportunities for linking the Centers with other Government-sponsored programs and nonprofit organizations.

Chris Rosheim, *Agency for Toxic Substances and Disease Registry (ATSDR)*
Jerome Paulson, M.D., *Children's Environmental Health Network Soros Advocacy Fellow and Co-Director of ATSDR's Region 3 Pediatric Environmental Health Specialty Unit (PEHSU) at George Washington University*

6:30 p.m. **Poster Session**

9:00 p.m. **Adjourn**

Monday, November 6 — Morning Session: Center Updates and Scientific Highlights

8:30 a.m. **Special Guest**
Joy Carlson, M.P.H.
The California Project

CENTER PRESENTATIONS

9:15 a.m. University of Southern California
Columbia University

10:15 a.m. **Break**

10:30 a.m. Mount Sinai School of Medicine
University of Washington
University of California–Berkeley

12:00 noon **Lunch**

Monday, November 6 — Afternoon Session: Continued Updates and Roundtables

1:30 p.m. The Johns Hopkins University
University of Iowa
University of Michigan

3:00 p.m. **Break**

3:30 p.m. **Cross-Center Roundtables**

The objective of this working session is to share cross-Center concerns to address specific issues that pertain to data quality, biological sampling/storage, and the ethical considerations of human subjects research. Each group will be facilitated through the process of identifying common obstacles and opportunities and encouraged to design an action plan to be presented and discussed in the plenary session on Tuesday morning.

Roundtable 1: Lung Disease Etiology and Prevention Research

Roundtable 2: Pesticide Exposure and Toxicity Research

6:30 p.m. **Adjourn**

7:00 p.m. **Director's Dinner**

Tuesday, November 7 — Morning Session: Report Outs and Wrap-Up

9:00 a.m.	**Agenda Review/Repair**
9:05 a.m.	**Report of Roundtable 1 and Discussion**
10:00 a.m.	**Report of Roundtable 2 and Discussion**
11:00 a.m.	**Wrap-Up**
11:30 a.m.	**Adjourn**
12:00 noon	**Leave for CHAMACOS de Salinas**

APPENDIX B

Report From Pesticide Breakout Session

Topics Addressed

I. QA/QC and Inter-Center Collaboration
II. Human Subjects
III. Pesticide Metabolism
IV. Linkages With EPA and NIEHS Laboratories

I. ***QA/QC and Inter-Center Collaboration***

Questionnaires
- Sharing and incorporating into study instruments
- Validation

Central Laboratory To Assure Commonality
- Dana Barr s laboratory at CDC
- One center to provide analytical service to other centers
- National laboratory

Sharing Methods/Protocols
- Clem Furlong-2D digital assay

Taking Initiative

QA Plan
- Audit (www.epa.gov/ncerqa) announcements
- EPA to provide guidance

Information Database
- Samples
- Promote inter-Center interaction

Common Language/Terminology

Exposures and Genetics
- Protocol to work with poison control center to obtain urine samples

Recommendation
- Project officers to examine means for inter-Center comparison of outcome data

➢ ***Human Subjects***

HHS Training Requirement
- All researchers dealing with human subjects
- Many venues for training
    - *NIH (http://ohsr.od.nih.gov/cbt)
    - *University (classroom and Web-based)

Reporting Findings of Illegal Activities
- Must address with university lawyers

Consent Forms and Sample Banking

III. Pesticide Metabolism

Pesticide Uses and Use Patterns
- Patterns constantly changing
- Regulatory action

Mixtures
- Challenges
- Technological advancements

Metabolite Analysis in Relation to Exposure
- Creatinine and creatine adjustment
- Children and pregnant women
- Metabolic pathways

Use California PUR Data
- Assumption of exposures

Urinary Metabolites
- Three Centers to examine sharing samples
- Data presentation and reporting

IV. Linkages With EPA and NIEHS Laboratories

Agricultural Health Study
- Desire for more information

National Children s Longitudinal Cohort Study
- Desire for more information

Two-Way Interaction
- Centers can offer input on study design and implementation

Pesticide Breakout Session

List of Participants

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APPENDIX C

EPA/NIEHS/CDC Centers for Children s Environmental Health and Disease Prevention Research Annual Meeting

List of Participants

Invited Guests

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