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RESEARCH ON ENVIRONMENTAL TOXINS AND PEOPLE WITH DISABILITIES

ASSESSMENTS

Development and validation of a test battery to assess subtle neurodevelopmental differences in children.

Davidson PW, Weiss B, Beck C, Cory-Slechta DA, Orlando M, Loiselle D, Young EC, Sloane-Reeves J, Myers GJ. University of Rochester School of Medicine, Rochester, NY, USA. phil_davidson@urmc.rochester.edu Neurotoxicology. 2006 Dec;27(6):951-69. Epub 2006 Apr 28.

There is increasing concern over the impact of low-dose exposures to environmental chemicals on children's neurobehavioral function. To determine subtle alterations in children's function, it is necessary to move beyond global measures such as IQ and employ tests that can detect small, subtle neurodevelopmental effects across a broad array of behavioral domains. We investigated the sensitivity and specificity of a battery of 63 neurodevelopmental tests or tasks designed to detect outcomes representing the type of subtle neurodevelopmental deficits caused by exposure to neurotoxicants in school-aged children. We studied Neonatal Intensive Care Unit (NICU) graduates, a population known to be at risk for both major and mild anomalies in perception, motor functioning, learning, memory and cognition. This population served as a surrogate to evaluate the capacity of these tests and tasks to predict such deficits. The subjects' histories of previous exposures to any environmental neurotoxicants was not ascertainable, but exposures to elevated levels was not suspected. Over one-third of the 63 measures proved capable of detecting pre-diagnosed lower IQ, the presence of a learning disability (LD) or a neonatal risk profile with at least 70% sensitivity and specificity. Some tests were differentially sensitive and specific, depending upon the presence or absence of one or more of several covariates such as gender, age, hearing status, or familiarity with computers. Tests were also eliminated from the battery if they were affected by too many covariates. We propose calling the final battery of tests that are specific and sensitive to subtle neurodevelopmental changes the Rochester test battery (RTB). Further studies are needed to confirm the capability of the RTB to detect subtle changes associated with neurotoxic exposures.

AUTISM SPECTRUM DISORDERS

Autism and environmental influences: review and commentary.

Bello SC. Developmental Pediatrics, PLLC, Latham, New York 12110, USA. Rev Environ Health. 2007 Apr-Jun;22(2):139-56.

Progress has been slow in identifying pre- and post-natal environmental exposures that might trigger the features that characterize autism. During the past thirty years, research in the field of autism has been conducted in a setting in which diagnostic criteria for this condition have changed and broadened, and differences of opinion regarding diagnostic issues and diagnostic terminology continue. The documented prevalence of all forms of autism has increased steadily during this time, suggesting one or more environmental contributors. Not established, however, is whether an increasing incidence of autism is responsible for increasing prevalence. The increase in documented prevalence could result from expanding and changing case definitions and increased reporting due to increased awareness on the part of professionals who work with children and by the public. This review provides a background for the evolving story of autism and describes the research on the relation between autism and the environment, with a particular focus on some of the more recently proposed environmental triggers. Critical analysis of this body of scientific research in a historical framework helps to explain the often controversial nature of the proposed relations between autism and environmental factors, as well as to rationalize some of the pitfalls in research design and in the often questionable interpretation of data so obtained.

Autism and the environment: challenges and opportunities for research.

Altevoigt BM, Hanson SL, Leshner AI. Institute of Medicine, Forum on Neuroscience and Nervous System Disorders, 500 Fifth St, NW, Washington, DC 20001, USA.

baltevoigt@nas.edu Pediatrics. 2008 Jun;121(6):1225-9.

Autism spectrum disorder is a complex developmental disorder that dramatically affects the lives of patients and their families and the broader community. The causes of autism are unknown; however, evidence increasingly suggests that a complex interplay among environmental stressors, genetic mutations, and other biological factors likely plays a significant role in the development and/or progression of autism spectrum disorder. On April 18 and 19, 2007, the Institute of Medicine's Forum on Neuroscience and Nervous System Disorders hosted a workshop to provide a venue to bring together scientists; major sponsors of autism-related research; and members of the autism patient, family, and advocacy community to discuss the most promising and urgent scientific questions and opportunities. Broad participation by the autism community enriched the meeting significantly by contributing a valuable and personal perspective that is often missing from scientific meetings. It also began a much improved public-private partnership in which all stakeholders are represented. On the basis of the presentations and the discussions that followed, an array of important scientific opportunities were identified in 5 general categories: (1) opportunities to advance clinical research; (2) opportunities to enhance epidemiologic studies; (3) opportunities to improve the understanding of autism's pathology and etiology; (4) tools and infrastructure needs; and (5) opportunities for public-private partnerships. This workshop demonstrated that full public engagement can greatly enhance activities such as this workshop and its outcomes. Furthermore, we expect that this listing of scientific challenges, needs, and opportunities will help to frame a more comprehensive research agenda.

The CHARGE study: an epidemiologic investigation of genetic and environmental factors contributing to autism.

Hertz-Picciotto I, Croen LA, Hansen R, Jones CR, van de Water J, Pessah IN. Division of Epidemiology, Department of Public Health Sciences, School of Medicine, and Medical Investigations of Neurodevelopmental Disorders (MIND) Institute, University of California-Davis, Davis, California, USA. ihp@ucdavis.edu Environ Health Perspect. 2006 Jul;114(7):1119-25.

Causes and contributing factors for autism are poorly understood. Evidence suggests that prevalence is rising, but the extent to which diagnostic changes and improvements in ascertainment contribute to this increase is unclear. Both genetic and environmental factors are likely to contribute etiologically. Evidence from twin, family, and genetic studies supports a role for an inherited predisposition to the development of autism. Nonetheless, clinical, neuroanatomic, neurophysiologic, and epidemiologic studies suggest that gene penetrance and expression may be influenced, in some cases strongly, by the prenatal and early postnatal environmental milieu. Sporadic studies link autism to xenobiotic chemicals and/or viruses, but few methodologically rigorous investigations have been undertaken. In light of major gaps in understanding of autism, a large case-control investigation of underlying environmental and genetic causes for autism and triggers of regression has been launched. The CHARGE (Childhood Autism Risks from Genetics and Environment) study will address a wide spectrum of chemical and biologic exposures, susceptibility factors, and their interactions. Phenotypic variation among children with autism will be explored, as will similarities and differences with developmental delay. The CHARGE study infrastructure includes detailed developmental assessments, medical information, questionnaire data, and biologic specimens. The CHARGE study is linked to University of California-Davis Center for Children's Environmental Health laboratories in immunology, xenobiotic measurement, cell signaling, genomics, and proteomics. The goals, study design, and data collection protocols are described, as well as preliminary demographic data on study participants and on diagnoses of those recruited through the California Department of Developmental Services Regional Center System.

Identifying environmental contributions to autism: provocative clues and false leads.

Lawler CP, Croen LA, Grether JK, Van de Water J. Division of Extramural Research and Training, National Institute of Environmental Health Sciences, PO Box 1123, MD EC-23, Research Triangle Park, NC 27709, USA. lawler@niehs.nih.gov Ment Retard Dev Disabil Res Rev. 2004;10(4):292-302.

The potential role of environmental factors in autism spectrum disorders (ASD) is an area of emerging interest within the public and scientific communities. The high degree of heritability of ASD suggests that environmental influences are likely to operate through their interaction with genetic susceptibility during vulnerable periods of development. Evaluation of the plausibility of specific neurotoxicants as etiological agents in ASD should be guided by toxicological principles, including dose-effect dependency and pharmacokinetic parameters. Clinical and epidemiological investigations require the use of sufficiently powered study designs with appropriate control groups and unbiased case ascertainment and exposure assessment. Although much of the existing data that have been used to implicate environmental agents in ASD

are limited by methodological shortcomings, a number of efforts are underway that will allow more rigorous evaluation of the role of environmental exposures in the etiology and/or phenotypic expression of the disorder. Surveillance systems are now in place that will provide reliable prevalence estimates going forward in time. Anticipated discoveries in genetics, brain pathology, and the molecular/cellular basis of functional impairment in ASD are likely to provide new opportunities to explore environmental aspects of this disorder.

CHILDHOOD EXPOSURE

In-home toxic chemical exposures and children with intellectual and developmental disabilities.

Graff JC, Murphy L, Ekvall S, Gagnon M. Boling Center for Developmental Disabilities, College of Nursing, University of Tennessee Health Science Center, Memphis, USA. Pediatr Nurs. 2006 Nov-Dec;32(6):596-603.

Despite the focus on preventing toxic chemical exposures during pregnancy, the perinatal period, and childhood, health professionals have given little attention to the risks and effects of toxic chemical exposures on children with intellectual and developmental disabilities (DD). Children with DD may be at higher risk due to behaviors that persist past a developmentally appropriate age, communication skills, motor skills, nutrition issues, and health problems related to DD. This article examines exposure of children to lead, mercury, and environmental tobacco smoke, three toxicants known to affect children's health and development. The authors identify sources of these toxicants, examine research documenting their effects on children, consider strategies to prevent and manage exposure, identify characteristics and behaviors placing children with DD at increased risk of exposure, and discuss implications for health providers.

Lessons learned for the National Children's Study from the National Institute of Environmental Health Sciences/U.S. Environmental Protection Agency Centers for Children's Environmental Health and Disease Prevention Research.

Kimmel CA, Collman GW, Fields N, Eskenazi B. National Children's Study Interagency Coordinating Committee, National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Washington, DC, USA. Environ Health Perspect. 2005 Oct;113(10):1414-8.

This mini-monograph was developed to highlight the experiences of the National Institute of Environmental Health Sciences (NIEHS)/U.S. Environmental Protection Agency (EPA) Centers for Children's Environmental Health and Disease Prevention Research, focusing particularly on several areas of interest for the National Children's Study. These include general methodologic issues for conducting longitudinal birth cohort studies and community-based participatory research and for measuring air pollution exposures, pesticide exposures, asthma, and neurobehavioral toxicity. Rather than a detailed description of the studies in each of the centers, this series of articles is intended to provide information on the practicalities of conducting such intensive studies and the lessons learned. This explication of lessons learned provides an outstanding opportunity for the planners of the National Children's Study to draw on past experiences

that provide information on what has and has not worked when studying diverse multiracial and multiethnic groups of children with unique urban and rural exposures. The Children's Centers have addressed and overcome many hurdles in their efforts to understand the link between environmental exposures and health outcomes as well as interactions between exposures and a variety of social and cultural factors. Some of the major lessons learned include the critical importance of long-term studies for assessing the full range of developmental consequences of environmental exposures, recognition of the unique challenges presented at different life stages for both outcome and exposure measurement, and the importance of ethical issues that must be dealt with in a changing medical and legal environment. It is hoped that these articles will be of value to others who are embarking on studies of children's environmental health.

The National Children's Study: a 21-year prospective study of 100,000 American children.

Landrigan PJ, Trasande L, Thorpe LE, Gwynn C, Lioy PJ, D'Alton ME, Lipkind HS, Swanson J, Wadhwa PD, Clark EB, Rauh VA, Perera FP, Susser E. Center for Children's Health and the Environment, Department of Community and Preventive Medicine, New York, New York, USA. phil.landrigan@mssm.edu Pediatrics. 2006 Nov;118(5):2173-86.

Prospective, multiyear epidemiologic studies have proven to be highly effective in discovering preventable risk factors for chronic disease. Investigations such as the Framingham Heart Study have produced blueprints for disease prevention and saved millions of lives and billions of dollars. To discover preventable environmental risk factors for disease in children, the US Congress directed the National Institute of Child Health and Human Development, through the Children's Health Act of 2000, to conduct the National Children's Study. The National Children's Study is hypothesis-driven and will seek information on environmental risks and individual susceptibility factors for asthma, birth defects, dyslexia, attention-deficit/hyperactivity disorder, autism, schizophrenia, and obesity, as well as for adverse birth outcomes. It will be conducted in a nationally representative, prospective cohort of 100,000 US-born children. Children will be followed from conception to 21 years of age. Environmental exposures (chemical, physical, biological, and psychosocial) will be assessed repeatedly during pregnancy and throughout childhood in children's homes, schools, and communities. Chemical assays will be performed by the Centers for Disease Control and Prevention, and banks of biological and environmental samples will be established for future analyses. Genetic material will be collected on each mother and child and banked to permit study of gene-environment interactions. Recruitment is scheduled to begin in 2007 at 7 Vanguard Sites and will extend to 105 sites across the United States. The National Children's Study will generate multiple satellite studies that explore methodologic issues, etiologic questions, and potential interventions. It will provide training for the next generation of researchers and practitioners in environmental pediatrics and will link to planned and ongoing prospective birth cohort studies in other nations. Data from the National Children's Study will guide development of a comprehensive blueprint for disease prevention in children.

Principles and practices of neurodevelopmental assessment in children: lessons

learned from the Centers for Children's Environmental Health and Disease Prevention Research.

Dietrich KN, Eskenazi B, Schantz S, Yolton K, Rauh VA, Johnson CB, Alkon A, Canfield RL, Pessah IN, Berman RF. University of Cincinnati College of Medicine, Division of Epidemiology and Biostatistics, Department of Environmental Health, and the Cincinnati Children's Environmental Health Center, Cincinnati, Ohio, USA. Environ Health Perspect. 2005 Oct;113(10):1437-46.

Principles and practices of pediatric neurotoxicology are reviewed here with the purpose of guiding the design and execution of the planned National Children's Study. The developing human central nervous system is the target organ most vulnerable to environmental chemicals. An investigation of the effects of environmental exposures on child development is a complex endeavor that requires consideration of numerous critical factors pertinent to a study's concept, design, and execution. These include the timing of neurodevelopmental assessment, matters of biologic plausibility, site, child and population factors, data quality assurance and control, the selection of appropriate domains and measures of neurobehavior, and data safety and monitoring. Here we summarize instruments for the assessment of the neonate, infant, and child that are being employed in the Centers for Children's Environmental Health and Disease Prevention Research, sponsored by the National Institute of Environmental Health Sciences and the U.S. Environmental Protection Agency, discuss neural and neurobiologic measures of development, and consider the promises of gene-environment studies. The vulnerability of the human central nervous system to environmental chemicals has been well established, but the contribution these exposures may make to problems such as attention deficit disorder, conduct problems, pervasive developmental disorder, or autism spectrum disorder remain uncertain. Large-scale studies such as the National Children's Study may provide some important clues. The human neurodevelopmental phenotype will be most clearly represented in models that include environmental chemical exposures, the social milieu, and complex human genetic characteristics that we are just beginning to understand.

DENTAL AMALGAM

A dose-effect analysis of children's exposure to dental amalgam and neuropsychological function: the New England Children's Amalgam Trial.

Bellinger DC, Trachtenberg F, Daniel D, Zhang A, Tavares MA, McKinlay S. Children's Hospital, Boston, MA, USA. J Am Dent Assoc. 2007 Sep;138(9):1210-6. Comment in: J Am Dent Assoc. 2007 Dec;138(12):1536-7; author reply 1537.

BACKGROUND: The New England Children's Amalgam Trial (NECAT) was a five-year randomized trial of 534 6- to 10-year-old children that compared the neuropsychological outcomes of those whose caries were restored using dental amalgam with the outcomes of those whose caries were restored using mercury-free resin-based composite. The primary intention-to-treat analyses did not reveal significant differences between the treatment groups on the primary or secondary outcomes of the administered psychological tests: Full-Scale IQ score on the Wechsler Intelligence Scale for Children-Third Edition, General Memory Index of the Wide Range Assessment of Memory and

Learning, and Visual-Motor Composite of the Wide Range Assessment of Visual Motor Abilities.

METHODS: To determine whether treatment group assignment, a dichotomous measure of exposure, was sufficiently sensitive to detect associations between mercury exposure and these outcomes, the authors conducted analyses to evaluate the associations between the primary and secondary outcomes and two continuously distributed indexes of potential exposure, surface-years of amalgam and urinary mercury excretion.

RESULTS: Neither index of mercury exposure was significantly associated with any of the three outcomes.

CONCLUSIONS: The authors found no evidence that exposure to mercury from dental amalgam was associated with any adverse neuropsychological effects over the five-year period after placement of amalgam restorations.

CLINICAL IMPLICATIONS: Analyses of the outcomes of the NECAT study indicate that use of dental amalgam was not associated with an increase in children's risk of experiencing neuropsychological dysfunction.

LEAD

Blood lead concentrations < 10 microg/d: and child intelligence at 6 years of age.

Jusko TA, Henderson CR, Lanphear BP, Cory-Slechta DA, Parsons PJ, Canfield RL.

Department of Epidemiology, School of Public Health and Community Medicine, University of Washington, Seattle, WA, USA. Environ Health Perspect. 2008

Feb;116(2):243-8. Comment in: Environ Health Perspect. 2008 Feb;116(2):A60-1.

BACKGROUND: Few studies provide data directly relevant to the question of whether blood lead concentrations < 10 microg/dL adversely affect children's cognitive function.

OBJECTIVE: We examined the association between blood lead concentrations assessed throughout early childhood and children's IQ at 6 years of age.

METHODS: Children were followed from 6 months to 6 years of age, with determination of blood lead concentrations at 6, 12, 18, and 24 months, and 3, 4, 5, and 6 years of age. At 6 years of age, intelligence was assessed in 194 children using the Wechsler Preschool and Primary Scale of Intelligence-Revised. We used general linear and semiparametric models to estimate and test the association between blood lead concentration and IQ.

RESULTS: After adjustment for maternal IQ, HOME scale scores, and other potential confounding factors, lifetime average blood lead concentration (mean = 7.2 microg/dL; median = 6.2 microg/dL) was inversely associated with Full-Scale IQ ($p = 0.006$) and Performance IQ scores ($p = 0.002$). Compared with children who had lifetime average blood lead concentrations < 5 microg/dL, children with lifetime average concentrations between 5 and 9.9 microg/dL scored 4.9 points lower on Full-Scale IQ (91.3 vs. 86.4, $p = 0.03$). Nonlinear modeling of the peak blood lead concentration revealed an inverse association ($p = 0.003$) between peak blood lead levels and Full-Scale IQ down to 2.1 microg/dL, the lowest observed peak blood lead concentration in our study.

CONCLUSIONS: Evidence from this cohort indicates that children's intellectual functioning at 6 years of age is impaired by blood lead concentrations well below 10 microg/dL, the Centers for Disease Control and Prevention definition of an elevated blood lead level.

Decreased brain volume in adults with childhood lead exposure.

Cecil KM, Brubaker CJ, Adler CM, Dietrich KN, Altaye M, Egelhoff JC, Wessel S, Elangovan I, Hornung R, Jarvis K, Lanphear BP. Cincinnati Children's Environmental Health Center, Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio, United States of America. kim.cecil@cchmc.org PLoS Med. 2008 May 27;5(5):e112. Comment in: PLoS Med. 2008 May 27;5(5):e115.

BACKGROUND: Although environmental lead exposure is associated with significant deficits in cognition, executive functions, social behaviors, and motor abilities, the neuroanatomical basis for these impairments remains poorly understood. In this study, we examined the relationship between childhood lead exposure and adult brain volume using magnetic resonance imaging (MRI). We also explored how volume changes correlate with historic neuropsychological assessments.

METHODS AND FINDINGS: Volumetric analyses of whole brain MRI data revealed significant decreases in brain volume associated with childhood blood lead concentrations. Using conservative, minimum contiguous cluster size and statistical criteria (700 voxels, unadjusted $p < 0.001$), approximately 1.2% of the total gray matter was significantly and inversely associated with mean childhood blood lead concentration. The most affected regions included frontal gray matter, specifically the anterior cingulate cortex (ACC). Areas of lead-associated gray matter volume loss were much larger and more significant in men than women. We found that fine motor factor scores positively correlated with gray matter volume in the cerebellar hemispheres; adding blood lead concentrations as a variable to the model attenuated this correlation.

CONCLUSIONS: Childhood lead exposure is associated with region-specific reductions in adult gray matter volume. Affected regions include the portions of the prefrontal cortex and ACC responsible for executive functions, mood regulation, and decision-making. These neuroanatomical findings were more pronounced for males, suggesting that lead-related atrophic changes have a disparate impact across sexes. This analysis suggests that adverse cognitive and behavioral outcomes may be related to lead's effect on brain development producing persistent alterations in structure. Using a simple model, we found that blood lead concentration mediates brain volume and fine motor function.

Exposures to environmental toxicants and attention deficit hyperactivity disorder in U.S. children.

Braun JM, Kahn RS, Froehlich T, Auinger P, Lanphear BP. College of Nursing, University of Wisconsin-Milwaukee, Milwaukee, Wisconsin, USA. Environ Health Perspect. 2006 Dec;114(12):1904-9. Comment in: Environ Health Perspect. 2007 Aug;115(8):A398-9; author reply A399. Environ Health Perspect. 2007 Aug;115(8):A398; author reply A399.

OBJECTIVE: The purpose of this study was to examine the association of exposures to tobacco smoke and environmental lead with attention deficit hyperactivity disorder (ADHD).

METHODS: Data were obtained from the National Health and Nutrition Examination Survey 1999-2002. Prenatal and postnatal tobacco exposure was based on parent report; lead exposure was measured using blood lead concentration. ADHD was defined

as having current stimulant medication use and parent report of ADHD diagnosed by a doctor or health professional.

RESULTS: Of 4,704 children 4-15 years of age, 4.2% were reported to have ADHD and stimulant medication use, equivalent to 1.8 million children in the United States. In multivariable analysis, prenatal tobacco exposure [odds ratio (OR) = 2.5; 95% confidence interval (CI), 1.2-5.2] and higher blood lead concentration (first vs. fifth quintile, OR = 4.1; 95% CI, 1.2-14.0) were significantly associated with ADHD. Postnatal tobacco smoke exposure was not associated with ADHD (OR = 0.6; 95% CI, 0.3-1.3; $p = 0.22$). If causally linked, these data suggest that prenatal tobacco exposure accounts for 270,000 excess cases of ADHD, and lead exposure accounts for 290,000 excess cases of ADHD in U.S. children.

CONCLUSIONS: We conclude that exposure to prenatal tobacco and environmental lead are risk factors for ADHD in U.S. children.

Impaired neuropsychological functioning in lead-exposed children.

Canfield RL, Gendle MH, Cory-Slechta DA. Division of Nutritional Sciences, College of Human Ecology, Cornell University, Savage Hall, Ithaca, NY 14853, USA. rlc@cornell.edu Dev Neuropsychol. 2004;26(1):513-40.

Neuropsychological functions were assessed in 174 children participating in a longitudinal study of low-level lead exposure. At age 5 1/2 years, children were administered the Working Memory and Planning Battery of the Cambridge Neuropsychological Testing Automated Battery. Measures of sociodemographic characteristics of the family, prenatal and perinatal risk, quality of caregiving and crowding in the home, and maternal and child intelligence were used as covariates to test the hypothesis that children with higher lifetime average blood lead concentrations would perform more poorly on tests of working memory, attentional flexibility, and planning and problem solving. The lifetime average blood lead level in this sample was 7.2 micrograms per deciliter (mug/dL; range: 0-20 mug/dL). Children with greater exposure performed more poorly on tests of executive processes. In both bivariate and multivariate analyses, children with higher lifetime average blood lead concentrations showed impaired performance on the tests of spatial working memory, spatial memory span, intradimensional and extradimensional shifts, and an analog of the Tower of London task. Many of the significant associations remained after controlling for children's intelligence test scores, in addition to the other covariates. These findings indicate that the effects of pediatric lead exposure are not restricted to global indexes of general intellectual functioning, and executive processes may be at particular risk of lead-induced neurotoxicity.

Intellectual impairment in children with blood lead concentrations below 10 microg per deciliter.

Canfield RL, Henderson CR Jr, Cory-Slechta DA, Cox C, Jusko TA, Lanphear BP. Division of Nutritional Sciences, College of Human Ecology, Cornell University, Ithaca, NY 14853, USA. rlc5@cornell.edu N Engl J Med. 2003 Apr 17;348(16):1517-26. Comment in: J Pediatr. 2003 Nov;143(5):687-8. N Engl J Med. 2003 Apr 17;348(16):1515-6. N Engl J Med. 2003 Jul 31;349(5):500-2; author reply 500-2.

BACKGROUND: Despite dramatic declines in children's blood lead concentrations and a lowering of the Centers for Disease Control and Prevention's level of concern to 10 microg per deciliter (0.483 micromol per liter), little is known about children's neurobehavioral functioning at lead concentrations below this level.

METHODS: We measured blood lead concentrations in 172 children at 6, 12, 18, 24, 36, 48, and 60 months of age and administered the Stanford-Binet Intelligence Scale at the ages of 3 and 5 years. The relation between IQ and blood lead concentration was estimated with the use of linear and nonlinear mixed models, with adjustment for maternal IQ, quality of the home environment, and other potential confounders.

RESULTS: The blood lead concentration was inversely and significantly associated with IQ. In the linear model, each increase of 10 microg per deciliter in the lifetime average blood lead concentration was associated with a 4.6-point decrease in IQ ($P=0.004$), whereas for the subsample of 101 children whose maximal lead concentrations remained below 10 microg per deciliter, the change in IQ associated with a given change in lead concentration was greater. When estimated in a nonlinear model with the full sample, IQ declined by 7.4 points as lifetime average blood lead concentrations increased from 1 to 10 microg per deciliter.

CONCLUSIONS: Blood lead concentrations, even those below 10 microg per deciliter, are inversely associated with children's IQ scores at three and five years of age, and associated declines in IQ are greater at these concentrations than at higher concentrations. These findings suggest that more U.S. children may be adversely affected by environmental lead than previously estimated.

Low-level environmental lead exposure and children's intellectual function: an International pooled analysis.

Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger DC, Canfield RL, Dietrich KN, Bornschein R, Greene T, Rothenberg SJ, Needleman HL, Schnaas L, Wasserman G, Graziano J, Roberts R. Cincinnati Children's Hospital Medical Center, Cincinnati, Ohio 45229-3039, USA. bruce.lanphear@cchmc.org Environ Health Perspect. 2005 Jul;113(7):894-9. Comment in: Environ Health Perspect. 2006 Feb;114(2):A85-6; author reply A86-7.

Lead is a confirmed neurotoxin, but questions remain about lead-associated intellectual deficits at blood lead levels < 10 microg/dL and whether lower exposures are, for a given change in exposure, associated with greater deficits. The objective of this study was to examine the association of intelligence test scores and blood lead concentration, especially for children who had maximal measured blood lead levels < 10 microg/dL. We examined data collected from 1,333 children who participated in seven international population-based longitudinal cohort studies, followed from birth or infancy until 5-10 years of age. The full-scale IQ score was the primary outcome measure. The geometric mean blood lead concentration of the children peaked at 17.8 microg/dL and declined to 9.4 microg/dL by 5-7 years of age; 244 (18%) children had a maximal blood lead concentration < 10 microg/dL, and 103 (8%) had a maximal blood lead concentration < 7.5 microg/dL. After adjustment for covariates, we found an inverse relationship between blood lead concentration and IQ score. Using a log-linear model, we found a 6.9 IQ point decrement [95% confidence interval (CI), 4.2-9.4] associated with an increase in concurrent blood lead levels from 2.4 to 30 microg/dL. The estimated IQ point decrements associated with an increase in blood lead from 2.4 to 10 microg/dL, 10 to 20

microg/dL, and 20 to 30 microg/dL were 3.9 (95% CI, 2.4-5.3), 1.9 (95% CI, 1.2-2.6), and 1.1 (95% CI, 0.7-1.5), respectively. For a given increase in blood lead, the lead-associated intellectual decrement for children with a maximal blood lead level < 7.5 microg/dL was significantly greater than that observed for those with a maximal blood lead level > or = 7.5 microg/dL ($p = 0.015$). We conclude that environmental lead exposure in children who have maximal blood lead levels < 7.5 microg/dL is associated with intellectual deficits.

Low-level lead exposure, executive functioning, and learning in early childhood.

Canfield RL, Kreher DA, Cornwell C, Henderson CR Jr. Division of Nutritional Sciences, Cornell University, Ithaca, NY 14850, USA. rlc5@cornell.edu Child Neuropsychol. 2003 Mar;9(1):35-53.

The current paper presents evidence relating low-level lead exposure to impaired executive functioning in young children. Using the Shape School task, we assessed focused attention, attention switching, working memory, and the ability to inhibit automatic responses in a cohort of 170 children. Participants performed the Shape School task at both 48 and 54 months of age; the mean blood lead level was 6.49 microg/dl at 48 months. After controlling for a wide range of sociodemographic, prenatal, and perinatal variables, blood lead level was negatively associated with children's focused attention while performing the tasks, efficiency at naming colors, and inhibition of automatic responding. In addition, children with higher blood lead levels completed fewer phases of the task and knew fewer color and shape names. There was no association between blood lead and performance on the most difficult tasks, those requiring attention switching or the combination of inhibition and switching. Children's IQ scores were strongly associated with blood lead and Shape School performance, and when entered as a covariate, only color knowledge and the number of tasks completed remained significant. Results provide only weak support for impaired executive functioning, but the deficits in color knowledge may indicate a primary sensory deficit or difficulty with forming conditional associations, both implicating disruptions in dopamine system function.

Metal concentrations in rural topsoil in South Carolina: potential for human health impact.

Aelion CM, Davis HT, McDermott S, Lawson AB. University of South Carolina, Department of Environmental Health Sciences, 921 Assembly Street, Columbia, SC 29208, United States. aelionm@sc.edu Sci Total Environ. 2008 Sep 1;402(2-3):149-56. Epub 2008 Jun 6.

Rural areas are often considered to have relatively uncontaminated soils; however few studies have measured metals in surface soil from low population areas. Many metals, i.e., arsenic (As), lead (Pb), and mercury (Hg), have well-documented negative neurological effects, and the developing fetus and young children are particularly at risk. Using a Medicaid database, two areas were identified: one with no increased prevalence of mental retardation and developmental delay (MR/DD) (Strip 1) and one with significantly higher prevalence of MR/DD (Strip 2) in children compared to the state-wide average. These areas were mapped and surface soil samples were collected from 0-5 cm depths from nodes of a uniform grid laid out across the sampling areas. Samples

were analyzed for As, barium (Ba), beryllium (Be), chromium (Cr), copper (Cu), Pb, manganese (Mn), nickel (Ni), and Hg. Inverse distance weighting (IDW) was used to estimate concentrations throughout each strip area, and a principal component analysis (PCA) was used to identify common sources. All metal concentrations in Strip 2, the MR/DD cluster area, were significantly greater than those in Strip 1 and similar to those found in more urban and highly agricultural areas. Both Strips 1 and 2 had a high number of significant correlations between metals (33 for Strip 1 and 25 for Strip 2), suggesting possible similar natural or anthropogenic sources which was corroborated by PCA. While exposures were not assessed and direct causation between environmental soil metal concentrations and MR/DD cannot be concluded, the high metal concentrations in areas with an elevated prevalence of MR/DD warrants further consideration.

Neuropsychological function in children with blood lead levels <10 microg/dL.

Surkan PJ, Zhang A, Trachtenberg F, Daniel DB, McKinlay S, Bellinger DC.

Department of Environmental Health, Harvard School of Public Health, Landmark Building, 4th Floor, 401 Park Drive, Boston, MA 02115, USA. Neurotoxicology. 2007 Nov;28(6):1170-7. Epub 2007 Jul 25.

Clear adverse effects of blood lead levels ≥ 10 microg/dL have been documented in children. Given that the majority of US children have levels below 10 microg/dL, clarification of adverse effects below this cutoff value is needed. Our study evaluated the associations between blood lead levels <10 microg/dL and a broad spectrum of children's cognitive abilities. Data were analyzed from 534 children aged 6-10, enrolled in the New England Children's Amalgam Trial (NECAT) from the urban area of Boston, Massachusetts and rural Farmington, Maine. Adjusting for covariates (age, race, socioeconomic status, and primary caregiver IQ), children with 5-10 microg/dL had 5.0 (S.D. 2.3) points lower IQ scores compared to children with blood lead levels of 1-2 microg/dL ($p=0.03$). Verbal IQ was more negatively affected than performance IQ, with the most prominent decrement occurring in children's vocabulary. Wechsler Individual Achievement Test scores were strongly negatively associated with blood lead levels of 5-10 microg/dL. In adjusted analyses, children with levels of 5-10 microg/dL scored 7.8 (S.D. 2.4) and 6.9 (S.D. 2.2) points lower on reading and math composite scores, respectively, compared to children with levels of 1-2 microg/dL ($p<0.01$). Finally, levels of 5-10 microg/dL were associated with decreased attention and working memory. Other than associations of lead exposure with achievement, which even persisted after adjustment for child IQ, the most pronounced deficits were in the areas of spatial attention and executive function. Overall, our analyses support prior research that children's blood levels <10 microg/dL are related to compromised cognition and highlight that these may especially be related to academic achievement.

Use of a general toxicity test to predict heavy metal concentrations in residential soils.

Aelion CM, Davis HT. Department of Environmental Health Sciences, Room 401, University of South Carolina, 921 Assembly Street, Columbia, SC 29208, USA. aelionm@sc.edu Chemosphere. 2007 Mar;67(5):1043-9. Epub 2006 Nov 30.

Significant clusters of developmental delay and mental retardation (DD/MR) were identified in children born in South Carolina. Although it is difficult to identify one factor that causes DD/MR, environmental insult including exposure of pregnant women to heavy metals can induce DD/MR in their children. Because it is expensive to measure the concentrations of individual metals in large numbers of environmental samples, the general Microtox toxicity test was used to identify highly toxic soil samples. Approximately 100 soil samples were collected from residential areas and analyzed to determine an effective concentration (EC(50)) of soil required to inhibit 50% light emission of the luminescent bacterial test organism (*Vibrio fischeri*). The EC(50) values were then transformed to relative toxicity units (RTU). A subset of 56 high and low toxicity soil samples was then analyzed by inductively coupled plasma-atomic emission spectrometry (EPA method 6010) for arsenic, lead, and chromium, which are known neurotoxins. The highest measured arsenic concentration was 30 times higher than the South Carolina residential soil limit. Significant correlations were found between the RTU and soil arsenic and chromium concentrations. Microtox also identified some low arsenic and chromium samples as toxic, presumably because additional unidentified toxicants were present in the soil. In general, however, the Microtox test was effective in identifying soils with elevated concentrations of arsenic and chromium, even in residential neighborhoods where limited soil toxicity was expected.

LIFE SPAN

Environmental Health and Developmental Disabilities: A Life Span Approach.

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Prenatal and childhood environmental exposures are an underrecognized primary cause of intellectual and other developmental disabilities. In addition, individuals with established disabilities are vulnerable to further harm from subsequent environmental exposures. In individuals with communicative impairment or limited ability to independently escape from hazards, these subsequent exposures, too, may occur undetected or untreated. This article introduces the subject of environmental health and developmental disabilities throughout the life span. In particular, we focus on ways that families, communities, and health professionals can prevent both primary and secondary disabilities through better awareness of common environmental health issues.

MERCURY

Applying cost analyses to drive policy that protects children: mercury as a case study.

Trasande L, Schechter C, Haynes KA, Landrigan PJ. Center for Children's Health and the Environment, Department of Community and Preventive Medicine, Mount Sinai School of Medicine, New York, NY 10029, USA. leo.trasande@mssm.edu Ann N Y Acad Sci. 2006 Sep;1076:911-23.

Exposure in prenatal life to methylmercury (MeHg) has become the topic of intense debate in the United States after the Environmental Protection Agency (EPA) announced a proposal in 2004 to reverse strict controls on emissions of mercury from coal-fired power plants that had been in effect for the preceding 15 years. This proposal failed to incorporate any consideration of the health impacts on children that would result from increased mercury emissions. We assessed the impact on children's health of industrial mercury emissions and found that between 316,588 and 637,233 babies are born with mercury-related losses of cognitive function ranging from 0.2 to 5.13 points. We calculated that decreased economic productivity resulting from diminished intelligence over a lifetime results in an aggregate economic cost in each annual birth cohort of \$8.7 billion annually (range: \$0.7-\$13.9 billion, 2000 dollars). \$1.3 billion (range: \$51 million-\$2.0 billion) of this cost is attributable to mercury emitted from American coal-fired power plants. Downward shifts in intellectual quotient (IQ) are also associated with 1566 (range: 115-2675) excess cases of mental retardation (MR defined as IQ < 70) annually. This number accounts for 3.2% (range: 0.2-5.4%) of MR cases in the United States. If the lifetime excess cost of a case of MR (excluding individual productivity losses) is \$1,248,648 in 2000 dollars, then the cost of these excess cases of MR is \$2.0 billion annually (range: \$143 million-\$3.3 billion). Preliminary data suggest that more stringent mercury policy options would prevent thousands of cases of MR and billions of dollars over the next 25 years.

Assessing and managing methylmercury risks associated with power plant mercury emissions in the United States.

Charnley G. HealthRisk Strategies, Washington, DC, USA. MedGenMed. 2006 Mar 9;8(1):64.

Until the Clean Air Mercury Rule was signed in March 2005, coal-fired electric utilities were the only remaining, unregulated major source of industrial mercury emissions in the United States. Proponents of coal-burning power plants assert that methylmercury is not a hazard at the current environmental levels, that current technologies for limiting emissions are unreliable, and that reducing mercury emissions from power plants in the United States will have little impact on environmental levels. Opponents of coal-burning plants assert that current methylmercury exposures from fish are damaging to the developing nervous system of infants, children, and the fetus; that current technology can significantly limit emissions; and that reducing emissions will reduce exposure and risk. One concern is that local mercury emissions from power plants may contribute to higher local exposure levels, or "hot spots." The impact of the Mercury Rule on potential hot spots is uncertain due to the highly site-specific nature of the relationship between plant emissions and local fish methylmercury levels. The impact on the primary source of exposure in the United States, ocean fish, is likely to be negligible due to the contribution of natural sources and industrial sources outside the United States. Another debate

centers on the toxic potency of methylmercury, with the scientific basis of the US Environmental Protection Agency's (EPA's) recommended exposure limit questioned by some and defended by others. It is likely that the EPA's exposure limit may be appropriate for combined exposure to methylmercury and polychlorinated biphenyls (PCBs), but may be lower than the available data suggest is necessary to protect children from methylmercury alone. Mercury emissions from power plants are a global problem. Without a global approach to developing and implementing clean coal technologies, limiting US power plant emissions alone will have little impact.

Associations of maternal long-chain polyunsaturated fatty acids, methyl mercury, and infant development in the Seychelles Child Development Nutrition Study.

Strain JJ, Davidson PW, Bonham MP, Duffy EM, Stokes-Riner A, Thurston SW, Wallace JM, Robson PJ, Shamlaye CF, Georger LA, Sloane-Reeves J, Cernichiari E, Canfield RL, Cox C, Huang LS, Janciuras J, Myers GJ, Clarkson TW. University of Ulster, United Kingdom. Neurotoxicology. 2008 Jun 11. [Epub ahead of print]

Fish consumption during gestation can provide the fetus with long-chain polyunsaturated fatty acids (LCPUFA) and other nutrients essential for growth and development of the brain. However, fish consumption also exposes the fetus to the neurotoxicant, methyl mercury (MeHg). We studied the association between these fetal exposures and early child development in the Seychelles Child Development Nutrition Study (SCDNS). Specifically, we examined a priori models of Omega-3 and Omega-6 LCPUFA measures in maternal serum to test the hypothesis that these LCPUFA families before or after adjusting for prenatal MeHg exposure would reveal associations with child development assessed by the BSID-II at ages 9 and 30 months. There were 229 children with complete outcome and covariate data available for analysis. At 9 months, the PDI was positively associated with total Omega-3 LCPUFA and negatively associated with the ratio of Omega-6/Omega-3 LCPUFA. These associations were stronger in models adjusted for prenatal MeHg exposure. Secondary models suggested that the MeHg effect at 9 months varied by the ratio of Omega-6/Omega-3 LCPUFA. There were no significant associations between LCPUFA measures and the PDI at 30 months. There were significant adverse associations, however, between prenatal MeHg and the 30-month PDI when the LCPUFA measures were included in the regression analysis. The BSID-II mental developmental index (MDI) was not associated with any exposure variable. These data support the potential importance to child development of prenatal availability of Omega-3 LCPUFA present in fish and of LCPUFA in the overall diet. Furthermore, they indicate that the beneficial effects of LCPUFA can obscure the determination of adverse effects of prenatal MeHg exposure in longitudinal observational studies.

Children's cognitive health: the influence of environmental chemical exposures.

Bellinger DC. Harvard Medical School, USA. Altern Ther Health Med. 2007 Mar-Apr;13(2):S140-4.

The potential exists for developmental exposure of children to myriad chemicals, many of which are known to be neurotoxic. Some, such as the organophosphate pesticides, are specifically designed to attack the central nervous system. Despite the known and suspected risks associated with such exposures, critical aspects of the dose-response

relationships are unknown or, at best, poorly characterized for the overwhelming majority of chemicals. Among the major knowledge gaps for most chemicals are the critical window(s) of vulnerability, the threshold or "no observed adverse effect level," and the host/environmental characteristics that modify individual vulnerability. Investigation of the role of genetic polymorphisms in determining vulnerability has barely begun. In the real-world, children are not exposed to a single chemical at a time but to complex mixtures of chemicals, and we have only a minimal understanding of the way in which exposures might interact with one another. Effective medical/environmental treatments for the adverse effects associated with chemical exposures are largely unknown, rendering primary prevention of exposure the most effective strategy for protecting children.

Do recent data from the Seychelles Islands alter the conclusions of the NRC Report on the toxicological effects of methylmercury?

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In 2000, the National Research Council (NRC), an arm of the National Academy of Sciences, released a report entitled, "Toxicological Effects of Methylmercury." The overall conclusion of that report was that, at levels of exposure in some fish- and marine mammal-consuming communities (including those in the Faroe Islands and New Zealand), subtle but significant adverse effects on neuropsychological development were occurring as a result of in utero exposure. Since the release of that report, there has been continuing discussion of the public health relevance of current levels of exposure to Methylmercury. Much of this discussion has been linked to the release of the most recent longitudinal update of the Seychelles Island study. It has recently been posited that these findings supercede those of the NRC committee, and that based on the Seychelles findings, there is little or no risk of adverse neurodevelopmental effects at current levels of exposure. In this commentary, members of the NRC committee address the conclusions from the NRC report in light of the recent Seychelles data. We conclude that no evidence has emerged since the publication of the NRC report that alters the findings of that report.

Is susceptibility to prenatal methylmercury exposure from fish consumption non-homogeneous? Tree-structured analysis for the Seychelles Child Development Study.

Huang LS, Myers GJ, Davidson PW, Cox C, Xiao E, Thurston SW, Cernichiari E, Shamlaye CF, Sloane-Reeves J, Georger L, Clarkson TW. Department of Biostatistics and Computational Biology, University of Rochester School of Medicine and Dentistry, Rochester, NY 14642, USA. Lhuang@bst.rochester.edu Neurotoxicology. 2007 Nov;28(6):1237-44. Epub 2007 Aug 25.

Studies of the association between prenatal methylmercury exposure from maternal fish consumption during pregnancy and neurodevelopmental test scores in the Seychelles Child Development Study have found no consistent pattern of associations through age 9 years. The analyses for the most recent 9-year data examined the population effects of prenatal exposure, but did not address the possibility of non-homogeneous

susceptibility. This paper presents a regression tree approach: covariate effects are treated non-linearly and non-additively and non-homogeneous effects of prenatal methylmercury exposure are permitted among the covariate clusters identified by the regression tree. The approach allows us to address whether children in the lower or higher ends of the developmental spectrum differ in susceptibility to subtle exposure effects. Of 21 endpoints available at age 9 years, we chose the Weschler Full Scale IQ and its associated covariates to construct the regression tree. The prenatal mercury effect in each of the nine resulting clusters was assessed linearly and non-homogeneously. In addition we reanalyzed five other 9-year endpoints that in the linear analysis had a two-tailed p-value <0.2 for the effect of prenatal exposure. In this analysis, motor proficiency and activity level improved significantly with increasing MeHg for 53% of the children who had an average home environment. Motor proficiency significantly decreased with increasing prenatal MeHg exposure in 7% of the children whose home environment was below average. The regression tree results support previous analyses of outcomes in this cohort. However, this analysis raises the intriguing possibility that an effect may be non-homogeneous among children with different backgrounds and IQ levels.

Maternal fish intake during pregnancy, blood mercury levels, and child cognition at age 3 years in a US cohort.

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Comment in: *Am J Epidemiol.* 2008 Jul 15;168(2):236.

The balance of contaminant risk and nutritional benefit from maternal prenatal fish consumption for child cognitive development is not known. Using data from a prospective cohort study of 341 mother-child pairs in Massachusetts enrolled in 1999-2002, the authors studied associations of maternal second-trimester fish intake and erythrocyte mercury levels with children's scores on the Peabody Picture Vocabulary Test (PPVT) and Wide Range Assessment of Visual Motor Abilities (WRAVMA) at age 3 years. Mean maternal total fish intake was 1.5 (standard deviation, 1.4) servings/week, and 40 (12%) mothers consumed >2 servings/week. Mean maternal mercury level was 3.8 (standard deviation, 3.8) ng/g. After adjustment using multivariable linear regression, higher fish intake was associated with better child cognitive test performance, and higher mercury levels with poorer test scores. Associations strengthened with inclusion of both fish and mercury: effect estimates for fish intake of >2 servings/week versus never were 2.2 (95% confidence interval (CI): -2.6, 7.0) for the PPVT and 6.4 (95% CI: 2.0, 10.8) for the WRAVMA; for mercury in the top decile, they were -4.5 (95% CI: -8.5, -0.4) for the PPVT and -4.6 (95% CI: -8.3, -0.9) for the WRAVMA. Fish consumption of < or =2 servings/week was not associated with a benefit. Dietary recommendations for pregnant women should incorporate the nutritional benefits as well as the risks of fish intake.

Mental retardation and prenatal methylmercury toxicity.

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BACKGROUND: Methylmercury (MeHg) is a developmental neurotoxicant; exposure results principally from consumption of seafood contaminated by mercury (Hg). In this analysis, the burden of mental retardation (MR) associated with methylmercury exposure in the 2000 U.S. birth cohort is estimated, and the portion of this burden attributable to mercury (Hg) emissions from coal-fired power plants is identified.

METHODS: The aggregate loss in cognition associated with MeHg exposure in the 2000 U.S. birth cohort was estimated using two previously published dose-response models that relate increases in cord blood Hg concentrations with decrements in IQ. MeHg exposure was assumed not to be correlated with native cognitive ability. Previously published estimates were used to estimate economic costs of MR caused by MeHg.

RESULTS: Downward shifts in IQ resulting from prenatal exposure to MeHg of anthropogenic origin are associated with 1,566 excess cases of MR annually (range: 376-14,293). This represents 3.2% of MR cases in the US (range: 0.8%-29.2%). The MR costs associated with decreases in IQ in these children amount to \$2.0 billion/year (range: \$0.5-17.9 billion). Hg from American power plants accounts for 231 of the excess MR cases/year (range: 28-2,109), or 0.5% (range: 0.06%-4.3%) of all MR. These cases cost \$289 million (range: \$35 million-2.6 billion).

CONCLUSIONS: Toxic injury to the fetal brain caused by Hg emitted from coal-fired power plants exacts a significant human and economic toll on American children.

Mercury exposure and child development outcomes.

Davidson PW, Myers GJ, Weiss B. Strong Center for Developmental Disabilities, Golisano Children's Hospital at Strong, University of Rochester School of Medicine and Dentistry, Rochester, New York 14642, USA. phil_davidson@urmc.rochester.edu Pediatrics. 2004 Apr;113(4 Suppl):1023-9.

Mercury is ubiquitous in the global environment, ensuring universal exposure. Some forms of mercury are especially neurotoxic, including clinical signs at high doses. However, typical human exposures occur at low to moderate doses. Only limited data about neurotoxicity at low doses are available, and scientists differ in their interpretation. Dose-response data on neurodevelopment are particularly limited. Despite or perhaps because of the lack of sufficient or consistent scientific data, public concern about a link between mercury exposure and developmental disabilities has been rising. After reviewing the data, the US Environmental Protection Agency proposed a reference dose (an estimate of a daily dose that is likely to be without a risk of adverse effects over a lifetime) for methyl mercury that is substantially lower than previous guidelines from the World Health Organization, the US Agency for Toxic Substances and Disease Registry, and the US Food and Drug Administration. Some questions have been raised about the Environmental Protection Agency's guidelines, but the issue remains unresolved. Meanwhile, consumer groups have raised questions about the potential link between mercury exposure and autism spectrum disorders as well as other adverse neurodevelopmental outcomes. This hypothesis has prompted some parents to seek regulatory, legal, or medical remedies in the absence of firm evidence. This article reviews what is known about mercury neurotoxicity and neurodevelopmental risk. Our intent is to focus the debate about mercury on 1) additional research that should be sought and 2) defining the principal issues that public policy makers face.

Methylmercury and neurodevelopment: longitudinal analysis of the Seychelles child development cohort.

Davidson PW, Myers GJ, Cox C, Wilding GE, Shamlaye CF, Huang LS, Cernichiari E, Sloane-Reeves J, Palumbo D, Clarkson TW. The Department of Pediatrics, University of Rochester School of Medicine and Dentistry, Rochester, New York, 14642, USA. phil_davidson@urmc.rochester.edu Neurotoxicol Teratol. 2006 Sep-Oct;28(5):529-35. Epub 2006 Jun 29.

BACKGROUND: The Seychelles Child Development Study (SCDS) has been longitudinally following a cohort of over 700 children enrolled in 1989. Their mothers consumed a diet high in fish during pregnancy. Repeated examination of the SCDS cohort at six different ages through age 11 years has shown no pattern of adverse effects. Some early appearing beneficial associations between both prenatal and postnatal hair MeHg and several child development endpoints were noted. We hypothesized these might be related to micronutrients in the fish, but they were not found when the children reached middle school age. These findings suggest that the associations observed between MeHg and developmental outcomes may vary with developmental stage.

METHOD: We examined the main cohort of the SCDS to determine if this might be true using a longitudinal multiple regression analysis design that focused on those endpoints that were repeatedly measured at different ages. The primary endpoint analyzed was global cognition, involving a measure of developmental quotient or IQ. Secondary analyses included other domains such as Reading and Mathematics scholastic achievement, social behavior, and memory. Analyses involved two different approaches, one including incorporation of a passage of time variable, the other including a difference of scores across time points.

RESULTS: No significant associations were found between prenatal MeHg exposure and any of the repeatedly measured endpoints.

CONCLUSIONS: These results suggest that even when individual subject variance is controlled there was no consistent pattern of associations between child development outcomes and prenatal exposures to MeHg from maternal consumption of a diet high in fish. The Seychellois diet contains about 10 times more ocean fish than is typically consumed by US citizens. Our primary focus on IQ should further inform growing scientific interest in the analysis of the risks and benefits of fish consumption on overall cognitive ability.

Methylmercury toxicity and functional programming.

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PURPOSE: Adverse health effects of developmental toxicants may induce abnormal functional programming that leads to lasting functional deficits. This notion is considered from epidemiological evidence using developmental methylmercury neurotoxicity as an example.

MOST IMPORTANT FINDINGS: Accumulating evidence indicates that adverse effects may occur even at low-level methylmercury exposures from seafood and freshwater fish. Neurobehavioral outcomes are usually non-specific, and imprecise exposure assessment results in a bias toward the null. Essential nutrients may promote the development of certain brain functions, thereby causing confounding bias. The functional deficits caused by prenatal methylmercury exposure appear to be permanent, and their extent may depend on the joint effect of toxicants and nutrients.

PRINCIPAL CONCLUSIONS: The lasting functional changes caused by neurodevelopmental methylmercury toxicity fit into the pattern of functional programming, with effects opposite to those linked to beneficial stimuli.

Neurodevelopmental effects of maternal nutritional status and exposure to methylmercury from eating fish during pregnancy.

Davidson PW, Strain JJ, Myers GJ, Thurston SW, Bonham MP, Shamlaye CF, Stokes-Riner A, Wallace JM, Robson PJ, Duffy EM, Georger LA, Sloane-Reeves J, Cernichiari E, Canfield RL, Cox C, Huang LS, Jancius J, Clarkson TW. University of Rochester, Rochester, NY, USA. *Neurotoxicology*. 2008 Jun 11. [Epub ahead of print]

Fish contain nutrients that promote optimal brain growth and development but also contain methylmercury (MeHg) that can have toxic effects. The present study tested the hypothesis that the intake of selected nutrients in fish or measures of maternal nutritional status may represent important confounders when estimating the effects of prenatal methylmercury exposure on child development. The study took place in the Republic of Seychelles, an Indian Ocean archipelago where fish consumption is high. A longitudinal cohort study design was used. A total of 300 mothers were enrolled early in pregnancy. Nutrients considered to be important for brain development were measured during pregnancy along with prenatal MeHg exposure. The children were evaluated periodically to age 30 months. There were 229 children with complete outcome and covariate data for analysis. The primary endpoint was the Bayley Scales of Infant Development-II (BSID-II), administered at 9 and 30 months of age. Combinations of four secondary measures of infant cognition and memory were also given at 5, 9 and 25 months. Cohort mothers consumed an average of 537g of fish (nine meals containing fish) per week. The average prenatal MeHg exposure was 5.9ppm in maternal hair. The primary analysis examined the associations between MeHg, maternal nutritional measures and children's scores on the BSID-II and showed an adverse association between MeHg and the mean Psychomotor Developmental Index (PDI) score at 30 months. Secondary analyses of the association between the PDI and only MeHg alone or nutritional factors alone showed only a borderline significant association between MeHg and the PDI at 30 months and no associations with nutritional factors. One experimental measure at 5 months of age was positively associated with iodine status, but not prenatal MeHg exposure. These findings suggest a possible confounding role of maternal nutrition in studies examining associations between prenatal MeHg exposures and developmental outcomes in children.

Nutrient and methyl mercury exposure from consuming fish.

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gary_myers@urmc.rochester.edu J Nutr. 2007 Dec;137(12):2805-8.

There is controversy about the risks and benefits of consuming fish. Fish consumption provides nutrients, some of which are essential for brain growth and development. All fish, however, contain methyl mercury (MeHg), a known neurotoxicant. The toxic effect of MeHg seems most damaging during brain development, and thus, prenatal exposure is of greatest concern. At present the level of prenatal exposure associated with risk to a child's neurodevelopment is not known. Balancing the rewards and possible risks of fish consumption presents a dilemma to consumers and regulatory authorities. We review the nutrients in fish that are important in brain development and the current evidence of risk from MeHg at exposure levels achieved by consuming fish. We then review the findings from a large prospective cohort study of a population that consumes fish daily, the Seychelles Child Development Study. The MeHg content of the fish consumed in the Seychelles is similar to that of ocean fish available in industrialized countries, so they represent a sentinel population for any risk from fish consumption. In the Seychelles, evaluations of the children through 9 y of age show no consistent pattern of adverse associations with prenatal MeHg exposure. Recent studies in the Seychelles have focused on nutrients in fish that might influence a child's development, including long-chain polyunsaturated fatty acids, iodine, iron, and choline. Preliminary findings from this study suggest that the beneficial influence of nutrients from fish may counter any adverse effects of MeHg on the developing nervous system.

Prenatal methylmercury exposure from ocean fish consumption in the Seychelles child development study.

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gary_myers@urmc.rochester.edu Lancet. 2003 May 17;361(9370):1686-92.

Comment in: Lancet. 2003 Aug 23;362(9384):664-5; author reply 665. Lancet. 2003 May 17;361(9370):1667-8.

INTRODUCTION: Exposure to methylmercury (MeHg) before birth can adversely affect children's neurodevelopment. The most common form of prenatal exposure is maternal fish consumption, but whether such exposure harms the fetus is unknown. We aimed to identify adverse neurodevelopmental effects in a fish-consuming population.

METHODS: We investigated 779 mother-infant pairs residing in the Republic of Seychelles. Mothers reported consuming fish on average 12 meals per week. Fish in Seychelles contain much the same concentrations of MeHg as commercial ocean fish elsewhere. Prenatal MeHg exposure was determined from maternal hair growing during pregnancy. We assessed neurocognitive, language, memory, motor, perceptual-motor, and behavioural functions in children at age 9 years. The association between prenatal MeHg exposure and the primary endpoints was investigated with multiple linear regression with adjustment for covariates that affect child development.

FINDINGS: Mean prenatal MeHg exposure was 6.9 parts per million (SD 4.5 ppm). Only two endpoints were associated with prenatal MeHg exposure. Increased exposure was associated with decreased performance in the grooved pegboard using the non-

dominant hand in males and improved scores in the hyperactivity index of the Conner's teacher rating scale. Covariates affecting child development were appropriately associated with endpoints.

INTERPRETATION: These data do not support the hypothesis that there is a neurodevelopmental risk from prenatal MeHg exposure resulting solely from ocean fish consumption.

Public health and economic consequences of methyl mercury toxicity to the developing brain.

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leo.trasande@mssm.edu Environ Health Perspect. 2005 May;113(5):590-6. Comment in: Environ Health Perspect. 2006 Jul;114(7):A399-400; author reply A400-1.

Methyl mercury is a developmental neurotoxicant. Exposure results principally from consumption by pregnant women of seafood contaminated by mercury from anthropogenic (70%) and natural (30%) sources. Throughout the 1990s, the U.S. Environmental Protection Agency (EPA) made steady progress in reducing mercury emissions from anthropogenic sources, especially from power plants, which account for 41% of anthropogenic emissions. However, the U.S. EPA recently proposed to slow this progress, citing high costs of pollution abatement. To put into perspective the costs of controlling emissions from American power plants, we have estimated the economic costs of methyl mercury toxicity attributable to mercury from these plants. We used an environmentally attributable fraction model and limited our analysis to the neurodevelopmental impacts--specifically loss of intelligence. Using national blood mercury prevalence data from the Centers for Disease Control and Prevention, we found that between 316,588 and 637,233 children each year have cord blood mercury levels > 5.8 microg/L, a level associated with loss of IQ. The resulting loss of intelligence causes diminished economic productivity that persists over the entire lifetime of these children. This lost productivity is the major cost of methyl mercury toxicity, and it amounts to \$8.7 billion annually (range, \$2.2-43.8 billion; all costs are in 2000 US\$). Of this total, \$1.3 billion (range, \$0.1-6.5 billion) each year is attributable to mercury emissions from American power plants. This significant toll threatens the economic health and security of the United States and should be considered in the debate on mercury pollution controls.

PEDIATRICIANS

The environment in pediatric practice: a study of New York pediatricians' attitudes, beliefs, and practices towards children's environmental health.

Trasande L, Boscarino J, Graber N, Falk R, Schechter C, Galvez M, Dunkel G, Geslani J, Moline J, Kaplan-Liss E, Miller RK, Korfmacher K, Carpenter D, Forman J, Balk SJ, Laraque D, Frumkin H, Landrigan P. Center for Children's Health and the Environment, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1057, New York, NY 10029, USA. leo.trasande@mssm.edu J Urban Health. 2006 Jul;83(4):760-72.

Chronic diseases of environmental origin are a significant and increasing public health problem among the children of New York State, yet few resources exist to address this growing burden. To assess New York State pediatricians self-perceived competency in dealing with common environmental exposures and diseases of environmental origin in children, we assessed their attitudes and beliefs about the role of the environment in children's health. A four-page survey was sent to 1,500 randomly selected members of the New York State American Academy of Pediatrics in February 2004. We obtained a 20.3% response rate after one follow-up mailing; respondents and nonrespondents did not differ in years of licensure or county of residence. Respondents agreed that the role of environment in children's health is significant (mean 4.44 +/- 0.72 on 1-5 Likert scale). They voiced high self-efficacy in dealing with lead exposure (mean 4.16-4.24 +/- 0.90-1.05), but their confidence in their skills for addressing pesticides, mercury and mold was much lower (means 2.51-3.21 +/- 0.90-1.23; $p < 0.001$). About 93.8% would send patients to a clinic "where pediatricians could refer patients for clinical evaluation and treatment of their environmental health concerns." These findings indicate that New York pediatricians agree that children are suffering preventable illnesses of environmental origin but feel ill-equipped to educate families about common exposures. Significant demand exists for specialized centers of excellence that can evaluate environmental health concerns, and for educational opportunities.

Pediatrician attitudes, clinical activities, and knowledge of environmental health in Wisconsin.

Trasande L, Schapiro ML, Falk R, Haynes KA, Behrmann A, Vohmann M, Stremski ES, Eisenberg C, Evenstad C, Anderson HA, Landrigan PJ. Center for Children's Health and the Environment, Mount Sinai School of Medicine, New York, NY 10029, USA. leo.trasande@mssm.edu WMJ. 2006 Mar;105(2):45-9.

Pediatricians can reduce exposures to environmental hazards but most have little training in environmental health. To assess whether Wisconsin pediatricians perceive a relative lack of self-efficacy for common environmental exposures and diseases of environmental origin, we assessed their attitudes and beliefs about the role of the environment in children's health. A 4-page survey was sent to the membership of the Wisconsin Chapter of the American Academy of Pediatrics. We obtained a 35.4% response rate after 1 follow-up mailing. Respondents agreed that the role of the environment in children's health is significant (mean 4.28 +/- .78 on 1-5 Likert scale). They expressed high confidence in dealing with lead exposure (means 4.22-4.27 +/- 1.01-1.09), but confidence in their skills for pesticide, mercury, and mold was much lower (means 2.49-3.09 +/- 1.06-1.26; $P < .001$). Of those surveyed, 88.6% would refer patients to a clinic "where pediatricians could refer patients for clinical evaluation and treatment of their environmental health concerns." These findings indicate that Wisconsin pediatricians agree that children are suffering preventable illnesses of environmental origin, but feel ill equipped to educate families about many common exposures. Significant demand exists for centers that can evaluate environmental health concerns, as well as for educational opportunities.

PESTICIDES

The conundrum of unmeasured confounding: Comment on: "Can some of the detrimental neurodevelopmental effects attributed to lead be due to pesticides? by Brian Gulson".

Lanphear BP, Hornung RW, Khoury J, Dietrich KN, Cory-Slechta DA, Canfield RL. Cincinnati Children's Environmental Health Center, Department of Pediatrics and of Environmental Health, Cincinnati Children's Hospital Medical Center, The University of Cincinnati, Cincinnati, Ohio, USA. bruce.lanphear@cchmc.org Sci Total Environ. 2008 Jun 25;396(2-3):196-200. Epub 2008 Mar 7. Comment on: Sci Total Environ. 2008 Jun 25;396(2-3):193-5.

The problem described by Dr. Brian Gulson - confounding by unmeasured exposures to pesticides - is only the most recent in a series of potential confounders cited to explain the observed effect of lead on children's intellectual abilities or behavioral problems. Despite the persistent problem of unmeasured confounders, there are several lines of evidence implicating lead as a toxicant at blood lead levels <10 microg/dL. First, in striking contrast with pesticides, there is considerable evidence from numerous studies linking low-level lead exposure with cognitive deficits and behavioral problems, even after controlling for a variety of potential confounders. Second, the consistency of evidence from diverse cohorts and distinct, if not always directly measured potential confounders - enhances our confidence that the lead effect observed at blood lead levels <10 microg/dL is not attributable to unmeasured confounders. Third, in our reanalysis of the Rochester Lead Study, the inclusion of parent-reported mouthing behaviors and breastfeeding status did not attenuate the effect of lead exposure on children's intellectual function. Finally, although we can never entirely dismiss unmeasured confounding in observational studies, we can rely on experimental studies of lead-exposed animals to confirm that lead is a toxicant. Thus, while we must remain vigilant for unmeasured or poorly measured confounders, it is crucial to balance the endless search for confounders with the evidence of toxicity and the need to take action to protect public health. The alternative, to perpetually permit children to be exposed to lead and other emerging toxicants, is both absurd and unacceptable.

Guidelines for developmental neurotoxicity and their impact on organophosphate pesticides: a personal view from an academic perspective.

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The appropriate regulation of drugs, chemicals and environmental contaminants requires the establishment of clear and accepted guidelines for developmental neurotoxicity. Ideally, these guidelines should encompass the ability to assess widely disparate classes of compounds through routine tests, with high throughput and low cost. Increasingly, however, the progress in primary research from academic laboratories deviates from this goal, focusing instead on categorizing novel effects of toxicants, development of new testing paradigms, and extension of techniques into molecular biology. The differing objectives of academic science as opposed to those of regulatory agencies or industry, are driven in part, by the priorities of the agencies that fund primary

research. Recent work on organophosphate pesticides (OPs) such as chlorpyrifos (CPF) illustrate this dichotomy. Originally, OPs were thought to affect brain development through their ability to elicit cholinesterase inhibition and consequent cholinergic hyperstimulation. This common mechanism allowed for parallels to be drawn between standard measures of systemic toxicity, gross morphological examinations, and exposure testing utilizing an easily-assessed surrogate endpoint, plasma cholinesterase activity. In the past decade, however, it has become increasingly evident that CPF, and probably other OPs, have direct effects on cellular processes that are unique to brain development, and that these effects are mechanistically unrelated to inhibition of cholinesterase. The identification and pursuit of these mechanisms and their consequences for brain development represent new and exciting scientific findings, while at the same obscuring the ability to sustain a uniform approach to neurotoxicity guidelines or biomarkers of exposure. In the future, a new set of test paradigms, relying on primary work in cell culture, invertebrates, or non-mammalian models, followed by more targeted examinations of specific processes in mammalian models, may unite cutting-edge academic research with the need for establishing flexible guidelines for developmental neurotoxicity.

In utero exposure to dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE) and neurodevelopment among young Mexican American children.

Eskenazi B, Marks AR, Bradman A, Fenster L, Johnson C, Barr DB, Jewell NP.

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OBJECTIVE: We investigated the relationship between prenatal exposure to dichlorodiphenyltrichloroethane (DDT) and dichlorodiphenyldichloroethylene (DDE) and neurodevelopment of Mexican farm-workers' children in California.

METHODS: Participants from the Center for the Health Assessment of Mothers and Children of Salinas study, a birth cohort study, included 360 singletons with maternal serum measures of p,p'-DDT, o,p'-DDT, and p,p'-DDE. Psychomotor development and mental development were assessed with the Bayley Scales of Infant Development at 6, 12, and 24 months.

RESULTS: We found a approximately 2-point decrease in Psychomotor Developmental Index scores with each 10-fold increase in p,p'-DDT levels at 6 and 12 months (but not 24 months) and p,p'-DDE levels at 6 months only. We found no association with mental development at 6 months but a 2- to 3-point decrease in Mental Developmental Index scores for p,p'-DDT and o,p'-DDT at 12 and 24 months, corresponding to 7- to 10-point decreases across the exposure range. Even when mothers had substantial exposure, breastfeeding was usually associated positively with Bayley scale scores.

CONCLUSIONS: Prenatal exposure to DDT, and to a lesser extent DDE, was associated with neurodevelopmental delays during early childhood, although breastfeeding was found to be beneficial even among women with high levels of exposure. Countries considering the use of DDT should weigh its benefit in eradicating malaria against the negative associations found in this first report on DDT and human neurodevelopment.

In utero exposure to DDT and performance on the Brazelton neonatal behavioral assessment scale.

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lfenster@dhs.ca.gov Neurotoxicology. 2007 May;28(3):471-7. Epub 2007 Jan 10.

We investigated whether decrements in neonatal neurodevelopment, as determined by the Brazelton neonatal behavioral assessment scale (BNBAS), were associated with in utero exposure to dichlorodiphenyltrichloroethane (DDT): p,p'-dichlorodiphenyl trichloroethane (p,p'-DDT), o,p'-dichlorodiphenyl trichloroethane (o,p'-DDT) and p,p'-DDT's primary breakdown product p,p'-dichlorodiphenyl dichloroethylene (p,p'-DDE) (heretofore collectively referred to as DDT/DDE). Our subjects were a birth cohort of 303 infants whose mothers were low-income Latinas living in the Salinas Valley, an agricultural community in California. We assessed neonates < or =2 months old using the seven BNBAS clusters (habituation, orientation, motor performance, range of state, regulation of state, autonomic stability, and reflex) and examined performance in relationship to DDT/DDE measures in maternal serum samples collected during pregnancy. We did not find any detrimental associations between in utero DDT/DDE levels and neonatal performance on the BNBAS. In this same cohort, we previously demonstrated that exposures to DDT/DDE were related to decrements in neurodevelopment at 6-24 months of age. The failure to observe effects on the BNBAS in these same children may be due to limited sensitivity of a single BNBAS assessment or a delay in the manifestations of neurodevelopmental effects of DDT/DDE until after the neonatal period.

Pesticide toxicity and the developing brain.

Eskenazi B, Rosas LG, Marks AR, Bradman A, Harley K, Holland N, Johnson C, Fenster L, Barr DB. Center for Children's Environmental Health Research, School of Public Health, University of California, Berkeley, CA 94704, USA. eskenazi@berkeley.edu Basic Clin Pharmacol Toxicol. 2008 Feb;102(2):228-36.

Organochlorine pesticides are used in some countries for malaria control and organophosphate pesticides are widely used in agriculture and in homes. Previous literature documents children's exposure to these chemicals both in utero and during development. Animal studies suggest that many of these chemicals are neurodevelopmental toxicants even in moderate doses, but there are few studies in human beings. Associations of children's pesticide exposure with neurodevelopment from studies being conducted worldwide are summarized. In addition, we present the work of the CHAMACOS study, a longitudinal birth cohort study of Mexican-American children living in the Salinas Valley of California. In this study, we investigated the relationship of children's neurodevelopment with maternal dichlorodiphenyltrichloroethane and dichlorodiphenyldichloroethylene serum levels, as well as prenatal and child organophosphate urinary metabolite levels. We have examined the association with children's performance on the Brazelton Neonatal Assessment Scales and at 6, 12 and 24 months on the Bayley Scales of Infant Development (mental development and psychomotor development) and mothers report on the Child Behaviour Checklist. We observed a negative association of prenatal

dichlorodiphenyltrichloroethane exposure and child mental development. We also observed adverse associations of prenatal but not postnatal organophosphate pesticide exposure with mental development and pervasive developmental disorder at 24 months.

Studying toxicants as single chemicals: does this strategy adequately identify neurotoxic risk?

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Despite the fact that virtually all chemicals exposure of humans are to mixtures, and that these mixed exposures occur in the context of numerous other risk modifiers, our current understanding of human health risks is based almost entirely on the evaluation of chemicals studied in isolation. This paper describes findings from our collaborative studies that prompt questions about these approaches in the context of neurotoxicology. The first section describes studies investigating the interactions of maternal Pb exposure with maternal stress. Examined across a range of outcome measures, it shows that maternal Pb can modulate the effects of maternal stress, and, conversely, stress modifies the effects of Pb. Further, effects of Pb+stress could be detected in the absence of an effect of either risk factor alone, and, moreover, the profile of effects of Pb alone differs notably from that of Pb+stress. Collectively, interactions were not systematic, but differed by brain region, gender and outcome measure. A second section describes outcomes of studies examining combined exposures to the pesticides paraquat (PQ) and maneb (MB) during development which likewise reveal potentiated effects of combined exposures. They also demonstrate examples of both progressive and cumulative neurotoxicity, including a marked vulnerability following gestational exposure to MB, to the effects of PQ, a pesticide with no structural relationship to MB. The ability of current hazard identification and risk assessment approaches to adequately identify and encompass such effects remains an important unanswered question. One consideration proposed for further evaluating potential interactions that may be of significance for the nervous system is based on a multi-hit hypothesis. It hypothesizes that the brain may readily compensate for the effects of an individual chemical itself acting on a particular target system, but when multiple target or functional sites within that one system are attacked by different mechanisms (i.e., multiple chemical exposures or chemical exposures combined with other risk factors), homeostatic capabilities may be restricted, thereby leading to sustained or cumulative damage.

POLYCHLORINATED BIPHENYLS

Cognitive development in preschool children prenatally exposed to PCBs and MeHg.

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A number of epidemiological studies have shown predictive relationships between prenatal exposure to polychlorinated biphenyls (PCBs) and subtle deficits in cognitive development in infancy through the preschool years [Child Dev. 56 (1985) 853; J. Pediatr. 116 (1990) 38; J. Pediatr. 134 (1999) 33; Toxicol. Lett. 102-103 (1998) 423; Neurotox. 21 (6) (2000) 1029-1038]. However, since not all studies have demonstrated these relationships (J. Pediatr. 119 (1991) 58-63), debate regarding the role of prenatal PCB exposure in cognitive development continues. The current study was designed to provide additional data to assist in resolving this question. Two hundred twelve children enrolled in the Oswego Newborn and Infant Development Project were assessed using the McCarthy Scales of Children's Abilities at 38 months of age, followed by a reassessment at 54 months of age. The relationship between prenatal exposure to PCBs (cord blood PCBs) and McCarthy performance was assessed at both ages after first controlling for a wide range of important predictors of cognitive development, including socioeconomic status (SES), maternal IQ, maternal education, home environment, cigarette smoking, and many others. Cord blood PCBs were statistically significant predictors of small but measurable deficits in McCarthy performance at 38 months of age. Moreover, a significant interaction between cord blood PCBs and maternal hair mercury (MeHg) was found, such that negative associations between prenatal MeHg exposure and McCarthy performance were found in subjects with higher levels of prenatal PCB exposure. No relationship between PCBs and/or MeHg and McCarthy performance was observed when the children were reassessed almost 1.5 years later (54 months of age). Inspection of the age-related trajectory of McCarthy performance revealed that the more highly exposed children caught up with the least exposed children by 54 months. Although the current data partially replicate the findings of Jacobson et al., Patandin et al., and Walkowiak et al. [J. Pediatr. 116 (1990) 38; J. Pediatr. 134 (1999) 33; Lancet 358 (2001) 1602], results reported here suggest that functional recovery may occur. Moreover, the interaction between PCB and MeHg cannot be considered conclusive until it has been replicated in subsequent investigations.

Polychlorinated biphenyls, organochlorine pesticides and neurodevelopment.

Korrick SA, Sagiv SK. Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts 02115, USA. susan.korrick@channing.harvard.edu Curr Opin Pediatr. 2008 Apr;20(2):198-204.

PURPOSE OF REVIEW: Although environmental levels of polychlorinated biphenyls and certain organochlorine pesticides--hexachlorobenzene, dichlorodiphenyl trichloroethane and its primary metabolite, dichlorodiphenyl dichloroethene--are generally on the decline, early-life exposures to these prevalent contaminants continue. The review will describe current understanding of the potential neurodevelopmental consequences of low-level exposures to these contaminants.

RECENT FINDINGS: Animal models suggest that early-life exposures to polychlorinated biphenyls, dichlorodiphenyl trichloroethane/dichlorodiphenyl dichloroethene or hexachlorobenzene are associated with decreased cognitive or behavioral function in later development. Despite almost 30 years of research, however, results of human studies are inconsistent regarding the nature of the observed effects and their persistence over time. Overall, epidemiologic studies support modest associations of primarily prenatal polychlorinated biphenyl exposures with differences in neuromotor

development, decrements in cognition and behavioral deficits, particularly regarding attention and impulse control. There are limited published human data regarding potential neurodevelopmental toxicities of early-life exposures to dichlorodiphenyl trichloroethane/dichlorodiphenyl dichloroethene and hexachlorobenzene.

SUMMARY: Exposures to polychlorinated biphenyls, dichlorodiphenyl trichloroethane/dichlorodiphenyl dichloroethene and hexachlorobenzene are likely detrimental to neurodevelopment. Effective control of exposure is complicated by variable exposure sources and variable contaminant levels in food, particularly fish, for which it is important to balance the risk of contaminants with nutritional benefits.

Prenatal exposure to low-level polychlorinated biphenyls in relation to mental and motor development at 8 months.

Daniels JL, Longnecker MP, Klebanoff MA, Gray KA, Brock JW, Zhou H, Chen Z, Needham LL. Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA. Julie.Daniels@unc.edu *Am J Epidemiol.* 2003 Mar 15;157(6):485-92.

The relation between exposure to low levels of polychlorinated biphenyls (PCBs), a class of persistent organic pollutants, and cognitive and motor development in young children has been examined in several studies, and results have varied. The authors evaluated the association between prenatal exposure to PCBs and children's neurodevelopment using data from the Collaborative Perinatal Project. Pregnant women were enrolled from 1959 to 1965 from 12 sites across the United States. PCBs were measured in maternal serum taken during pregnancy. To measure children's mental and psychomotor development at 8 months of age, the authors administered the Bayley Scales of Infant Development (means, 87 (standard deviation, 15) and 88 (standard deviation, 18), respectively). Overall, they did not observe a relation between prenatal PCB exposure and children's mental or psychomotor scores ($n = 1,207$; multivariate adjusted beta = 0.1 point per micro g/liter increase of PCB, $p = 0.71$, and beta = 0.5, $p = 0.14$, respectively). The PCB-psychomotor score relation varied by study center ($p < 0.05$): The association was direct in some centers, inverse in others. This could not be attributed to variation in the timing or measurement of the child's neurodevelopment or analysis of PCBs because these were standardized across centers. The reasons for variation in results within this study and across other studies remain unclear.

PSYCHOLOGISTS

Environmental toxicants and developmental disabilities: a challenge for psychologists.

Koger SM, Schettler T, Weiss B. Department of Psychology, Willamette University, Salem, OR 97301, USA. skoger@willamette.edu *Am Psychol.* 2005 Apr;60(3):243-55. Developmental, learning, and behavioral disabilities are a significant public health problem. Environmental chemicals can interfere with brain development during critical periods, thereby impacting sensory, motor, and cognitive function. Because regulation in the United States is based on limited testing protocols and essentially requires proof of harm rather than proof of lack of harm, some undefined fraction of these disabilities may

reflect adverse impacts of this "vast toxicological experiment" (H. L. Needleman, as quoted in B. Weiss & P. J. Landrigan, 2000, p. 373). Yet the hazards of environmental pollutants are inherently preventable. Psychologists can help prevent developmental disabilities by mobilizing and affecting public policy, educating and informing consumers, contributing to interdisciplinary research efforts, and taking action within their own homes and communities to reduce the toxic threat to children.

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