TESTIMONY

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HEARING ON

State of Research on Potential Environmental Health Factors with Autism and Related Neurodevelopment Disorders

Before the

U.S. Senate

COMMITTEE ON ENVIRONMENT AND PUBLIC WORKS
SUBCOMMITTEE ON CHILDREN'S HEALTH
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Good morning Chairman Klobuchar, Ranking Member Alexander and other members of the Committee. My name is Paul Anastas**.** I am the Assistant Administrator for Research and Development at EPA. It is a pleasure to be here with you this morning to discuss the state of EPA-funded research on the potential environmental factors related to autism and other neurodevelopmental disorders. As a father of two small children, I know that there is nothing more important than making sure we do everything we can so that all of America's children are safe and healthy.

Autism can be a heart breaking neurodevelopmental disorder that may prevent children from fully experiencing the typical social interactions so essential for family well-being and individual emotional and cognitive

development. ASDs are characterized by atypical development in socialization, communication, and behavior. The symptoms are often present before age 3 and are generally accompanied by changes in cognitive functioning, learning, attention, and sensory processing.

Autism spectrum disorder (ASD) is a range of complex neurodevelopment disorders, characterized by social impairments, communication difficulties, and restricted, repetitive, and stereotyped patterns of behavior.[1] Autistic disorder, sometimes called autism or classical ASD, is the most severe form of ASD, while other conditions along the spectrum include a milder form known as Asperger syndrome, the rare condition called Rett syndrome, and childhood disintegrative disorder and pervasive developmental disorder not otherwise specified (usually referred to as PDD-NOS).[1] In recent years, the term "autism" has been generally used to refer to ASDs as a whole.

Scientists aren't certain about what causes ASDs, however ASDs could result from a variety of factors, including combinations of genes, environmental exposures and gene-environment interactions. Evidence suggests that the rates of ASD are increasing in the United States (http://www.cdc.gov/ncbddd/autism/data.html) In fact – and this is of great concern to EPA – according to the most recent statistics from the Centers for Disease Control and Prevention (CDC), in 2006 an average of 1 in 110 children in the 11 sites examined (covering 11 states), or about 1%, have an autism spectrum disorder. The average is as high as 1 in 70 for boys. The average prevalence of ASDs among the 8-year-old children sampled increased by 57 percent from 2002 to 2006.[2]

Background

As you know, children are especially susceptible to the effects of chemicals in the environment because they eat, drink and breathe in more for their body weight than adults. They absorb a greater proportion of many chemicals in the environment than adults do, and due to hand to mouth behaviors, young children tend to have higher exposures to contaminants in dust and soil, such as pollutants deposited from the surrounding air, dust from lead paint, tobacco smoke, cleaning products, pesticides and other chemicals.[3, 4] Because of its extraordinary complexity, prenatal and early postnatal brain and nervous system development can be disrupted by environmental exposures at much lower levels than would affect adults.[5,6,7,8,9] We are learning that there are critical windows of susceptibility both prenatally and in early childhood, during which the effects of exposures to environmental contaminants, depending on dose and timing, can be significantly more severe and can lead to permanent and irreversible disability.[10,11,12] For these and many other reasons, EPA is especially concerned about potential effects of environmental chemicals on children's health and neurodevelopment.

It has been suggested that improvements in diagnosis may be contributing to the perceived increase in ASDs. However, one recent publication from researchers supported by EPA and the National Institute of Environmental Health Sciences (NIEHS) evaluated the rise in autism incidence in California from 1990 through 2006. They found that even when factors such as earlier diagnosis, changes in diagnostic criteria and inclusion of milder cases were taken into account, these did not fully explain the observed increase, and as a result the extent to which the continued rise represents a

true increase in the occurrence of autism remains unclear.[13] Additionally, through a recent evaluation of autistic disorder (AD) data from long-term (~ 10 years) studies , ORD scientists found significant and surprisingly uniform timing of increases in AD cumulative incidence (1988-1989) in Danish, California and worldwide data sets.[14] It is not clear if the observed increase in AD is real, and if so, for what reason; or whether the apparent increase is due to improved diagnosis, increased observations, or other factors. However, these researchers concluded that it seems prudent to assume that at least some portion of the observed increase is real and results from environmental factors interacting with susceptible populations.[14] Such exposures may be preventable; identification of candidate environmental factors should be a research priority.

The challenge is to determine what specific environmental factors may contribute to the onset or severity of autism and other neurodevelopmental disorders, so that exposure to these can be prevented. At EPA, we are conducting research to determine how environmental chemicals could impact the development and function of the human nervous system through our intramural and extramural research programs. Since 2002, EPA has invested $10.8 million in extramural dollars to support research on autism through the Centers for Children's Environmental Health and Disease Prevention Research, which we co-fund with NIEHS. Over the same time in our intramural program there has invested approximately 8-9 work years and $1 million in neurodevelopmental toxicology, along with an average of two postdoctoral fellows/ year.

EPA Intramural Research

Research at EPA's National Health and Environmental Effects Research

Laboratory (NHEERL) focuses on susceptibility to chemicals, the factors underlying this susceptibility, chemical mechanisms of action, and the relevance of effects detected by testing to human health.

EPA scientists are assessing the potential for environmental chemicals to alter processes essential for development of the nervous system, including how nerve cells grow, divide, make connections and communicate with each other, all of which are necessary for the nervous system to function.[15,16,17,18,19,20] Interference with any of these processes by environmental chemicals could predict neurodevelopmental disease in humans, the nature of which would depend on the extent and timing of exposure to the chemical.

Alternative Models and Approaches

Chemical testing approaches that can be used to test large numbers of chemicals in a short time (so-called "high-throughput" approaches) are being developed to provide information on chemicals that can adversely affect neurodevelopment.[21,22,23] The current emphasis is on methods that use laboratory cell cultures, including human cells, and non-mammalian species such as zebrafish [24,25] which share similarities in central nervous system development with other vertebrates and permit more rapid testing. EPA laboratories test suspected neurodevelopmental toxicants in rodents for effects on learning, memory, sensory function, and behavior.[26,27,28,29] Many of these endpoints are affected in autism. However, there are no well-accepted animal models of autism at present.

Computational Toxicology

Scientists in NHEERL have, to date, tested over 200 pesticides for developmental toxicity using cells in culture and zebrafish. Using these

data, we are developing the capacity for computational toxicology, or computer modeling of toxicity of environmental chemicals. Researchers at NHEERL and the National Center for Computational Toxicology (NCCT) are creating databases and approaches to predict the toxicity of new and untested chemicals (http://epa.gov/ncct/toxcast/index.html). This approach holds promise for identifying chemicals of most concern with respect to developmental toxicity and could be used to model the effects of real-world, complex mixtures of chemicals, such as we encounter in our daily lives, on human health.

Fundamental mechanisms by which chemical exposure during development can impact childhood and adult health

EPA investigators are also examining the possibility that chemical exposures to the fetus and infant may increase risk of disease later in life, and potentially affect subsequent generations. This research considers a broad range of potential health effects including high blood pressure, obesity, diabetes and behavioral changes. One potential mechanism for this is epigenetic alterations of chromatin, such as DNA methylation and histone modifications.[30] A current focus is to look for effects on the neuro-endocrine system, specifically the linkage between the brain and stress response, the so-called hypothalamic-pituitary-adrenal axis. This axis is common across species, is critical for the body's stress response and regulates physiological processes including the immune response.

Extramural Research -- Centers for Children's Environmental Health and Disease Prevention Research

In 1998, EPA and the National Institute of Environmental Health Sciences (NIEHS) together established the Centers for Children's Environmental

Health and Disease Prevention Research, or Children's Centers. The program has been highly successful and two of these Centers – at the University of California at Davis (or UC Davis) and the University of Medicine and Dentistry of New Jersey (or UMDNJ) – with funding from both agencies, have investigated how environmental factors may affect the development of autism spectrum disorder. A number of other Children's Centers are investigating how factors in the environment may affect a child's developing brain and nervous system.

UC Davis Center for Children's Environmental Health

The University of California at Davis Center for Children's Environmental Health is looking at possible genetic and environmental risk factors that may contribute to the incidence and severity of childhood autism, to understand and characterize common patterns of dysfunction in this disease. Part of the research focuses on how chemicals that are known to be toxic to the developing nervous and immune systems could contribute to atypical development of social behavior in children (see http://www.vetmed.ucdavis.edu/cceh/). The UC Davis Children's Center established the first, large-scale, epidemiologic investigation of the underlying causes of autism, the Childhood Autism Risk from Genetics and the Environment (CHARGE) Study, which includes nearly 1,400 families in California (see http://beincharge.ucdavis.edu/). Heavy metals are one of the classes of exposure being investigated in the CHARGE study. Children with autism in this study were found not to show an increase in mercury exposure when their current blood levels of mercury were compared to typically developing children (controls) after accounting for fish consumption, a common source of mercury exposure .[31]

The UC Davis Center is also looking at the potential relationship between exposure to flame retardants – polybrominated diphenyl ethers, or PBDEs – and autism. There has been some concern because PBDEs can affect development of the nervous system[32,33] and in animal studies, can affect behavior such as hyperactivity[34]. They can also have hormone-disrupting effects, particularly on estrogen and thyroid hormones.[35]

The UC Davis Children's Center identified several aspects of immune system differences in patients with autism compared to typically developing children. Some mothers of children with autism were found to carry antibodies against fetal brain tissue potentially setting up defensive mechanisms that could alter development of the child's nervous system[36]; and increased or decreased immune system function markers in children with autism (reduced total IgG levels , increased IgG4 levels, reduced TGF-beta levels[37.38,39].

In addition, the Children's Center at the University of Medicine and Dentistry of New Jersey(UMDNJ)has examined the effects of environmental chemicals on neurological health and development, with an emphasis on the interactions between exposure to environmental factors, learning disabilities and autism spectrum disorders.

Other Children's Centers Researching Environmental Effects on Neurodevelopment

There are other neurodevelopmental disorders of concern that include attention deficit disorder and ADHD, learning disabilities, sensory deficits and developmental delay. These disorders can cause lifelong disabilities and

the causes are likely to include both environmental and genetic factors.[40] We know that prenatal and early childhood exposures to chemicals such as methylmercury, lead, PCBs, and arsenic can affect development of the nervous system and lead to developmental disability.[43,44,45,46, 47,48,49,50.] Depending on the level and timing of exposure, these exposures can produce either obvious developmental disability or subclincal brain injury.

Research from a number of other Children's Centers is helping us understand how exposures to environmental chemicals could affect neurodevelopment. I'd like to highlight some examples of this research which we have co-funded with NIEHS through the Children's Centers program. Many of these and additional research findings are summarized in an EPA publication, "A Decade of Children's Environmental Health Research:Highlights from EPA's Science to Achieve Results Program".[40]

Researchers at the Columbia University Children's Center (http://www.ccceh.org/) have studied how prenatal exposure to air pollution, environmental tobacco smoke, polycyclic aromatic hydrocarbons or PAHs (chemicals from motor vehicles and other sources of combustion), and pesticides could adversely affect fetal growth and neurodevelopment. A recent publication from this Center showed that prenatal exposure to PAHs at levels found in New York City air can adversely affect children's IQ scores at age 5.[51] Another study from this Center showed that children with higher levels of PBDEs in cord blood scored lower on tests of mental and physical development, including IQ tests, between ages 1 and 6.[32]

The Cincinnati Children's Center looked at the effects of lead, pesticides, and environmental tobacco smoke on neurodevelopment. They concluded that prenatal tobacco and childhood lead exposures are associated with

ADHD in US children, especially among those with both exposures.[52] For additional information on the Cincinnati Children's Center see their website at http://www.cincinnatichildrens.org/research/project/enviro/default.htm.

Researchers at the Mount Sinai Children's Center showed that prenatal exposures to phthalates (measured by prenatal maternal urinary concentrations of phthalate metabolites, were associated with lower scores on neonatal behavioral tests among girls.[53] Phthalates are plasticizers found in food packaging materials as well as cosmetics and personal care products. Mount Sinai researchers also found an association between prenatal phthalate exposure and poor behavioral outcomes such as conduct disorder, ADHD and depression.[54] For additional information on the Mount Sinai Children's Center see their website at http://www.mountsinai.org/patient-care/service-areas/children/areas-of-care/childrens-environmental-health-center).

Researchers from the CHAMACOS study (see http://ehs.sph.berkeley.edu/chamacos/) at the University of California at Berkeley Children's Center showed that prenatal exposure to common agricultural insecticides is associated with a higher frequency of abnormal reflexes in newborns and lower scores on standard tests of mental development in 2-year-old children and attention deficits in preschoolers.[55,56] They showed that early exposure to these chemicals in a population living in an agricultural area is associated with PDD, which is on the autism spectrum, based on a standardized questionnaire administered to parents.[56]

Conclusion

Research supported by EPA, has enabled us to learn a great deal about the effects of environmental chemicals on children's health and neurological

disorders. As you can see, there is a lot of excellent research that has been done or is underway. EPA's Administrator has emphasized strengthened chemical management as one of her top priorities. Research to better understand the environmental contributions to ASD and other disorders will help us develop policies and actions to reduce them. A key part of preventative strategies will be our focus on creating a more sustainable environment for our children and grandchildren. We must also develop safer chemicals to reduce and prevent adverse effects to children's health.

Thank you for the opportunity to appear before you today. I will be happy to answer your questions.

References

1. National Institute of Neurological Disorders and Stroke. 2010. Available at http://www.ninds.nih.gov/disorders/autism/detail_autism.htm. Accesses July 30, 2010

2. Centers for Disease Control and Prevention. Prevalence of Autism Spectrum Disorders --- Autism and Developmental Disabilities Monitoring Network, United States, 2006. *Morbidity and Mortality Weekly Report (MMWR) Surveillance Summaries.* December 2009. Available at http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5810a1.htm.

3. National Research Council. 1993. Pesticides in the Diets of Infants and Children. National Academy of Sciences Press, Washington, DC.

4. U.S. Environmental Protection Agency (EPA). 2005 Guidance on selecting age groups for monitoring and assessing childhood exposures to environmental contaminants. National Center for Environmental Assessment, Washington, DC; EPA/630/P-03/003F.

5. (ATSDR). 2007. Toxicological profile for Lead. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. http://www.atsdr.cdc.gov/ToxProfiles/tp13-c3.pdf

6.Grandjean P, and Landrigan PJ. 2006. Developmental neurotoxicity of industrial chemicals. Lancet.;368(9553):2167-78.

7.Jett DA, Kuhlmann AC, Farmer SJ, Guilarte TR.1997. Age-dependent effects of developmental lead exposure on performance in the Morris water maze. Pharmacol Biochem Behav.57(1-2):271-9

8.Sanders T, Liu Y, Buchner V, Tchounwou PB. 2009.Neurotoxic effects and biomarkers of lead exposure: a review. Rev Environ Health. 24(1):15-45.

9.Ted Schettler.2001. Toxic threats to neurologic development of children. Environmental Health Perspectives 109, suppl. 6 813-816.

10.Deborah Rice and Stan Barone Jr. 2000. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environmental Health Perspectives 108, suppl. 3: 511-533.

11.Gilbert & Epel, Ecological Developmental Biology, Sinauer Press, 2009

12.Dale Purves et al. 2008 Neuroscience, Fourth Edition, Sinauer Press, 2008 (see Unit IV, The Changing Brain)

13.Hertz-Picciotto, I and Delwiche, L. 2009. The rise in autism and the role of age at diagnosis. Epidemiology 20, no. 1. 84-90.

14 .McDonald ME and Paul JF. 2010. Timing of increased autistic disorder cumulative incidence.Environ Sci Technol. 44(6):2112-8.

15.Breier JM, Radio NM, Mundy WR, Shafer TJ. 2008. Development of a high-throughput screening assay for chemical effects on proliferation and viability of immortalized human neural progenitor cells. Toxicol Sci. 105:119-33.

16.Radio NM, Breier JM, Shafer TJ, Mundy WR. 2008. Assessment of chemical effects on neurite outgrowth in PC12 cells using high content screening. Toxicol Sci.105:106-18.

17.Radio NM, Freudenrich TM, Robinette BL, Crofton KM, Mundy WR. 2010. Comparison of PC12 and cerebellar granule cell cultures for evaluating neurite outgrowth using high content analysis. Neurotoxicol Teratol. 32:25-35.

18. Meyer DA, Carter JM, Johnstone AF, Shafer TJ. 2008. Pyrethroid modulation of spontaneous neuronal excitability and neurotransmission in hippocampal neurons in culture. Neurotoxicology. 29:213-25.

19.Harrill JA, Freudenrich TM, Machacek DW, Stice SL, Mundy WR. 2010. Quantitative assessment of neurite outgrowth in human embryonic stem cell-derived hN2 cells using automated high-content image analysis. Neurotoxicology 31:277-90.

20.Mundy WR, Radio NM, Freudenrich TM. 2010. Neuronal models for evaluation of proliferation in vitro using high content screening. Toxicology 270:121-30.

21.Johnstone AF, Gross GW, Weiss DG, Schroeder OH, Gramowski A, Shafer TJ. 2010. Microelectrode arrays: a physiologically based neurotoxicity testing platform for the 21st century. Neurotoxicology 31:331-50.

22.Breier JM, Gassmann K, Kayser R, Stegeman H, De Groot D, Fritsche E, Shafer TJ. 2010.

Neural progenitor cells as models for high-throughput screens of developmental neurotoxicity: state of the science. Neurotoxicol Teratol. 32:4-15.

23.Kuegler PB, Zimmer B, Waldmann T, Baudis B, Ilmjärv S, Hescheler J, Gaughwin P, Brundin P, Mundy W, Bal-Price AK, Schrattenholz A, Krause KH, van Thriel C, Rao MS, Kadereit S, Leist M. 2010. Markers of murine embryonic and neural stem cells, neurons and astrocytes: reference points for developmental neurotoxicity testing. ALTEX. 27:17-42.

24.MacPhail RC, Brooks J, Hunter DL, Padnos B, Irons TD, Padilla S. 2009. Locomotion in larval zebrafish: Influence of time of day, lighting and ethanol. Neurotoxicology. 30:52-8.

25.Fan CY, Cowden J, Simmons SO, Padilla S, Ramabhadran R. 2010. Gene expression changes in developing zebrafish as potential markers for rapid developmental neurotoxicity screening. Neurotoxicol Teratol.32:91-8.

26.Gee JR, Moser VC. 2008. Acute postnatal exposure to brominated diphenylether 47 delays neuromotor ontogeny and alters motor activity in mice. Neurotoxicol Teratol. 30:79-87.

27.Gilbert ME, Sui L. 2008. Developmental exposure to perchlorate alters synaptic transmission in hippocampus of the adult rat. Environ Health Perspect. 116:752-60.

28.Kodavanti PR, Coburn CG, Moser VC, MacPhail RC, Fenton SE, Stoker TE, Rayner JL, Kannan K, Birnbaum LS. 2010. Developmental exposure to a commercial PBDE mixture, DE-71: neurobehavioral, hormonal, and reproductive effects. Toxicol Sci. 116:297-312.

29.Moser VC, McDaniel KL, Phillips PM, Lowit AB. 2010. Time-course, dose-response, and age comparative sensitivity of N-methyl carbamates in rats. Toxicol Sci. 114:113-23.

30.Rogers JM, Ellis-Hutchings RG, Lau, C. 2010. Epigenetics and the developmental origins of health and disease. In: Comprehensive Toxicology, CA McQueen, editor-in-chief. Volume 12, pp. 69-88.

31.Hertz-Picciotto I, Green PG, Delwiche L, Hansen R, Walker C, Pessah IN. 2010. Blood mercury concentrations in CHARGE study children with and without autism. Environ Health Perspect 118:161-166.

32Herbstman JB, Sjodin A, Kurzon M, Lederman SA, Jones RS, Rauh V, Needham LL, Tang D, Niedzwiecki M, Wang RI, Perera F. 2010. Prenatal exposure to PBDEs and neurodevelopment. Environ Health Perspect. 118(5):712-9.

33.Schreiber T, Gassmann K, Götz C, Hübenthal U, Moors M, Krause G, Merk HF, Nguyen NH, Scanlan TS, Abel J, Rose CR, Fritsche E. 2010. .Polybrominated diphenyl ethers induce developmental neurotoxicity in a human in vitro model: evidence for endocrine disruption. Environ Health Perspect.118(4):572-8.

34. Costa LG, Giordano G. 2007. Developmental neurotoxicity of polybrominated diphenyl ether (PBDE) flame retardants.Neurotoxicology. 28(6):1047-67.

35. Chevrier J, Harley KG, Bradman A, Gharbi M, Sjödin A, Eskenazi B. 2010. Polybrominated Diphenylether (PBDE) Flame Retardants and Thyroid Hormone during Pregnancy. Environ Health Perspect. 2010 Jun 21. [Epub ahead of print]

36.Braunschweig D, Ashwood P, Krakowiak P, Hertz-Picciotto I, Hansen R, Croen LA, Pessah IN, Van de Water J. 2008.. Autism: maternally derived antibodies specific for fetal brain proteins. Neurotoxicology 29(2):226-31.

37. Heuer L, Ashwood P, Schauer J, Goines P, Krakowiak P, Hertz-Picciotto I, Hansen R, Croen LA, Pessah IN, Van de Water J. 2008. Reduced levels of immunoglobulin in children with autism correlates with behavioral symptoms. Autism Res 1(5):275-283.

38. Enstrom AM, Onore CE, Van de Water JA, Ashwood P. 2010. Differential monocyte responses to TLR ligands in children with autism spectrum disorders. Brain Behav Immun 24(1):64-71.

39. Ashwood P, Enstrom A, Krakowiak P, Hertz-Picciotto I, Hansen RL, Croen LA, Ozonoff S, Pessah IN, Van de Water J. 2008. Decreased transforming growth factor beta1 in autism: a potential link between immune dysregulation and impairment in clinical behavioral outcomes. J Neuroimmunol. 204(1-2):149-153.

40. U.S. Environmental Protection Agency (EPA). 2007. A Decade of Children's Environmental Health Research:Highlights from EPA's Science to Achieve Results Program. Office of Research and Development Washington, DC. EPA/600/S-07/038.

41..National Research Council. "Scientific Frontiers in Developmental Toxicology and Risk Assessment". National Academy Press. Washington, D.C. 2000.

42.Goldman LR and Koduru S. 2000. Chemical in the enviroment and developmental toxicity to children: a public health perspective.Environ Health Perspect. 108, no. 3 443-448.

43.Wasserman GA, Liu X, Parvez F, Ahsan H, Factor-Litvak P, Kline J, van Geen A, Slavkovich V, Loiacono NJ, Levy D, Cheng Z, Graziano JH. 2007. Water arsenic exposure and intellectual function in 6-year-old children in Araihazar, Bangladesh. Environ Health Perspect. 115(2):285-9.

44.Wasserman GA, Liu X, Parvez F, Ahsan H, Levy D, Factor-Litvak P, Kline J, van Geen A, Slavkovich V, LoIacono NJ, Cheng Z, Zheng Y, Graziano JH. 2006. Water manganese exposure and children's intellectual function in Araihazar, Bangladesh. Environ Health Perspect. 114(1):124-9.

45.Landrigan PJ, Whitworth RH, Baloh RW, Barthel WF, Staehling NW, Rosenblum BF. 1975. Neuropsychological dysfunction in children with chronic low-level lead absorption. Lancet 1:708-712.

46.Needleman HL, Gunnoe C, Leviton A, et al. 1979. Deficits in psychologic and classroom peformance of children with elevated dentine lead levels. N Engl J Med. 300 (13):689-695.

47.Baghurst PA, McMichael AJ, Wigg NR, et al. 1992. Environmental exposure to lead and children's intelligence at the age of seven years: the Port Pirie Cohort Study. N Engl J Med. 327:1279-1284.

48. Bellinger D, Dietrich KN. 1994. Low-level lead exposure and cognitive function in children. Pediatr Ann.23:600-605.

49. Rogan WJ, Ware JH. 2003. Exposure to lead in children – how low is low enough? N Engl J Med. 348:1515-1516.

50.Harada H. 1978. Congenital Minamata Disease: intrauterine methylmercury poisoning. Teratol. 18:285-288.

51.Perrera FP, Zhigang L, Whyatt R, Hoepner L, Wang S, Camann D, Rauh V. 2009. Prenatal airborne polycyclic aromatic hydrocarbon exposure and child IQ at age 5 years. Pediatrics. 124(2):e195-202.

52.Froehlich TE, Lanphear BP, Auinger P, Hornung R, Epstein JN, Braun J, Kahn RS. 2009. Association of tobacco and lead exposures with attention-deficit/hyperactivity disorder. Pediatrics. 124(6):e1054-63.

55.Engel SM, Zhu C, Berkowitz GS, Calafat AM, Silva MJ, Miodovnik A, Wolff MS.2009. Prenatal phthalate exposure and performance on the Neonatal Behavioral Assessment Scale in a multiethnic birth cohort. Neurotoxicology.. 30(4):522-8.

54.Engel SM, Miodovnik A, Canfield RL, Zhu C, Silva MJ, Calafat AM, Wolff MS. 2010Prenatal phthalate exposure is associated with childhood behavior and executive functioning. Environ Health Perspect. 118(4):565-71.

55.Brenda Eskenazi, Kim Harley, Asa Bradman, Erin Weltzien, Nicholas P. Jewell, Dana B. Barr, Clement E. Furlong, and Nina T. Holland. 2004. Association of in utero organophosphate pesticide exposure and fetal growth and length of gestation in an agricultural population. *Environmental Health Perspectives.* 112(10):1116–1124.

56.Eskenazi B, Marks AR, Bradman A, Harley K, Barr DB, Johnson C, Morga N, Jewell NP. 2007. Organophosphate pesticide exposure and neurodevelopment in young Mexican-American children. Environ Health Perspect. 115(5):792-8.