

TESTIMONY

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HEARING ON

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

Before the

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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 hyperactivity³⁴. 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 system³⁶; 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 subclinical 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.

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