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STATE OF RESEARCH ON POTENTIAL ENVIRONMENTAL HEALTH FACTORS WITH AUTISM AND RELATED NEURODEVELOPMENT DISORDERS

HEARING

BEFORE THE

SUBCOMMITTEE ON CHILDREN'S HEALTH

OF THE

COMMITTEE ON ENVIRONMENT AND PUBLIC WORKS UNITED STATES SENATE

ONE HUNDRED ELEVENTH CONGRESS

SECOND SESSION

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C O N T E N T S

STATE OF RESEARCH ON POTENTIAL ENVIRONMENTAL HEALTH FACTORS WITH AUTISM AND RELATED NEURODEVELOPMENT DISORDERS

TUESDAY, AUGUST 3, 2010

U.S. SENATE,
COMMITTEE ON ENVIRONMENT AND PUBLIC WORKS,
SUBCOMMITTEE ON CHILDREN'S HEALTH,
Washington, DC.

The Subcommittee met, pursuant to notice, at 10 a.m. in room 406, Dirksen Senate Office Building, Hon. Amy Klobuchar (Chair of the Subcommittee) presiding.

Present: Senators Klobuchar, Boxer, and Udall.

OPENING STATEMENT OF HON. AMY KLOBUCHAR, U.S. SENATOR FROM THE STATE OF MINNESOTA

Senator KLOBUCHAR. Call the hearing to order.

I want to thank all of you for being here today for this important hearing. As a mother of a 15-year-old daughter and as the Chair of this Subcommittee, protecting our children from exposure to harmful substances is an issue that is extremely important to me. I also know that it is very important to Chairman Boxer, who has made this a cause for much of the work that she's done for California and for the country. So I am honored to have her here as well today.

This is why we are here, and it is to highlight the latest scientific research on the environmental impacts on autism and other neurodevelopmental disorders. Before we consider policy changes, we need to understand the latest science.

Two decades ago autism and other neurodevelopment disorders were little-known, uncommon diseases. Today they affect 1 million to 1.5 million Americans, and 1 in every 110 children born in the U.S. will be diagnosed with autism. That means that there will be more kids with autism than juvenile diabetes. Yet there is still so little known about the disease, its causes, or treatments.

I know personally many of my friends have kids with autism. I know that they struggle not only with the treatment, but it is always so difficult because they never really know the cause.

Sometimes when we are here in Washington, we don't realize that the abstract numbers that I just mentioned, those 1 million to 1.5 million Americans, 1 in every 110 children, that those abstract numbers have very real implications in people's lives.

I know this because I meet Minnesota families like the Moens, who are here with us today, that deal with the challenges of having an autistic child, and the frustrations of not having the answers. There is no cure for autism yet, so it is clear more research is needed. We need to look at the various factors that could contribute to autism so that we can find a cure and develop better services and treatments for those living with the disease.

With the rapid growth in the incidence of autism, Congress took action and passed the Combating Autism Act of 2006, providing nearly $1 billion to combat neurological disorders through screening, education, early intervention, prompt referrals for treatment and services, and research. In last year's Recovery Act we invested over $10 billion in NIH for new research on mental health, including at least $60 million devoted to autism diagnosis and treatment.

But even with this increase in research funding, we must continue to do our part to ensure that our researchers and medical professionals are better equipped to recognize and diagnose autism and other neurodevelopment disorders. We also need to increase awareness of autism. Early diagnosis and intervention can greatly help kid with autism. And it can reduce the cost of lifelong care by two-thirds.

While we don't have a cure, there are treatments and therapies that can help improve the quality of life of kids with autism. As we know, children are more susceptible to environmental dangers than adults. Children consume more food and water, touch more dirt, because they are closer to the ground, and can be exposed to toxins easier than adults. Because their immune systems are still developing, kids are more likely to become sick when exposed to environmental risks.

Along with the EPA, the National Institute of Environmental Health Centers for Children's Environmental Health and Disease Prevention Research are studying how exposure to chemicals in the environment could lead to neurodevelopment disorders in children, including autism spectrum disease. The research that these agencies are conducting will further our knowledge in the potential causes of autism and other neurodevelopmental disorders. In turn, these results will help us stem the increasing prevalence of these diseases and eliminate potential environmental dangers facing our kids.

Your testimony today will go a long way in helping us better understand potential environmental factors related to autism and what the state of the research is today. Your stories will help us understand the urgency behind the research.

I thank you all for joining us today, and I look forward to hearing from all of you.

Now I will turn it over to the Chair of this Committee, Chairman Boxer.

OPENING STATEMENT OF HON. BARBARA BOXER, U.S. SENATOR FROM THE STATE OF CALIFORNIA

Senator BOXER. Senator Klobuchar, Madam Chair, thank you very much.

I want to begin by saying that we were all deeply saddened to learn of the passing of your mom, Senator. Our thoughts and prayers are with you and your family at this time.

I want to note that Amy's mom dedicated her life to teaching children. I know how proud she must have been when her daughter founded the first subcommittee on this Committee dealing with children's health. So we dedicate this hearing to her mom.

Today's hearing will look at the latest research on potential environmental factors that might harm the health of our children, including the ability to learn and think and interact with families and other people in society. The EPA and the National Institute of Environmental Health Science fund a variety of studies on neurodevelopmental disorders, including autism.

I would like to extend a special welcome to Professor Isaac Pessah from the University of California Davis' Mind Institute, who will testify in the second panel. The Mind Institute receives Federal agency funding to conduct research on these very important issues.

While science is still working to identify the cause of autism, exposure to toxic chemicals in the environment is one crucial area of inquiry. The Children's Center at UC Davis is conducting research on environmental health factors with autism, including chemicals' potential impacts on brain development on social behaviors, and immune system function. Their research is especially important now, since some data indicates that the occurrence of autism is growing.

The Federal Centers for Disease Control estimates that on average 1 in 110 children in the United States has symptoms of autism spectrum disorder, or ASD. In California, State agencies are reporting an apparent rise in the incidence of ASD. In its most recent report, the California Department of Developmental Services found that from 1997 to 2007—while the total number of people served by the department increased 56 percent—the number of people with autism grew 321 percent.

Autism can affect entire families and have financial and other effects throughout society. The Federal Interagency Autism Coordinating Committee estimates that autism spectrum disorders' cost to society is currently between $35 billion to $90 billion annually.

Today's hearing focuses on research, but there are a number of other ways this Committee is working to protect children and families from toxic chemicals. For example, communities need help dealing with the impacts of autism and other disorders that may have connections to environmental health. When these disorders appear in concentrations or clusters, it may be an indication that environmental factors are playing a role in making people sick.

I am introducing a bill this week to ensure that Federal agencies are coordinating their efforts on disease clusters as effectively as possible and that the resources are there to help the people in the areas that need them. This will include making sure communities that suspect they have a cluster of disease can call on the Government to investigate and address their concerns.

My bill will also require EPA to upgrade their data tracking systems to strengthen the Federal Government's ability to investigate disease clusters. In addition, Senator Lautenberg's bill—the Safe

Chemicals Act of 2010, introduced earlier this year—would take an important step toward testing and identifying chemicals that could harm our children before them come to market, instead of having to deal with consequences after the fact.

What we want to do is require that the chemical industry prove that their chemicals are safe to use before they are allowed on the market, rather than the reverse. Right now society has to prove that the chemicals are not safe. We think the producers should have to prove they are safe before they get on the market.

So today's hearing—and I thank Senator Klobuchar for her leadership on this—will help inform our efforts to protect America's children from environmental dangers. I look forward to hearing from the witnesses. I have about—I can stay until about 11, and then I will read the rest of the testimony. But I am very grateful to Senator Klobuchar for her leadership.

Senator KLOBUCHAR. Thank you very much, and thank you for your kind words about my mom, who devoted herself to kids. She had 30 second graders, when she was 70 years old, in her class. But lately, in her last few years, she was mostly watching C-SPAN, and loved watching Senator Boxer give speeches.

[Laughter.]

Senator KLOBUCHAR. She would always say, where were you? I saw Senator Boxer.

[Laughter.]

Senator KLOBUCHAR. So we have two great witnesses to begin here. Our first witness is Dr. Paul Anastas with the EPA Office of Research and Development. Dr. Anastas is the Assistant Administrator for the Environmental Protection Agency's Office of Research and Development and the science advisor to the agency.

Our second witness is Dr. Linda Birnbaum with the National Institutes of Health. Dr. Birnbaum is the Director of the National Institute of Environmental Health Sciences, overseeing research relating to autism and other neurodevelopmental disorders.

I will introduce our second panel. Senator Boxer already mentioned one of the witnesses, as well as the Moens from Minnesota, which is what guided me to make the decision I would be here this morning for this hearing. Because I came all the way in, and the work must go on.

So we will start with you, Dr. Anastas.

STATEMENT OF PAUL ANASTAS, PH.D., ASSISTANT ADMINISTRATOR, OFFICE OF RESEARCH AND DEVELOPMENT, AND SCIENCE ADVISOR, U.S. ENVIRONMENTAL PROTECTION AGENCY

Mr. ANASTAS. Thank you, Chairman Klobuchar, Chairman Boxer. It is a pleasure to be with you here this morning.

My name is Paul Anastas, the Assistant Administrator for the Office of Research and Development in EPA. It is a pleasure to discuss this important issue. It is also a pleasure to be here with my esteemed colleague from the NIEHS and the other panelists.

This issue is tremendously important, when we talk about the potential environmental factors related to autism and other neurodevelopmental disorders. I am a father of two small children. I know how essential it is that we do everything we can to ensure

the health and the safety and the well-being of our children going forward.

Autism can be a heartbreaking neurodevelopmental disorder that may prevent children from fully experiencing typically social interactions essential for well-being, for individual emotional and cognitive development. Autism spectrum disorder is a range of complex neurodevelopmental disorders characterized by social impairments, communication difficulties, and restricted and repetitive pattern disorders.

Autistic disorders, sometimes called autism disorders, or classical autism, is the most severe form of ASD. Other conditions along the spectrum include the milder form of ASD known as Asperger's Syndrome.

Scientists are uncertain about what causes ASD. However, many believe it could result from a variety of factors, including a combination of genes, environmental exposures, and gene-environment interactions. Evidence suggests that the rates of ASD are increasing in the United States as both of you mentioned in your opening statements.

As you know, children are especially susceptible to the effects of chemicals in the environment, because they eat, drink, and breathe far more than their body weight than adults. They absorb a greater proportion of many of the chemicals in the environment than adults do, and due to hand-mouth behavior, young children tend to have higher exposures to these contaminants.

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. We are learning that there are critical windows of susceptibility, both prenatally and in early childhood, in which the effects of exposures to environmental contaminants can be significantly more severe and can lead to permanent and irreversible disability. For these and many other reasons EPA is especially concerned about the potential effects of environmental chemicals on children's health and neurodevelopment.

Now, it has been suggested that improvements in diagnosis may be contributing to the perceived increase in ASDs. However, one recent publication from research supported by the EPA and NIEHS evaluated the rise in autism incidence in California from 1990 to 2006. They found that even when factors such as early diagnosis, changes in diagnostic criteria, and milder cases were taken into account they did not fully explain the observed increase. As a result, the extent to which the continued rise represents a true increase in the occurrence of autism still remains unclear.

Additionally, through a recent evaluation of autistic disorder data from long-term, approximately 10-year studies, EPA scientists found significant and surprisingly uniform timing of increases and cumulative incidence from 1988 to 1989, in Danish, Californian, and worldwide data sets. 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 reduced.

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. EPA's intramural research program focuses on susceptibility to chemicals and the factors underlying the susceptibility, the chemical mechanisms of action, and the relevance of effects to human health.

There are now alternative models and methods, including computational toxicology, which allows us to evaluate a much larger number of substances in the same amount of time. We have an extensive extramural research program that includes the children's research centers that we work hand in hand with our partners at NIEHS. And we are going to hear far more about those today, including the research of the University of California at Davis Center for Children's Environmental Health, which 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.

Also, we have studies in the Children's Center at the University of Medicine and Dentistry of New Jersey and several other centers, which we will be happy to discuss and are detailed in our written testimony.

Thank you for the opportunity to speak to you here this morning.

[The prepared statement of Mr. Anastas follows:]

TESTIMONY

Paul Anastas, PhD

Assistant Administrator for Research and Development and Science Advisor

U.S. Environmental Protection Agency (EPA)

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
August 3, 2010

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.

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Paul Anastas, Ph.D. is the Assistant Administrator for EPA's Office of Research and Development (ORD) and the Science Advisor to the Agency. Known widely as the "Father of Green Chemistry" for his groundbreaking research on the design, manufacture, and use of minimally-toxic, environmentally-friendly chemicals, Dr. Anastas has an extensive record of leadership in government, academia, and the private sector. At the time he was nominated by President Obama to lead ORD, Dr. Anastas was the Director of the Center for Green Chemistry and Green Engineering, and the inaugural Teresa and H. John Heinz III Professor in the Practice of Chemistry for the Environment at Yale University's School of Forestry and Environmental Studies. Prior to joining the Yale faculty, Dr. Anastas was the founding Director of the Green Chemistry Institute, headquartered at the American Chemical Society in Washington, D.C. From 1999 to 2004 he worked at the White House Office of Science and Technology Policy, concluding his service there as the assistant director for the environment. Dr. Anastas began his career as a staff chemist at EPA, where he rose to the positions of chief of the Industrial Chemistry Branch, and director of the U.S. Green Chemistry Program. It was during his work at EPA that Dr. Anastas coined the term "green chemistry."

Trained as a synthetic organic chemist, Dr. Anastas' research interests have focused on the design of safer chemicals, bio-based polymers, and new methodologies of chemical synthesis that are more efficient and less hazardous to the environment. A leading writer on the subjects of sustainability, green chemistry, and green engineering, he has published ten books, including "Benign by Design," Designing Safer Polymers," "Green Engineering" and his seminal work with co-author John Warner, "Green Chemistry: Theory and Practice."

Dr. Anastas has been recognized for his pioneering work with a host of awards and accolades including the Vice President's Hammer Award, the Joseph Seifter Award for Scientific Excellence, the Nolan Sommer Award for Distinguished Contributions to Chemistry, the Greek Chemical Society Award for Contributions to Chemistry, the Inaugural Canadian Green Chemistry Award, a Scientific American 50 Award for Policy Innovation, the John Jeyes Award from the Royal Society of Chemistry, and an Annual Leadership in Science Award from the Council of Scientific Society Presidents. He was a Special Professor at the University of Nottingham and an Honorary Professor at Queens University in Belfast where he was also was awarded an Honorary Doctorate.

Dr. Anastas earned his B.S. from the University of Massachusetts at Boston and his M.A. and Ph.D. in chemistry from Brandeis University.

Senate Environmental and Public Works Committee
Subcommittee on Children's Health Hearing
"State of Research on Potential Environmental Health Factors with Autism and Related Neurodevelopment Disorders"
Tuesday, August 3, 2010

Follow-up Questions for the Record

Senator Barbara Boxer

1. Assistant Administrator Anastas, your testimony states that 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 ... "

Can you give us an idea about how sensitive this development process is and what the science is showing regarding the ability of chemicals to impact such development?

Answer: Based on decades of research in animal models and in humans, we know that the development of the human brain is very sensitive to changes in these processes. For example, recent work examining human brain tissue found physical evidence for short-range over-connectivity of neurons in the outer layer of the brain's cortex in people that had been diagnosed with autism spectrum disorders (Avino and Hutsler in press).

A few industrial chemicals (e.g., lead, methylmercury, PCBs, arsenic, and toluene) are recognized causes of neurodevelopmental disorders and subclinical brain dysfunction (Grandjean and Landrigan 2006). It is critical to understand such impacts, because the nervous system, once damaged, has very little ability to repair itself. Therefore, in most situations, alterations in brain development, such as those that might result from exposures during fetal life or childhood, are permanent and cannot be reversed. For example, the developmental toxicity of acute exposure to methylmercury was evident from the large number of cases of spasticity, blindness and profound mental retardation in infants born to mothers who consumed fish from waters contaminated with high levels of mercury compounds released by a plastics plant into Minamata Bay, Minamata, Japan (Harada 1995), similar profound neurodevelopmental disorders were found in Iraqi infants after their mothers mistakenly consumed seed grain treated with high levels of methyl mercury fungicides during pregnancy (Elhassani 1982).

We currently lack toxicology data and mechanistic information on many of the chemicals registered for commerce in the United States with regard to their potential neurodevelopmental impacts, particularly at environmental exposure levels. To address the need for such information, EPA scientists are developing tools and models needed to assess the impact of environmental chemicals on the processes that are critical for nervous system and brain development, including how nerve cells grow, divide, make connections and communicate.

EPA's current research efforts in this arena focus on chemicals that may impact development of the nervous system, although not specific to autism, and are aimed at developing new, more efficient testing methods, using cell cultures that will allow rapid and cost-effective screening of thousands of chemicals. EPA recently completed testing of over 300 chemicals, mostly pesticides, for their potential impact on some of these processes (see for example, Radio et al., 2010; Brier, et al, 2010). A major future focus is on interpretation of these data to better inform decisions on how to prioritize the thousands of untested chemicals for further, more intense testing in whole animal studies. An advantage of this strategy is that the same chemicals can be screened for a wide variety of potential effects, and this will enable us to determine which chemicals specifically affect the nervous system as opposed to other systems and at what exposure levels. These results will help prioritize chemicals for further study in selected human populations to better understand potential associations between specific chemical or environmental exposures and the development of neurological disorders such as autism in human populations. Although epidemiology studies do not usually directly identify causation, they provide a body of evidence that helps regulators identify risk factors and inform decisions that may prevent exposures with potentially high risk.

2. Assistant Administrator Anastas, could you please describe what the current research is telling us about the potential for exposure to environmental toxins to increase the risk of disease impacts in future generations?

Answer: Many of the diseases that have been showing recent increases could have environmental factor(s) associated with them (e.g., autism (Rapin 1999; Ingram et al. 2000; Cambell et al 2006), ADHD (Bouchard et al. 2010; Hoffman et al. 2010), thyroid cancer (Ward et al. 2010)). In the case of autism, because we have limited national outcome tracking data and limited data on causation, it is difficult to determine whether the observed increases are actual increases in the incidence of autism, or are only apparent increases due to changes in the way autism is diagnosed and/or reported and tracked (see McDonald and Paul 2010).

Exposures to pregnant woman can impact development of the nervous system in their unborn child without measureable effects in the mother.. For example, recent research funded by EPA and the Department of Health and Human Services National Institutes of Health's National Institute of Environmental Health Services (NIEHS) showed that children born to women exposed during pregnancy to above average levels of polycyclic aromatic hydrocarbons in urban air pollution later had small but statistically significant decrements in IQs compared with those exposed to lower levels (Perera et al., 2009). Furthermore, exposure to pregnant inner city women in New York City to chlorpyrifos, used largely for cockroach control, has been associated with delayed neurodevelopment in inner-city infants (Rauh et al 2006), and smaller head circumference in newborns (Berkowitz et al 2004). A recent review summarizes what is known about associations between prenatal exposures to environmental contaminants such as lead, ethyl alcohol, methyl mercury and chlorpyrifos and autism (Landrigan 2010). Because such exposures

affect developmental processes in the fetus without inducing genetic changes, affected children do not typically pass these deficits on to their children. As you can see from the above studies, this topic remains and active area of research

Senator James M. Inhofe

1. Are the Autism Spectrum Disorders prevalence rates in other countries growing similarly to the rates in the U.S.? If not, can you explain this difference?

Answer: Autistic disorder (that is, classic or infantile autism, one of the most severe forms of autism spectrum disorders), appears to be increasing worldwide, and the increases in cumulative incidence of autistic disorder for these countries is different (see McDonald and Paul 2010, and their Supplemental Table 1, and citations there in). Some of the differences between countries may not be real, but rather apparent due to differences in access to health care and public health tracking methods. However, in the few long term studies where there this possibility has been examined, at least some of the observed increases in autistic disorder are due to an actual increase of autistic disorder in these populations over time (California (Hertz-Picciotto and Delwiche 2009) and Denmark (Parner et al. 2008). Possible factors associated with the differential increases in cumulative incidence between the different countries are unknown, but such differences could be due to different inherent genetic vulnerabilities of the populations in the different countries, or to differences in exposure of the populations in the countries to some environmental factor(s) associated with autistic disorder, or possibly both (see McDonald and Paul, 2010).

2. I am concerned that, in our federal research efforts, potential environmental causes are identified, but whether they actually contribute, or don't contribute, to autism is a question that, in many cases, is never finally resolved. Is there a way we can prioritize existing resources to exclude certain environmental causes, or confirm them once and for all, so researchers can move on to ask new research questions to advance our understanding of the causes of autism?

Answer: There are no current, formal approaches for rapidly screening all possible environmental factors for their possible association with autism per se. The lack of a reliable animal model of autism severely hampers our ability to screen or test chemicals for their potential to cause autism. However, EPA is developing improved approaches for rapidly screening large numbers of chemicals for their ability to alter development of nerve cells in culture, as described above (Radio et al., 2010). Rapid and cost-effective screening of thousands of chemicals will make it feasible to prioritize chemicals for further study, thus focusing resources on those chemicals most likely to impact the nervous system. Based on those results, more strategic and biologically plausible epidemiology and human health outcome studies can be designed to evaluate the relationship between the environment and autism. Over time longitudinal studies, such as the National Children's Study (www.nationalchildrensstudy.gov), may also provide insights into the root causes of diseases such as autism. The National Children's Study, led by the *Eunice Kennedy Shriver* National Institute of Child Health and Human

Development of the National Institutes of Health (NIH) in collaboration with a consortium of federal government partners including EPA, will examine effects of environmental influences on the health and development of 100,000 children across the United States, following them from before birth until age 21 (www.nationalchildrensstudy.gov). Data from the study may inform research into behavioral, learning, and mental health disorders like autism, as well as many other health conditions.

An alternative approach for reducing the number of potential environmental factors that may be associated with autism is to apply a weight-of-evidence approach to existing human data. This approach would include screening for novel or increasing exposures to chemicals (or other environmental factors) that specifically occurred around the period of time over in which measured increases in autistic disorders were detected (e.g., 1988-1989 birth cohorts in data examined by McDonald and Paul, 2010). This, coupled with toxicological and differential exposure information in different countries, could potentially allow some environmental factors to be excluded.

3. Would you characterize the environmental factors which may contribute to the rise in Autism Spectrum Disorders incidence as being predominantly a mixture of pollutants or single pollutants?

Answer: We don't know the answer to that question yet. There is a genetic component to autism (Hertz-Picciotto et al. 2006), but it does not follow a simple model of inheritance (Risch et al. 1999), and more than 29 genes currently are implicated (Sutcliffe 2008). Environmental exposures to exogenous environmental factors (e.g., intrauterine rubella, thalidomide, and valproate) during pregnancy have also been linked to the development of autism in some children, but not in all cases of exposure does this occur (Rapin 1999). Thus, it may be a complex interaction between exposure to environmental stressors with genetically susceptible subpopulations that leads to the phenotypic expression of autism (Altevogt et al. 2008, Hertz-Picciotto et al. 2006, Lawler et al. 2004). Also, a further complicating factor is that human populations are rarely exposed to a single environmental factor.

4. Would you suggest any additions to the Interagency Autism Coordinating Committee's Strategic Plan with regards to environmental pollutants as significant factors in causing Autism Spectrum Disorders? What about EPA's research program?

Answer: The Interagency Autism Coordinating Committee's 2010 Strategic Plan (http://iacc.hhs.gov/strategic-plan/2010/IACC_2010_Strategic_Plan.pdf) recognizes the potential role of environmental pollutants in the spectrum of suspected risk factors for autism. In the cross-cutting theme "Prevention," the document states, "Additionally, if one views ASD as a biological disorder triggered in genetically susceptible people by environmental factors, then prevention can include prevention of new cases of ASD through the identification and elimination of environmental causes" (p. 5). The Plan outlines a comprehensive and well thought out approach for exploring environmental factors in the context of the complexity of this disorder. It stresses the importance of

examining these factors during pregnancy and early childhood when susceptibility to environmental factors would be greatest, and calls for longitudinal studies to address the relationship between environmental factors and the likelihood of disease, while also examining known and emerging genetic susceptibility and gene-environment interactions. While EPA is not represented on this coordinating committee, the report notes that studies like those conducted in the NIEHS-EPA Children's Environmental Health and Disease Prevention Program are highly relevant to the issues raised in the report and should continue to be of high priority for Federal support. The latter is the only research funded by EPA that specifically addresses autism in children. EPA is a primary partner in and provides advice and assistance to the National Children's Study, a longitudinal study with enormous potential to address many of the recommendations in this autism strategy.

References

Altevogt, B. M.; Hanson, S. L.; Leshner, A. I. Autism and the environment: challenges and opportunities for research. *Pediatrics* **2008**, *121*, 1225-1229.

Avino TA and JJ Hutsler. Abnormal cell patterning at the cortical gray–white matter boundary in autism spectrum disorders. *Brain Research*, **2010**,*1360*:138-46.

Berkowitz GS, Wetmur JG, Birman-Deych E, Obel J, Lapinski RH, Godbold JH, Holzman IR, Wolff MS. In utero pesticide exposure, maternal paraoxonase activity, and head circumference. *Environ Health Perspect.*, **2004**, *112*:388-91.

Bouchard, MF, DC Bellinger, RO Wright, MG Weisskopf. Attention-deficit/hyperactivity disorder and urinary metabolites of organophosphate pesticides. *Pediatrics* **2010**, *125*:e1270-7.

Breier JM, Gassmann K, Kayser R, Stegeman H, De Groot D, Fritsche E, Shafer TJ.
Neural progenitor cells as models for high-throughput screens of developmental neurotoxicity: state of the science. *Neurotoxicol Teratol.* **2010**, 32:4-15.

Campbell, D. B; Sutcliffe, J. S.; Ebert, P. J.; Militerni, R.; Bravaccio, C,; Trillo, S.; Elia, M.; Schneider, C.; Melmed, R.; Sacco, R.; Persico, A. M.; Levitt, P. A genetic variant that disrupts *MET* transcription is associated with autism. *PNAS.* **2006**, *103*, 16834-16839.

Elhassani SB. The many faces of methylmercury poisoning. *J Toxicol Clin Toxicol* **1982**, 19:875-906.

Grandjean P and PJ Landrigan. Developmental neurotoxicity of industrial chemicals. *Lancet* **2006**, *368*:2167-2178.

Harada M. Minamata disease: methylmercury poisoning in Japan caused by environmental pollution. *Crit Rev Toxicol* **1995**, 25:1-24.

Hertz-Picciotto, I.; Croen, L. A.; Hansen, R.; Jones, C. R.; van de Water, J.; Pessah, I. N. The CHARGE Study: an epidemiologic investigation of genetic and environmental factors contributing to autism. *Environ. Health Perspect.* **2006**, *114*, 1119-1125.

Hertz-Picciotto, I.; Delwiche, L. The rise in autism and the role of age at diagnosis. *Epidemiology.* **2009**, *20*, 84-90.

Hoffman K, TF Webster, MG Weisskopf, J Weinberg, VM Vieira. 2010. Exposure to polyfluoroalkyl chemicals and Attention Deficit Hyperactivity Disorder in U.S. children aged 12-15 years. Environ Health Perspect online 15 June 2010.

Ingram, J. L.; Stodgell, C. J.; Hyman, S. L.; Figlewicz, D. A.; Weitkamp, L. R.; Rodier, P. M. Discovery of allelic variants of HOXA1and HOXB1: genetic susceptibility to autism spectrum disorders. *Teratology.* **2000,** *62,* 393-405.

Landrigan, PJ, What causes autism? Exploring the environmental contribution. *Curr Opin Pediatr,* **2010** *22,* 219-25.

Lawler, C. P.; Croen, L. A.; Grether, J. K.; Van de Water, J. Identifying environmental contributions to autism: Provocative clues and false leads. *Ment. Retard. Dev. Disabil. Res. Rev.* **2004,** *10,* 292-302.

McDonald ME and JF Paul. 2010. Timing of increased autistic disorder cumulative incidence. *Environ. Sci. Technol.* 44:2112-2118.

Parner, E. T; Schendel, D. E.; Thorsen, P. Autism prevalence trends over time in Denmark. *Arch. Pediatr. Adolesc. Med.* **2008,** *162,* 1150-1156.

Perera FP, Li Z, Whyatt R, Hoepner L, Wang S, Camann D, Rauh V. Prenatal airborne polycyclic aromatic hydrocarbon exposure and child IQ at age 5 years. *Pediatrics,* **2009** 124:e195-202.

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

Rapin, I. Autism in search of a home in the brain. *Neurology.* **1999,** *52,* 902-904.

Rauh VA, Garfinkel R, Perera FP, Andrews HF, Hoepner L, Barr DB, Whitehead R, Tang D, Whyatt RW. Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children. Pediatrics. **2006,** *118*:e1845-59.

Risch, N.; Spiker, D.; Lotspeich, L.; Nouri, N.; Hinds, D.; Hallmayer, J.; Kalaydjieva, L.; McCague, P.; Dimiceli, S.; Pitts, T.; Nguyen, L.; Yang, J.; Harper, C.; Thorpe, D.; Vermeer, S.; Young, H.; Hebert, J.; Lin, A.; Ferguson, J.; Chiotti, C.; Wiese-Slater, S.; Rogers, T.; Salmon, B.; Nicholas, P.; Petersen, P. B.; Pingree, C.; McMahon, W.; Wong, D. L.; Cavalli-Sforza, L. L.; Kraemer, H. C.; Myers, R. M. A genomic screen of autism: evidence for multilocus etiology. *Am. J. Hum. Genet.* **1999,** *65,* 493-507.

Sutcliffe, J. S. Insights into the pathogenesis of autism. *Science.* **2008,** *321,* 208-209.

Ward MH, BA Kilfoy, PJ Weyer, KE Anderson, AR Folsom, JR Cerhan. Nitrate intake and the risk of thyroid cancer and thyroid disease. *Epidemiology* **2010,** 21: 389-395.

Senator KLOBUCHAR. Thank you very much.
Dr. Birnbaum.

STATEMENT OF LINDA BIRNBAUM, PH.D., D.A.B.T., A.T.S., DIRECTOR, NATIONAL INSTITUTE OF ENVIRONMENTAL HEALTH SCIENCES, NATIONAL INSTITUTES OF HEALTH, AND DIRECTOR, NATIONAL TOXICOLOGY PROGRAM, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

Ms. BIRNBAUM. Chairman Klobuchar, Chairman Boxer, and Senator Udall, I am pleased to present testimony today on research related to neurodevelopmental disorders and to specifically discuss if environmental exposures are linked to the development of autism spectrum disorders.

My name is Linda Birnbaum. I am the Director of the National Institute of Environmental Health Sciences at the National Institutes of Health and the Director of the National Toxicology Program at the Department of Health and Human Services.

Scientists have made considerable progress in understanding how the brain and nervous system grow and function. It is becoming clear that neurodevelopmental disorders, such as autism spectrum disorders, attention deficit hyperactivity disorder, and learning disorders are likely due to a complex interplay of both genetics and the environment. Our research indicates that environmental exposures, including low-dose exposures, and lifestyle choices before a baby's birth and during early childhood do have an effect on the developing brain.

Autism spectrum disorders are developmental conditions that have increased in U.S. children in the past several years. NIEHS has significantly increased our funding this year to $9.3 million. I am also an active member of the Interagency Autism Coordinating Committee, a group of Federal agencies, autism advocates and parents who plan and coordinate a research agenda.

Our two largest efforts on autism are the EARLI study and CHARGE. In the EARLI study researchers at the Drexel University, University of California, and Johns Hopkins University are studying mothers who already have one child with autism and who are pregnant again. This study is one of the largest studies of its kind. It will follow 1,200 mothers during their pregnancy and their new babies until the age of 3 to identify prenatal and postnatal exposures that may be linked to autism.

The CHARGE study, which you will much more about from Dr. Pessah, which is coordinated by the NIEHS EPA Children's Centers at the University of California Davis, is looking at a wide range of environmental exposures and their effects on early neurodevelopment. This study is following more than 1,600 children in California from three groups: children with autism, children with other developmental days, and normally developing children.

So far, the most striking findings relate immune system alterations in children with autism, which points to the need for further study of the immune and nervous systems in the etiology of autism spectrum disorder. It is also important to note that the CHARGE study found no difference in mercury levels between children with autism and normally developing children.

I am happy to report that the American Recovery and Reinvestment Act allowed NIH to increase its support for autism research. Our funding is being used to study air pollution, polyfluoroalkyl compounds, better known as PFCs, and PFOA is the most common one; PFCs are the ones we think about, endocrine disrupting chemicals, smoking, alcohol use, medication, and infections as potential risk factors for autism.

The work we fund on autism and ASD is an important part of our overall investment in children's neurological development, which totaled more than $29 million last year, almost $18 million from the regular NIEHS appropriations, plus $11.5 million in ARRA funds. Development of the nervous system begins in the womb and extends throughout childhood.

During periods of rapid development, the brain is vulnerable. Even small changes in the timing of critical developmental events can have major consequences for brain structure and function. We call these critical developmental periods windows of susceptibility, during which different chemicals can affect the brain in specific and damaging ways.

For example, the amount of lead that is toxic to an infant is much less than the amount that would be toxic for an adult. So infancy, in this case, is a window of susceptibility.

Many studies have shown that mercury is also a developmental neurotoxicant. Studies in Bangladesh have found that arsenic and manganese in drinking water are associated with decreases in intelligence.

But metals are not the only toxic agents to affect IQ, learning, and memory. A study published last year from Columbia University showed that a mother's exposure to PAHS released from burning fossil fuels and tobacco can adversely affect a child's IQ. The IQ scores of children exposed in utero to high levels of PAHS were almost five points lower than those of less exposed children. In another report, Columbia University examined prenatal exposure to a common flame retardant, PBDEs. Core blood specimens were analyzed for selected flame retardant chemicals. The same children were examined for neurodevelopment at ages 1, 2, 3, 4, and 6. The research showed that these children, who had higher blood concentrations of the flame retardants, scored lower on tests of mental and physical development.

In addition to effects on learning, these same chemicals can also affect behavior. Early lead exposure has been associated with aggressive behavior at different age levels, from toddler to adolescent. Researchers at our Cincinnati Children's Center found that childhood exposure to lead and prenatal exposure to tobacco are risk factors for ADHD, possibly accounting for one-third of the cases in U.S. children.

A recent study from Mount Sinai's Children's Environmental Health Study found that increased concentration of pthalates in the mothers during pregnancy were associated with increased aggression as well as conduct problems, attention problems, and depression in the children. Pesticides are also being investigated in relation to ADHD. Our Harvard Center just released a report showing an association between exposure to organophosphate pesticides and development of ADHD.

In summary, environmental influences on brain development, behavior, and other neurological outcomes of public health concern are a rapidly growing area of environmental health sciences and a high priority for NIEHS. We believe that our research will advance our understanding of these conditions, including autism, providing new information for prevention and treatment for children.

Thank you for the opportunity to testify. I would be happy to answer questions.

[The prepared statement of Ms. Birnbaum follows:]

Testimony before the
Subcommittee on Children's Health
Committee on Environment and Public Works
United States Senate

Statement for hearing entitled, "State of Research on Potential Environmental Health Factors with Autism and Related Neurodevelopment Disorders"

Statement of
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Chairman Klobuchar, Ranking Member Alexander, and distinguished members of the Subcommittee—I am pleased to appear before you today to present testimony on and the state of research efforts regarding potential environmental factors related to the development of autism and other neurodevelopmental disorders. My name is Linda Birnbaum; I am the Director of the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health and the National Toxicology Program (NTP) within the Department of Health and Human Services (HHS).

Scientists have made tremendous progress in understanding how the brain and nervous system grow and function. Research supported by NIEHS has clearly shown that it is not just genetics, but the complicated interplay of both genes and the environment that determines the risk of many neurodevelopmental disorders. We now have new information on the role that early environmental exposures may play in the development of a broad spectrum of childhood and adult disorders, including autism, attention deficit hyperactivity disorder (ADHD), and learning disorders. NIEHS-supported researchers are beginning to unravel some of the mysteries of how neurodevelopment may be impaired by looking at the possible effects of timing and concentration of environmental and lifestyle exposures (e.g., diet or smoking), including low-dose exposures before birth and during early childhood, on the vulnerability of the developing brain.

Environment and Autism

Autism spectrum disorder (ASD) is a neurodevelopmental condition whose rates have increased significantly in U.S. children in the past several years.[1] Much research is now focused on this disorder, and NIEHS has significantly increased its funding in this area in recent years. NIEHS spent $9.3M on autism in FY 2009, of which $4.4M was from our regular appropriation and $4.9M was from funds provided under the American Recovery and Reinvestment Act (ARRA). I am an active member of the Interagency Autism Coordinating Committee (IACC), a group of Federal agencies and public members (parents and people living with autism) that works to plan and coordinate a research agenda that simultaneously meets the goals of science and reflects the input and concerns of the autism community.

NIEHS's two largest efforts on autism are the Childhood Autism Risks from Genes and the Environment, or CHARGE study, and the Early Autism Risk Longitudinal Investigation, or EARLI study. In the EARLI study, researchers at the Drexel University School of Public Health are enrolling mothers who have a child with autism and who are pregnant again. One of the largest studies of its kind, this longitudinal study will follow 1,000 mothers during their pregnancy and their new babies through age three to identify prenatal, neonatal, and early postnatal exposures that may influence their risk of developing autism. The EARLI study is based on the theory that detection of autism risk factors will be enhanced by prospective data collection during the pregnancy period, and that a cohort of pregnancies at higher risk for autism (because the mothers have a previous child with autism) provides an efficient strategy for detecting such risk factors. This study is part of the trans-NIH Autism Centers of Excellence (ACE) Program and is jointly funded by NIEHS and three other NIH Institutes (the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), the

[1] http://www.cdc.gov/ncbddd/autism/data.html

National Institute of Mental Health (NIMH), and the National Institute of Neurological Disorders and Stroke (NINDS)) and the advocacy group Autism Speaks.

The CHARGE study is coordinated by the Children's Center at the University of California at Davis and co-funded by NIEHS and EPA. Launched in 2003, it is the first large-scale human population case-control study of children with autism. Researchers are looking at a wide range of environmental exposures and their effects on early development in more than 1,600 California children. Three groups of children are enrolled in the CHARGE study: children with autism, children with developmental delay who do not have autism, and children from the general population. All of the children are evaluated for a broad array of exposures and susceptibilities with the goal of better understanding the causes and contributing factors for autism or developmental delay.

Heavy metals are one of the classes of exposure being investigated in the CHARGE study. A recent paper discussed study findings that demonstrated that current blood levels of mercury do not differ in children with autism versus controls when adjustments for fish consumption are made.[2] Additional analyses of mercury are underway to more directly address its role in development of autism and to better understand the mechanism of action. Perhaps the most interesting new findings from the CHARGE study relate immune system alterations in children to the development of autism. These findings point to the need for further study on the interface of the immune and nervous systems in autism etiology. [3 4 5 6]

ARRA provided a key opportunity to increase NIH support for autism research. NIEHS joined four other NIH institutes (the National Institute of Mental Health, , the National Institute of Neurological Disorders and Stroke, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, and the National Institute on Deafness and Other Communication Disorders) in a broad initiative soliciting applications to address the IACC strategic plan, including objectives related to potential environmental contributors to autism. Four ARRA grants were awarded by NIEHS through this initiative. These grants capitalize on existing studies, including the CDC Study to Explore Early Development (SEED), CHARGE, the Finnish National Birth cohort, and the Early Markers of Autism Risk (EMAR) study. ARRA funding is being provided:

- To examine whether air pollution due to traffic, a common environmental exposure, increases risk for ASD. This study will also look at genes that process pollutants in the

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[2] Hertz-Picciotto I, Green PG, Delwiche L, Hansen R, Walker C, Pessah IN. Blood mercury concentrations in CHARGE study children with and without autism. Environ Health Perspect 2010;118:161-166.
[3] Gregg JP, Lit L, Baron CA, Hertz-Picciotto I, Walker W, Davis RA, Croen LA, Ozonoff S, Hansen R, Pessah IN, Sharp FR. Gene expression changes in children with autism. Genomics. 2008 Jan;91(1):22-9.
[4] Heuer L, Ashwood P, Schauer J, Goines P, Krakowiak P, Hertz-Picciotto I, Hansen R, Croen LA, Pessah IN, Van de Water J. Reduced levels of immunoglobulin in children with autism correlates with behavioral symptoms. Autism Res 2008 Oct;1(5):275-283.
[5] Enstrom AM, Onore CE, Van de Water JA, Ashwood P. Differential monocyte responses to TLR ligands in children with autism spectrum disorders. Brain Behav Immun 2010 Jan;24(1):64-71.
[6] Ashwood P, Enstrom A, Krakowiak P, Hertz-Picciotto I, Hansen RL, Croen LA, Ozonoff S, Pessah IN, Van de Water J. Decreased transforming growth factor beta1 in autism: a potential link between immune dysregulation and impairment in clinical behavioral outcomes. J Neuroimmunol. 2008 Nov 15;204(1-2):149-153.

body to determine if they are different in children with and without autism, and to see if they interact with air pollution to increase autism risk.[7]

- To determine whether polyfluoroalkyl compounds, or PFCs, which are widespread and persistent industrial pollutants that may interfere with the actions of hormones, are found at higher levels in samples from newborns who are later diagnosed with autism as compared to samples from newborns that develop normally.[8]

- To analyze several types of chemicals—including pyrethroid pesticides, flame retardants (such as PBDEs), and plasticizers (such as bisphenol A and phthalates)—that are being found in greater amounts in the environment but have not previously been looked at in relation to their potential effects on autism. This study will expand an existing autism study by adding collection and analysis of household dust and a food frequency questionnaire to determine exposures.[9]

- To identify genes whose effects on ASD may vary depending on the mother's exposures during pregnancy (including smoking and alcohol use, medication, and infection) using data obtained on 500 autism cases and controls through SEED, a large epidemiologic investigation of autism.[10]

NIEHS also provided ARRA supplements to autism investigators, including a supplement to hire additional outreach coordinators for the EARLI study, new personnel to speed up analysis and publication of pending CHARGE study findings, and support for home visits to CHARGE families to collect dust samples for analysis of additional exposures.

Neurodevelopment and Cognition

The work we fund on autism spectrum disorders is an important part of our overall investment in children's neurological development, which totaled over $29 million in FY2009 (almost $18M from the regular NIEHS appropriation plus $11.5 million in ARRA funds.) With this investment, NIEHS supports a wide range of studies covering the role of environmental effects on children's neurological development and behavior. While the research mentioned below is not specific for disorders related to autism spectrum disorders, the research will provide us with a better general understanding of neurological development and behavior in children.
Development of the nervous system begins in the womb and extends throughout childhood. During these periods of rapid development, the brain is vulnerable to some environmental exposures that may have the potential to disrupt the chemical signals that organize development. Even small changes in the timing of critical developmental events can potentially have major consequences for brain structure and function. Thus, even brief adverse exposures at these vulnerable stages can have lasting effects on adult brain function .[11] [12] We refer to "windows of

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[7] 1 R21 ES019002-01 -- Investigating Gene-Environment Interaction in Autism: Air Pollution – McConnell, Robert S. (CA)
[8] 1 R01 ES019003-01 -- Prenatal Exposure to Polyfluoroalkyl Compounds in the EMA Study – Croen, Lisa A. (CA)
[9] 1 R01 ES015359-03S2 – The CHARGE Study—Autism Risk from Genetics and the Environment – Hertz-Picciotto, Irva (CA)
[10] 1 R01 ES019001-01 -- Genome-wide Environment Interaction Study for Autism: The SEED study – Fallin, Danielle (contact); Newschaffer, Craig (MD)

[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)

susceptibility" to mean the life stage at which the brain is exposed, during which different agents can affect the brain in specific and deleterious ways. For example, the dose of lead that is neurotoxic to an infant is much less than the dose that would be neurotoxic for an adult, so infancy in this case is a "window of susceptibility."[13] [14] [15] Our full research portfolio on environmental impacts on brain and nervous system development gives us a full scientific context that may help us interpret results from our autism studies.

Learning disabilities are on the rise in the United States[16], and we now have a significant body of information on how exposure to certain environmental agents can affect children's intelligence quotients (IQs). For example, scientific literature attests to the effects of lead exposure in early life on IQ. [17] [18] The more recent studies of lead have detected cognitive effects even below the CDC action level of 10 micrograms of lead per deciliter of blood.[19] CDC's National Health and Nutrition Examination Survey (NHANES) from 1999-2000 estimated that 434,000 children ages 1-5 years had blood lead levels greater than or equal to 10 micrograms per deciliter.[20] Mercury also has been shown in multiple studies to be a developmental neurotoxicant. And studies in Bangladesh have found that concentrations of arsenic[21] and manganese[22] in drinking water are associated in a dose-dependent fashion with decreases in intelligence.

We are finding that metals are not the only toxic agents to affect IQ, learning, and memory. A study published last year from Columbia University showed that a mother's exposure to urban air pollutants known as polycyclic aromatic hydrocarbons (PAHs) can adversely affect a child's IQ. PAHs are released into the air from the burning of coal, diesel, oil, gas, and other organic substances such as tobacco. In urban areas, motor vehicles are a major source of PAHs. The researchers found that children in New York City who were exposed *in utero* to high levels of PAHs had full-scale and verbal IQ scores that were 4.31 and 4.67 points lower than those of less exposed children.[23]

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[13] (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

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

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

[16] http://www.cdc.gov/nchs/data/series/sr_10/Sr10_237.pdf

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

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

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

[20] http://www.cdc.gov/mmwr/preview/mmwrhtml/ss5210a1.htm

[21] Wasserman, G.A., X. Liu, F. Parves, H. Ahsan, P. Factor-Litvak, A. van Geen, V. Slavkovich, N.J. LoIacono, Z. Cheng, I. Hussain, H. Momataj, and J.H. Graziano. September 2004. Water Arsenic Exposure and Children's Intellectual Function in Araihazar, Bangladesh. *Environmental Health Perspectives* 112(13):1329-1333.

[22] Wasserman, G.A., X. Liu, F. Parvez, H. Ahsan, D. Levy, P. Factor-Litvak, J. Kline, A. van Geen, V. Slavkovich, N.J. LoIacono, Z. Cheng, Y. Zheng, J.H. Graziano. 2005. Water Manganese Exposure and Children's Intellectual Function in Araihazar, Bangladesh. *Environmental Health Perspectives*. 114(1):124-129.

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

In another report, Columbia University researchers examined the association of prenatal exposure to a common flame retardant called PBDE (polybrominated diphenyl ether) with neurodevelopment. Two hundred and ten cord blood specimens were analyzed for selected PBDE chemical varieties and neurodevelopmental effects in the children were assessed at ages 1, 2, 3, 4, and 6 years. The findings demonstrated that adverse effects on neurodevelopment were related to cord blood PBDE concentrations.[24] [25] These investigators are currently leading a longitudinal cohort study initiated following the 9/11 attacks that includes 329 participants who were pregnant at the time of the event and delivered babies in one of three hospitals in lower Manhattan, to look at potential effects of prenatal toxic air exposures on neurodevelopment.

In a very different community, NIEHS funded researchers have been conducting a long-term, ongoing study of effects on growth, intellectual function, and ADHD of Inuit children exposed pre-and post-natally to polychlorinated biphenyls (PCBs), methylmercury, lead, and docosahexaenoic acid (DHA), which is the omega-3 fatty acid that is critically important for growth and development of neurons and retinal cells. The study, which was designed to be culturally appropriate to ensure accurate findings (cognitive tests were translated into the native Inuit language and adjusted for cultural understanding), has produced several unpublished findings concerning the transmission of pollutants in breastfeeding and the benefits of DHA during pregnancy. Although these findings will be published in the fall, specifics cannot be shared at this time, since our researchers agreed at the beginning of the study to review their findings first with the Nunavik Nutrition and Health Committee and the Municipal Councils of the three major Inuit villages where data collection took place. This study also is looking at transmission of methylmercury through breastfeeding; child body burdens from birth through 11 years of age; and the potential beneficial effects for children of increased intake of DHA by mothers, particularly during the third trimester of pregnancy.

Neurobehavioral Outcomes: ADHD

In addition to effects on learning, NIEHS scientists have found that early environmental exposure to some of these same chemicals, such as lead and mercury, can affect behavior. Early lead exposure, for example, has been associated with aggressive behavior at different age levels from toddler to adolescent.[26] Investigators at Cincinnati Children's Hospital, one of NIEHS's Centers for Children's Environmental Health and Disease Prevention, co-funded by NIEHS and the Environmental Protection Agency, are conducting research on childhood lead and prenatal tobacco exposure and the potential connection to development of ADHD in children. These investigators have shown that such exposures, when linked with certain genes for susceptibility, may act as precursors to development of ADHD. These investigators also found that childhood

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

[25] The plasma samples were analyzed for the following PBDE congeners (by International Union of Pure and Applied Chemistry numbers): 2,2,2',4,4'-tetraBDE (BDE-47); 2,2',3,4,4'-pentaBDE (BDE-85); 2,2',4,4',5-pentaBDE (BDE-99); 2,2',4,4',6-pentaBDE (BDE-100); 2,2',4,4',5,5'-hexaBDE (BDE-153); 2,2',4,4',5,6'-hexaBDE (BDE-154); 2,2',3,4,4',5',6-heptaBDE (BDE-183); and 2,2',4,4',5,5'-hexaBB (BB-153).

[26] Hornung RW, Lanphear BP, Dietrich KN. Age of greatest susceptibility to childhood lead exposure: a new statistical approach. Environ Health Perspect. 2009 Aug;117(8):1309-12

exposure to lead and prenatal exposure to tobacco are risk factors for ADHD, accounting for about one out of three cases of ADHD in U.S. children.[27]

A recent report in NIEHS's journal *Environmental Health Perspectives* (*EHP*) looked at the association of prenatal phthalate exposure with behavior and executive function[28] at 4-9 years of age in the Mt. Sinai Children's Environmental Health Study cohort. The study found that increased concentrations of certain byproducts of phthalate exposure in the urine of mothers during pregnancy were associated with poorer scores on a variety of measures of aggression, as well as conduct problems, attention problems, and depression in their children.[29] Another *EHP* publication just released online, by NIEHS-funded investigators at Boston University School of Public Health, measured exposures to four types of polyfluoralkyl compounds (PFCs) and their relation to ADHD, using data from almost 600 children taken from the National Health and Nutrition Examination Survey (NHANES) from HHS's Centers for Disease Control and Prevention (CDC). PFCs are widely used in consumer products and have been shown in animal data to be potential neurotoxicants. This study has shown increased risk of ADHD in children with higher serum PFC concentrations.[30]

NIEHS-funded researchers at Harvard University have recently published compelling findings showing associations between prenatal exposure to methylmercury, in some cases combined with PCBs, and memory and learning impairment, as well as adverse behavior and decreased impulse control in adolescents.[31] This work has provided the basis for a pilot project within a Children's Environmental Health and Disease Prevention Research Formative Center that NIEHS recently funded, which will focus on the relationship of exposure to bisphenol A and phthalates with neurobehavioral outcomes in adolescents.

Pesticides, both agricultural and home use, are also being investigated in relation to ADHD. The center at Harvard University has just released a report showing an association between exposure to organophosphate pesticides and development of ADHD.[32] Although we do not yet know the mechanism underlying these associations, these researchers are actively investigating these questions.

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[27] Froehlich TE, Lanphear BP, Auinger P, Hornung R, Epstein JN, Braun J, Kahn RS. Association of tobacco and lead exposures with attention-deficit/hyperactivity disorder. Pediatrics 2009 Dec;124(6):e1054-1063

[28] The term executive function describes a set of cognitive abilities that control and regulate other abilities and behaviors. Executive functions are necessary for goal-directed behavior. They include the ability to initiate and stop actions, to monitor and change behavior as needed, and to plan future behavior when faced with novel tasks and situations.

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

[30] Hoffman K, Webster TF, Weisskopf MG, Weinberg J, Vieira VM, 2010 Exposure to Polyfluoroalkyl Chemicals and Attention Deficit Hyperactivity Disorder in U.S. Children Aged 12-15 Years. Environ Health Perspect doi:10.1289/ehp.1001898 Link to article

[31] Sagiv SK, Thurston SW, Bellinger DC, Tolbert PE, Altshul LM, Korrick SA. Prenatal organochlorine exposure and behaviors associated with Attention Deficit Hyperactivity Disorder in schoolaged children. Am J Epidemiol 2010;171:593-601.

[32] Bouchard MF, Bellinger DC, Wright RO, Weisskopf MG. Attention-deficit/hyperactivity disorder and urinary metabolites of organophosphate pesticides. Pediatrics 2010;125(6):e1270-e1277.

In summary, environmental influences on brain development, behavior, and other neurological outcomes of public health concern are a rapidly growing area of environmental health sciences and a high priority for NIEHS. We believe that our investments will help to advance our understanding of these conditions, and provide critically needed information to drive prevention and treatment options for children. Thank you for the opportunity to testify; I would be very happy to answer your questions.

Responses to Questions for the Record
submitted to
Linda Birnbaum, Ph.D.
Director
National Institute of Environmental Health Sciences
National Institutes of Health
and Director, National Toxicology Program
U.S. Department of Health and Human Services

following August 3, 2010, hearing entitled,
"State of Research on Potential Environmental Health Factors with Autism and Related Neurodevelopment Disorders"
Subcommittee on Children's Health
Committee on Environment and Public Works
United States Senate

Questions from Senator Barbara Boxer

1. Director Birnbaum, could you please go into more detail on the "Childhood Autism Risks from Genes and the Environment" study, which is based at the University of California at Davis, and jointly funded by EPA and NIEHS? In particular, could you please describe the types of environmental toxins this study is researching and the issues this research has raised regarding the potential effect of the immune system on the development of autism?

   Response: The Child Autism Risk for Genetics and Environment (CHARGE) is led by investigators at the University of California at Davis. CHARGE is a comprehensive, population-based case-control investigation of underlying causes for autism and triggers of regression. The study includes three groups: children with autism, children with developmental delay but not autism, and children selected at random from the general population. Since the study was launched in 2003, more than 1200 children, their parents and siblings have been enrolled. This includes 641 children with a diagnosis of autism, 281 children with developmental delay, and 355 children from the general population.

   The major classes of exposures under consideration in CHARGE are: pesticides; metals; persistent pollutants that act as endocrine disrupters; infections; medical treatments and procedures; and medications. These cover a range of hypothesized mechanisms that might interfere with development of the central nervous system including: direct interference with cell differentiation and migration; synaptogenesis (the formation of connections between nerve cells) or dendritic branching and pruning; effects on

immune function and/or induction of inflammatory responses; alterations in the hormonal milieu; or other actions affecting brain chemistry. The CHARGE study has the ability to assess exposures from all of these five groups, using biological specimens, medical records, interview and other directly collected information, and existing exposure-related databases.

A large body of work generated from CHARGE investigators has strengthened the hypothesis that significant alterations in the immune system may play a critical role in some individuals with autism.[1] One finding of special note is the presence of a unique pattern of circulating autoantibodies that target fetal brain in a subset of mothers of children with autism.[2] This finding may have use in biomarker development and could suggest new avenues for future therapeutics and prevention. Other recent findings point to potential interactions between environmental exposures and immune alterations observed in autism.

Other important findings emerging from the CHARGE study involve the relationship between immune alterations and behavioral symptoms in children with autism. Elevated plasma levels of cytokines (IL-1β, IL-6, IL-8 and IL-12p40), i.e., regulatory proteins released by immune system cells, were correlated with behavioral severity in these children (Ashwood et al., 2010).[3] The characterization of immunological parameters in autism may help to identify mechanisms that are important in the etiology of autism spectrum disorders (ASDs) in a subgroup of subjects. The relationship between environmental exposures and altered immune function in children with autism, and the association of these alterations with specific behavioral impairments, are continuing areas of high priority by CHARGE investigators.

2. Director Birnbaum, your testimony refers to the National Institutes of Environmental Health Sciences' use of funds from the American Recovery and Reinvestment Act to facilitate research on autism. Can you describe in a little more detail some of the benefits that this money provided to autism research that NIEHS is helping to fund?

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[1] Goines P, Van de Water J. The immune system's role in the biology of autism. *Curr Opin Neurol.* 2010 Apr;23(2):111-7.

[2] Braunschweig D, Ashwood P, Krakowiak P, Hertz-Picciotto I, Hansen R, Croen LA, Pessah IN, Van de Water J. Autism: maternally derived antibodies specific for fetal brain proteins. *Neurotoxicology.* 2008 Mar;29(2):226-31. Epub 2007 Nov 6

[3] Ashwood P, Krakowiak P, hertz-Picciotto I, Hansen R, Pessah I, Van de Water J. Elevated plasma cytokines in autism spectrum disorders provide evidence of immune dysfunction and are associated with impaired behavioral outcome. *Brain Behav Immun* 2010 Aug 10.

Response: NIEHS used funds from the American Recovery and Reinvestment Act (ARRA) to fund four new grants on autism and three supplements to existing autism grants. Further descriptions of the four new grant awards can be found in the ARRA section on our website at http://tools.niehs.nih.gov/recovery/index.cfm?action=recovery.search, but a brief description of each is below:

- *R01ES019001, Genome-wide Environment Interaction Study for Autism: the SEED Study* is being done at Johns Hopkins University, using the Study to Explore Early Development (SEED), a multisite case-control investigation of 900 children with ASDs, 900 typically developing controls, and 900 children with non-autism developmental impairments. ARRA funds are enabling these investigators to extend the analysis of this study cohort to identify single-nucleotide polymorphisms (SNPs) within genes, whose effects on ASDs may vary in combination with exposure categories related to maternal exposures such as smoking and alcohol use during pregnancy, infections, and use of medications.

- *R21ES019002-01, Investigating Gene-Environment Interaction in Autism: Air Pollution* is a study at the University of Southern California that is investigating the association of air pollution, with autism. Using data collected as part of the CHARGE study, these investigators are assessing the role of traffic-related air pollutants in autism risk; they also are genotyping 384 SNPs in 17 candidate genes to examine air pollutant-SNP interactions.

- *R01ES019003, Prenatal Exposure to Polyfluoroalkyl Compounds in the EMA Study* is being done at the Kaiser Foundation Research Institute in Oakland, CA. This study is extending an earlier project called the Early Markers for Autism (EMA) study, an innovative investigation of biologic markers for autism that banks samples from mother-baby pairs and compares three groups: children with ASDs, children with developmental disabilities but not autism, and children selected at random from the general population. The ARRA award will permit analysis of maternal samples for polyfluoroalkyl compounds (PFCs), which are ubiquitous persistent organic compounds that have developmental toxicity and may be endocrine disruptors.

- *R01ES019004, Prenatal Factors and Risk of Autism in a Finnish National Birth Cohort* is being done at the New York State Psychiatric Institute, drawing upon data and samples from pregnancies in Finland between 1987 and 2007. Samples from mothers of autism cases and mothers of healthy controls will be analyzed

for environmental factors including infections, immune abnormalities, hormones, and smoking.

The three supplements to existing grants were targeted to provide extra resources to ongoing autism studies, either for collection of additional samples or to speed analysis and publication. Two are supplements to the CHARGE study, based at the University of California-Davis. To date, this study has collected data from medical records, questionnaires, and biological specimens such as blood and urine from more than 1200 children with autism and controls. One funding supplement was awarded to expand and improve on environmental assessment for this cohort, adding collection and laboratory analysis of dust samples from their homes; quantitative analysis of pyrethroid and organophosphate pesticides, phthalates, and Bisphenol-A, as well as some of their metabolites; and a food frequency questionnaire for the pregnancy and early childhood periods. The second supplement provides for additional staff for data analysis, writing and publication of the enormous amount of data being amassed through the study.

The third supplement is augmenting the work on the Early Autism Risk Longitudinal Investigation, or EARLI, to increase outreach and accelerate recruitment and enrollment. In particular, activities are being undertaken to expand enrollment diversity and enhance retention. The supplemental funds are being used for additional field worker positions as well as website development and Spanish-language translation.

3. Director Linda Birnbaum, could you please go into more detail on the current state of research on the types of toxic substances, including heavy metals and air pollution, which may be harming IQ, learning, and memory?

Response: The National Institutes of Environmental Health Sciences (NIEHS) has a robust investment in this area, investigating a wide range of neurotoxicants and their effects on neurological development. In FY 2009, we funded research on children's neurological health at a level of close to $30 million dollars ($17.8 million through our regular appropriation and $11.6 million through ARRA). Researchers are studying the neurotoxic properties of metals such as lead, arsenic, tin, mercury, and manganese, as well as other chemicals and exposures such as pesticides, tobacco smoke, polychlorinated biphenyls (PCBs), and PBDEs. NIEHS-funded research is using the latest brain imaging techniques in adults and children, to determine the impact of early life exposure on the structure and function of the brain. NIEHS's investment also includes basic research on the mechanisms and pathways by which toxicants may cause damage to the developing brain, including pathways that work through endocrine or immune mechanisms.

Questions from Senator James M. Inhofe

1. Do you feel that federal agencies like the Center for Disease Control and Health Resources and Services Administration could better direct some of their resources to more adequately serve and protect our nation's children?

   Response: Although you would need to discuss this issue with the agencies themselves for more specific information, I am confident that our sister Department of Health and Human Services agencies are working hard to make sure that their decisions for prioritization of resources are informed by the best and most recent scientific and public health information.

2. I am concerned that, in our federal research efforts, potential environmental causes are identified, but whether they actually contribute, or don't contribute, to autism is a question that, in many cases, is never finally resolved. Is there a way we can prioritize existing resources to exclude certain environmental causes, or confirm them once and for all, so researchers can move on to ask new research questions to advance our understanding of the causes of autism?

   Response: In fact, the process you describe is happening all the time as part of the scientific enterprise. Scientists generate and test hypotheses, new data emerge, and gradually an overall consensus forms that moves the entire field forward. It is not a top-down process but an organic synthesis that occurs across an entire field; the emerging consensus may not be 100%, but over time, as more data accumulate, the curve begins to approach 100%. NIEHS strives to stay on top of the most recent scientific publications and thinking as we assess the upcoming needs of any particular area of science. To help our scientific staff do this, we convene workshops with outside scientists to help us evaluate the latest information and identify areas of science for new investment. In addition, NIH convenes committees of outside scientists to help us review the applications we receive and judge whether the proposed research is well-founded and worthy of support. In the case of autism, we also have the Interagency Autism Coordinating Committee, which provides a forum for scientists and public members to meet, discuss the latest science, and identify areas of research for further exploration.

Senator KLOBUCHAR. Thank you very much to both of you.

I was just trying to put myself in the shoes of like a pregnant mom right now, or someone who has a baby that they are afraid has autism, and they don't know what is wrong, and trying to figure out exactly what the state of the research is. I thought your comment at the end, Dr. Birnbaum, was something we all believe, that chemicals do affect children's development and their brain. That is why I worked so hard on that children's product bill with the lead, and the Chairman and others and Senator Udall have worked on lead paint and other issues like that.

But I wanted to just narrow in on this autism issue. You mentioned two things specifically, was that one of the studies had shown no difference in the mercury levels of kids with autism and with not. Is that right?

Ms. BIRNBAUM. That is correct. That is from the CHARGE study. I think maybe Dr. Pessah will talk more about that.

Senator KLOBUCHAR. Then the other thing you mentioned, though, there was a difference in the immune systems. Do you want to elaborate on that?

Ms. BIRNBAUM. I think I can just kind of give you the bottom line. It appears that the immune systems of these children may be altered. They appear that they may be showing more symptoms, or symptoms that may develop into autoimmunity.

And again, I think Dr. Pessah will talk more about those findings. But I think it is important to understand that autoimmunity is another of the conditions in our country which is rapidly increasing over the past 10 to 20 years.

Senator KLOBUCHAR. So, could that have something to do—could that be the key for us trying to figure out the cause here because of the difference that has been found, or not?

Ms. BIRNBAUM. No, no, I think the point is that there is growing suggestion that environmental factors may be playing a role in the increase in autoimmunity. Part of the syndrome, if you want to use that word, for autism spectrum disorders, may involve alterations in the immune system.

Senator KLOBUCHAR. OK. So what you are saying is, and I will let you answer this, too, Dr. Anastas, is that it is finding that there is a difference with the autoimmune systems. We know that autoimmune system differences can be attributed to environmental factors, and that that could lead us to believe that the environmental factors could have something to do with who has autism and who doesn't.

Ms. BIRNBAUM. I think alterations in the immune system may be one part of the autism puzzle. I think the role of environmental factors in the increase in autism is in large part because you can't—our genes don't change over a generation. Our genes take multiple generations to change. And the rapid increase in autism, which was indicated by work that was done at UC Davis. The CDC has done continual analyses indicating that 1 in 70 boys is developing autism.

Senator KLOBUCHAR. I take it that you both believe there has actually been an increase? Some people say, oh, it is diagnosing that they didn't do before. But you both believe there has been an increase?

Ms. BIRNBAUM. Right. I think the study that, again, that is coming out of the UC Davis group that Dr. Anastas referred to, clearly shows that at least in California only 30 percent of the increased incidence can be potentially due to differential diagnosis.

Senator KLOBUCHAR. Dr. Anastas.

Mr. ANASTAS. Thank you.

Yes, and I would just add that in addition to the study that was just referred to, there is an additional study worldwide that shows that the rise in incidence cannot be attributed to changes in diagnosis alone.

There are a couple of very important points that have been made that I just wanted to emphasize. This window of susceptibility is something that can't be overemphasized. When we talk about what the doses or the levels of mercury, for example, might be the same, we need to recognize that that is not the entirety of the story. When you are exposed, whether it is in utero or in early childhood, it can be a difference in reaction because of the level and the stage of development that you are in.

So merely because one person may be exposed to the same levels as another, that is not the entirety, and that is something that is a very important area for research.

The other is we often get into this discussion about whether it is environment or genetics. I think there is a growing body of knowledge that it is not one or the other. As Dr. Birnbaum just stated, our genetics can't change this quickly in order to explain the increase in incidence. So what we are saying is that it is an interaction of the environment and genetic susceptibility, where certain triggers are released because of environmental exposures.

Senator KLOBUCHAR. Thank you.

Senator Boxer.

Senator BOXER. First of all, thank you very much, both of you, for your clarity. I remember many years ago meeting, when I was in local government, meeting parents who had children with autism. And then, they were being told it was the way they were raising their children, that there was something with the mother-child relationship. Honestly, I saw the look on parents' faces. They were devastated. That is where the science was.

We clearly have moved to a different place now, where we are looking at the genes, and we are looking at the chemicals that either the parents or the child have been exposed to. So I think there is a very important message to parents out there: do not give up hope. We are going to figure this thing out.

The fact that we are only spending $9 million on autism, something that affects 1 out of 110 children, is just amazing to me. And it goes to where our priorities are. So I wanted to ask Director Birnbaum, again, just if you could lay out for me how much did you get in the Economic Recovery and Reinvestment Act to facilitate the research. And if you could slowly tell me what that is exactly.

Ms. BIRNBAUM. NIH has, as you know, got $10 billion, or $10.4 billion, including the comparative effectiveness research dollars under the Stimulus Act. NIEHS, including our Superfund program, got about $190 million to conduct research under the Stimulus Act. Our funding that we have committed of our ARRA funds was about $9 million, no, $11.5 million, excuse me, related to

neurodevelopmental disorders. About $4.9 million of that was stimulus funding.

Senator BOXER. I am really confused. How much of the Economic Recovery Act funds that went to NIEHS autism research?

Ms. BIRNBAUM. Specifically, of the $190 million, let's say, put about $5 million of that $190 million.

Senator BOXER. Five million in addition to the $9 million?

Ms. BIRNBAUM. No, that is part of the $9 million. Our base funding was, in 2009, was $4.3 million for autism.

Senator BOXER. So the base funding is about $4 million. And you added $5 million. So you doubled the amount. So without the ARRA funding, we go back to $4 million, $4.5 million research on autism, is that right?

Mr. BIRNBAUM. I think it is hard to say exactly, because we do see autism as a priority, and we are trying to increase our amount of funding to look at neurodevelopmental effects.

Senator BOXER. Well, I hope you will let us know, all of us here care a lot about this, and others who are not here who do care. If you feel that we could do a lot more, if we had a little more funding here. Because following Chair Klobuchar's questions, it is clear to me that there are, we are coming along, we are narrowing down. It may be this, some susceptibility to certain chemicals and toxins because of certain genes or other factors.

So I think, and that is why putting that together with our cluster bill that we are introducing, and Senator Lautenberg's bill on making sure the chemicals are safe before they are introduced, I think we are kind of having a fairly clear path here to where we are going.

That really covers my questions. Thank you.

Senator KLOBUCHAR. Thank you very much.

Senator Udall.

Senator UDALL. Thank you, Chairman Klobuchar, and thank you, both of you, for focusing in on this issue.

I would like to put my opening statement in the record and go directly to questions, if that is acceptable here.

Senator KLOBUCHAR. Without objection, so ordered.

[The prepared statement of Senator Udall follows:]

STATEMENT OF HON. TOM UDALL,
U.S. SENATOR FROM THE STATE OF NEW MEXICO

Thank you, Chairman Klobuchar, for calling this hearing into an issue that is of great concern to families in New Mexico and around the country.

A number of my constituents have contacted my office, describing their families' challenges with autism and our frustrating inability to learn more about the causes and cures for this condition.

According to our testimony here today, our top researchers believe that there is a significant environmental component to autism. Genetics cannot explain the rapid rise in autism, so they suspect chemical exposure may trigger or worsen neuro-developmental disorders.

I hope this hearing will support those ongoing efforts, and I think that it is important to put the unknown links between autism and environmental toxic exposure in the bigger picture.

As I and others on this Committee have stated, Federal toxic chemical regulation is broken and needs to be addressed.

Our Nation's laws that are supposed to regulate toxic chemicals do not even require chemical companies to submit health and safety studies for the chemicals that are included in everyday household products.

The Washington Post published an article yesterday titled "U.S. regulators lack data on health risks of most chemicals," which I would like to include in the record.

The article references the recent recall of 28 million boxes of the Nation's most popular children's cereals because a petrochemical known as "2-methyl naphthalene" accidentally ended up in cereal. The chemical is apparently used in the foil packaging.

According to the article, "the Food and Drug Administration has no scientific data on its impact on human health. The Environmental Protection Agency also lacks basic health and safety data even though the EPA has been seeking that information from the chemical industry for 16 years."

We have had several hearings already this year underlining the need to reform the Toxics Substances Control Act, and I hope we will continue to make the case for action.

I believe that we can all agree that science should drive decisionmaking and that we should take precautions when we expose children to potentially toxic chemicals. The need for testing is basic and obvious.

If we do not, our children and our grandchildren will continue to be guinea pigs in an uncontrolled experiment testing the impacts of thousands of industrial chemicals on the human body.

[The referenced article follows:]

The Washington Post

U.S. regulators lack data on health risks of most chemicals

By Lyndsey Layton
Washington Post Staff Writer
Monday, August 2, 2010; A01

This summer, when Kellogg recalled 28 million boxes of Froot Loops, Apple Jacks, Corn Pops and Honey Smacks, the company blamed elevated levels of a chemical in the packaging.

Dozens of consumers reported a strange taste and odor, and some complained of nausea and diarrhea. But Kellogg said a team of experts it hired determined that there was "no harmful material" in the products.

Federal regulators, who are charged with ensuring the safety of food and consumer products, are in the dark about the suspected chemical, 2-methylnaphthalene. The Food and Drug Administration has no scientific data on its impact on human health. The Environmental Protection Agency also lacks basic health and safety data for 2-methylnaphthalene -- even though the EPA has been seeking that information from the chemical industry for 16 years.

The cereal recall hints at a larger issue: huge gaps in the government's knowledge about chemicals in everyday consumer products, from furniture to clothing to children's products. Under current laws, the government has little or no information about the health risks posed by most of the 80,000 chemicals on the U.S. market today.

"It is really troubling that you've got this form of naphthalene that's produced in millions of pounds a year and we don't have some of the basic information about how toxic it is," said Erik Olson, an expert at the Pew Charitable Trusts, which is advocating an overhaul of U.S. chemical laws. "In so many cases, government agencies are missing data they need on even widely used chemicals about whether they pose a health risk."

The information gap is hardly new. When the Toxic Substances Control Act was passed in 1976, it exempted from regulation about 62,000 chemicals that were in commercial use -- including 2-methylnaphthalene. In addition, chemicals developed since the law's passage do not have to be tested for safety. Instead, companies are asked to volunteer information on the health effects of their compounds, and the government can decide whether additional tests are needed.

In 1994, the EPA invited the chemical industry to submit health and safety data for 2-methylnaphthalene because it was being produced in large quantities, said Mary F. Dominiak of the EPA. Chemical manufacturers have yet to disclose that information, she said.

And they may not even have it. If a manufacturer possesses data showing that a chemical harms health or the environment, it is required to turn over the findings to the EPA. Critics say that creates a disincentive for manufacturers to test their chemicals.

Kellogg responded to a request for comment by referring to the statement it issued with its recall, which said, "While the potential for serious health problems is low, some consumers are sensitive to the uncharacteristic off-flavor and smell and should not eat the recalled products because of possible temporary symptoms including nausea and diarrhea."

Bills pending in Congress would revamp the way the government regulates chemicals, forcing companies to prove that new chemicals are safe before using them and requiring health and safety assessments of existing chemicals, such as 2-methylnaphthalene. The chemical industry has said it agrees the law should be revamped, but it also has expressed concern that new restrictions might hamper innovation and competitiveness.

One federal agency has minimal information about 2-methylnaphthalene -- the Agency for Toxic Substances and Disease Registry, which reviewed the scientific literature on the chemical in 2005. It concluded that nothing is known about its use related to food. "You are not likely to be exposed . . . eating foods or drinking beverages" and risk exposure only "if you live near a hazardous waste site," according to the agency's Web site.

A natural component of crude oil, 2-methylnaphthalene is structurally related to naphthalene, an ingredient in mothballs and toilet-deodorant blocks that is considered a possible human carcinogen by the EPA. Kay Cooksey, a packaging expert at Clemson University, said 2-methylnaphthalene likely ended up in cereal because something went awry in the manufacturing of the foil-lined bags. The foil is attached to the paper bag with an adhesive that is heated, she said. If too much heat is applied or if the composition of the adhesive is incorrect, 2-methylnaphthalene could form, she said.

The chemical "is not supposed to be in food," said Mitchell Cheeseman of the FDA's office of food safety. The agency allows a minute amount of the chemical in food packaging if it is produced as a "contaminant" during the manufacturing process, but it is not supposed to transfer to the food, he said.

Because the FDA does not know anything about the toxicity of 2-methylnaphthalene, the agency set its limit based on what it knows about the toxic effects of similar chemicals, Cheeseman said.

He added that the FDA does not know what caused the Kellogg contamination, how much 2-methylnaphthalene might have migrated into the cereals or if it was the only contaminant. The agency did not perform its own tests on the cereals.

Roberta Wagner of the FDA's Office of Regulatory Affairs said Kellogg destroyed most of the tainted liners before it contacted the agency and announced a recall.

"Basically, Kellogg's investigated the situation before they made the decision to do the recall," Wagner said. "They did their own testing." She said the agency continues to investigate.

The company submitted a copy of its health risk assessment to the FDA, but neither Kellogg nor the agency would release it.

Cheeseman said it is unusual for contaminants to migrate from packaging into foods.

But others are less certain. "In this case, it had an odor and it had a taste, so it was detected," said David Andrews, a senior scientist at the Environmental Working Group, an advocacy organization. "But there are hundreds of other potential impurities that we can't smell and taste, chemicals that we know very little about and the government knows little about."

Senator UDALL. One of the things that I would like to ask about, and I would like to cite a few facts to set the stage, an April article in the journal Current Opinion in Pediatrics states that children today are surrounded by thousands of synthetic chemicals. Two hundred of them are neurotoxic in adult humans and a thousand more in laboratory models. Yet fewer than 20 percent of high volume chemicals have been tested for neurodevelopmental toxicity.

According to the EPA, there are 3,000 chemicals that are classified as high production volume. These are chemicals that the U.S. imports or produces at a rate of more than 1 million pounds per year. According to the EPA, over 40 percent of these have not been tested for basic toxicity.

And I would like to ask both of you, do you think the suspected links between chemical exposure and autism and other neurodevelopmental disorders show the need for chemical makers to provide more information and health studies about their products? And part of that, yesterday part of that question, I don't know whether you saw the post yesterday, but on the first page was an article that in cereal, boxes of cereal, which—kids are eating most of the cereal, an unsettling surprise. The Kellogg recall shows that U.S. lacks data on risks of many chemicals. And there is a chemical in there.

And one of the things it highlighted in the story is the chemical companies do not test, they do not test these kinds of chemicals. Because if they test, they are required to turn it over to the Government. So they just decide, well, we don't want to know what is in it, so we don't want to turn it over.

Would you talk a little bit about that, and what you think we need to do to get to the bottom of this and try to do everything we can to protect our children?

Ms. BIRNBAUM. First of all, I think you know that I am not in a regulatory agency, but in a research agency.

Senator UDALL. That is right.

Ms. BIRNBAUM. I may have had many years at EPA, but I would like to stick to the research.

I think the issue is that there is growing evidence, lots of evidence that chemicals can cause effects. We have known for years that pharmaceuticals, or the drugs—there are always black box warnings on drugs, do not take if pregnant. And the reason you don't take them is because they can harm the fetus as it grows.

So we know that chemicals can impact things. Many chemicals are not tested at all. I think many of us do believe that it would be much better to have chemicals fully evaluated for their safety before they go on the market. The chemical that was of concern that was talked about in the cereal boxes yesterday is the chemical that my NTP actually has done some very limited testing on to test whether it was a mutagen or not, it caused genetic damage. But that is the extent of the testing that has been done for that.

So I think it would be very important to have the testing done first. I think we have to really work on what we mean by testing. Because there is a pattern that has emerged that there are guidelines for how you do testing. And the problem is that guidelines that were established for science in the 1970s are really not up to what is needed in this century. We need to focus our efforts on

using all the newest information, not necessarily things that were required 20 or 30 years ago to do these tests.

The other point I would like to make, which is referring to something Dr. Anastas just talked about, which was the susceptibility and the interaction between genes and the environment, I think it is very, very clear that depending on your genetics, as well as maybe what your past exposures were, can alter your susceptibility. There is a paper that I just saw that is coming out that shows that some of the flame retardants, whether or not you see developmental neurotoxicity, at least in animal studies, is totally dependent on the genetics of the mouse that you test.

So while mice are not men, they provide us a great deal of information about what may be possible in the human population.

I think I will let Paul talk a little bit more about the regulatory agenda.

Mr. ANASTAS. I will just say that prior to coming to the Environmental Protection Agency, I taught chemistry at Yale University. One of the things that we always taught our students is that when you introduce a new chemical into the world, when you make a new chemical in the lab, you need to characterize that chemical. And there is a wide range of analyses that are done in order to describe exactly what that chemical is.

But yet traditionally part of that chemical characterization has not included its impact on human health or the environment. As long as that exists, where when we are describing a chemical, it doesn't include its impacts on humans, on the environment, on developing children, then we are going to be in the same situation. We need to have a fuller understanding. And the definition of performance when we are talking about chemicals, and even commercial chemicals, needs to include how it performs in terms of its role in the world, interacting with humans and the environment.

Senator UDALL. Thank you both for those answers.

I am sorry, I have to leave, and I won't be able to hear the second panel. I have to preside over the Senate, but I am leaving you in the hands of two very capable Senators that I know are very concerned about this issue.

Thank you very much.

Senator KLOBUCHAR. Thank you.

First, Dr. Birnbaum, I am just trying to figure out the exact amount of money and trying to mesh these numbers here. You said it to Senator Boxer, it is like $9 million on research?

Ms. BIRNBAUM. Nine million on autism research in fiscal year 2009. And approximately that in fiscal year 2010. But that is, in our total portfolio for all our neurodevelopmental work, is about $29 million.

Senator KLOBUCHAR. Right. That is what I just saw in your testimony.

Ms. BIRNBAUM. It is about a third of the total neurodevelopment.

Senator KLOBUCHAR. So there is $29 million for research for neurodevelopmental work, and about a third of that is specifically for autism?

Ms. BIRNBAUM. That is correct.

Senator KLOBUCHAR. I am just trying to figure out, we got from NIH the statistic that in the recovery act, we invested over $10 bil-

lion in NIH on new research on mental health, including at least $60 million devoted to autism diagnosis and treatment.

Ms. BIRNBAUM. Under the stimulus package, NIH did have an initiative and has funded about $60 million of stimulus funds on autism. Much of that has to do with treatment and diagnosis.

Senator KLOBUCHAR. So you are differentiating that from the research of causes?

Ms. BIRNBAUM. Our—for example, approximately $5 million of stimulus funding in autism is part of that $60 million that NIH as a whole was spending. There are about four or five NIH institutes that are very involved, for example, in the Interagency Autism Coordinating Committee and involved in autism research. So it is not just NIEHS.

Senator KLOBUCHAR. That makes a difference.

The other thing I wanted to ask about was, we have had an incident in Minnesota, and I talked with these families in the Somalian community, we have a very large Somalian community in Minnesota. And they have had a very high incidence of autism. I don't know if you have heard about it, but the diagnosis is 1 out of 28 of their children have autism.

So I was just wondering how this possibly could fit in with the research that is going on. Of course they are searching for answers. What Senator Boxer has been talking about with clusters, although this is, they live in a similar area, but other kids that aren't Somalian don't have that high rate.

Dr. Birnbaum and then Dr. Anastas.

Ms. BIRNBAUM. There are some recent hypotheses that Vitamin D, or the absence of Vitamin D may be associated with an increase in autism. My understanding is that there are essentially no reports of autism in Somalia. Again, it is a developing country, they might not have the diagnosis.

But the phenomenal cluster, I would say, actually of Somali children being reported with ASD in Minnesota and I think in some other Somali communities in the northern United States, people are at least suggesting that that might be related to not having enough Vitamin D. So that is a hypothesis that people are beginning to look at.

Senator KLOBUCHAR. Dr. Anastas.

Mr. ANASTAS. I would just suggest that while this is certainly an important area of research, it does lend itself to something we discussed earlier, which is the genetic-environment interactions rather than one or the other. This dance, if you will, would lend itself to people with genetic predispositions, not necessarily exhibiting a certain disorder in the absence of being exposed to certain triggers. Yet when they are exposed to certain triggers, they could exhibit those disorders.

So it is an active area, or I should say, an important area of research that in my opinion needs to be emphasized.

Senator KLOBUCHAR. This interaction, and I suppose this could be an example where if, in fact, and I do believe the diagnosis in Somalia might be very limited. But if in fact they get more autism, the kids do, in the U.S., that it could be an interaction between some genetic component and then some kind of triggering factor, environmental factor.

Ms. BIRNBAUM. This is the beauty of the EARLI study, which is recruiting 1,200 women who already have one autistic child. Because we know that if you have one autistic child you have a higher likelihood that a second child might be autistic, suggesting that there is clearly some genetic component to it.

However, it is a little bit hard to—usually if you have one child, your environment doesn't change that much if you have a second child. So there is also the interaction going on here. But in the EARLI study, not only are we looking at every kind of environmental factor that we can think of, and that includes diet and it includes stress, but we are also looking at the genomics of these women and their children and their partners as well.

Senator KLOBUCHAR. Senator Boxer.

Senator BOXER. A couple of questions. I want to home in on the one child, two child, three child; doctors studying that. What do we know? What are the chances, if you have had one autistic child, of having a second?

Ms. BIRNBAUM. I believe you have about 10 percent chance that your next child might be. I think that is the approximate statistics, that about 1 in 10. So that is much higher than the 1 in 110.

Senator BOXER. Than the 1 in 110. So that leads you further to suspect that it is something either in the genes or the environment combined?

Ms. BIRNBAUM. Right. When you have a genetic input, and not every child is impacted, then it says that there has to be something in addition to genetics that is causing the condition to appear.

Senator BOXER. Do we have other neurological conditions that have been found to be caused by both genes and environment?

Ms. BIRNBAUM. There is suggestion that many different certain things like schizophrenia or bipolar disorder, for example, an adult clearly may have an interaction. And we know that, for example, when you look at something like lead, which is a clear neurodevelopmental toxicant, that not every child has the IQ loss. You have to look at a whole population of children to see the shift.

Senator BOXER. So is the ultimate—down the road cure for this, if this proves out, we don't know that, gene therapy?

Ms. BIRNBAUM. I think that the importance of understanding environmental triggers of disease is that you can change your environment. But at least at this point, you can't change your genes.

Senator BOXER. But isn't one of the goals of the reason we did all that funding for genes is to eventually do gene therapy?

Ms. BIRNBAUM. That is certainly a possibility. But I think we can get to the environmental impacts more easily and more readily. And again, as Dr. Anastas has said several times, the effect of a gene may only be expressed in a given environment.

Senator BOXER. Yes, sir.

Mr. ANASTAS. I would just like to add that this area of epigenetics is emerging and being understood——

Senator BOXER. What do you call it?

Mr. ANASTAS. It is called epigenetics.

Senator BOXER. E-P-I?

Mr. ANASTAS. E-P-I. It is an emerging area of investigation. I would certainly describe it as in its early stages.

But this is showing that having certain environmental interactions may trigger these genes to perhaps impair a gene's ability to the expression of a certain gene. The point that I want to make is that the early suggestions are that it wouldn't necessarily stop with the individual, but can be translated into future generations as well.

Now, I would never suggest that this is an established, concluded science. I am saying that this is emerging science in an important research area.

Senator BOXER. Let me just ask my last question. We know in America 1 in every 110 kids is born with autism. What do we know about other countries' data?

Ms. BIRNBAUM. I don't know the exact statistics in other countries. I do know that there appears to be—the increase in autism appears to be in many, many countries. I think one of the issues that we keep getting is the differential diagnosis, are we changing our criteria, are we looking in a different way. It is clear in the U.S. that that doesn't explain the increase.

Senator BOXER. So you would say, from what you know, there is a worldwide increase?

Ms. BIRNBAUM. Certainly in many countries there appears to be. Certainly in developed countries anyway.

Senator BOXER. I doubt that they have a lot of statistics in Somalia just because I don't think they have a health care system that is capable of doing what we do. But I certainly think, given what Senator Klobuchar has discussed about that cluster, it might be very interesting to look at at least the gene situation, and if that is somehow making these children in your State more vulnerable. I don't know if we have any data from Somalia.

Ms. BIRNBAUM. We would certainly be eager to entertain a grant where someone proposed to study that population; it needs to be done, really, in a prospective fashion. And again, since there are so many children being diagnosed with autism in that population, you might be able to do something similar to what we are doing in Philadelphia and California and Maryland as far as recruiting in that population.

Senator BOXER. The reason I think it is important—I was stunned with that number you said, 1 in 28 children.

Ms. BIRNBAUM. Yes.

Senator BOXER. That is a cluster. And I think we could maybe learn quite a bit.

Anyway, I need to run off to my next obligation. I just wanted to say how much I will look forward to hearing about the next panel from today's Chair, and to thank everybody for being here. We are going to be taking action on a lot of these matters. I wanted to note when you mentioned pthalates; did you mention pthalates?

Ms. BIRNBAUM. Yes, I did.

Senator BOXER. We passed some very tough legislation; Senator Klobuchar and I serve on the Commerce Committee. We were able to ban pthalates in children's products. It was an enormous fight. It was an enormous, enormous, terrible, awful fight. We got into fights about rubber duckies and how, one of the people said, well, you know, these rubber duckies are fine. Well, yes, but if they have pthalates, they are not.

So we managed to do it. But it is very tough to regulate this one chemical at a time. That is why the work you do is so very important. Because hopefully you are going to be able to I.D. for us a class of chemicals that may be problematic or will give us the road map we need so we don't have to just get into these arguments one particular chemical at a time.

Thank you very much, Senator Klobuchar.

Senator KLOBUCHAR. Thank you.

I want to thank our witnesses. It was enlightening. We know there is a lot more work to be done. Thank you for this update; I think it helps us to understand the funding but also the status of the research and learn some new things, like epigenetics.

We look forward to our next panel. Thank you very much to both of you.

If we could have our next panel come up.

Welcome to our second panel. I see you are staying here, Dr. Anastas. Thank you for that, and Dr. Birnbaum, so we can hear your reaction to this later as well.

Our first witness in this second panel, as has already been mentioned, is Dr. Isaac Pessah, who is the director of UC Davis Children's Center for Environmental Health and Disease Prevention. He is an expert on how environmental factors interact to influence neurodevelopment.

Dr. Bruce Lanphear, in the middle, is the Director of the Cincinnati Children's Environmental Health Center, and is the principal investigator for research examining fetal and early childhood exposures to prevalent environmental hazards.

Finally, I would like to extend a warm welcome to Mary Moen. Mary is a fellow Minnesota mother and is here today to share her and her family's experience of living with an autistic son.

Is Max with you today? There you are, Max. Thank you for being with us.

I understand, Max, that you are a real whiz with maps and directions; is that right? Maybe you could help my husband. Maybe I can hook you guys up.

As well as your dad, and Mary's husband, Steve. Thank you for being here. And Mary is here with her family to help us put a real face on the stories behind autism and other neurodevelopment disorders. Thank you so much for coming from Minnesota.

So we will get started with Dr. Pessah.

STATEMENT OF ISAAC N. PESSAH, PH.D., DIRECTOR, DEPARTMENT OF MOLECULAR BIOSCIENCES, COLLEGE OF VETERINARY MEDICINE, AND DIRECTOR, UNIVERSITY OF CALIFORNIA DAVIS CHILDREN'S CENTER FOR ENVIRONMENTAL HEALTH AND DISEASE PREVENTION

Mr. PESSAH. Senator Klobuchar, thank you for giving me the opportunity to present testimony regarding environmental factors in autism risk.

As you have already heard, autism spectrum disorders encompass a wide range of what we call phenotypic severities and comorbidities, such as a high rate of seizure disorder and anxiety. ASD likely encompasses several disorders with distinct ways of get-

ting there, or etiologies, and pathologies that converge on a common set of behavioral criteria.

Although autism risk has strong heritability, it turns out that no single locus alone, or genetic address, is sufficient to account for the full clinical phenotype. Results from many genome-wide autism screens indicate that potential susceptibility genes are spread across the entire genome.

Recently, several very rare genetic mutations, single nucleotide polymorphisms, de novo copy number variations and as you have heard, epigenetic factors which influence DNA methylation, and therefore expression of the DNA's message, were shown to contribute to the complex transmission of autism risk. So genetics alone cannot account for the majority of autism cases currently being diagnosed.

There is a lack of full concordance between identical or monozygotic twins with some estimates ranging as low as 60 percent, which leaves wide room for environmental triggers. Interactions among multiple genes are likely to contribute to various types of autism. Inheritable epigenetic factors and/or non-heritable environmental exposures are likely to significantly contribute to susceptibility and variable expression of autism and autism-related traits. It is therefore likely that constellations of epigenetic and environmental factors are contributing to the increased prevalence of ASD, as we have heard. And the rise cannot be fully accounted for by changes in diagnostic criteria.

There is a critical need to identify environmental factors, including exposures to foreign chemicals or anthropogenic source and changes to the diet that contribute to autism risk and severity. The vast majority of public and private resources has and continues to support work on identifying genetic impairments associated with autism risk. From these studies we have learned that genetics alone cannot predict the majority of autism cases, the patterns of impairments, severity, nor can they predict the success for current treatment modalities.

Moreover, we have learned that many of the molecular and cellular systems that have been associated with autism risk are the very same ones that are targets of environmental chemicals currently of concern to human health, and children's health in particular because of their widespread use. Current research is needed on definable factors that contribute to causing or protecting against autism.

It is accepted that autism is a multi-factorial, meaning that there are multiple factors contributing to risk. Therefore, it is essential to bring together both studies of genes and environment to fully understand autism risk.

We know that autism prevalence continues to increase dramatically, clearly implicating environmental factors in autism risk. We must identify which environmental exposures and combinations of exposures are contributing to the increased overall risk in the population and identify the most susceptible group within children, which are in themselves a highly susceptible group.

Only by bringing together the concerted effort of multi-disciplinary teams of scientists can we identify which of the more than 80,000 commercially important chemicals, and a subset of those, a

very small subset have actually received sufficient study, contribute to neurological impairments with idiopathic autism. It is clear that there is a critical need to identify which chemicals in the environment influenced the same biological pathways known to be affected in autism and how this contributes to susceptibility. By far, limiting exposures to these chemicals is the only current way to mitigate and prevent autism susceptibility in individuals.

Thank you. I would be happy to answer any questions.

[The prepared statement of Mr. Pessah follows:]

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TO: U.S. Senate Committee on Environment and Public Works

FROM: Dr. Isaac N. Pessah, Director
UC Davis Center for Children's Environmental Health and Disease Prevention
Professor of Toxicology

Re: State of Research on Potential Environmental Health Factors With Autism and Related Neurodevelopment Disorders

Autism Spectrum Disorders (ASD) are highly heterogeneous conditions that are diagnosed using only behavioral criteria due to a lack of concrete biological markers. The American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV) defines ASD as a disorder characterized by deficits in verbal and nonverbal communication, stereotyped behaviors and interests, and impaired social interactions. ASD encompasses a wide range of phenotypic severities and co-morbidities. ASD likely encompasses several disorders with distinct etiologies and pathologies that converge on a common set of behavioral diagnostic criteria. Although autism risk has strong heritability, no single locus alone appears to be sufficient to account for the full clinical phenotype. Results from many genome-wide autism screens indicate that potential susceptibility genes are spread across the entire genome. Recently several very rare genetic mutations, single nucleotide polymorphisms (SNPs), *de novo* copy number variations, and epigenetic factors that influence DNA methylation were shown to contribute complexity in the transmission of autism risk. Yet genetics alone cannot account for the majority of autism cases currently being diagnosed. There is lack of full concordance between monozygotic twins, with some estimate ranging as low as 60%, and the prevalence of ASD among siblings has been reported as high as 14%. Interactions among multiple genes are likely to contribute to various types of autism, and heritable epigenetic factors and/or non-heritable environmental exposures are likely to significantly contribute to susceptibility and variable expression of autism and autism-related traits. It is therefore likely that constellations of epigenetic and environmental factors are contributing to the increasing prevalence of ASD, a rise that cannot be fully accounted for by changes in diagnostic criteria.

There is a critical need to identify environmental factors, including exposure to xenobiotic chemicals and changes in diet that contribute to autism risk and severity. The vast majority of public and private resources has, and continues, to support work on identifying genetic impairments associated with autism risk. From these studies we have learned that genetics alone cannot predict the majority of autism cases, the patterns of impairments, severity, nor can they predict success for current treatment modalities. Moreover, we have learned that many of the molecular and cellular systems that are associated with autism are the very same ones that are the target of environmental chemicals currently of concern to human health because of their widespread use. Further research is needed on modifiable factors that contribute to causing or protecting against autism. It is accepted that autism is 'multi-factorial,' meaning that there are multiple factors that combine to impair brain development. Increased efforts to identify environmental factors that contribute risk to developing autism spectrum are therefore essential to improve our understanding of the constellations of genes that confer differential sensitivity to distinct environmental exposures during gestational and neonatal development. Such approaches will likely prove useful in defining subgroups of children that differ in susceptibility to specific types of environmental exposures that promote autism risk, severity, and responsiveness to clinical and behavioral interventions.

We know that autism prevalence continues to increase dramatically clearly implicating environmental factors in autism risk. We must identify which environmental exposures and combination of exposures are contributing to increased overall risk in the population and identify the most susceptible groups. Only by bringing together the concerted effort of multidisciplinary teams of scientists can we identify which of the >80,000 commercially important chemicals currently in production promote developmental neurotoxicity consistent with the immunological and neurological impairments identified in individuals with idiopathic autism. It is clear that their is a critical need to identify which chemicals in the environment that influence the same biological pathways known to be affected in autism. Limiting exposure to these chemicals is the only way to mitigate or prevent autism in susceptible individuals.

Respectfully Submitted,

Isaac N. Pessah

Isaac N. Pessah, Ph.D.
Professor of Toxicology

Questions for Pessah
Questions from:
Senator Barbara Boxer

1. Doctor Pessah, your testimony states "genetics alone cannot account for the majority of autism cases currently being diagnosed." What other factors is the research showing that might be contributing to the incidents of autism?

Senator Boxer, no single gene defect can fully account for the spectrum of autisms currently being diagnosed. Even if we consider highly penetrant gene mutations (including missense mutations, copy number variations (CNVs), and single nucleotide polymorphisms (SNPs)) that have been identified in very large genome-wide association studies, each mutation accounts for a very small fraction (less than 1%) of the 1:100 ASD cases being diagnosed today. Many of these mutations occur in a few extended families afflicted with autism. These very same rare mutations can occur in some families that have no history of ASD. Most scientists working on understanding complex disorders (e.g., cancer, metabolic disorders, asthma) incorporate in their research strategy the fundamental paradigm that genes provide the substrate for susceptibility to environment triggers. The occurrence and severity of autisms, like other complex disorders, are determined by both genetic susceptibility and environment triggers.

Current knowledge about the neurobiology of autisms implicates environmental triggers influence autism risk. Many pesticides, including organophosphates, pyrethroids, and organochlorines are known to promote brain over-excitation through the same neurobiological substrates known to be impaired in autism. Persistent organic pollutants, such as PCBs, brominated flame retardants, and related chemicals have been shown in upset the delicate balance between excitatory and inhibitory circuits in the brain thereby altering neuronal networks known to be impaired in autism.

2. Doctor Pessah, could you please describe what scientific methods are currently available or are being developed that would better enable researchers to screen large numbers of chemicals for potential impacts on human health?

Senator Boxer, recent technological advances in cellular imaging, along with the development of vital dyes that specifically query the status of key signaling molecules and cellular functions, simultaneously, have permitted High Content Analysis (HCA). HCA is a multiplex approach specifically adapted to assess the health of thousands of primary adherent cells (macrophage/monocytes; hepatocytes, neural and muscle cells) and their sensitivity to environmental changes. This new approach is especially valuable in large population based studies where cells from thousands of patients are collected and cryopreserved for later expansion. The advantages of HCA within the context of identifying developmental neurotoxicants and immunotoxicants relevant to autism risk include:

1. Detection of sub-lethal damage that can occur one or two logs lower in concentration than that identified with an IC50 curve of a classic cytoxicity assay.

2. Detection of chronic damage to cellular organelles (such as abnormal growth and membrane

transport, damage to endoplasmic reticulum, mitochondria, and nuclear chromatin). Damage relevant to developmental neurotoxicity frequently is triggered by chronic exposures to low doses, and these can be mimicked using HCA.

3. Detection of cellular damage to cells of human origin, not only primary immune cells not typically amenable to flow cytometry, but also induced pluripotent stem cells (iPSC) and neural cells derived from them, and tissues collected at the time of delivery.

Senator James M. Inhofe

1. In your testimony you mentioned that the vast majority of public and private resources have gone to support work on identifying genetic impairments associated with autism risk and that further research is needed on other factors that cause autism. How beneficial do you think it would be for autism research to start melding the two together and looking at how certain genetic markers coincide with specific outside risk factors in autism cases?

Senator Inhofe, research into the pathophysiology and genetics of autism has already informed scientist about which environmental exposures are most likely to promote adverse outcomes in brain development that influence risk and severity to these debilitating disorders. Conversely, understanding how low-level chemical exposure influences molecular, cellular, and behavioral outcomes relevant to the development of autism will enlighten geneticists, neuroscientists, and immunologists about autism's complex etiologies and possibly yield novel intervention strategies. The inherent imbalances in neuronal connectivity in children at risk for autism are likely to provide the biological substrate for enhanced susceptibility to environmental triggers that are known to target signaling systems. These systems establish the basic patterns of connectivity, from early neuronal migration and axonal pathfinding to postnatal refining of neuronal connections. Three examples of gene x environment interactions that likely contribute to autism risk can be illustrated: pesticides that interfere with (1) acetylcholine (ACh) and (2) γ-aminobutyric acid (GABA) neurotransmission; and (3) the persistent organic pollutants that directly alter Ca^{2+} signaling pathways and Ca^{2+}-dependent effectors. One fundamental way in which heritable genetic vulnerabilities can amplify the adverse effects triggered by environmental exposures is if both factors (genes and environment) converge to dysregulate the same neurotransmitter and/or signaling systems at critical times during development.

Senator KLOBUCHAR. Thank you very much.
Dr. Lanphear.

STATEMENT OF BRUCE LANPHEAR, M.D., MPH, SENIOR SCIENTIST, CHILD AND FAMILY RESEARCH INSTITUTE, AND PROFESSOR, SIMON FRASER UNIVERSITY, VANCOUVER, BRITISH COLUMBIA, AND ADJUNCT PROFESSOR, CINCINNATI CHILDREN'S HOSPITAL MEDICAL CENTER

Dr. LANPHEAR. Thank you very much for the opportunity to be here today.

I wanted to focus my testimony on other neurodevelopmental disorders, because we have talked quite a bit about autism as a window into why we should be concerned about chemicals, particularly as they might relate to autism.

Children's environmental health has grown tremendously in the past decade or two. It has been fueled by the emergence of new morbidities or diseases in children. Research has shown that fetus and child are particularly vulnerable to environmental influences and toxicants in particular. Mounting evidence is implicating environmental exposures as major risk factors for some of the most common diseases and disabilities in children. Finally, research indicating that many diseases of industrialized societies in adults have their origins in early childhood. So what happens during childhood has implications for a person's ability throughout life to contribute.

In short, and in contrast—and this is important—in contrast with many other types of research, this field of research offers tremendous promise and potential to prevent many of the diseases affecting America's children.

One in six American children has a developmental problem, from a subtle learning disability to overt behavioral disorders such as ADHD or autism. Although the data are sparse, many of these diseases appear to be rising. The findings from some of the most thoroughly studied and widely dispersed environmental toxicants—such as lead, tobacco, PCBs, and mercury—indicate that exposures to exceedingly low levels are risk factors for deficits in intellectual abilities and executive functions. Executive functions are those things that distinguish us most clearly from other animals. None of us would be sitting here today if we didn't have good executive functions.

So this is becoming increasingly important, if we want to try to make sure that children can contribute to society.

We also know that they are major risk factors for behavior problems such as ADHD and criminal behavior. These conditions can severely impair a child's ability to succeed in school, to interact socially. They can elevate a child's risk for violent and criminal behaviors. And they can dramatically diminish their ability to contribute to society.

We have heard about several other new emerging toxicants. And there is indeed emerging evidence that a whole host of new environmental chemicals, many of which are routinely found in pregnant women and children, such as bisphenol-A, flame retardants, pesticides, pthalates, and airborne pollutants, are associated in early studies with intellectual deficits or behavior problems al-

though the evidence is not as conclusive as some of the more established toxicants.

Much of the research I quoted from was from the NIEHS USEPA Children's Centers in collaboration with the Centers for Disease Control.

I wanted to share just a few highlights of the Cincinnati Children's Environmental Health Center to highlight the impact of a low-level toxicant, lead, on both children and society as an indicator of the extent of the seriousness of what we have always thought of as a subtle problem. In a series of studies we found an increase in blood lead levels from less than 1 microgram per deciliter to 10 micrograms per decaliter, which is well below the CDC's level of concern, were associated with a 6 to 7 IQ point decrement. On a population level a shift in IQ of 5 points across a population in the United States would mean 3 and a half million more children who qualify as being mentally retarded. These are not subtle effects.

We also confirmed early reports implicating childhood lead exposure in the epigenesis of ADHD. As Dr. Birnbaum pointed out, we estimated that one in three cases of ADHD in U.S. children—that is over 1.5 million cases—could be attributed to prenatal tobacco exposure—that is when the mom smokes—or childhood lead exposure.

Finally, we have confirmed that childhood lead exposure is a risk factor for impaired brain development, using brain imaging studies, again, focused in particular on the prefrontal cortex, that area responsible for executive function, as well as criminal arrests in young adults. Collectively, these and other studies suggest that a large proportion of crimes and homicides in the United States over the past century can be attributed to lead toxicity.

Now, we don't tend to think of low-level chemical exposures as being of any consequence. But the levels we are talking about are the same concentrations that we try to achieve with therapeutic doses of anti-psychotics. We know these low-level chemicals can have an impact on behavior.

It has been estimated, using these studies, that for every dollar we invest in preventing lead exposure, we would benefit by $17 to $20, or annually, somewhere between $30 billion to $34 billion. I focused on just one toxicant. But I think they indicate the importance of this kind of exposures that occur.

Finally, let me just end by saying that we have talked a bit about the research. That is increasingly important. Still, we can't ignore the pattern of pathology we have seen with these other established toxicants: lead, tobacco, PCBs, and so forth. It is clear to me that we know enough to require pre-market testing for a whole host of other environmental chemicals, particularly those that are used in high volumes. The alternative, to continue to experiment on our children, is no longer tenable.

We should also look back to the history of drug regulations. For 50 years prior to drug regulations taking effect in the 1960s, there was a handful of people arguing that we needed better regulations. It took the thalidomide epidemic for us to take action. Perhaps autism is the equivalent for environmental chemicals.

Thank you.

[The prepared statement of Dr. Lanphear follows:]

Prepared Statement of Dr. Bruce Lanphear
Senior Scientist, Child & Family Research Institute,
Professor, Faculty of Health Sciences, Simon Fraser University
Adjunct Professor, Cincinnati Children's Hospital Medical Center

Children's environmental health -- the study and prevention of disease and disabilities in children from exposures to social, physical, biologic, and chemical agents -- has emerged as a new field of research, policy, and clinical practice (Landrigan et al. 1998). The growth of this field has been fueled by the emergence of new morbidities in children, research showing that the fetus and child are particularly vulnerable to environmental influences, and mounting evidence implicating environmental exposures as major risk factors for prevalent diseases and disabilities in children (Lanphear, 2005).

One in six American children have a developmental problem, from a subtle learning disability to overt behavioral disorders, such as attention deficit hyperactivity disorder (ADHD) or autism (Boyle et al. 1994; Hertz-Picciotto, 2009). These conditions can severely impair a child's ability to succeed in school, elevate their risk for violent and criminal behaviors, and dramatically diminish their ability to contribute to society.

The findings from some of the most thoroughly studied and widely dispersed environmental toxicants indicate that exposure to exceedingly low levels are risk factors for the "new morbidities" of childhood -- intellectual impairments, behavioral problems, asthma and preterm birth (Lanphear, 2005). Indeed, there is often no apparent threshold and, in some cases the effects appear to be greater at the lowest levels of exposure (England et al. 2001; Canfield et al. 2003; Lanphear et al. 2005; Yolton et al. 2005).

Exposures to established environmental toxicants -- such as lead, tobacco, PCBs and mercury -- have consistently been linked with higher rates of intellectual impairment or behavioral problems, such as conduct disorder and ADHD (Needleman et al. 1990; Schantz et al. 2003; Kahn et al. 2003; Wakschlag et al. 2002; Stewart et al. 2003; Needleman et al. 1979; Lanphear et al. 2005; Yolton et al. 2005). There is emerging evidence that a whole host of new environmental chemicals – such as Bisphenol A, PBDEs, pesticides, phthalates, and airborne pollutants – are associated with intellectual deficits or behavioral problems in children, but the evidence is not as conclusive (Rauh, 2006; Engel, 2010; Eskenazi, 2007; Braun, 2009; Perera 2009; Herbstman, 2010). Much of this research was done by the NIEHS/US EPA Children's Environmental Health Research Centers working collaboratively with the Centers for Disease Control and Prevention.

Children's developing brains are more vulnerable to certain toxicants and pollutants than adults. The central nervous systems of the fetus and young child, which are undergoing rapid changes, are particularly vulnerable to some toxicants. The fetus is a recipient of toxicants through placental transfer (Perera et al. 2003; Whyatt and Perera 1995; Bearer 2003). In some cases, such as mercury, the fetus is exposed to a larger dose than the mother (Ramirez et al. 2000). In other cases, such as organophosphate pesticides, the fetus may lack critical enzymes to metabolize environmental toxicants (Chen et al. 2003). Toddlers are often at greater risk for exposure to many environmental toxicants because they have a high degree of hand-to-mouth activity and they absorb some toxicants more efficiently (Bearer 1995).

Biomarkers are revolutionizing our ability to study the impact of environmental chemicals on neurodevelopmental disabilities (Perera, 1997; Lanphear and Bearer 2005; CDC 2003; Sexton et al. 2004). Historically, scientists and clinicians relied on indirect markers -- housing condition, poverty, questionnaires, and community-level monitoring of water and air -- to quantify the effect of environmental influences on children's health (Sexton et al. 2004). Biomarkers are making it possible to directly measure the internal dose for many environmental chemicals and test causal associations of environmental exposures with disease and disability in children.

I wanted to share some of the results of the Cincinnati Children's Environmental Health Center to highlight the impact of low-level toxicity on children. In a 2003 study, published in the *New England Journal of Medicine*, we estimated that an increase in blood levels from <1 μg/dL to 10 μg/dL was associated with a 7 IQ point decrease (Canfield, 2003). Because of the policy implications, we convened an international group of experts to conduct a pooled analysis of seven cohort studies. We estimated that an increase in blood levels from <1 μg/dL to 10 μg/dL was associated with a 6 IQ point decrement (Lanphear, 2005). These studies have been confirmed by over ten studies conducted around the world.

We also confirmed earlier reports implicating childhood lead exposure in the epigenesis of psychopathology in children. We estimated that one in five cases of ADHD in US children were due to childhood lead exposure (Froehlich, 2009). We also found joint effects of prenatal tobacco exposure and childhood lead exposure. Although each toxicant was associated with a 2.5-fold elevated risk for ADHD, children with higher exposures to both toxicants had a 8-fold elevated risk for ADHD (Froehlich, 2009).

Finally, we confirmed that childhood lead exposure is a risk factor for criminal arrests in young adults. We found that lead exposure is associated with conduct disorder, criminal arrest and impaired brain development using magnetic brain imaging (Braun, 2008; Cecil 2008; Wright, 2008; Brubaker 2009). These and other studies suggest that much of the criminal and violent behaviors in the US can be attributed to lead toxicity (Nevin, 2000; Reyes, 2007).

Gould used these studies to conduct a cost-benefit analysis of lead toxicity. She estimated that for every dollar spent to reduce lead exposure, society would benefit by $17 to $220, a net annual benefit of $30 billion to $44 billion (Gould, 2009).

Over the past century, increasing evidence has emerged linking chronic, low-level exposure to environmental influences and industrial pollutants with many of the most prevalent and disabling learning and behavioral problems in children. But questions remain. It is critical, for example, to examine the interactions of multiple environmental toxins or pollutants and to identify how genetic susceptibility or other markers of susceptibility elevate the risk for disease or disability. It is critical to discern whether the new chemicals are risk factors for autism and other emerging behavioral problems in children. Funding that is directed to children's environmental health research – the Children's Environmental Health Centers, the National Children's Study and other research awards -- offers us the opportunity to resolve many of the unanswered questions and prevent some of the most serious problems that impact children's learning abilities and behavioral problems, but much more needs to be done.

References

1. Bearer CF. 1995. How are children different from adults? Environ Health Perspect 103(suppl 6): 7-12.
2. Boyle CA, Decoufle P, Yeargin-Allsopp M. 1994. Prevalence and health impact of developmental disabilities in US children. Pediatrics 93:399-403.
3. Braun JM, Froehlich TE, Daniels JL, et al. Association of environmental toxicants and conduct disorder in U.S. children: NHANES 2001-2004. Environ Health Perspect 2008;116:956-962.
4. Braun J, Yolton K, Dietrich K, et al. Prenatal Bisphenol A exposure and early childhood behavior. Environ Health Persp 2009;117:1945-1952.
5. Brubaker CJ, Schmithorst VJ, Haynes EN, et al. Altered Myelination and axonal integrity in Adults with Childhood Lead Exposure: A Diffusion Tensor Imaging Study. Neurotoxicology 2009;30:867-875.
6. Canfield RL, Henderson CR, Cory-Slechta DA, Cox C, Jusko TA, Lanphear BP. Intellectual impairment in children with blood lead concentrations below 10 micrograms per deciliter. N Engl J Med 2003;348:1517-1526.
7. Cecil KM, Brubaker CJ, Adler CM, et al. Decreased brain volume in adults with childhood lead exposure. PLoS Med 2008;5:e112.
8. CDC. 2003. Second National Report on Human Exposure to Environmental Chemicals. Atlanta, GA:Centers for Disease Control and Prevention.
9. Chen J, Kumar M, Chan W, Berkowitz G, Wetmur JG. 2003. Increased influence of genetic variation on PON1 activity in neonates. Environ Health Perspect 111: 1403-1409.
10. Engel SM, Miodovnik A, Canfield RL, et al. Prenatal phthalate exposure is associated with childhood behavior and executive functioning. Environ Health Perspect 2010;118:565-71.
11. England LJ, Kendrick JS, Wilson HG, Merritt RK, Gargiullo PM, Zahniser SC. 2001. Effects of smoking reduction during pregnancy on the birth weight of term infants. Am J Epidemiol 154:694-701.
12. Eskenazi B, Marks AR, Bradman A, et al. Organophosphate pesticide exposure and neurodevelopment in young Mexican-American children. Environ Health Perspect 2007;115:792-798.
13. Froehlich T, Lanphear BP, Auinger P, et al. The Association of Tobacco and Lead Exposure with Attention-Deficit/Hyperactivity Disorder in a National Sample of US Children. Pediatrics 2009;124:e1054-1063.
14. Gould E. Childhood lead poisoning: Conservative estimates of the social an economic benefits of lead hazard control. Environ Health Perspectives 2009;117:1162-1167.
15. Herbstman JB, Sjödin A, Kurzon M, et al. Prenatal exposure to PBDEs and neuro-development. Environ Health Perspect 2010;118:712-719.
16. Hertz-Picciotto I, Delwiche L. The rise in autism and the role of age at diagnosis. Epidemiology. 2009 Jan;20(1):84-90.19:417-428.
17. Jaakkola JJ, Jaakkola N, Zahlsen K. 2001. Fetal growth and length of gestation in relation to prenatal exposure to environmental tobacco smoke assessed by hair nicotine concentration. Environ Health Perspect 109: 557-561.

18. Jacobson JL, Jacobson SW. 1996. Intellectual impairment in children exposed to polychlorinated biphenyls in utero. N Engl J Med 335:783-789.
19. Kahn RS, Khoury J, Nichols WC, Lanphear BP. 2003. Role of dopamine transporter genotype and maternal prenatal smoking in childhood hyperactive-impulsive, inattentive, and oppositional behaviors. J Pediatr 143: 104-110.
20. Landrigan PJ, Carlson JE, Bearer CF, et al. 1998. Children's health and the environment: a new agenda for prevention research. Environ Health Perspect 106(suppl 3):787-794.
21. Lanphear BP, Hornung R, Khoury J, et al. Low-level environmental lead exposure and children's intellectual function: An international pooled analysis. Environ Health Perspect 2005;113:894-899.
22. Needleman HL, Schell A, Bellinger D, Leviton A, Allred EN. 1990. The long-trm effects of exposure to low doses of lead in childhood. An 11-year follow-up report. N Engl J Med 322:83-88.
23. Needleman HL, Gunnoe C, Leviton A, et al. 1979. Deficits in psychologic and classroom performance of children with elevated dentine lead levels. N Engl J Med 300:689-695.
24. Nevin R. How lead exposure relates to temporal changes in IQ, violent crime, and unwed pregnancy. Environ Res 2000;83:1-22.
25. Perera FP. 1997. Environment and cancer: who are susceptible? Science 278:1068-1073.
26. Perera FP, Li Z, Whyatt R, Hoepner L, Wang S, Camann D, Rauh V. Prenatal airborne polycyclic aromatic hydrocarbon exposure and child IQ at age 5 years. Pediatrics. 2009;124:e195-202.
27. Ramirez GB, Cruz MC, Pagulayan O, Ostrea E, Dalisay C. 2000. The Tagum study I: analysis and clinical correlates of mercury in maternal and cord blood, breast milk, meconium, and infants' hair. Pediatrics 106:774-781.
28. Rauh VA, Garfinkel R, Perera FP, et al. Impact of Prenatal Chlorpyrifos Exposure on Neurodevelopment in the First 3 Years of Life Among Inner-City Children *Pediatrics* 2006;118;e1845-e1859.
29. Reyes JW. Environmental policy as social policy? The impact of childhood lead exposure on crime. The BE Journal of Economic Analysis & Policy 2007;7:1 Article 51.
30. Schantz SL, Widholm JJ, Rice DC. 2003. Effects of PCB exposure on neuropsychological function in children. Environ Health Perspect 111:357-576.
31. Sexton K, Needham LL, Pirkle JL. 2004. Human biomonitoring of environmental chemicals. Am Sci 92: 38-45.
32. Stewart PW, Reihman J, Lonky EI, Darvill TJ, Pagano J. 2003. Cognitive development in preschool children prenatally exposed to PCBs and MeHg. Neurotoxicol Teratol 25: 11-22.
33. Wakschlag LS, Pickett KE, Cook E Jr, Benowitz NL, Leventhal BL. 2002. Maternal smoking during pregnancy and severe antisocial behavior in offspring: a review. Am J Public Health 92:966-974.
34. Wright JP, Dietrich KN, Ris MD, et al. Association of prenatal and childhood blood lead concentrations with criminal arrests in early adulthood. PLoS Med 2008;5:e101.
35. Yolton K, Auinger P, Dietrich K, Lanphear B, Hornung R. 2005. Exposure to environmental tobacco smoke and cognitive abilities among U.S. children and adolescents. Environ Health Perspect 113:98-103.

Questions for Lanphear

Questions from:

Senator Barbara Boxer

1. Doctor Lanphear, your testimony states that research on the impacts of environmental toxins is showing that "in some cases the effects appear to be greater at the lowest levels of exposure ... "

Could you please give me some examples of what the research is finding on this issue?

There are over five studies that have reported greater decrements in IQ or other intellectual abilities in children at the lowest levels of lead exposure. In other words, while having a blood lead level of 20 micrograms per deciliter is associated with greater cumulative IQ decrements than having a blood lead level of 10 micrograms per deciliter, an increase in blood lead from <1 micrograms per deciliter to 10 micrograms per deciliter is associated with greater IQ decrements (an estimated 6 IQ points) compared with the decrements associated with an increase from 10 micrograms to 20 micrograms per deciliter (an estimated 2 IQ points). This surprising finding indicates that there is no safe level of lead in blood.

Two studies of tobacco exposure showed the greatest decrements in newborn birth weight and reading abilities in school age children at the lowest levels.

Other studies, such as those studying mercury toxicity, have not yet found a threshold. One study suggests that there are greater cognitive deficits at lower levels of arsenic exposure, but it has not been confirmed.

Why are these studies important? Because, with the exceptions of carcinogens, most regulations for chemical and metals assume that there are thresholds; that they are not toxic at the lowest levels of exposure. This emerging research indicates that for a given increase in exposure, there may be substantial damage at the lowest levels with no evidence for a threshold. If chemicals are toxic at the lowest measurable levels, this means that a far greater number of children or Americans will be adversely affected. Finally, subtle effects which affect millions of Americans results in substantial health impacts and costs. For example, our own research has been used to show that for every $1 invested to reduce children's exposure to residential lead hazards, society would benefit by $17 to $220, a cost-benefit ratio that is better than vaccines. This is equivalent to over $30 billion in annual savings for the United States.

2. Doctor Lanphear, how important do you think it is for researchers to better understand how to assess the interactions of multiple environmental toxins on the health and development of our children?

It is extraordinarily important to understand how interactions of multiple toxins, or toxicants, impact children's development. If we do not take into account the joint effect of various toxicants, we will, in many cases, erroneously dismiss or underestimate the effects of potent toxicants on children and adults in the United States.

For example, in a national US study, we recently found that children who were prenatally exposed to tobacco (i.e., the mother was an active smoker) or who had blood lead levels in excess of 1.4 micrograms per deciliter (virtually all of the children had blood lead levels < 10 micrograms per deciliter, the current CDC level of concern), were 2.5-times more likely to meet criteria for ADHD, using a validated instrument. But children who had high exposures to both tobacco and lead were *8-times* more likely to have ADHD.

This study also estimated that one out of every three children who met diagnostic criteria for ADHD could be attributed to either lead or tobacco exposure. Although less definitive, other studies of this same data set found that pesticides were associated with ADHD symptoms.

3. Doctor Lanphear, what does the current state of research on the potential impacts of environmental toxins, including lead, tell you about the need for policymakers to use this type of information to protect children's health?

The current state of the science is sufficient for us to revise the Toxic Substances Control Act of 1976. One essential measure of these new regulations would be to require industry to prove that chemicals sold or used in products are safe – before they are marketed.

Although there are some uncertainties about whether any particular chemical is toxic, the pattern of pathology or toxicity that has been confirmed for numerous metals or chemicals (e.g., mercury, lead, PCBs, tobacco, arsenic) is sufficient for us to conclude with absolute certainty that low-level exposures to these chemicals have the potential to be toxic, especially for the developing fetus or child.

This situation is analogous with the recognition that drugs should be tested for safety and efficacy BEFORE they are marketed. Although there were scientists who argued for stronger regulations on drugs since the early 1900s, they were only introduced after the thalidomide epidemic. The European Union has already acknowledged this by shifting the burden of proof to industry. If US manufacturers want to sell their products to the EU, we will have to meet the EU standards.

Senator James M. Inhofe

1. You mention an example that used cohort studies to look at blood concentrations and IQ. Given that cohort studies are subject to many biases and not suited to study rare diseases (or in this case very small changes in IQ), do you think it is appropriate to look at different methodology?

There are ways to accelerate or augment the existing types of studies or study designs to enhance our ability to make more definitive conclusions about the safety or toxicity of chemicals. First, we can rely on validated animal toxicity studies without requiring human studies. Indeed, if we are to require industries to prove that their products are safe before marketing, we will have to rely on this type of study. There is a tremendous track record showing that most (but not all) animal toxicity studies are relevant to human health. (If anyone argues otherwise, they would also have to acknowledge that a sizable fraction of NIH-funded studies are of questionable merit because many NIH-funded studies rely on animal models.)

Second, there are newer, alternative types of toxicity testing that were recently reviewed by the National Academies of Sciences, but many of these tests are still being validated.

Third, whenever possible and ethically acceptable, we can reduce exposures to *existing* (and persistent) environmental chemicals in an experimental or randomized fashion and examine whether the participants who were assigned to the reduced exposure group benefit. This type of study can benefit the participants of the study by reducing exposure at the same time as testing preventive interventions (e.g., increasing dietary intake of fish low in mercury during pregnancy).

Senator KLOBUCHAR. Thank you very much.
Ms. Moen, thank you for being here.

STATEMENT OF MARY MOEN

Ms. MOEN. Thank you, Senator Klobuchar.

I am happy to be here today with my husband, Steven, and my 10-year-old son, Max, from our home in Minneapolis, Minnesota. Thank you for the opportunity to speak with you about the effect of autism on my family.

When Max was 3 years old he was diagnosed with an autism spectrum disorder. The diagnosis came after a year of fear and frustration as our bright and active baby had become increasingly agitated and aggressive as a toddler. As a pre-schooler any social situation was very challenging for Max. He became difficult to manage outside the home safely and was increasingly bothered by loud and high pitched noises, smells, and touch.

His reactions to things he didn't like were explosive and often dangerous. His brother, Theo, was born during this time. And the stress of a new baby and an uncontrollable 3-year-old was more than we could bear.

We took Max for lengthy evaluations through Minneapolis public schools and medical assessments at two different autism specialty centers. The school district gave him an educational label of autism spectrum disorder at age 3 and a half. The doctors' and psychologists' reports gave similar findings.

At the time he was diagnosed, many around me were asking how Max got autism. We suspect a genetic link, but the time it didn't matter. I was focused on moving forward to help my son, who was by now so obviously different from his peers. Everything we read about treating autism told us that early intervention was key. We bought books, went to conferences and begged for consultations with over-scheduled experts in the field. We learned what methods would be most effective for Max but were frustrated to find waiting lists as long as 6 to 12 months at facilities that offered these services.

I quit my teaching job, and my husband cut back on his orthopedic surgery practice. It became our mission to put together an appropriate treatment plan that would address Max's unique needs. We worked to tweak this plan for the next few years of Max's life.

When he began kindergarten at age 6, we learned that our local community school did not have an autism program. Although Max's reading and math skills were far above grade level, his poor social skills and lack of self-control meant he needed more support. We had to send him to a school outside of our community. And doing so created even more impediments to making friends, and his social isolation was not improved.

Our goal was to bring his skills to a point where he could be fully mainstreamed and moved to our community school by first grade. This took a lot of hard work, including doubling up on therapy and intensive summer programing. He has now been at the school for 3 years.

Life was somewhat easier now, but not without struggles. We made the difficult decision to give Max medication to control his

impulses and stay calm. Meltdowns come weekly, rather than daily. Things like playing on a sports team, making friends, and going to summer camp that are just natural steps in a neurotypical child's life come carefully planned and prepared for Max. Setting him up for success takes understanding his challenges as well as a tremendous amount of time and forethought.

So while things look pretty good right now, we never really know what will set Max back or how long he will need our help. We hope he will continue to excel academically and go on to college and be a productive and happy adult.

In contrast, Max's 48-year-old aunt, who we suspect is also in the autism spectrum, is unemployed, socially isolated, and entirely dependent on her aging parents. People like her, with undiagnosed and untreated autism, are an example of autism's costs to our economy and society.

I now feel like I can look beyond our situation and address some of the questions others were asking me when Max was first diagnosed. There are many unanswered questions that can only be answered through more research. As families of children with autism, we each struggle with the why. The manifestations of autism are as diverse as the families and communities from which children with autism come.

I do not believe we can come to a simple conclusion when it comes to the cause and effects of such a complex disorder as autism. While there is an urgent and growing need for resources for early identification and intervention, ongoing treatment, medical care, and social services for children and adults with autism, it is also imperative that we focus resources on continued research so that we can one day identify its cause. Until we have done the extensive research necessary to understand autism, we cannot leave any stone unturned or rule out any possible factors as a cause of this disorder.

Thank you for the opportunity to share my story with you today. I welcome any questions you may have.

[The prepared statement of Ms. Moen follows:]

Senator Klobuchar and Distinguished members of the Subcommittee:

My name is Mary Moen. My husband Steve and my 10 year-old son, Max, are here with me today from our home in Minneapolis, MN. When Max was three years-old he was diagnosed with an Autism Spectrum Disorder called Pervasive Developmental Disorder-Not Otherwise Specified. The diagnosis came after a year of fear and frustration as our bright and active baby had become increasingly agitated and aggressive as a toddler.

As a preschooler, any social situation was very challenging for Max. He became difficult to manage outside the home safely and was increasingly bothered by loud and high-pitched noises, smells and touch. His reactions to things he didn't like were explosive and often dangerous. His brother, Theo, was born during this time and the stress of a new baby and an uncontrollable 3 year-old was more than we could bear.

We took him for lengthy evaluations through Minneapolis Public Schools and medical assessments at two different autism specialty centers. The school district gave him an educational label of autism spectrum disorder. The doctors' and psychologists' reports gave similar findings.

At the time he was diagnosed, many around me were asking how Max got autism. We suspected a genetic link and I wondered about the effects of the infertility medications I had taken for the two years previous to his birth, but at the time it didn't matter. I was focused on moving forward to help my son who was, by now, so obviously different from his peers.
Everything we read about treating autism told us that early intervention was key so we could not wait for services to come to us. We bought books, went to conferences and begged for consultations with over-scheduled experts in the field. We learned what methods would be most effective for Max, but were frustrated to find waiting lists as long as 6 to 12 months at facilities that offered these treatments. We sought out private therapies until we could get into an autism program. These therapies often were not covered by insurance. Thankfully we live near Fraser Child and Family Center, the largest provider of Autism Services in the Midwest. At Fraser I was assigned a case manager and Max was admitted into a day treatment program for children with autism. The words of one psychologist haunted me. "You're going to have to teach your son many of the developmental things that other kids learn naturally." I wondered, "What were those things?" and "What if I missed something?". I quit my teaching job and threw myself into this full-time. My husband also cut back on his orthopaedic surgery practice to be home more. It became our mission to put together an appropriate treatment plan that would address Max's unique needs and we worked and tweaked this plan for the next few years of Max's life.

When he began kindergarten at age 6, we learned that our local community school did not have an autism program and although Max's reading and math skills were

far above grade level, his poor social skills and lack of self-control meant he needed more support. We had to send him to a school outside of our community that had an Autism Program. We always thought it was strange to take kids with a social disorder and send them to a school outside of their community, where there are even more impediments to making friends.

Our goal was to bring his skills to a point where he could be fully mainstreamed and moved to our community school with no autism support by first grade. It took a lot of hard work to make this happen-including doubling-up on therapy and intensive summer programming.

Moving to our community school was an extremely difficult transition despite some very well-meaning teachers. The staff was not experienced in working with kids on the autism spectrum. Despite these challenges, we felt it was important for Max to experience a mainstream school setting instead of being accommodated in a special education program. My husband calls it the "school of hard knocks", and there have been plenty of hard knocks. Max works so hard each day that it is not uncommon for him to fall asleep in exhaustion before dinner.

Life is somewhat easier now, but not without struggles. We made the difficult decision start medication to help control his impulses and stay calm. Meltdowns come weekly rather than daily. Max's interests are not like his peers and making friends is very difficult. Teaching him tools to resolve conflict is an ongoing lesson. He is often inflexible and resistant to change. Things like playing on a sports team, making friends and going to summer camp, that are just natural steps in a neuro-typical child's life come carefully planned and prepared for Max. Setting him up for success takes understanding his challenges as well as a tremendous amount of time and forethought.

Max turned 10 last Sunday and will be starting 4th grade in a few weeks. He is a bright, outgoing star at school. He is known and loved by his teachers and staff. He is beginning to have success in age appropriate experiences after 6 years of Special Education, therapies, medication and social skills training. He plays on basketball, baseball and soccer teams and joined the chess club. He would tell you that he has a few friends. He is going to sleep away camp for the first time next week , which is a milestone for any child, but particularly for a child with autism that has difficulty making friends and adapting to change.

So while things look pretty good right now, we never really know what will set Max back or how long he will need our help. We hope he will continue to excel academically and go on to college and be a productive and happy adult. In contrast, Max's 48 year-old aunt who we suspect is also on the autism spectrum, is unemployed, socially isolated and entirely dependent on her aging parents. People like her, with undiagnosed or untreated autism, are an example of autism's cost to our economy and society.

Our family is at a point now where I feel like I can look beyond our situation and address some of those questions others were asking me when Max was first diagnosed. How did Max get autism? Why is autism increasing? And what can I do to help so other parents and children can be spared this difficult path? There are many unanswered questions that can only be answered with more research. As families of children with autism we each struggle with the "why". The manifestations of autism are as diverse as the families and communities from which children with autism come. I do not believe we can come to simple conclusions when it comes to the cause and effects of such a complex disorder as autism. While there is an urgent and growing need for resources for early identification and intervention, on-going treatment, medical care and social services for children and adults with autism, it is also imperative that we focus resources on continued research so that we can one day identify its cause. Until we have done the extensive research necessary to understand autism, we cannot leave any stone unturned or rule out any possible factors as a cause of this disorder.

Thank you for the opportunity to share my story with you today.

Dear Senator Boxer:

In response to your question:
"Ms. Moen, you've heard government officials and researchers from across the country describe the importance of the studying environmental factors in potentially triggering neurological disorders.
What would you tell these people about the importance of their research--in terms of helping people in our society impacted by this disorder?"

To government officials: Please continue to fund autism research and hold researchers accountable for quality studies and findings. Please listen to researchers if there is any suspect food or chemical on the market and fight to have it removed. Also please continue to support programs for early diagnosis and intervention for children with autism.

To researchers studying autism: I am not sure that you can help my son, but for all the babies yet to be born, please let us know if you suspect anything mother's are ingesting or living near may possibly impact their child. I know that we do not want to create hysteria similar to the vaccine/mercury case, but, for example, if there is any question about chemicals in food, at least doctors could be suggesting that natural foods only be ingested by pregnant mothers and small children. Many assume that if a food is on the shelf, it is harmless to eat.

I advocate constantly for my son. I am at school, on the soccer field and in my neighborhood, ensuring that he has equal opportunities and positive experiences. I want to know that someone is out there advocating for me and all the children and adults affected by autism and other neurological disorders. I felt that at the Senate Hearing from you, Senator Boxer, and Senator Kolbuchar. Although finding the true cause of this disease has been desribed as very large in scope, I pray that the researchers realize the huge economic and social impact of their work as well.

Thank you for the opportunity to speak at the hearing.
Sincerely,
Mary Moen

Senator KLOBUCHAR. Thank you so much. Thank you for your courage.

She did a pretty good, right, Max? You liked it. You were good.

So thank you for that, and all the work that you have done. Your story sounds eerily similar to some of my friends who basically gave up their jobs as well and focused on trying to figure out what was wrong and then how to fix it. I would think knowing the root cause would obviously make it a lot easier in figuring out the treatment.

Could you just talk first about some of the impediments you had in getting treatment? I know Minnesota is one of the medical meccas and a good place to be when things go wrong. But do you want to talk about some of the obstacles and what you think could be done to improve that?

Ms. MOEN. Definitely. Initially, there is a lot of shame. Because the behaviors he was exhibiting were more embarrassing than anything else. We called it the walk of shame, when we would go walk down the hall to the preschool teacher to find out what happened that day. So at first, just admitting that there was something that was different from his peers.

It was fairly easy, living in a metro area, with the Minneapolis public schools doing early childhood screening as early as we needed it, to get him to special education. But the appointments to get in with an autism specialist were 6 months long, just to get a diagnosis. We didn't know it was autism at that time, but we were looking at all of our different options.

Senator KLOBUCHAR. And when you are here today, when you listened to the testimony, I know you are out there about some of the research that is going on, and this complex interaction, as you have acknowledged, that it may not be just one silver bullet, the solution, between genetics and environmental factors, what is your reaction to that? You mentioned that you thought it could have a genetic link, because of this aunt, I assume.

Ms. MOEN. Yes.

Senator KLOBUCHAR. So what has been your own journey in trying to follow the research and figure out what is going on?

Ms. MOEN. My journey has been very recent, because I truly haven't felt that I have been able to look outside of my little world until very recently. I am not surprised, because I have two sons. They both have the same aunt. One of them is neurotypical; one of them is not. And there have always been questions about what it could be, beyond that. I don't think we can stop looking at that.

Senator KLOBUCHAR. Thank you.

Dr. Pessah, we were talking earlier with Dr. Birnbaum about this, the CHARGE study and what has been going on there. She mentioned that you could help to further illuminate, there must be preliminary findings, because it is not completed?

Mr. PESSAH. There are.

Senator KLOBUCHAR. On the immune system and the relation.

Mr. PESSAH. The immune disregulation in children with autism seems to be standing out based on comparisons with case control comparison groups, including those with developmental delays in the study without autism and neurotypical children. If I had to sort of summarize what the major impairments are in the immune sys-

tem, it would be a pro-inflammatory sort of—pro-inflammatory behavior of the immune cells in the presence of antibodies that direct or recognize proteins within the brain.

We found these, or immunologists found these both in the children, but also in the mothers. We have no idea how these auto-antibodies, as they were called——

Senator KLOBUCHAR. I got an A in high school chemistry, but then I forgot everything the next week after the test. So could you just try to explain that a little in layman's terms, what you are talking about here?

Mr. PESSAH. Sure. Pro-inflammatory behavior of the immune system is essentially one hallmark of immune dysfunction. Pro-inflammatory immune system can damage both immune responses but also is now known to influence neurodevelopment, especially if it occurs at very precise times during development.

Senator KLOBUCHAR. So pro-inflammatory, is it kind of a hyper-immune system, or it reacts a lot?

Mr. PESSAH. Essentially hyper-responsive in a particular way.

Senator KLOBUCHAR. All right, so you have this hyper-responsive immune system, and you mentioned that which, I guess one could argue that, is that possibly it reacts to some environmental factor?

Mr. PESSAH. That is a very good point. We have actually started to examine whether immune cells from children with autism respond differently to what we call zenobiotic exposures. The two that we have examined thus far is mercury, and the other are the flame retardants. We picked the latter because we now have evidence that flame retardants and others have presented that flame retardants interfere with both the developing nervous system and the immune system, possibly through common mechanisms.

Senator KLOBUCHAR. And what was the thing you said about the protein in the cells? What was that about?

Mr. PESSAH. That auto-antibodies are those antibodies which recognize self. That is not really supposed to happen. Because it can promote disease.

So in the mothers at risk for giving birth to an autistic child, we found that a subset of them have antibodies that actually can react with fetal proteins. What that means is that during gestation these antibodies can cross the placental barrier and have an influence, or have the possibility of having an influence on the developing fetus.

Again, we don't know why mothers at risk would have these auto-antibodies. This is something that we are examining now.

Senator KLOBUCHAR. In your testimony, and this is along the same lines, you said that genetics alone cannot account for the majority of autism cases currently being diagnosed. Do you want to elaborate on that?

Mr. PESSAH. Yes. There are some genes that have been associated with autism. But when you look at the percent of cases which have these genetic malfunctions, for each gene it is typically less than 1 percent. And in cumulative total, I think the estimate may be as high but probably no greater than 20 percent, if you add all those up.

So there is a large fraction of autism that really, at least at this point, has not been attributed to genetic contribution.

Senator KLOBUCHAR. I think you heard my story of these Somalian kids in Minnesota. Maybe you have heard about this before. Do you have any opinion on that and what could be going on there?

Mr. PESSAH. It is certainly intriguing and deserves more study.

Senator KLOBUCHAR. We will get you the information on it. That would be helpful.

UC Davis is working on a project called MARBLES, right, Markers of Autism Risk in Babies Learning Early Signs, to identify early predictors of autism, whether genetic or environmental? Can you be more specific in describing the aspects of this project and what the intended goals are?

Mr. PESSAH. This project, MARBLES, is recruiting women at high risk of giving birth to an autistic child. This is based on having inclusion criteria that the women must have already at least one autistic child—biological child—in the family. The goals of the study are to study the biology of the women involved, including taking blood samples, urine samples, labor and delivery samples, as well as following the child for the first 3 years after birth.

Such a longitudinal study is now being modeled. It was the predecessor of the EARLI study which Dr. Birnbaum described. Thus far, we have about 170 women enrolled. Our target is about 200, at least for this project period. The retention of women in the study, because it is a very arduous study for the participants, has been better than 90 percent. So we are very pleased.

Senator KLOBUCHAR. Very good.

I guess this could be both of you, I will start with Dr. Lanphear.

You mentioned the emerging evidence that new environmental chemicals have been associated with autism or other neurodevelopmental disorders. I think you focused on some of the other ones. But that more research is needed. Can you elaborate on the information gap, and do you think the NIH priorities are on track, or the research that is being done across the country?

Dr. LANPHEAR. Yes. First, I should say that using the same framework, it is going to be extraordinarily important to begin to understand mechanisms about how these chemicals may impact children and at different stages of life. What we have begun to do much more carefully over the last decade or so is to use biomarkers, measure how much of a chemical actually a child or an unborn child is exposed to, and then to see how that plays out, how it impacts the trajectory of learning behaviors and so forth.

So those kinds of studies will continue to be extraordinarily important. One example has an interaction that we have talked about, I think Dr. Anastas mentioned, if we look at children and ADHD, if the mother smokes, the child is about 2 and a half times more likely to have ADHD. If the child is exposed to lead, higher levels of lead in childhood, again about a 2 and a half-fold increased risk.

Together, if they are exposed to high levels of both tobacco and lead, which are both dopaminergic toxins, impacting particular areas of the brain, they are over 8 times more likely. So this idea of looking at interactions is really quite important. In a sense, you could think of it in very much the same way as genes and the environment. When they come together there can be tremendous risks for different kinds of problems.

Having said all that, while it is critical to do more of this research it seems to me that we do know enough to take action and develop regulations. Now, even if we develop all those regulations, there is still going to be plenty for all of us to do. We are not going to be out of work, although that would be wonderful, if you could develop regulations that would put me out of work.

[Laughter.]

Dr. LANPHEAR. But I do think the balance here is making sure that we act on the evidence that we have. And that doesn't mean that each new chemical has to be studied to death. We could look at the pattern that we have seen with other environmental toxicants. And based on that, just like we took regulations, took and developed regulations based on drugs, we can develop the regulations. And yet of course there is still quite a bit that needs to be done to look at these new emerging chemicals, some of which are acting as endocrine disruptors, others as neurotoxicants, or traditionally, like lead, impact other parts of the body.

Senator KLOBUCHAR. You mentioned the biomarkers. Could you go into a little detail about how that will help, not only with trying to find root causes, but prevention, diagnosis, treatment?

Dr. LANPHEAR. That is extraordinarily important. In the past we might have to rely on asking a pregnant woman, how close did you live to this plastics plant. That is not a very good way of measuring exposure. Now what we can do is take exquisite measures of exposures that might occur over pregnancy, for example.

So in our Cincinnati home study, what we have done is by——

Senator KLOBUCHAR. By exquisite, you don't mean like jewelry. What do you mean?

Dr. LANPHEAR. Exquisitely accurate measures of chemicals that the pregnant woman is exposed to in either her diet or airborne exposures. And look at those at different times. So we have measures three times during pregnancy in the Cincinnati home study, at 16 weeks gestation, 26 weeks, and at delivery. What we can do is begin to ask questions, not only about exposures throughout pregnancy, by taking the sum of those, but whether there is a difference, for example, in the timing of exposure.

So when we looked at bisphenol-A, a plastic, we found that exposures at 16 weeks gestation were associated with acting out type behaviors in the daughters but not in the sons. Now, that needs to be confirmed. That is the type of research that we can't make policy based upon one study. But what it suggests is the timing is important, looking sometimes at gender differences or sexually dimorphic behavior differences, based on a chemical.

But we couldn't have done that without a biomarker. So it is really critical to be able to measure exposures to chemicals.

Senator KLOBUCHAR. I get that.

Dr. Pessah, do you want to add anything with the biomarkers? Because I understand them now. We are almost on equal footing. I am kidding.

[Laughter.]

Mr. PESSAH. I think that by identifying classes of compounds, in the future we may be able to invoke a precautionary principle where, if a chemical has chemical properties that will know to be bioaccumulated—that is, retained in the body—if children are more

exposed, as you mentioned, that we might be able to predict, as opposed to having to test every chemical.

There are various levels of testing chemicals, from the cellular, the mechanistic, to the epidemiological approach. Given the vast number of high volume and even greater number of other chemicals in the environment, it behooves us to try to find some commonalities amongst chemicals in their mechanism of producing harm.

Senator KLOBUCHAR. What about this fact that Dr. Lanphear was talking about, that boys seem to have a higher rate of autism? I think that is correct. I am just trying to understand this. He talked about the interrelationship with gender. Any ideas there?

Mr. PESSAH. I think that is an important factor that needs to be acknowledged in current and future research, that obtaining cells from males may be different than obtaining cells from females, in terms of the level of susceptibility, or the nature of the response to environmental chemicals. So we need to keep that in mind.

Senator KLOBUCHAR. So if we could just write you a blank check right now, which sadly we can't, what would you most, if you could just conduct the research that you wanted to, in a big way, and I know there are limits on research, but if you could do that, where would you want to focus the research? No constraints from anyone about telling you what it should be or what pot of money it comes from. If you just wanted to figure out an answer for Mary Moen's question about why, what would you do?

Mr. PESSAH. Because of the complexity of autism spectrum disorders, our lesson learned at UC Davis is that you need a multidisciplinary approach. You need to have immunologists talk to neuroscientists talk to toxicologists and pool their efforts, integrate their efforts in understanding this very complex disorder. So granted, very large science will address more global issues.

I think concerted studies of specific populations will give you valuable answers that could lead to mitigation of autism.

Senator KLOBUCHAR. Do you want to answer that, Dr. Lanphear?

Dr. LANPHEAR. Yes. Given the prevalence of autism, even though it has risen in recent years, I think the kind of study you would want to do would be prospective, it would be large. And you would have multiple measures of various chemical exposures, or the opportunity to go back, using a repository, collecting blood or urine and so forth and storing it. And looking at the children as they develop.

That would of course be augmented by a whole host of other types of studies, looking very specifically at questions. But that kind of large birth cohort study, like the National Children's Study, I think is going to be an essential part of understanding the risk factors for the development of autism and ASD.

Senator KLOBUCHAR. Very good.

I want to thank all of you for coming. We will keep the record open for 2 weeks, and I am sure my colleagues may have some follow up questions. But I wanted to commend you for the work you are doing. I think that Ms. Moen said it best when she said she is just now, after struggling and doing everything for Max, gotten out of that. I know how that one feels, that one box, to start step-

ping back and asking why. I think that is what a lot of us are doing on behalf of moms and dads like her across the country.

It does appear that the solution may not be an easy one, but that this interaction with genetics and the immunology as well as the environmental factors is where we should head. So I want to thank you for all the research you have done.

Dr. Pessah, I think you should try to go head to head with Max on a math question when we are done, and see how he does there. Because he is supposed to be a math whiz. We will see how he does.

So thank you, everyone, for coming. The hearing is adjourned.

[Whereupon, at 11:35 a.m., the Subcommittee was adjourned.]

[An additional statement submitted for the record follows:]

STATEMENT OF HON. JAMES M. INHOFE,
U.S. SENATOR FROM THE STATE OF OKLAHOMA

As a father and grandfather, protecting the health of children—born and unborn—is a personal priority for me. I would like to thank Senator Klobuchar for scheduling this important hearing to discuss new developments in autism and other neuro-development disorders.

Autism and related developmental disorders affect approximately 1 in 110 births and are growing at an alarming rate of 10 to 17 percent per year. At this rate, there are estimates that the prevalence of autism could reach 4 million Americans in the next decade. Autism and similar disorders have no ethnic, racial, or social boundaries and can affect any family or child indiscriminately. Autism has increasingly been identified as a mostly complex genetic disorder, but some environmental factors may also be linked to its causes.

I have always championed the use of the best available science to properly assess the risks these devastating disorders have on children and families. Due to the increasing rates of autism in children, the Committee must ensure that the best available scientific research is conducted and appropriate funding is directed toward these causes.

Both the Environmental Protection Agency and the National Institute of Environmental Health Sciences have dedicated resources to research the environmental health factors associated with autism, and I look forward to hearing from the witnesses on the status of these ongoing studies. I invite the agencies and experts to identify areas where there may be inefficiencies or lack of sufficient information so we can address these issues and make certain that proper resources are being dedicated to the most appropriate areas of study.

The rise in autism is a very serious problem facing our Nation's children and families, and I will stay committed to discovering the causes and finding treatments. I look forward to hearing the results of the agencies' findings and how the Federal Government can enhance and improve its research efforts.

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