S. HRG. 110–1265

OVERSIGHT ON EPA'S CHILDREN'S HEALTH PROTECTION EFFORTS

HEARING

BEFORE THE

COMMITTEE ON ENVIRONMENT AND PUBLIC WORKS UNITED STATES SENATE

ONE HUNDRED TENTH CONGRESS

SECOND SESSION

SEPTEMBER 16, 2008

Printed for the use of the Committee on Environment and Public Works

Available via the World Wide Web: http://www.access.gpo.gov/congress.senate

U.S. GOVERNMENT PUBLISHING OFFICE
88–909 PDF WASHINGTON : 2015

For sale by the Superintendent of Documents, U.S. Government Publishing Office
Internet: bookstore.gpo.gov Phone: toll free (866) 512–1800; DC area (202) 512–1800
Fax: (202) 512–2104 Mail: Stop IDCC, Washington, DC 20402–0001

COMMITTEE ON ENVIRONMENT AND PUBLIC WORKS

ONE HUNDRED TENTH CONGRESS
SECOND SESSION

BARBARA BOXER, California, *Chairman*

MAX BAUCUS, Montana	JAMES M. INHOFE, Oklahoma
JOSEPH I. LIEBERMAN, Connecticut	JOHN W. WARNER, Virginia
THOMAS R. CARPER, Delaware	GEORGE V. VOINOVICH, Ohio
HILLARY RODHAM CLINTON, New York	JOHNNY ISAKSON, Georgia
FRANK R. LAUTENBERG, New Jersey	DAVID VITTER, Louisiana
BENJAMIN L. CARDIN, Maryland	JOHN BARRASSO, Wyoming
BERNARD SANDERS, Vermont	LARRY E. CRAIG, Idaho
AMY KLOBUCHAR, Minnesota	LAMAR ALEXANDER, Tennessee
SHELDON WHITEHOUSE, Rhode Island	CHRISTOPHER S. BOND, Missouri

BETTINA POIRIER, *Majority Staff Director and Chief Counsel*
ANDREW WHEELER, *Minority Staff Director*

C O N T E N T S

OVERSIGHT ON EPA'S CHILDREN'S HEALTH PROTECTION EFFORTS

TUESDAY, SEPTEMBER 16, 2008

U.S. SENATE,
COMMITTEE ON ENVIRONMENT AND PUBLIC WORKS,
Washington, DC.

The full committee met, pursuant to notice, at 10 a.m. in room 406, Dirksen Senate Office Building, Hon. Barbara Boxer (chairman of the full committee) presiding.

Present: Senators Boxer, Lautenberg, Cardin, Klobuchar, Clinton, Whitehouse, and Barrasso.

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

Senator BOXER. Good morning. I understand from Senator Barrasso that he will be joining in. Why don't you join us up here then, Senator? We would love to have you.

I believe this oversight hearing on the Environmental Protection Agency's Children's health protection record is key to our work. Protecting children's health should be a top-level priority for every EPA program. Children are not little adults; they can be extremely vulnerable to harm from toxic chemicals, often far more vulnerable and more exposed to pollutants than adults. Their rapidly growing bodies, complex and developing nervous and immune systems, their way of exploring their environment, including by putting just about everything they find into their mouths, all make children more vulnerable to harm from toxic pollutants than adults.

Their small size means they also consume more air, they drink more liquids, they eat more food for their body weight than do adults. A ten-pound infant may not be able to withstand the same amount of air pollution as a 170-pound adult male without suffering life-long injury.

On April 21, 1997, President Clinton issued Executive Order 13045 titled, Protection of Children from Environmental Health Risks and Safety Risks. This order established a national policy requiring all Federal agencies to "make it a high priority" to assess environmental health risks that may disproportionately affect children and to ensure agencies' policies, programs, activities, and standards address such risks.

The order also created an inter-agency task force that reported to the President with recommendations on ways to better protect children's health.

In May 1997 Administrator Browner established the Office of Children's Health Protection to help EPA implement the order and

to make the protection of children's health a fundamental goal of public health and environmental protection in the United States.

EPA also created a Federal Advisory Committee on Children's Health Protection to advise EPA on children's environmental health issues, as it develops standards, communicates with the public, and conducts research.

When it was first created, EPA used the Office of Children's Health Protection and the Children's Health Protection Advisory Committee in a proactive way to help the Agency better protect our children. Unfortunately, it has become clear that EPA has taken a dangerous u-turn on children's health protection.

My colleagues and I have spoken out and fought against EPA decisions that put our children's health at risk. Many of us have introduced bills. Many of us have fought against these regulations on perchlorate, on mercury, dangerous air pollutants such as smog and toxic soot and lead. We all know that children are more vulnerable than adults to these threats, and we know that these contaminants are in the air we breathe, the water we drink, and the land that we live in, and I am tired of people saying our children are our future as they roll back protections and don't do everything they can to protect our children.

Because of the disturbing pattern in rollback after rollback in this Administration, Senator Clinton joined me in asking the GAO to investigate EPA's record on children's health. Today they are going to give their interim findings.

The early results of GAO's investigation could not be more deeply troubling. GAO has found that EPA has failed to followup on recommendations of its own children's health experts and has weakened the Office of Children's Health Protection. Who are they listening to? The special interests. That is the answer, and it is absolutely unacceptable.

You may also remember the infamous Cheers program that EPA proposed jointly with the pesticide industry in 2005. It would have provided gifts to low-income families to participate in a study to evaluate children's exposure to toxic pesticides in their homes. They actually had kids crawling around in pesticides that were sprayed as part of the experiment. That is what they did. And then they were going to pay the families money, give them a camera, a video camera to follow the children around while they crawled around the sprayed areas. That is the reason I voted against Johnson when his vote came up.

We forced EPA to cancel that unethical study. We required EPA to issue new rules banning these types of tests. However, EPA's rules failed to sufficiently protect children. I have joined other colleagues in filing an amicus brief and a court challenge to EPA's rules, and EPA has a string of losses in the courts, and we trust they will lose this one, too.

I was stunned when EPA recently tried to quietly issue a proposal that could have allowed studies very similar to the Cheer's program. At my request, my Committee staff asked EPA a series of detailed questions about the ethical and other aspects of this proposal. EPA was unable to defend this program and answer these questions, so last week they canceled the proposal. Good. But why would EPA consider it in the first place?

We know that the failure to protect children's health has consequences, and when you hear the sound of my voice it is not happy because I am not only a Senator, but I am also a mother and I am a grandmother and I am going to be a grandmother again. Senator Lautenberg and Senator Cardin, if you would please give me this moment—I know that when my daughter has to consider what she can eat because of the levels of mercury in the food, where she can go, what she can do, we already know that premature babies are coming more and more often because of a lot of these exposures. This is not the time to pull back from protecting the public.

My colleagues, I know you are with me 100 percent on this, because we know the failure to protect our children has consequences.

Senator Lautenberg in every hearing we have had has gone through chapter and verse the experience of his own grandchild due to asthma, and I hope he will do it again, because he can't do it enough times for me, because that makes it real.

We will hear testimony from Dr. Trasande of Mount Sinai Medical Center today that "chronic diseases of environmental origin have become epidemic in American children. These diseases include, one, asthma; two, birth defects; three, neurodevelopmental disorders; four, leukemia; five, brain cancer in children; six, testicular cancer in adolescents; and, last but not least, pre-term birth.

We also will hear from GAO that EPA no longer has high-level infrastructure or mandates to coordinate Federal strategies for children's environmental health. Let me repeat that. We will hear from GAO that EPA no longer has high-level infrastructure or mandate to coordinate Federal strategies for children's environmental health. Now that does not reflect the values of the American people and our families. Children's health should be our top priority.

I will do everything in my power, and I know I speak for others on this committee, to ensure that EPA's inexcusable policies of neglecting children's health and carrying out its mission is reversed either now or when the next Administration takes over from this dismal, dismal record.

I would ask Senator Barrasso to now speak.

OPENING STATEMENT OF HON. JOHN A. BARRASSO, U.S. SENATOR FROM THE STATE OF WYOMING

Senator BARRASSO. Thank you, Madam Chairman.

Protecting children's health is a serious issue. As the father of three, I understand the concerns of parents wanting to protect their children from illness, from disease. As a doctor also and a trauma surgeon, a doctor who takes care of young children, I have treated children so that they can grow up to lead productive lives. I have taken an oath both as a Senator and as a doctor to work to improve the lives of people, and especially children. Our children must be protected. We must do whatever we can to achieve this goal.

But I think we can all agree that protecting children is a bipartisan issue. There may be different approaches to how to do it best, but it is a bipartisan issue. There is nothing that we wouldn't do to provide for our children. Children need safe drinking water.

Children need lifesaving medication. They need safe food to eat and clean air to breathe.

One way we provide these things for our children and our communities is through scientific innovation. Every day American ingenuity is generating the next generation of child safety products and medical devices. They are being created under a risk-based regulatory process under the EPA. But there is risk, unfortunately, that this next generation of life-saving innovations will not be developed. That is because some believe that the best way to protect our communities is to ban any chemical that might, even in the most remote instance, have a negative health effect.

This approach is designed to instill fear and precaution in families which will prevent future technologies that can make a real difference in the lives of children. Chlorine, for example, is a base ingredient. It is in disinfectants. You can read the possible harmful effects on a bottle of Lysol. In large doses, chlorine is toxic. And we often say in the medical world the dose makes the poison. Despite this, chlorine-based disinfectants are used every day to clean day care child centers, as disinfectants in hospitals across the Country. That is because chlorine kills e-coli, salmonella, other food-borne illnesses and bacteria that are a threat to infants, to toddlers, and to pre-teen children.

But in addition to disinfectants, chlorine chemicals are used to make prosthetic devices, PVC, which is a common chlorine-containing plastic used to construct prosthetic legs and arms for children who have lost legs because of birth defects. Thanks to these devices, many of the children can now lead normal lives and participate in most activities. PVC is used in blood bags and IV fluid bags and tubing to help deliver medication needed to care for young patients.

These things all improve people's lives.

I believe that the approach that the EPA uses is a correct approach, setting standards for clean water or for clean air or for what chemicals can be approved. You need to have a risk-based approach. Such an approach has peer review, it verifies data, it takes laboratory work and applies that to what you know about real-world exposures. Then you make a determination as to what is the best benefit to the environment and public health in making regulations.

In a previous hearing earlier this year I highlighted an article that ran in the Washington Post. The story is entitled, For Children, A Better Beginning. In brief, it says, "In a wide-ranging look at how children have fared in the first decade of life, a study released offers a promising picture of American childhood. Sixth graders feel safer at school. Reading and math scores are up for 9-year-olds. More pre-schoolers are vaccinated. Fewer are poisoned by lead."

The analysis was created as a composite index of more than 25 key national indicators reports an almost 10 percent boost in children's well-being between 1994 and 2006.

Now, the article mentioned possible reasons for the trend: better medical care, better nutrition, mandatory use of car seats, safer playground equipment. All of these things were brought about by

new innovation, the kind of innovation that comes about when you operate under a risk-based regulatory approach.

There is still more work that needs to be done. Children across the globe face new dangers from new diseases and other health threats. We must continue to review our regulations using a risk-based regulatory system to make sure we are adequately protecting our children. But the evidence clearly shows that the EPA is doing something right. Let's make sure that we are prepared here at home to address these challenges by keeping America the world leader in innovations that protect our children.

Thank you, Madam Chairman.

Senator BOXER. Thank you, Senator.

Let me just say for the record there isn't anyone on the Democratic side of the aisle that doesn't support risk-based analysis. What we do not support is tainted risk-based analysis by taking the scientists out and putting the special interests in, so let's be clear. Let's not set up a straw person here.

Senator Cardin.

OPENING STATEMENT OF HON. BENJAMIN CARDIN, U.S. SENATOR FROM THE STATE OF MARYLAND

Senator CARDIN. Well, let me thank my colleague for his courtesy and thank our Chairman for calling this hearing and for your dedication to the responsible of this Committee for oversight, which is one of the principal responsibilities we have as to whether the Office of Children's Health Protection is carrying out its mission to provide adequate protection for our children.

Madam Chair, I would ask my entire statement be made part of the record and let me just comment on a conference that I attended yesterday in Baltimore dealing with healthy homes in which agencies were represented. I think we had a good group there. I look forward to their recommendations.

It pointed out something that should be obvious in our Country, and that is that children have a right to expect a healthy environment. Children are not miniature adults. They deal with contaminants differently. Their bodies are growing. It is for that reason that we set up special protection for our children. They need our special protection.

We have a responsibility to make sure that the issues the that chairman referred to in regards to mercury, or an area that I have been involved with for many years, lead contaminant where we have lead poisoning of our children. You know, when a child suffers from a high level of lead in his or her blood, it robs that child of their full potential. They are more likely to drop out of school. They are more likely to have learning disabilities and are not able to achieve their full God-given potential. That is something that each one of us should be concerned about, because lead poisoning is totally preventable. This is a preventable disease.

Yes, I am proud that in Maryland we have made progress. We have reduced actually the children exposed to lead by about one-third over the last 12 years, and that is good numbers, but there are still too many children in my State and too many children in this Country that have a high level of lead in their blood that could have been prevented. We need to do more.

We can talk about the sub-standard housing in America where children are exposed to mold and mildew and pests and rodents, and it aggravates their ability, and we have asthma, and we have children being denied their full potential because we haven't dealt with that environmental risk.

So I think the frustration you are going to hear today is the fact that we have an interim report from the GAO that confirms what we, I think, knew from our own gut, and that is that the agency that was created to protect our children and speak up for our children, the Office of Children's Health Protection, has not utilized the services of its own advisory group, has not followed the recommendations that are important to protect our children, and that this Administration is not putting our children first and protecting them from environmental risks, which was the clear intent of Congress in establishing this agency and the responsibility of this Committee to make sure that the agency is aggressive in looking for ways. Rather than avoiding its responsibility, it should be using its Advisory Committee, it should be looking for creative ways to help our children so that we can be more aggressive in eliminating the risks that are out there.

Madam Chairman, again I thank you for holding this hearing.

[The prepared statement of Senator Cardin follows:]

STATEMENT OF HON. BENJAMIN L. CARDIN, U.S. SENATOR
FROM THE STATE OF MARYLAND

Madam Chairman, thank you for calling this hearing on a topic of great importance to me. I have been involved in children's environmental health issues, especially lead-poisoning of our children, dating back to my time in the State legislature. I appreciate the opportunity to address this key issue.

Children are not miniature adults. They are exposed to different environmental threats and their growing bodies process some contaminants differently than adults in important ways. The Office of Children's Health Protection was established following the recognition that children are affected uniquely by environmental risk factors and therefore need special protection. The goal of the office's creation was to ensure that the EPA established protections to specifically address threats to children's health and ensure a safe environment for every child.

Today we have reason to believe that this goal is not being achieved. The interim findings of the Government Accountability Office suggest that OCHP has failed to utilize the Children's Health Protection Advisory Committee, and has ignored the recommendations of this committee. The office has failed to take actions that would reduce the risks children face from environmental threats and has shown a lack of focus on children's health issues.

Environmental threats affect all children, but we have increasingly seen that they are most detrimental to infants and children who live in low income areas. There is significant evidence that environmental risks have negative impacts prenatally when pregnant women are exposed to unhealthy conditions. The impact on these populations, often unrepresented and under served, highlights the critical nature of OCHP's task. To ensure safe environments for all children is to encourage the equality of opportunity that is fundamental to America's ideals.

In my home State of Maryland, as in many states, children are at risk of being exposed to mercury through our waterways, lead in housing and commercial products, and untested pesticides, all of which have the potential for long-term health consequences. As a State we have attempted to address several of these issues, and have succeeded in decreasing childhood exposure to lead by thirty-three percent since 1995. However, we continue to see trends of the greatest impact in infants and low-income populations. It is critical that the Federal Government address these issues to lead and assist states in making children's health a demonstrated priority nationwide.

EPA has not done enough to protect children's health. I look forward to hearing from today's witnesses and to a recommitment from EPA to meet the special needs of America's children.

Thank you.

Senator BOXER. Thank you very much.
Senator Lautenberg.

OPENING STATEMENT OF HON. FRANK LAUTENBERG, U.S. SENATOR FROM THE STATE OF NEW JERSEY

Senator LAUTENBERG. Thank you, Madam Chairman.

One who serves on this Committee with any exposure to the operation of the Committee knows how forceful, how concerned our chairperson is to these things that endanger children or that permit us to lower our standards for what ought to be a good air quality standard or anything that presents risk.

When we talk about risk based, I think there is another way to view this, and that is on a precautionary basis, because when you say risk based it means that there are a group of kids who might become terribly affected, but the numbers aren't that great. Any child, any family that has children coming and knows that the risk is one in a thousand versus one in a hundred may be left out of the calculation because it doesn't furnish the fullest risk consideration.

This Committee once again finds itself forced to bring attention to dangerous shortcomings of the Bush administration's EPA. Simply put, this Administration repeatedly failed to do what they can do to protect the health of our children, and yet the EPA doesn't seem at all fazed by it. They could have set higher air quality standards so that our children are protected from asthma.

Senator Boxer was kind enough to remember that I have a grandchild who suffers from asthma, and it presents a lot of problems when my daughter takes her son to play soccer or another sport. The first thing she does is check where the nearest clinic is, emergency clinic, in case he starts to wheeze. She has to get him over there, regardless of where they stand in their games. That is her first concern, and I agree with that.

EPA could have made sure toxics and other industrial chemicals used in thousands of everyday products, from plastics to children's toys, were finally regulated, but they failed to act.

In fact, both of these changes were recommended by the EPA's own expert committee, the Children's Health Advisory Committee, and, as GAO will testify today, the EPA has chronically ignored the advice of these experts and repeatedly set standards too low to protect our children's health.

Out of the 80,000 chemicals and products that are found in our homes, around our children, the EPA has only tested 200. This statistic is the reason that I was joined by Chairman Boxer, Senators Clinton, Menendez, Carey, Schumer, Whitehouse to introduce the Kid-Safe Chemical Act instead of waiting for a chemical to make someone sick, are hoping for the EPA to prevent that from happening. We need to prove that chemicals are safe before they get into the hands of consumers. Precaution.

Our bill would direct the EPA to make sure that every chemical in every product is safe before it ends up on the store shelves or in our homes, and would put special emphasis on chemicals that are used by children.

We already regulate pesticides and pharmaceuticals this way. It is simply common sense that we do the same for chemicals that are used in consumer products.

We have so many other contingent things that concern us, and that is the lack of health care coverage for lots of young mothers-to-be, particularly in the teenage area. Some of those women see a doctor for the first time when labor begins. So we have an obligation to make sure that they are carrying a healthy child, to whatever extent we can.

Also, as we look at things, we have to note that in the State of California, for instance, Senator Boxer, in the last 10 years autism has increased as an incident over 200 percent, and in the State of New Jersey we know it is believed that one out of ninety-four males being born will be autistic. It is a terrible thing.

We need whatever help we can get. For the EPA to ignore the recommendations of the Committee is absolutely unacceptable.

I thank you.

Senator BOXER. Senator, thank you so much for your constancy on this issue.

We are joined by Senator Whitehouse. Senator Clinton is also on the way, so I told her staff that when she gets here we will finish whoever is speaking on the panel and let her make her opening statement, since she joined with me in calling for the GAO investigation.

I want to make a point that Senator Whitehouse, before he came here he was Attorney General in his State, and he took the leadership on the lead issue, protecting children from lead, so I am just so pleased you are here, Senator. Please go ahead.

OPENING STATEMENT OF HON. SHELDON WHITEHOUSE, U.S. SENATOR FROM THE STATE OF RHODE ISLAND

Senator WHITEHOUSE. Thank you, Chairman. And thank you for holding this hearing.

It is, in many respects, unpleasant that we have to be here, and I hope very much that whoever is elected President they put in place leadership at EPA so that these sorts of hearings are no longer necessary, because my at this point very strongly held view is that they represent an absolutely abject failure of governance and integrity at the Environmental Protection Agency right now. I have mentioned this on many occasions.

I will address the ozone issue briefly in my remarks right now because it is so important to Rhode Island's children. We get huge ozone load from midwestern power plants. As Attorney General I had to file suit to try to get action, and it continues to the point where Rhode Island, which is a beautiful State where people come to visit, which has a wonderful Atlantic shore, from time to time in the summer you drive in to work and you hear on the radio the announcements that this is not a safe day to breathe the air if you are elderly or if you are an infant or if you have breathing difficulties, and it is because of the level of ozone.

Here is the agency that is supposed to champion environmental protection. It is supposed to be their sole mission. It is right in their founding statement by the first administrator that that is supposed to be the case. And when you look what they did on

ozone, they got the answer substantively wrong, as they have on many environmental standards. They disregarded the advice of their own scientists and others. The procedures, as we have shown, in many of their decisionmaking have been deliberately manipulated to allow interference. So they have actually undercut the very administrative integrity and structure of the organization.

Finally, on other issues, we have had the administrator come in and, in my opinion, lie to this Committee as part of a calculated scheme to obscure the White House's political fingerprints on the decision that EPA purported to have made itself in the California waiver decision.

So the rot is very serious over there, in my estimation, at this point in its leadership. It looks very much like what people talked early on as the regulatory infrastructure was built in the United States, the great danger was a regulatory capture. This looks like an agency that is now captive in the hands of industry and is led by people whose job is not to follow the science, is not to protect the public, but is to deliver for the industry and then say whatever nonsense is necessary to try to cover their tracks to try to hang on to it. Because the American people certainly aren't going to put up with somebody who says, I am here to ruin this agency. I am here to hurt children's health protection. I am here to deliver for industry polluters. You can't be dumb about it; you have got to be clever. You have got to be crafty. You have got to be familiar with the kind of phony science that has become a minor industry in this Country to create doubt where no doubt should lie.

That is the strategy right now, and it makes it very awkward to have these hearings, because what we get it the screen of falsehood and prevarication that is designed to cover up the fact that this is an agency that has sold out at the highest levels.

I have called for the Administrator's resignation. I did it with great reluctance. The Chairman was gracious enough to join me and, in fact, lead that call, along with other members of the Committee, including Senator Lautenberg. I think we have kind of had it.

In the limited time remaining in this Administration it is a hard call to know whether it is worth just looking forward, moving on, and hoping it will be clean next time, or try to continue to root at the problem. I am very proud that, despite the limited time remaining, our Chairman has decided to root out this problem, because it is not just a problem of environmental protection; it is a problem of the integrity of Government at this stage, and we need to make sure this sort of thing doesn't happen again in American governmental organizations.

I thank the Chair.

Senator BOXER. I thank you for your very strong statement. I share every bit of what you said. I believe that you are right on target here.

I think I want the record to show that we invited Administrator Johnson again. Is this the fifth time? He hasn't been here since March. Senators Lautenberg and Whitehouse and my friends on the other side who aren't here, we have an Administrator, as I understand it—correct me if I am wrong—when he came to testify said he was thrilled to be the choice for Administrator. We asked

him, as we do everyone, will you come before this Committee whenever this Committee needs you to be here? He said yes.

Well, Senators, I am looking at that, because if somebody says yes—and I believe he was under oath at the time because it was in testimony—and he hasn't shown up since March, April, May, June, July, August, September—six months, and we have asked him to come to a number of hearings, and so far we have not received an affirmative response.

I am pursuing my remedies on that. You would think he would show up to talk about children. He said, I remember so clearly when we interviewed him when he came forward and he was before the Committee how proud he was of his kids and his grandkids were his biggest joy, and I believe that. Well, why isn't he here? He is hiding from this Committee and the American people. He is hiding from the American people.

So we are going to hear from The Honorable George Gray, Assistant Administrator for research and development at the EPA, and John Stephenson, GAO, Director, Environment and Natural Resources. We will ask each of you to speak for 5 minutes, please, and we will ask questions.

Mr. Gray.

STATEMENT OF HON. GEORGE GRAY, ASSISTANT ADMINISTRATOR FOR THE OFFICE OF RESEARCH AND DEVELOPMENT, UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

Mr. GRAY. Thank you, Madam Chair and members of the Committee. My name is George Gray and I am the Assistant Administrator for the Office of Research and Development and EPA, and I also serve as Agency Science Advisor.

Thank you for the opportunity to appear before the Committee to discuss an issue that is critically important to the American people and the future of our Nation, our children's health. As a Federal agency whose mission is to protect health and the environment, safeguarding children from unsafe exposures to chemicals and other toxic substances is a top priority at EPA.

On a personal note, as a parent with two growing children of my own, I know how important it is that we base our decisions on sound science to make sure that our children are safe from environmental harm. That is why EPA is constantly seeking ways to enhance children's health and why my office is producing and funding the best science to inform regulatory decisions.

Today I will highlight several key programs and regulations which were put in place to ensure that EPA continues to protect human health and children's health, and I will also discuss some of EPA's ongoing scientific research and analyses on this topic, as well as some publicly available resource guides for the public.

Because children are different from adults in several important ways, they may be more vulnerable to some health and developmental risks. Since EPA was established in 1970, we have taken leadership in the Nation's efforts to protect children's health. We all know, of course, of our early actions that mandated the removal of lead from gasoline, which continues to represent a landmark achievement in protecting children's health. Blood lead levels of

children born today are significantly lower than those born when EPA took action.

In 1995 EPA established an Agency-wide policy to ensure that unique vulnerabilities of children be explicitly and consistently considered in our risk assessments, risk characterizations, and our health standards. In 1996, the national agenda to protect children's health from environmental threats expanded the Agency's activities to specifically address risks for children.

As previously mentioned, in 1997 the President signed an Executive Order, protection of children's health from environmental health risks and safety risks. The order requires all Federal agencies to address a high priority to addressing health and safety risks to children.

EPA established the Office of Children's Health Protection in 1997 to support the agency as it embraced our 1996 agenda and the 1997 Executive Order. The mission of EPA's children's office is to make the health protection of children a fundamental goal of public health and environmental protection in the United States.

The office ensures that risks to children are considered in agency activities, standards, and regulations. It also works to advance science relating to children's exposure and risk.

To continually inform Agency initiatives related to children's health, EPA established the Children's Health Protection Advisory Committee in 1997. Through this Committee, leading researchers, academics, health care providers, NGO's, industry representatives, as well as representatives of State and local governments, regularly advise EPA on regulations, research, and communication's that are related to children's health.

EPA has worked to ensure that standards and regulations consider the potential risks that children face from exposure to chemicals and toxic substances.

I would like to highlight some examples of how the regulatory process has addressed children's health concerns.

You know that the Clean Air Act requires EPA to set national ambient air quality standards for widespread pollutants from diverse sources that are considered harmful to public health and the environment. Primary NOX standards are designed to protect the health of sensitive populations, including children. These ambient air quality standards are an important mechanism for reducing children's exposure. For example, in September 2006 EPA issued the Agency's most protective set of NOX ever for particular matter.

Our estimates indicate that attaining the new 24-hour PM 2.5 standards will result in the following improvements in children's health each year compared to 2006: we predict there will be 1,200 fewer emergency room visits for asthma, 7,300 fewer cases of acute bronchitis, 97,000 fewer cases of upper and lower respiratory symptoms, and 51,000 fewer cases of aggravated asthma. And the NAAQS for lead, ozone, nitrogen, and sulfur oxides also provide important benefits for children's health.

In addition, under the Safe Drinking Water Act Amendments of 1996 the EPA must consider segments of the population at risk from drinking water contaminants. In setting standards for drinking water, EPA conducts detailed analyses of available data to determine children's health risk.

Protecting children from potential effects of pesticides is an important aspect of EPA's pesticide program.

The Food Quality Protection Act requires EPA to place particular interest in children when making regulatory decisions about pesticides.

Risk assessments include evaluations for children in various age groups, since children's feeding and activity patterns change as they grow up.

In another area of critical important to children's health, EPA recently published its lead renovation and remodeling and painting rule. This rule is designed to minimize children's lead exposure as a result of renovation activities by ensuring that safe occupational practices are used by renovaters and that workers are properly trained.

EPA also conducts and facilitates research that provides essential information on children's health. In addition to intramural research in our Office of Research and Development, EPA's National Center for Environmental Research actively supports extramural research on topics related to children's environmental health through its Science to Achieve Results, or STAR, program.

From a read of our 2007 report, A Decade of Children's Environmental Health Research, you can see impressive results——

Senator BOXER. Mr. Gray, can you just sum up, because you have gone a minute over and we have a lot of questions. If you could sum up it would be great.

Mr. GRAY. We have an impressive portfolio of 100 projects that have resulted in more than 1,000 peer review publications.

In addition, we have guidance on conduct of risk assessment and the ways in which children's health should be considered, guidance on exposure assessment and the ways in which children's health can be considered, all of which are developed through a rigorous Agency-driven process, go through a complete peer review, and are available to those who are interested.

So thank you, Chairman Boxer, members of the Committee. I appreciate your dedication to children's health and your interest in EPA's efforts. EPA embraces its mission to protect the environment and public health, and we take extra care to protect those who may be most vulnerable, especially children.

I look forward to answering any questions that you may have. Thank you.

[The prepared statement of Mr. Gray follows:]

TESTIMONY OF

GEORGE GRAY, PhD
ASSISTANT ADMINISTRATOR FOR RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
BEFORE THE
COMMITTEE ON ENVIRONMENT AND PUBLIC WORKS
UNITED STATES SENATE

September 16, 2008

Good morning, Madam Chair and Members of the Committee. My name is Dr. George Gray, and I am the Assistant Administrator for Research and Development (ORD) at the U.S. Environmental Protection Agency (EPA). I also serve as the Agency's Science Advisor. Thank you for this opportunity to appear before the Committee to discuss an issue that is critically important to the American people and the future of our nation: the health of our children. EPA is committed to protecting children from exposures to harmful substances, and I appreciate your continued interest in our efforts. Today I will highlight several key EPA programs and regulations, which were put in place to ensure that we continue to protect children's health. I will also discuss some of EPA's ongoing scientific research and analyses on this topic, as well as publicly available resource guides related to children's health.

Focusing on Children: The Right Thing to Do

As a federal agency whose mission is to protect human health and the environment, safeguarding children from unsafe exposure to chemicals and other toxic substances is a top priority at EPA.

Because children are different from adults in several important ways, they may be more vulnerable to some health and developmental risks. First, because children are still growing and their neurological, immunological, respiratory, digestive, and other physical systems are still forming, they may be more at risk from harmful exposures that can disrupt their normal

development. Pound for pound, children also eat more, drink more, and breathe more than adults, so their food, water, and air must be safe. The way children play, infants crawl, and toddlers explore their world by placing things in their mouths increases the chances for exposure to environmental contaminants. Finally, children can be exposed to harmful substances in unique ways, such as through the placenta and breast milk. These special circumstances can make children more vulnerable to toxic substances in their environment.

On a personal note, as a parent with two growing children of my own, I know how important it is to base decisions on sound science and ensure our children are safe from environmental harm. That is why EPA is constantly seeking ways to enhance children's health, and why my office is producing and funding the best science to inform regulatory decisions.

EPA: A History of Protecting Children's Health

Since the establishment of EPA in 1970, we have taken leadership in the nation's efforts to protect children's health. For example, one of our earliest regulations mandated the removal of lead from gasoline, which continues to represent a landmark achievement in protecting children's health. The median concentration of lead in the blood of children 5 years old and under declined by 89 percent over the past 25 years.

In 1995, EPA established an Agency-wide policy to ensure that the unique vulnerabilities of children would be explicitly and consistently considered in our risk assessments, risk characterizations, and health standards. In 1996, the *National Agenda to Protect Children's Health from Environmental Threats* expanded the Agency's activities to specifically address risks for children. The Agenda directed EPA to:

- Ensure that all standards set by EPA are protective of any heightened risks faced by children.
- Develop a scientific research strategy focused on the gaps in knowledge regarding child-specific susceptibility and exposure to environmental pollutants.
- Develop new, comprehensive policies to address cumulative and simultaneous exposures faced by children.
- Expand community right-to-know, allowing families to make informed choices concerning environmental exposures to their children.

- Encourage parental responsibility for protecting children from environmental health threats by providing parents with basic information.
- Encourage and expand educational efforts with health-care providers and environmental professionals, so they can identify, prevent, and reduce environmental health threats to children.
- Provide the necessary funding to address children's environmental health as a top priority among relative health risks.

In 1997, the President signed Executive Order 13045: *Protection of Children's Health from Environmental Health Risks and Safety Risks.* The Order requires all federal agencies to assign a high priority to addressing health and safety risks to children, coordinate research priorities on children's health, and ensure that standards take into account special risks to children.

EPA established the Office of Children's Health Protection (OCHP) in 1997 to support the Agency as it embraced the 1996 National Agenda and the 1997 Executive Order. The mission of EPA's Children's Office is to make the health protection of children a fundamental goal of public health and environmental protection in the United States. The Office ensures that risks to children are considered in Agency activities, standards, and regulations. It also works to advance science relating to children's exposures and risks. For example, the Children's Office educates health care providers and jointly supports the Pediatric Environmental Health Specialty Units in partnership with the Agency for Toxic Substances and Disease Registry. The Office also supports critical efforts to develop indicators of children's environmental health, both domestically and internationally, and is an important partner with EPA on science and research related to children. Finally, the Office raises general awareness about children's environmental health issues and has been a leader in the Agency's efforts to address environmental health in schools.

To continually inform Agency initiatives related to children's health, EPA established the Children's Health and Protection Advisory Committee in 1997. Through the Committee, leading researchers, academics, health care providers, NGOs, industry representatives, as well as state and local government representatives advise EPA on regulations, research, and communications issues important to children's health.

Standards and Regulations

The Agency has worked to ensure that its standards and regulations consider the potential risks that children face from exposure to harmful chemicals and toxic substances. To assist in that effort, two publications help EPA staff determine whether the Executive Order or EPA's policy apply to specific Agency actions: *The Guide to Considering Children's Health When Developing EPA Actions: Implementing Executive Order 13045* and *EPA's Policy on Evaluating Health Risks to Children.* Since the 1998 issuance of the *Rule Writer's Guide to Executive Order 13405*, EPA has published several guidance documents related to risk assessment, regulatory policy, and action development.

The revision of the guide reflects new developments and more clearly integrates EPA's children's health policy with the action-development process for clean air, clean water, drinking water, pesticides, and toxics programs. The action-development process provides the framework for developing EPA regulations, and I would like to highlight some examples of how our regulatory process has addressed children's health concerns.

The Clean Air Act requires EPA to set National Ambient Air Quality Standards (NAAQS) for widespread pollutants from numerous and diverse sources considered harmful to public health and the environment. The Clean Air Act established two types of NAAQS. Primary standards set limits to protect public health, including the health of sensitive groups of the population. Secondary standards set limits to protect public welfare, including protection against visibility impairment, damage to animals, crops, vegetation, and buildings. The Clean Air Act requires periodic review of the science upon which the standards are based and the standards themselves. The NAAQS are an important mechanism for reducing children's exposure to pollutants that cause asthma and other health effects.

In September 2006, EPA issued the Agency's most protective set ever of NAAQS for particulate pollution, also called particulate matter, or PM. EPA selected levels for the final standards after completing an extensive evaluation of thousands of scientific studies about the potential impact of fine and coarse particulates on public health and welfare. EPA considered the advice provided by its Clean Air Scientific Advisory Committee at various points during this evaluation process. The Agency also carefully reviewed and considered public comment on the proposed

standards. Our estimates indicate that, in 2020, attaining the new 24-hour PM 2.5 standards have the potential to result in the following improvements in children's health:[1]

- 1,200 fewer emergency room visits for asthma;
- 7,300 fewer cases of acute bronchitis;
- 97,000 fewer cases of upper and lower respiratory symptoms; and
- 51,000 fewer cases of aggravated asthma.

On March 12, 2008, EPA significantly strengthened its NAAQS for ground-level ozone, the primary component of smog. As compared to the previous 8-hour NAAQS of 0.8 parts per million, the revised standard of 0.75 parts per million is estimated to provide the following benefits to children's health in 2020:[2]

- 4,900 fewer emergency room visits for asthma;
- 43,000 fewer cases of acute bronchitis;
- 1,000 fewer cases of lower respiratory symptoms; and
- 6,100 fewer cases of upper respiratory symptoms.

Finally, the Agency is in the process of reviewing the NOx and SOx NAAQS; among the health impacts being evaluated are the potential to exacerbate children's asthma. EPA will propose potential revisions to these standards in mid-2009.

Under the 1996 Amendments to the Safe Drinking Water Act, when EPA sets drinking water standards designed to strengthen protection of the public from the potential effects of contaminants in drinking water, EPA must consider segments of the population that are most at risk from the drinking water contaminants. In setting standards for drinking water contaminants, EPA conducts detailed analyses of available data to determine children's health risk. In the past few years, EPA has focused on setting or strengthening standards for controlling microbes, disinfection byproducts, and lead in drinking water. These include the Long Term 2 Enhanced Surface Water Treatment Rule, the Stage 2 Disinfectants and Disinfection Byproducts Rule and the Ground Water Rule, all promulgated in 2006, and Revisions to the Lead and Copper Rule, promulgated in 2007.

---

[1] For additional information and assumptions, see the regulatory impact analysis at the following website: http://www.epa.gov/air/particlepollution/fs20061006.html, http://www.epa.gov/ttn/ecas/regdata/RIAs/Chapter%205--Benefits.pdf

[2] For additional information and assumptions, see the regulatory impact analysis at the following website: http://www.epa.gov/ttn/ecas/regdata/RIAs/6-ozoneriachapter6.pdf

EPA is concerned about the potential sensitivity of children to exposure from pesticides compared to adults. Protecting children from potential effects of pesticides is an important aspect of EPA's Pesticide Program. The Food Quality Protection Act requires EPA to place particular emphasis on children in making regulatory decisions about pesticides. Risk assessments include evaluations for children in various age groups, since children's eating and activity patterns change as they grow up.

Another area of critical importance to children's health is lead exposure In the past 30 years, the average blood-lead concentration in children has declined dramatically from 15 micro-grams per deciliter to less than 2 micro-grams per deciliter due changes in product formulation (gasoline and house paint). However, studies continue to show health problems related to lead exposure, so there is more work to be done to reduce children's exposure. This need led EPA to promulgate its Renovation, Remodeling, and Painting Rule regarding lead. This rule is designed to minimize children's lead exposure as a result of renovation activities by ensuring that safe occupational practices are used by renovators in these homes, and providing training for workers. The rule's estimates of lead exposure and its estimates of health effects to children from lead are based on extensive research and modeling conducted by EPA's Office of Research and Development. Additionally, Agency researchers are working with outside vendors to develop lead-paint test kits to meet the specifications of the rule. Performance of the test kits will be independently verified through EPA's Environmental Technology Verification program.

The Agency is also currently reviewing and revising the NAAQS for lead. The Agency has reviewed thousands of studies on the health and environmental impacts of lead as part of the NAAQS process and has obtained advice from its expert scientific panel. Several of the studies evaluated focus on lead exposure to children, and these studies will be an important factor in the Agency's decision on a revised lead NAAQS. We anticipate issuing the final rule on the revised lead NAAQS in mid-October.

Research, Analysis, and Resource Guides

EPA has conducted and facilitated, at our own labs and research centers, and also through extramural grants, research projects that provide essential information related to children's health. EPA has worked collaboratively with other Agencies to support basic research on children's health issues in order to better understand child-specific risk factors and identify opportunities to reduce children's risks. EPA has developed, and made publicly available, a number of documents that provide guidance to researchers and the public about how to use scientific data when assessing children's exposures or health risks. The following section highlights several key examples of our children's health accomplishments related to research, analysis, and resource guides.

EPA's National Center for Environmental Research actively supports extramural research on topics related to children's environmental health through its Science to Achieve Results (STAR) program. EPA's 2007 report, *A Decade of Children's Environmental Health Research*, summarizes many of the accomplishments of EPA's grants in this area. Examples of research topics include the effects of pesticides on neurodevelopment; impacts of the ban of chlorpyrifos and diazinon; link between immune system abnormalities and autism; genetic vulnerability of children to the effects of organophosphate pesticides; and the relationship between children raised near major roadways and the risk of developing asthma.

Since 1998, EPA and the National Institute of Environmental Health Sciences (NIEHS) have funded fourteen independent, academic Centers for Children's Environmental Health and Disease Prevention Research. These Centers are dedicated to the study of children's environmental health hazards; they translate their scientific findings into intervention and prevention strategies by working with communities. The first eight centers were funded in 1998 to study the effects of environmental factors, such as pesticides and air pollution, on childhood asthma as well as children's growth and development. Four more Centers were funded in 2001 to study the basis of neuro-developmental and behavioral disorders, such as autism. Additional Centers were funded in 2004 and 2007 to investigate how exposure to mixtures of chemicals affects children's health, and also how environmental, social, and other factors contribute to health disparities in birth outcomes. Each Center fosters community participation in one or more studies.

EPA's intramural research program is complementary to, and integrated with, its extramural STAR program. This research informs current risk assessments and ongoing epidemiological and observations studies. EPA is identifying critical windows of exposure during fetal and early life; revealing how endocrine-active compounds mimic hormones and disrupt normal development of the nervous and reproductive systems; determining the importance of allergens, such as mold and air pollution, in inducing or exacerbating childhood asthma; improving experimental protocols and test methods to identify and characterize contaminants that might impact children's health; and developing better methods and models to assess cumulative exposures and toxicity.

EPA, as part of a consortium of federal partners, has contributed to the planning of the *National Children's Study*. This first-of-a-kind study will examine the influence of the social and physical environment, as well as the genetic influences on the health and development of more than 100,000 children across the United States, following them from before birth until age 21. The goal of the study is to improve the health and well-being of children. The National Children's Study (then called the Children's Longitudinal Cohort Study) was authorized by the U.S. Congress and signed into law on October 17, 2000 as a part of the Children's Health Act of 2000 (Public Law 106-310).

EPA has developed many publications and resource guides to assist researchers and the public in collecting data, identifying the best available science, and characterizing potential exposures and risks to children. For example, EPA's 2002 *Child-Specific Exposure Factors Handbook* provides a well-researched summary of data and recommendations for the use of specific exposure factors or activity patterns when assessing exposures to children. These exposures include those related the following: drinking water consumption, soil ingestion and mouthing behavior, inhalation rates, dermal factors, breast milk intake, and time spent in different locations or performing different activities.

EPA guidelines are developed with cross-Agency concurrence to ensure consistency and transparency in risk assessment, and they undergo external peer review and public comment. EPA's 2005 *Guidelines for Carcinogen Risk Assessment* and *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* describe how quantitative scientific data can be used to inform risk assessments. These assessments cover exposure to carcinogens during infancy and childhood and, under the Guidelines, help identify when an

assessor should apply age-dependent adjustment factors to provide additional protection for children. In 2007, EPA released a draft report entitled *Framework for Determining a Mutagenic Mode of Action for Carcinogenicity* for public comment and expert peer review. This proposed Framework provides guidance on the application of age-dependent adjustment factors for children by presenting a methodology for evaluating whether a chemical has a mutagenic mode of action for carcinogenicity.

EPA's 2005 *Guidance on Selecting Groups for Monitoring and Assessing Childhood Exposures to Environmental Contaminants* also provides guidance on how to select appropriate age groups when assessing childhood exposures to environmental contaminants. EPA's 2006 report, *A Framework for Assessing Health Risks of Environmental Exposures to Children* provides additional information on how to assess children's health risks based on existing EPA guidelines and policies. The Framework serves as a guide for conducting more complete assessments of the health risks to children during all stages of development. In *Scientific and Ethical Approaches for Observational Exposure Studies*, released in May 2008, EPA identifies key scientific and ethical issues and provides information and resources to assist researchers as they plan and implement observational exposure studies, including those that involve children.

Conclusion

Thank you, Chairwoman Boxer, and members of the Committee. I appreciate your dedication to children's health and your interest in EPA's efforts. EPA embraces its mission to protect the environment and safeguard human health. We take extra precaution to protect those who are most vulnerable to contaminants in the environment, especially children. I look forward to answering any questions you may have. Thank you for your time.

Senator BOXER. Thank you.
Mr. Stephenson, welcome.

STATEMENT OF JOHN B. STEPHENSON, DIRECTOR, NATURAL RESOURCES AND ENVIRONMENT, GOVERNMENT ACCOUNTABILITY OFFICE

Mr. STEPHENSON. Welcome. Madam Chairman, members of the Committee, I am pleased to be here today to discuss our work of evaluating EPA's efforts to protect children from environmental health risks. Many of the Nation's 74 million children are exposed to hazardous chemicals daily. In 2006, for example, 55 percent of children lived in counties that exceeded one or more of the six principal air pollutants, two of which, ozone and particulate matter, are known to cause respiratory diseases such as asthma.

Asthma is the third most common cause of hospitalizations among children, resulting in 3.2 billion for treatment and 14 million lost days of school annually.

In April, 1997, as you have mentioned, the President signed Executive Order 13045 establishing an inter-agency task force to ensure that Federal regulations recognize, explicitly account for health and safety risks to children. The President's task force was co-chaired by the Administrator of EPA and the Secretary of Health and Human Services at the time and included the heads of at least 14 other departments, agencies, commissions, and councils.

Also in 1997 EPA established the Children's Health Protection Advisory Committee to advise the Agency on regulations, guidance, and policy relevant to children's health.

My testimony is based on ongoing work for this Committee. We are reporting today on how well EPA is using the Advisory Committee and responding to its recommendations.

In summary, we found that, although the Advisory Committee is a FACA chartered specifically to ensure that the Agency's regulations, guidance, and policies address the disproportionate risks to children that result from environmental contaminants, EPA is not effectively using its expertise. The Advisory Committee met more than thirty times over the last 10 years and discussed a variety of environmental health issues with dozens of officials from EPA program offices; however, we identified just seven instances where EPA program offices actually asked the Committee's advice. Rather, in the absence of such requests, the Advisory Committee, itself, has taken the initiative to write more than 70 letters to the Administrator since 1998 offering recommendations on a wide variety of children's environmental health concerns.

I have a chart here that depicts this over 600 recommendations categorized in terms of the subject they wrote on. It was very difficult to get these recommendations gleaned out of these 70 letters because it is not generally tracked by EPA.

In addition, in April 2007, to mark its tenth anniversary, the Advisory Committee wrote a letter to the EPA Administrator highlighting progress, but also identifying seven key areas of concern. That is depicted in this next chart. They include the need for EPA to eliminate environmental health disparities among low-income and minority children, the need to strengthen the national approach to regulating toxic chemicals, and the need to provide the

necessary leadership and infrastructure to protect children's health.

Our preliminary analysis shows that in about half the cases EPA's response to the Advisory Committee's 70 letters was non-responsive. We also found that the Administrator has not yet honored the commitment he made in his June 2007 letter for EPA program offices to review the recommendations in the Advisory Committee's letter. It has been over a year since he made this commitment, but this first step has not yet been completed.

While we are still in the process of evaluating EPA's response to all of the over 600 Advisory Committee recommendations, we have examined in detail recommendations pertaining to three air quality standards: particulate matter, ozone, and lead. We selected these air standards because of their affects on the rising rates of asthma, one of the most critical children's health concerns in the U.S.

We found that the Advisory Committee has written seven letters containing 27 recommendations on these air pollutants, alone because scientific evidence suggests that standards were not sufficiently protective of children's health. However, in analyzing EPA's response to these recommendations, we found that EPA either did not acknowledge, was non-committal, rejected, or offered only to consider them along with comments from the general public.

As shown in my last chart, EPA ultimately set the standards for these air toxins at less stringent levels than those recommended by not only the Children's Advisory Committee, but its own Clean Air Advisory Committee, as well.

Finally, nearly every children's health expert we have spoken to in the course of our work has suggested the need for an inter-agency group to provide important high-level leadership and coordination on children's environmental health issues. The President's Task Force on Environmental Health Risks and Safety Risks to Children had been providing this leadership from 1997 until it was allowed to expire in April 2005. The Task Force championed several important initiatives such as the National Children's Study and the healthy schools environmental assessment tool and developed national strategies to coordinate Federal programs for asthma, developmental disorders, cancer, and unintentional injuries, four major environmental health threats to children that it identified.

In conclusion, we believe that EPA should take steps to reinvigorate and more proactively use the expertise of its Advisory Committee and its Office of Children's Health, and it should honor the Administrator's commitment to act on the Advisory Committee's numerous recommendations.

Madam Chairman, that concludes my statement. I will be happy to take questions.

[The prepared statement of Mr. Stephenson follows:]

United States Government Accountability Office

GAO

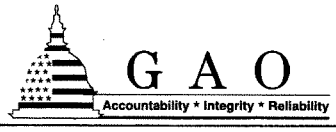
Testimony
Before the Committee on Environment and Public Works, U.S. Senate

For Release on Delivery
Expected at 10:00 a.m. EDT
Tuesday, September 16, 2008

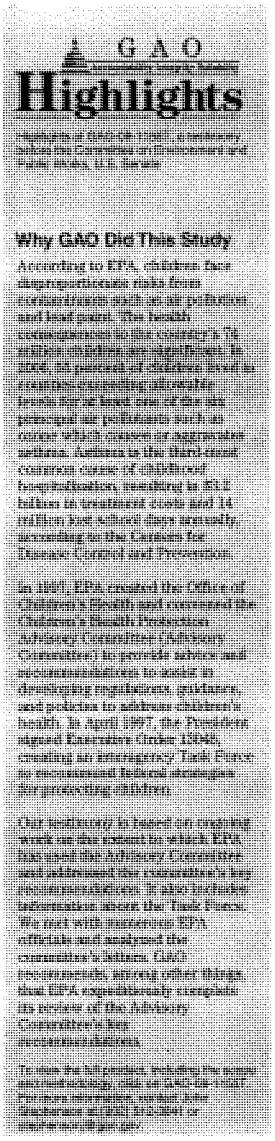
ENVIRONMENTAL HEALTH

EPA Efforts to Address Children's Health Issues Need Greater Focus, Direction, and Top-level Commitment

Statement of John B. Stephenson, Director
Natural Resources and Environment



GAO-08-1155T



GAO

Highlights

Why GAO Did This Study

According to EPA, children face disproportionate risks from contaminants such as air pollution and lead paint. The health consequences to the country's 73 million children are significant. In 2000, 35 percent of children lived in counties exceeding allowable levels for at least one of the six principal air pollutants, such as ozone which causes or aggravates asthma. Asthma is the third most common cause of childhood hospitalization, resulting in $3.2 billion in treatment costs and 14 million lost school days annually, according to the Centers for Disease Control and Prevention.

In 1997, EPA created the Office of Children's Health and convened the Children's Health Protection Advisory Committee (Advisory Committee) to provide advice and recommendations to assist in developing regulations, guidance, and policies to address children's health. In April 1997, the President signed Executive Order 13045, creating an interagency Task Force to recommend federal strategies for protecting children.

Our testimony is based on ongoing work on the extent to which EPA has used the Advisory Committee and addressed the committee's key recommendations. It also includes information about the Task Force. We met with numerous EPA officials and reviewed the committee's letters. Our preliminary results, among other things, show that EPA unintentionally suspended its review of the Advisory Committee's key recommendations.

To view the full product, including the scope and methodology, click on GAO-08-1165T. For more information, contact Anu Mittal at (202) 512-3841 or mittala@gao.gov.

September 16, 2008

ENVIRONMENTAL HEALTH

EPA Efforts to Address Children's Health Issues Need Greater Focus, Direction, and Top-level Commitment

What GAO Found

EPA has not proactively used the Advisory Committee to ensure that the agency's regulations, guidance, and policies address the disproportionate risks that environmental contaminants pose to children. Our analysis found that the Advisory Committee met more than 30 times and discussed a variety of environmental health issues with dozens of officials from EPA offices such as Pesticides and Toxic Substances, and Research and Development. However, we identified just three instances where EPA specifically asked the committee for recommendations and advice on regulations—most notably an October 1997 request that the committee identify five regulations or standards for EPA to re-evaluate in order to better protect children. In the absence of focus and direction from EPA, the Advisory Committee has taken the initiative to write more than 70 letters to the Administrator since 1998 containing hundreds of recommendations on a wide variety of children's health concerns.

EPA has not addressed key recommendations from its Advisory Committee, particularly those in a major April 2007 letter and in recent letters advising EPA on proposed revisions to national air quality standards. The April 2007 letter, which marked the 10th anniversary of the Executive Order, provided recommendations in seven key areas. These included the need for EPA to eliminate environmental health disparities among low-income and minority children. While EPA generally responds to the Advisory Committee's letters, the agency has not fulfilled the Administrator's commitment in his response to the 10th anniversary letter to collaboratively review recommendations from the advisory committee. The Office of Children's Health had begun forming internal workgroups, but a new acting director stopped the process in late 2007 to hold individual meetings with EPA's assistant administrators, and the process remains stalled. We also analyzed EPA's responses to the committee's specific recommendations on three recently-considered EPA air quality standards—the National Ambient Air Quality Standards for particulate matter, ozone, and lead—and we found that EPA either offered to consider the committee's recommendations as part of the public comment process or rejected them.

The President's Task Force, which was authorized in April 1997, provided high-level interagency leadership and coordination on children's environmental health, but it expired in April 2005. According to the children's health experts with whom we spoke, the task force provided important leadership on initiatives such as the National Children's Study and the Healthy Schools Environmental Assessment Tool. The task force also developed federal strategies to address four threats to children—asthma, developmental disorders, cancer, and unintentional injuries. In 2003, the President ordered the task force to be extended by 2 years, but the order eliminated the provision for reassessing the task force. Since the task force's expiration, EPA no longer has a high-level infrastructure or mandate to coordinate federal strategies for children's environmental health and safety.

Madam Chairman and Members of the Committee:

I am pleased to appear here today to discuss our ongoing work regarding the Environmental Protection Agency's (EPA) efforts to protect children from environmental health risks such as pollution in the air, lead paint in homes, pesticide residues on food, and treatment-resistant microbes in drinking water. Many of the nation's 74 million children are exposed to such hazards daily. In 2006, for example, 55 percent of children lived in counties that exceeded one or more of the six principal air pollutants, two of which—ozone and particulate matter—are known to cause or aggravate respiratory diseases such as asthma. Asthma is the third most common cause of hospitalizations among children, resulting in $3.2 billion for treatment and 14 million lost days of school annually, according to the Centers for Disease Control and Prevention.

Children's environmental health is a complex but vitally important subject. The federal government has therefore taken several steps to make it a priority and to ensure that it has access to the best available expert advice. In April 1997, for example, the President signed Executive Order 13045, Protection of Children from Environmental Health Risks and Safety Risks (Executive Order), which mandated a concerted federal effort to address children's environmental health and safety risks. Among other things, the Executive Order established an interagency President's Task Force on Environmental Health Risks and Safety Risks to Children (President's Task Force) for a period of 4 years and charged it with recommending strategies to the President for protecting children's environmental health and safety. The President's Task Force was co-chaired by the Administrator of EPA and the Secretary of Health and Human Services and included the heads of at least 14 other departments, agencies, commissions, and councils.

Also in 1997, EPA established the Office of Children's Health Protection to support its efforts. In addition, EPA formed the Children's Health Protection Advisory Committee (Advisory Committee) to provide advice, information, and recommendations to assist the agency in the development of regulations, guidance, and policies relevant to children's health. Instead of a panel of experts on a single academic discipline, the Advisory Committee is made up of a broad cross-section of children's health experts from the academic, healthcare, industry, local government, and non-profit sectors.

In April 2007, the Advisory Committee wrote to the Administrator to reflect on EPA's achievements protecting children from environmental

health threats in the 10 years since the Executive Order was signed. The committee cited successes such as increased margins of safety for pesticides mandated under the Food Quality Protection Act and the creation of the National Children's Study.[1] However, the committee also expressed serious concerns about EPA's continued lack of focus on children's environmental health issues and the lack of progress in addressing its many recommendations.

My testimony is based on ongoing work for the Senate Committee on Environment and Public Works, which we expect to complete in mid-2009, that examines the extent to which EPA has maintained its focus on children's environmental health issues and capitalized on opportunities to solve some significant and emerging environmental health challenges in the decade since the Executive Order was signed. My statement today addresses: (1) the extent to which EPA has used the Children's Health Advisory Committee and (2) the extent to which EPA has addressed the Advisory Committee's key recommendations. In addition, as you requested, my statement includes information about the activities and status of the President's Task Force on Environmental Health Risks and Safety Risks to Children. In conducting our work, we met with EPA and Advisory Committee officials and analyzed documents—including committee meeting agendas, summary documents, letters to the EPA Administrator, and EPA's response letters—using the content analysis software NVivo. We also reviewed key documents and interviewed agency officials to determine the major activities and current status of the President's Task Force. We also obtained EPA's views on the facts presented in my statement and made minor modifications based on the agency's comments. Our ongoing work for this performance audit began in December 2007, and continues in accordance with generally accepted government auditing standards.

[1]The National Children's Study, led by multiple federal, state and local agencies, as well as research institutions, will examine the effects of environmental influences on the health and development of more than 100,000 children across the nation, following them from before birth until age 21. By studying children through their different phases of growth and development, researchers will be better able to understand the role of these environmental factors on health and disease.

In summary:

- EPA has not proactively used the Advisory Committee to ensure that the agency's regulations, guidance, and policies address the disproportionate risks to children that result from environmental contaminants. Our analysis found that the Advisory Committee met more than 30 times since 1997 and discussed a variety of environmental health issues with dozens of officials from EPA offices such as Pesticides and Toxic Substances, Air and Radiation, and Research and Development. However, we identified just three instances where EPA specifically asked the committee for recommendations and advice on regulations—most notably an October 1997 request that the committee identify five regulations or standards for EPA to re-evaluate in order to better protect children. In the absence of focus and direction from EPA, the committee has taken the initiative to write more than 70 letters to the Administrator since 1998 offering hundreds of recommendations on a wide variety of children's environmental health concerns.

- EPA has largely disregarded key recommendations from its Advisory Committee, particularly those in its 10th anniversary letter and in several recent letters advising EPA on proposed revisions to national air quality standards. In April 2007, to mark the 10th anniversary of the Executive Order, the Advisory Committee provided recommendations in seven key areas of concern, including the need for EPA to eliminate environmental health disparities among low-income and minority children, strengthen the national approach to regulating toxic chemicals, and provide necessary leadership and infrastructure to protect children's health. While EPA generally provides a letter in response to the committee, the agency has not fulfilled the Administrator's commitment in his June 2007 response letter to review the advisory committee's recommendations and EPA's children's environmental health activities. In his response to the Advisory Committee's letter, the Administrator agreed that the 10th anniversary of the Executive Order was an appropriate time to review EPA's children's health activities. He directed the Office of Children's Health to collaborate with EPA's program offices and the Advisory Committee to review their recommendations. In addition, the acting director of the office committed to engage the staff involved with Children's Health Advisory Management Partners (CHAMPS)—actions which have yet to happen. We also analyzed EPA's response to the committee's specific recommendations related to three recently-considered EPA air quality standards, and we found that EPA did not acknowledge, was noncommittal, rejected, or offered only to consider them along with comments from the general public.

- The President's Task Force on Environmental Health Risks and Safety Risks to Children provided important high-level leadership and interagency coordination on children's environmental health from 1997 until it expired in April 2005. According to the EPA staff and children's health experts we spoke with, the President's Task Force provided critical leadership on several important initiatives such as the National Children's Study and the Healthy Schools Environmental Assessment Tool. The task force also developed national strategies to coordinate federal programs to address the four major environmental and safety threats to children that it identified—asthma, developmental disorders, cancer, and unintentional injuries. Since the task force's expiration, EPA no longer has a high-level infrastructure to coordinate federal strategies for children's environmental health and safety. According to the experts, the task force could have helped the federal government respond to the recent health and safety concerns that prompted the recall of 45 million toys and children's products in 2007.

Background

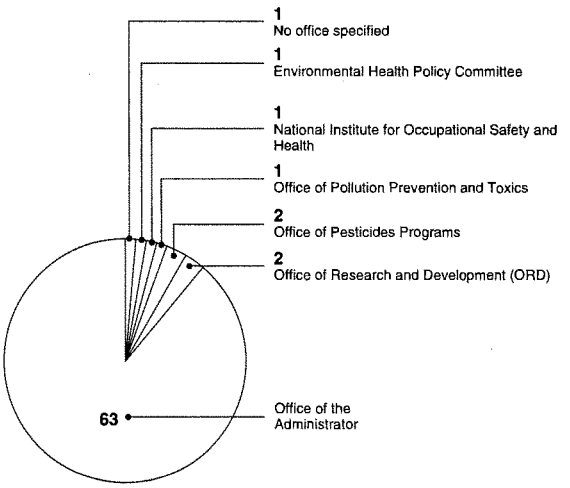
According to EPA, children face disproportionate and unique threats from environmental hazards for many reasons. For example, EPA has noted that children may receive higher doses of environmental contaminants because they spend more time close to the ground, touch their hands to their mouths more often, and, in proportion to their body weight, breathe more air, consume more food, and drink more water than adults. Contaminants may also affect children disproportionately because they have unique exposure pathways—through the placenta and breast milk. Furthermore, children are more vulnerable to contaminants than adults because of the relative immaturity of their biochemical and physiological functions. For example, air pollutants that would produce slight breathing difficulties in adults may contribute to more serious breathing problems in young children because of their smaller airways. Also, EPA has noted that children have limited ability to communicate and urge action about protecting their environment, so others must act on their behalf.

The Children's Health Protection Advisory Committee, as a committee chartered under the Federal Advisory Committee Act must follow broad requirements for balance, independence and transparency. The membership of the Advisory Committee includes a diverse range of viewpoints from 29 individuals including researchers, academicians, health care providers, environmentalists, children's advocates, professionals, and government employees who advise EPA on regulations, research, and communication issues relevant to children. The current chairman of the Advisory Committee, only the second since the committee

began meeting in 1998, has been in place since 2003. As required under FACA, a designated federal official from EPA's Office of Children's Health oversees the Advisory Committee's activities, including approving meeting agendas and attending all meetings. To ensure that suitable speakers are invited to committee meetings, the meeting agendas and speakers are set by a steering committee comprised of the director of EPA's Office of Children's Health, the chairman of the Advisory Committee, and the chairs of any active workgroups created by the committee to examine a specific children's issue. According to the Advisory Committee's charter, the committee is to send its letters to the EPA Administrator. In addition, the Advisory Committee announces meetings ahead of time and gives notice to interested parties about such meetings. The plenary sessions of meetings are open to the public and EPA ensures that meeting minutes are prepared and posted to their website.

As shown in figure 1, the committee has directed the vast majority of its letters to the EPA Administrator but periodically directs letters to other EPA officials such as the Director of the Office of Research and Development.

Figure 1: Advisory Committee Letter Addressees



Source: GAO analysis of Advisory Committee letters.

According to the committee's operating procedures and principles, "all recommendations must reflect the consensus of the committee and that in achieving consensus, all relevant perspectives, interests and concerns of committee members are reflected." To accomplish detailed reviews of children's health issues in order to achieve consensus, the committee typically forms a taskgroup from its members that meets separately with staff from the Office of Children's Health. Taskgroups consider information presented during full committee meetings, identify relevant recommendations, and draft letters for full committee review. The committee has formed nearly three dozen such taskgroups over its history, including taskgroups that considered EPA's proposed revisions to air quality standards for particulate matter, ozone, and lead. Although the committee typically reviews these letters during plenary sessions, the committee uses a between-meeting process—to ensure that the full

committee has an opportunity to review materials, provide input, and reach consensus without a plenary session—when a letter must be written before the next meeting, as was the case for the letters that addressed the air quality standards.

EPA Has Not Proactively Used the Children's Health Protection Advisory Committee in the Development of Regulations, Guidance, and Policies

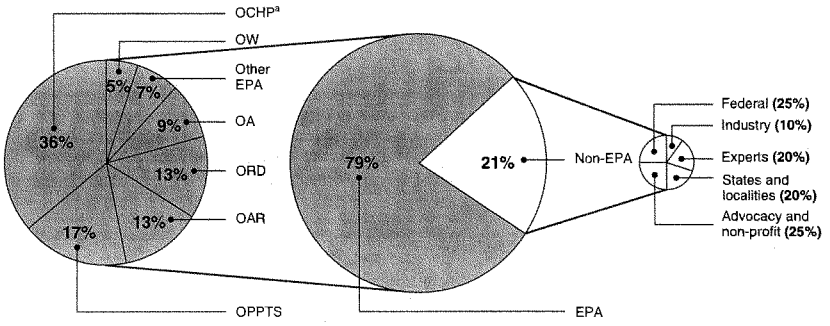
While EPA has convened the committee for dozens of presentations and discussions with EPA and non-EPA officials, the agency has made few requests for the committee's advice or recommendations on regulations, guidance or policies to address the disproportionate risks to children's health. Nonetheless, the committee has sent more than 70 letters to the Administrator offering hundreds of recommendations on a wide range of children's health concerns.

The Advisory Committee Has Met With Many Officials from EPA and Other Agencies

Since 1997, EPA has convened the Advisory Committee 32 times for meetings which included presentations and discussions with many EPA and non-EPA officials on a wide variety of children's health topics. Staff from the EPA Office of Children's Health told us that the committee's value comes, in part, from the verbal input that committee members provide to EPA officials during the discussions surrounding those presentations. According to our analysis of agendas and meeting summaries, EPA and non-EPA speakers made 189 presentations for the committee during the past decade. As shown in figure 2, EPA officials made 79 percent of the presentations to the advisory committee, with the Office of Children's Health (OCHP) accounting for the largest proportion. Since 2006, for example, officials from OCHP have given regular updates to the committee on EPA's revisions to the National Ambient Air Quality Standards for particulate matter, ozone, and lead. In addition, the Office of the Administrator (OA) has given a number of presentations, and three of the four EPA Administrators since 1997 have met with the committee.[2]

[2]The Advisory Committee met with Administrator Browner on July 6, 1998; Administrator Whitman on February 27, 2002; and Administrator Johnson on July 17, 2007.

Figure 2: Presentations Made to the Children's Health Protection Advisory Committee, 1998-2008 (Percentage)



Source: GAO analysis of Advisory Committee meeting summaries and agendas.

[a]The Office of Children's Health (OCHP) is part of the Office of the Administrator (OA) but is shown separately in the figure.

The figure also shows that EPA's program offices made regular presentations to the Advisory Committee, including the agency's Office of Prevention, Pesticides and Toxic Substances (OPPTS), Office of Air and Radiation (OAR), Office of Research and Development (ORD), and Office of Water (OW). For example, officials from the Office of Air and Radiation, and the Administrator himself, gave three presentations to the committee on the air quality standards between 2005 and 2007.

Although the Advisory Committee was established to provide EPA with advice, information and recommendations—and reports directly to the Administrator—it also regularly hears from non-EPA officials to gather additional information. As the figure also shows, 21 percent of Advisory Committee presentations were made by representatives from other federal agencies, industry, academic experts, states and localities, and advocacy and non-profits. For example, the committee has heard from representatives from the Centers for Disease Control and Prevention and the National Academy of Sciences.

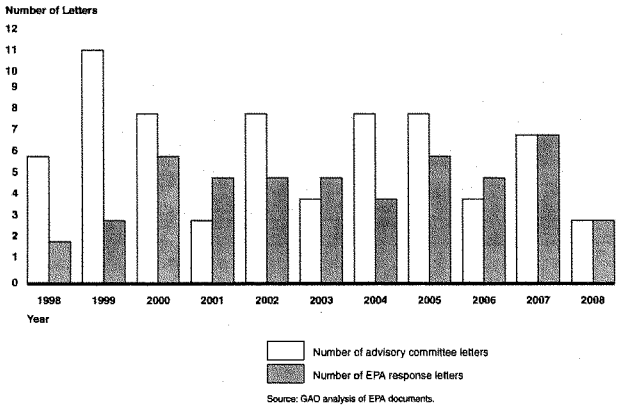
EPA Has Rarely Sought the Advisory Committee's Advice on Regulations, Guidance, and Policies that Address Children's Health

Despite convening the Advisory Committee more than 30 times over the last 10 years for discussions with a variety of speakers, EPA has rarely sought out the committee's advice and recommendations to assist it in developing regulations, guidance, and policies that address children's health. We identified only three instances where EPA specifically asked the committee for advice on regulations, three instances on guidance, and one instance on policies. The clearest example is EPA's request in October 1997—prior to the committee's first meeting—that the committee identify five regulations or standards for the agency to re-evaluate in order to better protect children. In another instance, in 2005, EPA asked CHPAC for comments on data that the agency planned to use to support the Clean Air Mercury Rule. In addition to these requests regarding regulations, guidance, and policies, we identified 14 other instances where EPA asked for the committee's advice on programs, plans, or other issues. The requests varied in topic and scope, ranging from a 2005 request for advice on evaluating EPA's pilot version of the Voluntary Children's Chemical Evaluation Program (VCCEP) to a request in 2002 to suggest a health organization to be asked to join EPA's Smart Growth Network.

Although EPA has not proactively requested the Advisory Committee's advice on regulations, guidance, and policies, the members of the committee have nonetheless devoted considerable time to drafting and reviewing 70 letters that the committee has sent to the Administrator since 1998. Those letters contained a range of advice, information and recommendations, to which EPA has responded a total of 51 times.[3] As figure 3 shows, the committee typically sends 8 or fewer letters a year.

[3]The number of letters reviewed reflects the period between May 1998 and June 2008.

Figure 3: Number of Advisory Committee and EPA Response Letters (1998-2008)



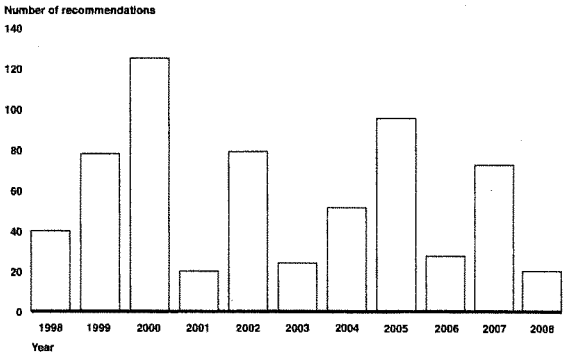
Source: GAO analysis of EPA documents.

The Advisory Committee Has Offered Hundreds of Recommendations to EPA on a Range of Children's Health Issues

The Advisory Committee's letters offered EPA hundreds of recommendations about a variety of topics related to reducing environmental health risks to children. We identified over 600 recommendations during our review of the committee's letters.[4] A small number of letters contained recommendations relating to multiple children's environmental health issues, such as a May 2008 letter with recommendations about mercury regulation, farm worker protection standards, organophosphate pesticides, and air quality. However, most letters contained recommendations on a single issue. As shown in figure 4, the number of recommendations varied from year to year, ranging from more than 120 recommendations in 2000 to 20 thus far in 2008.

[4]For the purposes of our review, we defined a recommendation as "any and all statements made in Advisory Committee letters that advise and ask/request/suggest/urge EPA to take action".

Figure 4: Number of Advisory Committee Recommendations by Year (1998-2008)

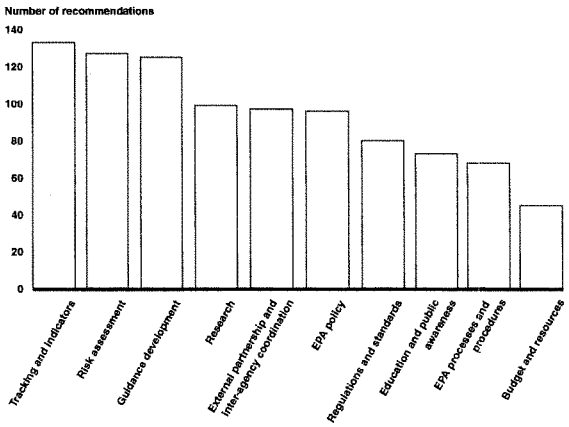


Source: GAO analysis of Advisory Committee letters.

In addition, we organized the Advisory Committee's recommendations into 10 categories to help demonstrate the breadth and depth of children's health issues that have concerned the committee[5] Figure 5 shows that the largest number of recommendations were focused on improving indicators and data used for tracking children's health information (133), urging that children's health vulnerabilities are considered in EPA risk assessments (127), and improving or developing agency guidance documents (125). The committee also offered many recommendations on topics such as research (99), external partnerships and inter-agency coordination (97), policy (96), and regulations and standards (80).

[5]Some recommendations were considered to emphasize more than one subject area and as such the categories are not mutually exclusive.

Figure 5: Advisory Committee Recommendations by Category



Source: GAO analysis of Advisory Committee letters.

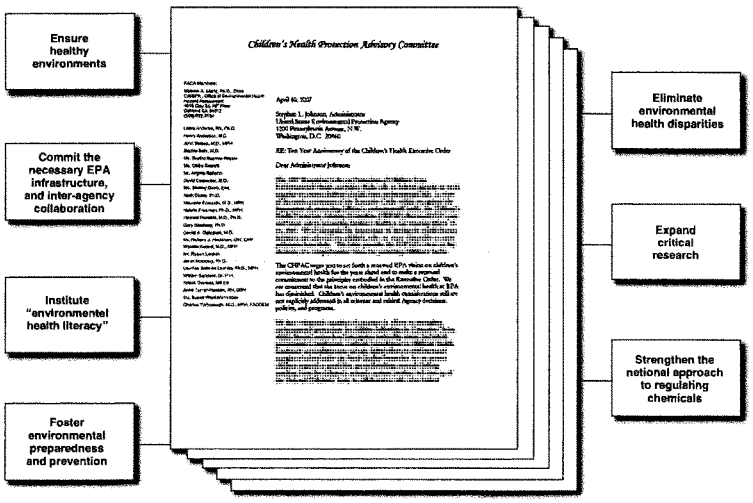
EPA Has Largely Disregarded Key Recommendations from the Children's Health Protection Advisory Committee

The process that EPA initiated to carry out the Administrator's commitment, in a June 2007 letter, to address the Advisory Committee's key recommendations has stalled. In addition, EPA has largely disregarded the advisory committee's recommendations on air quality standards, mercury, and the Voluntary Children's Chemical Evaluation Program.

EPA Commitment to Review Key Advisory Committee Recommendations Has Stalled

On the 10th anniversary of the Executive Order, the Advisory Committee wrote to EPA to express its views on key elements of a comprehensive vision for protecting children's health and made recommendations for action. The committee's April 10, 2007 letter provided recommendations in seven areas for renewing EPA's vision on children's environmental health and its commitment to the principles outlined in the Executive Order. As illustrated in figure 6, the areas of concern to the committee included the need for EPA to (1) eliminate environmental health disparities among low-income and minority children, (2) strengthen the national approach to regulating toxic chemicals, and (3) provide necessary leadership and infrastructure to protect children's health.

Figure 6: Seven Key Recommendations to EPA from its Advisory Committee's 10th Anniversary Letter, April 2007



Source: GAO analysis of Advisory Committee's April 10, 2007 letter.

The Administrator's June 13, 2007 response letter directed the Office of Children's Health to work collaboratively with program offices across the agency and committed the agency to working with the committee to review these recommendations. However, EPA has not yet fulfilled the Administrator's commitment. The Office of Children's Health had established workgroups within its Children's Health Advisory Management Partners (CHAMPS) to address each of the seven areas outlined by the committee, and the program offices had begun identifying representatives to serve on the workgroups.[6] However, a new acting office director stopped the process in late 2007, opting instead to hold individual meetings with EPA's assistant administrators. The acting director decided that strengthening relationships with senior management would be a quicker way to identify leadership issues related to children's health, ensuring that they would be engaged and invested in the agency's response. In March 2008, a new permanent director replaced the acting director. At present, the process of addressing the Administrator's commitment remains stalled.

Advisory Committee Recommendations on Air Quality Standards Have Not Been Substantially Addressed

We also examined the Advisory Committee's recommendations related to three air quality standards—the National Ambient Air Quality Standards (NAAQS) for particulate matter, ozone, and lead, which EPA recently reviewed.[7] The committee was particularly concerned about the air quality standards because of rising rates of asthma among U.S. children and the relationship between poor air quality and the incidence and severity of asthma. To express its concern, the committee wrote a number of letters to urge EPA to tighten the standards based on scientific evidence that they were not sufficiently protective of children's health. Specifically, we identified seven letters containing 23 recommendations with respect to EPA's proposed revisions to the particulate matter, ozone, and lead standards. In general, the committee's recommendations were further supported by recommendations from EPA's Clean Air Science Advisory Committee (CASAC), which also has been sharply critical of several of EPA's decisions.[8] For example, CASAC wrote to the administrator stating

[6]CHAMPS is a cross-agency group of headquarters and regional staff who work on children's issues that was formed by the Children's Health Office to discuss projects and share information.

[7]EPA sets Primary National Ambient Air Quality Standards for ozone, particulate matter, sulfur dioxide, nitrogen dioxide, carbon monoxide, and lead.

[8]CASAC is an independent committee of scientists that advises the EPA Administrator and was established by statute in 1977 to review the agency's work in setting NAAQS.

unanimously that the revised air quality standard for particulate matter "does not provide an adequate margin of safety ... requisite to protect the public health." Table 1 shows that EPA's revised air quality standards for particulate matter, ozone, and lead are at or above the upper limits of recommendations from both advisory committees.

Table 1: Advisory Committees Recommendations for Revisions to NAAQS Compared to EPA's Finalized Standards

Standard (μg/m³ unless noted)		EPA Previous Standard[c]	Clean Air Science Advisory committee	Children's Advisory committee	EPA Final Standard
Particulate Matter[a] (PM)	Fine PM (annual)	15	13-14	Less than 15	15
	Fine PM (daily)	65	30-35	Less than 35	35
	Course PM (daily)	150	No recommendation[d]	Less than 70	150
Ozone (in parts per million)	Human Health standard (8-hour average)	0.08	0.060-0.070	0.060	0.075
Lead[b]	Human Health standard (3-month average)	1.5	≤ 0.2	0.02	0.10-0.30 (proposed)

Sources: GAO review of Advisory Committee letters and EPA air quality regulations.

[a]EPA defines the standard for fine PM as consisting of particulate matter 2.5 micrometers or less in diameter, abbreviated as $PM_{2.5}$.

[b]EPA was under court order to complete the review of lead NAAQS by September 15, 2008, but the agency received an order extending the deadline to October 15, 2008.

[c]Although these standards were promulgated in 1997, they are only now coming into effect, because of legal challenges, the need to establish a monitoring network, and various administrative factors.

[d]In its September 15, 2005 letter, CASAC recommended a new course PM indicator ($PM_{10-2.5}$), which EPA put forward in its proposed rule. CASAC did not discuss the option of retaining the existing daily standard for course PM (i.e., PM_{10}) of 150 ppm during its advisory process.

While EPA provided the Advisory Committee with official response letters to six of its seven NAAQS-related letters, we found that the agency generally did not acknowledge or was noncommittal to the committee's recommendations, or that it offered merely to consider them as part of the public comment process. EPA did not specifically acknowledge 11 of the committee's 23 recommendations, but provided a generic statement about considering the recommendations with all others.[9] For example, EPA did

[9]EPA did not provide a response to address 6 out of the 23 recommendations that we identified.

not directly address the committee's recommendations related to the lead standards or the ability of a national lead-monitoring system to accurately measure and facilitate effective control of the complex exposure routes of airborne lead. Instead, EPA responded that it would consider the committee's recommendations along with all other public comments. EPA acknowledged another 5 of the committee's recommendations, although it was noncommittal, providing no details about whether or how the agency would address them. In one instance, EPA rejected a committee recommendation. In its February 2007 letter, the committee recommended that EPA reinstate the opportunities for public review and input provided for in the previous NAAQS process to allow for scientific input and public review. This letter, as well as a similar one from CASAC, warned that the new process could significantly reduce opportunities for scientists to provide input, as they had at key steps of previous NAAQS reviews. In its response, EPA stated that changes to the review process would enhance the agency's ability to issue timely decisions while promoting participation by scientific experts and the public. While there are periods in the rulemaking process where EPA officials are in ongoing deliberations and may not commit to actions until a standard is finalized, EPA did not provide the Advisory Committee with any explanation after deliberations were complete and officials were free to comment.

Advisory Committee Recommendations on Mercury and Voluntary Children's Chemical Evaluation Program

We also reviewed the Advisory Committee's recommendations on mercury and EPA's Voluntary Children's Chemical Evaluation Program (VCCEP). As with the air quality recommendations, EPA either did not acknowledge or remained noncommittal toward most of the committee's recommendations related to mercury and VCCEP. Specifically, we identified five Advisory Committee letters containing 29 recommendations focused on the need to protect children from the risks posed by mercury and three EPA response letters. Our review of EPA's response letters indicates that the agency did not acknowledge 10 of the recommendations. For example, EPA did not acknowledge the recommendation that EPA create incentives in its proposed Interstate Air Quality Rule to reduce children's exposure to mercury. Furthermore, EPA acknowledged but provided no details about how the agency would address another 4 recommendations.[10] For example, the committee recommended to EPA that hot spots—areas disproportionately affected by mercury emissions—

[10]EPA did not provide a response to address 13 of the 29 recommendations that we identified.

be prevented under any Interstate Air Quality Rule. EPA acknowledged the recommendation in its response, but did not address how this would be ensured, stating instead that in implementing cap-and-trade programs in the past, the agency has not observed the creation of hot spots, and that a cap-and-trade program creates incentives for the utility sector to aggressively seek reductions in nitrogen oxides (NO_x) and sulfur dioxide (SO_2), which ultimately provide early mercury reductions.[11] Only in its 1998 response to the committee's mercury-related recommendations did EPA acknowledge the recommendations offered by the committee and detail how it had addressed or intended to address each of the recommendations raised. For example, to address the committee's recommendation about the need to take a holistic approach to evaluate all sources of mercury emissions, EPA pointed to a November 1998 draft strategy that addressed the multimedia nature of mercury. With respect to the committee's recommendation to consider mercury releases from municipal and medical waste combustion sources, EPA described actions that, once fully implemented, would reduce mercury emissions caused by human activities at these types of sources by 50 percent from 1990 levels.[12]

Similarly, our review of EPA's responses to the Advisory Committee's 14 recommendations regarding VCCEP indicates that the agency largely did not acknowledge the committee's recommendations. Half of the recommendations were in a June 2006 letter to EPA. In its response, EPA stated that it would carefully consider the committee's comments and undertake a thorough evaluation of the program in the coming months, but, stopped short of providing detail or information on if or how it would address six of the seven recommendations in this committee letter.[13] Moreover, in addition to its specific recommendations, the committee concluded in its letter to EPA that the pilot program, as implemented, was

[11]We have reported previously on major shortcomings in EPA's proposed mercury rule that limit its usefulness for informing decision makers and the public. Among other things, we found that EPA did not consistently analyze its mercury policy options or provide estimates of the total costs and benefits, and that EPA did not estimate economic benefits directly related to decreased mercury emissions (GAO-05-252).

[12]In addition, EPA described final regulations for hazardous waste combustion facilities (e.g., incinerators, cement kilns, lightweight aggregate kilns) that were expected to be promulgated in February 1999.

[13]EPA did acknowledge the importance of public review and stated that it would address the committee's recommendation to publish a Federal Register notice later that year, announcing a formal evaluation of the VCCEP pilot and how it intended to seek stakeholder views and comments like those provided by the committee.

not on track to fulfilling its stated goal, and that there has been limited information on specific chemicals relevant to children's health provided to the public. The Advisory Committee added that an opportunity had been lost to develop and disseminate more advanced methods for assessing children's exposures and consequent risks.

President's Task Force on Children's Environmental Health Risks and Safety Risks Expired in 2005, Eliminating An Important Opportunity for EPA Leadership and Interagency Coordination

The President's Task Force was authorized by executive order in April 1997 for a period of 4 years to provide high-level leadership and interagency coordination on children's environmental health. It was comprised of nine cabinet officials and seven White House office directors and was co-chaired by the Administrator of EPA and the Secretary of Health and Human Services.[14] The task force convened for meetings five times—in October 1997, April 1998, January 1999, September 1999, and in October 2001 after the President extended it until April 2003. At the urging of the EPA Administrator in April 2003, the President ordered the task force to be extended for a final 2 years. However, this order eliminated the provision for reassessing the need for continuance of the task force, which was not convened after October 2001. Nonetheless, a senior-staff steering committee continued to meet until 2005 to provide coordination and draft strategies to address the threats to children's health.

The President's Task Force identified four major environmental and safety threats to children—asthma, developmental disabilities (including lead poisoning), cancer, and unintentional injuries, and it recommended national strategies for each of them. The task force recognized that an integrated solution was needed across the federal government to address the complex interaction between a child's biology, behavior, and the physical, chemical, biological, and social environment. According to the children's health experts with whom we spoke, the task force provided critical leadership on several important initiatives such as the National

[14]The Executive Order states, "The Task Force shall be composed of the Secretary of Health and Human Services, who shall serve as a Co-Chair of the Council; Administrator of the Environmental Protection Agency, who shall serve as a Co-Chair of the Council; Secretary of Education; Secretary of Labor; Attorney General; Secretary of Energy; Secretary of Housing and Urban Development; Secretary of Agriculture; Secretary of Transportation; Director of the Office of Management and Budget; Chair of the Council on Environmental Quality; Chair of the Consumer Product Safety Commission; Assistant to the President for Economic Policy; Assistant to the President for Domestic Policy; Assistant to the President and Director of the Office of Science and Technology Policy; Chair of the Council of Economic Advisers; and such other officials of executive departments and agencies as the President may, from time to time, designate."

Children's Study and the Healthy Schools Environments Assessment Tool (Healthy SEAT). These national programs focus heavily on the environmental influences on children, with the National Children's Study examining the role of environmental factors on health and disease and Healthy SEAT offering school districts a self assessment tool for evaluating environment, safety and health hazards. In addition, the departments and agencies that made up the task force partnered to prepare a fiscal year 2001 interagency budget initiative to fund the task force's initiatives in the four priority areas. The Secretary of Health and Human Services and the Administrator of EPA submitted the request to the Office of Management and Budget with the recommendation that it be included as part of the President's budget request that year. Officials told us that OMB's involvement helped ensure that adequate funds were available to these agencies to address children's health.

Since the task force's expiration, EPA and HHS no longer have a high-level infrastructure or mandate to coordinate federal strategies for children's environmental health and safety. According to the EPA staff and children's health experts with whom we spoke, the task force could have helped the federal government respond to the health and safety concerns that prompted the 2007 recall of 45 million toys and children's products, 30 million of them from China. Furthermore, since the provision of the executive order expired in 2005, the task force no longer reports the results of its efforts to the President. Those reports collected and detailed the interagency research, data, and other information necessary to enhance the country's ability to understand, analyze, and respond to environmental health risks to children.

Conclusions

In 1997, the President issued an executive order on Protection of Children from Environmental Health and Safety Risks calling on federal agencies to work together to protect children's health from environmental risk. In the same year, EPA established an Office of Children's Health Protection and formed its Children's Health Protection Advisory Committee. In the intervening decade, we have seen a number of successful efforts to strengthen environmental protections for children, including the landmark Food Quality Protection Act, which provides protections from pesticides. However, we also have seen growing evidence that children's environmental experience before birth, early in life, and through adolescence may have lifelong consequences and may affect subsequent generations.

EPA's Advisory Committee and others have recently raised concerns that the agency's focus on children's environmental health has diminished since the executive order was signed. Based on our review of EPA's use of the Advisory Committee and the agency's general unresponsiveness to the committee's key recommendations, coupled with the expiration of the President's Task Force, we believe the agency needs to reinvigorate its focus and leadership on children's environmental health in order to meet current and emerging challenges facing the nation's children.

Recommendations for Executive Action

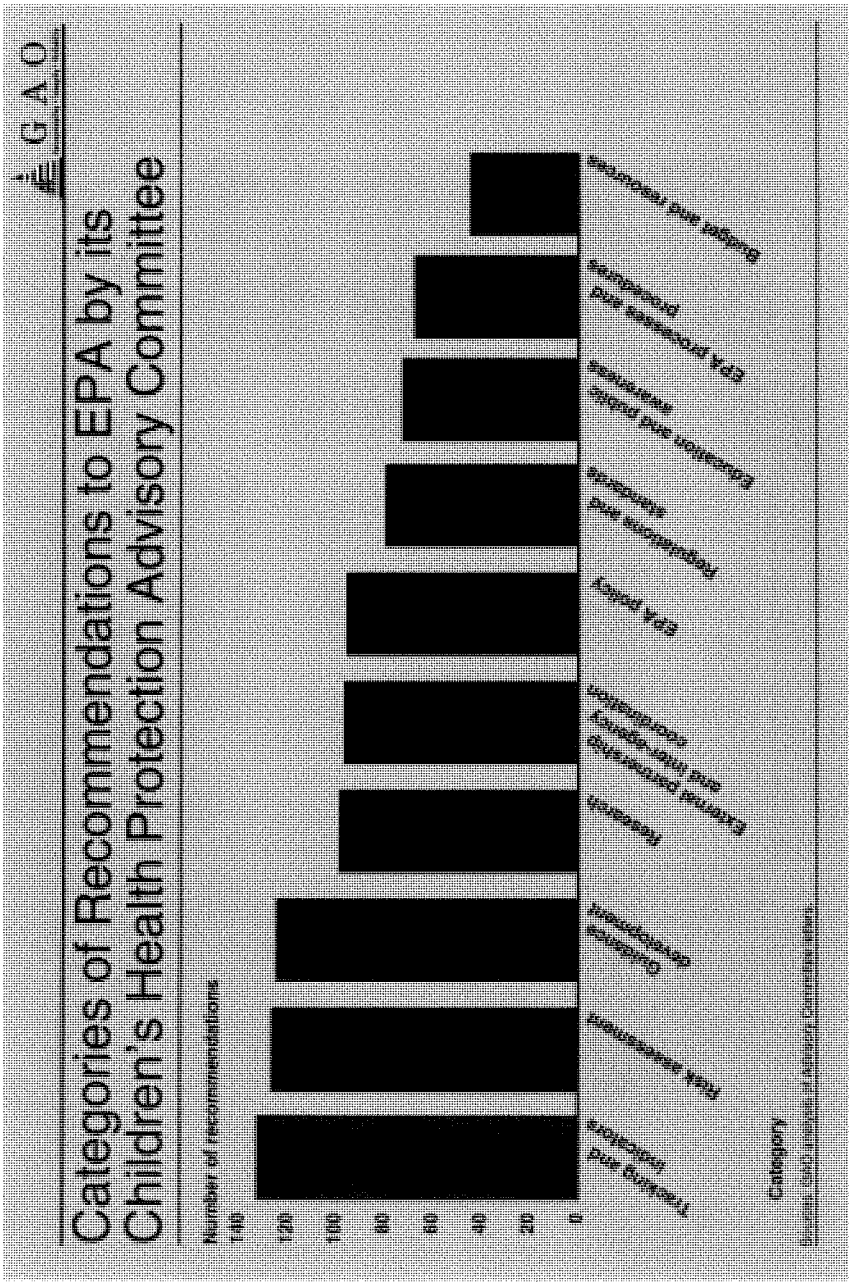
To honor the Administrator's commitment to the Children's Health Protection Advisory Committee, we are recommending that the Office of Children's Health Protection expeditiously complete the cross-agency process to review the committee's key recommendations. We are further recommending that the Administrator examine ways to more proactively use the committee to reinvigorate its focus on protecting children's environmental health.

Madam Chairman, this concludes my prepared statement. I would be happy to respond to any questions that you or members of the Committee may have at this time.

Contact and Staff Acknowledgments

Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this statement. For further information about this testimony, please contact John Stephenson at (202) 512-3841 or stephensonj@gao.gov. Key contributors to this testimony were Diane Raynes, Terrance Horner, Aaron Shiffrin, and Corissa Kiyan. Other contributors included Elizabeth Beardsley, Mark Braza, Muriel Brown, and Benjamin Shouse.

GAO's Mission	The Government Accountability Office, the audit, evaluation, and investigative arm of Congress, exists to support Congress in meeting its constitutional responsibilities and to help improve the performance and accountability of the federal government for the American people. GAO examines the use of public funds; evaluates federal programs and policies; and provides analyses, recommendations, and other assistance to help Congress make informed oversight, policy, and funding decisions. GAO's commitment to good government is reflected in its core values of accountability, integrity, and reliability.
Obtaining Copies of GAO Reports and Testimony	The fastest and easiest way to obtain copies of GAO documents at no cost is through GAO's Web site (www.gao.gov). Each weekday, GAO posts newly released reports, testimony, and correspondence on its Web site. To have GAO e-mail you a list of newly posted products every afternoon, go to www.gao.gov and select "E-mail Updates."
Order by Mail or Phone	The first copy of each printed report is free. Additional copies are $2 each. A check or money order should be made out to the Superintendent of Documents. GAO also accepts VISA and Mastercard. Orders for 100 or more copies mailed to a single address are discounted 25 percent. Orders should be sent to: U.S. Government Accountability Office 441 G Street NW, Room LM Washington, DC 20548 To order by Phone: Voice: (202) 512-6000 TDD: (202) 512-2537 Fax: (202) 512-6061
To Report Fraud, Waste, and Abuse in Federal Programs	Contact: Web site: www.gao.gov/fraudnet/fraudnet.htm E-mail: fraudnet@gao.gov Automated answering system: (800) 424-5454 or (202) 512-7470
Congressional Relations	Ralph Dawn, Managing Director, dawnr@gao.gov, (202) 512-4400 U.S. Government Accountability Office, 441 G Street NW, Room 7125 Washington, DC 20548
Public Affairs	Chuck Young, Managing Director, youngc1@gao.gov, (202) 512-4800 U.S. Government Accountability Office, 441 G Street NW, Room 7149 Washington, DC 20548


GAO
Categories of Recommendations to EPA by its Children's Health Protection Advisory Committee
Number of recommendations
Category
Tracking and surveillance
Risk assessment
Outreach and communication
Research
External partnership and intergovernmental coordination
EPA policy
Regulations and standards
Education and public awareness
EPA Programs and procedures
Budget and resources

G A O
Seven Key Recommendations to EPA from its Children's Health Protection Advisory Committee's 10th Anniversary Letter, April 2007
Eliminate environmental health disparities
Expand critical research
Strengthen the national approach to regulating chemicals
Ensure a healthy environment
Commit the necessary EPA infrastructure, and inter-agency collaboration
Institute "environmental health literacy"
Foster environmental stewardship and prevention

Senator BOXER. Thank you very much.

Here is what we are going to do. First, we need to just take down that chart, please, because people can't see Senator Clinton for her statement. If you could put it right in front of the table so we can look at it, it would be very helpful.

Here is what we are going to do. As I promised Senator Clinton, I am going to give her 5 minutes for an opening, and I am going to give up my questioning time to her. She and I worked together on this GAO report, and I will come last on my questions, so we will go to Senator Clinton for 10 minutes, and Senator Lautenberg, Senator Whitehouse.

Please proceed.

OPENING STATEMENT OF HON. HILLARY CLINTON, U.S. SENATOR FROM THE STATE OF NEW YORK

Senator CLINTON. Thank you so much, Chairman Boxer, and thank you for your lifetime commitment, really, to the health and well-being of our children.

This is such an important hearing, because obviously many of us believe strongly that there are direct links between environmental contaminants, pollution, stresses, and our children's health. We thought that we were on the right track in our Country and our Government in focusing on these concerns, and we learn, unfortunately, but not unexpectedly, that the Bush administration has basically undermined much of what we were trying to accomplish.

Now, for me this is a very significant finding that the GAO has presented in its report. It reveals a systematic failure to prioritize children's health in the Bush administration. The specifics of this are, unfortunately, clear for all to see.

The Bush administration disbanded a critical inter-agency task force in our Government that was focused on bringing agencies together to protect children's health against threats in the environment. While disbanding the group that spearheaded the major children's health reforms of the past decade, it ignored its own panel of experts, disregarded recommendations to ensure our children have access to clean air and water, safe homes, safe schools, and healthy food.

It is time to sound the alarm. This cannot be permitted to continue.

More than 40 years ago, Rachel Carson wrote, "For the first time in the history of the world, every human being is now subjected to contact with dangerous chemicals from the moment of conception until death." Environmental contamination and pollution presents an insidious threat to children's health, a silent but ever-present factor in childhood asthma, cancer rates, and other serious health problems.

Cancer rates, asthma, people think, Well, what does that have to do with the environment? Well, asthma rates have more than doubled since 1985. The CDC estimates that more than 300,000 children currently have elevated levels of lead in their blood. We know that children living near very obvious sites of pollution have other serious diseases, including cancer, in a higher than expected rate. We cannot allow this to continue.

In the Clinton administration more than a decade ago we issued an Executive Order on the protection of children from environmental health risks and safety risks. EPA established the Office of Children's Health Protection and created the Children's Health Advisory Committee. That was an important set of decisions and represented a milestone in making sure we did not ignore the scientific evidence and linkage between environmental exposure and children's health, adverse effects.

These actions helped make schools safer for kids and helped reduce pesticide exposure and focused attention on the growing asthma epidemic and expanded lead poisoning prevention. The task force established under the Executive Order was instrumental in the creation of the landmark National Children's Study, a long-term effort that will help us better understand the links between chronic disease and the environment.

So it defies common sense that the Bush administration quietly disbanded the task force in 2005, undercut the Children's Health Protection Office, and failed to follow through ton the Clinton administration's efforts on children's health.

I mean, this would be laughable if it weren't so serious. In 2002 EPA made the Office of Children's Health Protection responsible for the aging initiative, focused on issues facing seniors, equally important but undermining the mission of that office, and doing so despite recommendations to the contrary by the Children's Health Protection Advisory Committee.

Later, the Office of Children's Health, having incorporated aging issues, was combined with the Office of Environmental Education. Until recently, the Administration refused to appoint anyone to actually be the director of the office, essentially and purposefully leaving it rudderless.

So it is time we restored the mission of this office, the function of the inter-agency task force, and nation spirit of the orders issued by the Clinton administration.

Today I will be introducing the Children's Environmental Health and Safety Risk Reduction Act, which will once again ensure that we have the entire Federal Government working together to protect the health of our children. The Children's Health Protection Advisory Committee made seven recommendations for action EPA should take to recommit the Agency to children's health. I echoed those findings in a letter to Administrator Johnson, asking him to take action. He responded that he would ask the Office of Children's Health to review the recommendations. But, according to the GAO, no progress has been made more than a year after the initial promise of a review by Administrator Johnson. It is no wonder he wouldn't come to testify today.

Ten years after the landmark executive order, this is the State of children's health protection at the EPA: no leadership, no resources, no initiative, no real mission. It is a disaster and it is a disgrace, and we intend to fix it.

I hope that today's hearing will galvanize advocates, parents, as well as the EPA, itself, to take action. I look forward to continuing to work with our chairman and other colleagues to try to push forward an agenda that will protect our children.

[The prepared statement of Senator Clinton follows:]

STATEMENT OF HON. HILLARY RODHAM CLINTON, U.S. SENATOR
FROM THE STATE OF NEW YORK

Thank you so much, Chairman Boxer, and thank you for your lifetime commitment, really, to the health and well-being of our children.

This is such an important hearing because obviously many of us believe strongly that there are direct links between environmental contaminants, pollution, stresses, and our children's health. And we thought we were on the right track in our country and our government in focusing on these concerns, and we learn unfortunately but not unexpectedly that the Bush administration has basically undermined much of what we were trying to accomplish.

Now for me, this is a very significant finding that the GAO has presented in its report. It reveals a systematic failure to prioritize children's health in the Bush administration. And the specifics of this are unfortunately clear for all to see. The Bush administration disbanded a critical interagency Task Force in our government that was focused on bringing agencies together to protect children's health against threats in the environment. While disbanding the group that spearheaded the major children's health reforms of the past decade, it ignored its own panel of experts, disregarded recommendations to ensure our children have access to clean air and water, safe homes, safe schools, and healthy food.

It is time to sound the alarm. This cannot be permitted to continue. More than 40 years ago, Rachel Carson wrote, "For the first time in the history of the world, every human being is now subjected to contact with dangerous chemicals from the moment of conception until death." Environmental contamination and pollution presents an insidious threat to children's health—a silent, but ever present factor in childhood asthma, cancer rates, and other serious health problems.

Cancer rates, asthma, people think, "Well what does this have to do with the environment?" Well, asthma rates have more than doubled since 1985. The CDC estimates that more than 300,000 children currently have elevated levels of lead in their blood. We know that children living near very obvious sites of pollution have other serious diseases, including cancer, at a higher than expected rate.

We cannot allow this to continue. In the Clinton administration, more than a decade ago, we issued an Executive Order on the protection of children from environmental health risks and safety risks. The EPA established the office of Children's Health Protection and created the Children's Health [Protection] Advisory Committee. That was an important set of decisions and represented a milestone in making sure we did not ignore the scientific evidence and linkage between environmental exposure and children's health adverse effects.

These actions helped make schools safer for kids and helped reduce pesticide exposure and focused attention on the growing asthma epidemic and expanded lead poisoning prevention. The Task Force established under the Executive Order was instrumental in the creation of the landmark National Children's Study, a long-term effort that will help us better understand the links between chronic disease and the environment.

So it defies common sense that the Bush administration quietly disbanded the taskforce in 2005, undercut the Children's Health Protection Office, and failed to follow through on the Clinton administration's efforts on children's health. I mean, this would be laughable if it weren't so serious.

In 2002, EPA made the Office of Children's Health Protection responsible for the Aging Initiative, focused on issues facing seniors—equally important, but undermining the mission of that office and doing so despite recommendations to the contrary by the Children's Health Protection Advisory Committee. Later the Office of Children's Health, having incorporating aging issues, was combined with the Office on Environmental Education. And until recently, the administration refused to appoint anyone to actually be the director of the office, essentially and purposefully leaving it rudderless.

So it's time we restored the mission of this office, the function of the interagency Task Force, and the spirit of the orders issued by Clinton administration.

Today I will be introducing the Children's Environmental Health and Safety Risk Reduction Act, which will once again ensure that we have the entire Federal Government working together to protect the health of our children.

The Children's Health Protection Advisory Committee made seven recommendations for actions EPA should take to recommit the agency to children's health. I echoed those findings in a letter to Administrator Johnson, asking him to take action. He responded that he would ask the Office of Children's Health to review the recommendations. But according to the GAO, no progress had been made more than a year after the initial promise of a review by Administrator Johnson. It's no wonder he wouldn't come to testify today.

Ten years after the landmark Executive Order, this is the State of children's health protection at the EPA: no leadership, no resources, no initiative, no real mission. It's a disaster and it's a disgrace, and we intend to fix it.

I hope today's hearing will galvanize advocates, parents, as well as the EPA itself to take action, and I look forward to continuing to work with our Chairman and other colleagues to try to push forward an agenda that will protect our children.

Senator CLINTON. Now, there is so much to be talked about here that it is almost hard to know where to start, but let me begin, Mr. Stephenson. Your testimony notes that if the inter-agency task force created by President Clinton's Executive Order 13045 were still in existence, it could have helped address the multiple toy recalls last year. Would you please elaborate on the importance of that task force and the ways that it contributes to children's health protection.

Mr. STEPHENSON. That is, of course, hypothetical, but nevertheless, without the inter-agency task force you don't have Housing and Urban Development working with the EPA. You simply don't have a high-level infrastructure with which to coordinate Federal programs. Even in the EPA's annual operating plan for Fiscal Year 2009 it recognizes the importance of the task force and its contribution to removing lead. That was just in this year's plan, even though the task force was disbanded over 3 years ago.

Senator CLINTON. Dr. Gray, can you explain why the President chose to disband the task force?

Mr. GRAY. Well, Senator, I think it is important to realize that there is high-level coordination in the Federal Government. It has been focused for the last several years, however, on the National Children's Study, which is an outgrowth of the task force.

Senator CLINTON. Well, isn't it true that in the President's budget of the last several years it was recommended to cut the funding for the National Children's Study?

Mr. GRAY. The funding for the National Children's Study has continued. There are recommendations for cuts, but that is an effort to make sure that we have just the resources that we need to do the highest priority work. That high-priority work comes from an inter-agency process that is co-chaired by the EPA, and it also involves an ongoing consortium that coordinates between all of the Federal agencies, including Housing and Urban Development, who are interested in children's affairs. So there is coordination.

Senator CLINTON. Well, it is somewhat confusing to follow your testimony, because the fact is that President Bush had sought to zero out the National Children's Study in his budgets, and it is interesting that your testimony touts programs spearheaded by the task force such as the National Children's Study, so it is very difficult to understand exactly what the priorities of this Administration are when it comes to children's health.

I don't hold you responsible. You are here representing the EPA, but, unfortunately, the bottom line is that actions speak louder than words, and the efforts to zero out the funding, to disband the task force I think speaks volumes about what we can expect from this Administration, thankfully not for very much longer.

Dr. Gray, in June 2007 Administrator Johnson promised to implement an inter-agency review of the Children's Health Protection Advisory Committee regarding a renewed focus on children's health. In a letter I sent to him in October 2007 I asked for a time

line. In December 2007 I was told that there were preliminary discussions and we would be hearing something soon. It has been roughly 10 months since that response. What progress has been made in reviewing these recommendations and what is a time line for the completion of that review?

Mr. GRAY. Well, thank you for an opportunity to make clear that, in fact, the Agency is working to understand and to consider those recommendations that came from the Children's Health Protection Advisory Committee. There have been conversations between at the time the acting head of the Office of Children's Health Protection, and a variety of the program offices. There are staff-level collaborations that are going on. There has been a change, as was mentioned. We have a permanent head for the Office of Children's Health Protection, and as that person has the opportunity to get settled and organize things, we will be moving forward.

I can't give you a time line right now, but I would be happy to get back to you with a time line.

Senator CLINTON. Well, the time line is that nothing has happened.

Just to followup quickly, Mr. Stephenson, what progress has EPA made in reviewing the recommendations of the tenth anniversary letter since December 2007?

Mr. STEPHENSON. Really, none. There is a new director of the Children's Health Office. That is true. But under the acting director they had actually established task groups to work on the recommendations, and those were pretty much disbanded by the current director when she took office. I know she has held meetings with each of the program offices and so forth, but there has really been nothing concrete that has come out of that, to my knowledge.

Senator CLINTON. Thank you.

Senator BOXER. Thank you so much, Senator Clinton.

Senator Lautenberg.

Senator LAUTENBERG. Thank you, Madam Chairman.

Mr. Stephenson, in your testimony you highlight very clearly the fact that there has been virtually no response to many things that the Committee has recommended. Has EPA explained to your agency why they haven't implemented the Committee's recommendations or why they haven't? Do they acknowledge in any way receipt of letters or communication from your Agency that recommendations made are either being ignored, not understood? What do they say?

Mr. STEPHENSON. One of the advantages of having an actual FACA Advisory Committee is that the Agency is required to respond in writing to each of the letters written to it by the Advisory Committee. They have done so, but what I was suggesting is that a quarter of the time no response was delivered. About a quarter of the time the response was a, Thank you very much for your interest. And, to be fair, half the time there was a detailed response.

What is more alarming is that we had to work very, very hard to pull the recommendations out of these 70 letters to even determine that there were 600 recommendations. Nobody is tracking that. There is no rigor in what the Advisory Committee has recommended and what actions we might do. There is no proactive asking of the Advisory Committee, What do you think about this

regulation? What do you think about that policy? It is all push; there is no pull.

That is what we noticed. We just think they need to invigorate and use in a more concrete way the valuable input that they are getting from this 29-member scientific Advisory Committee.

Senator LAUTENBERG. You are very kind to say re-invigorate. No response. How do you invigorate the no-response kind of thing? What does that say to you? Are they asleep over there? Do they think that your recommendations are useless? What about you got some responses here and there, and thank you very much, as you said, for your interest. What do they say? do you followup when there are letters sent, recommendations made, and you hear nothing?

Mr. STEPHENSON. Well, the Office of Children's Health is assigned to the Office of the Administrator, and it is an Advisory Committee. Nevertheless, it exists because of the unique needs of children, and simply to say that we have improved this clean air program or we have improved this drinking water program for the general public is not good enough. The office exists for the explicit needs of children, and we just don't see it being used in that manner.

Senator LAUTENBERG. So if you had to grade their report card, what kind of a grade would you give them for their attention to children's health needs, as described by your agency and by the Committee and your commentary?

Mr. STEPHENSON. Probably an incomplete.

Senator LAUTENBERG. Incomplete is like failure, right?

Mr. STEPHENSON. You haven't asked.

Senator LAUTENBERG. Yes. Recently the EPA put forward air quality standards that are less protective than what the Children's Health Advisory Panel [sic] called for. Is there any evidence that EPA even considered this recommendation or is it, as has happened so often in the past, ignored?

Mr. STEPHENSON. I am sure they considered it, but, again, when you are looking at the Advisory Committee's contribution toward these air standards, they made, as we said, over 20 specific recommendations concerned with the high level of these standards. The chart is right in front of you here that shows that ultimately where the standard was set is above not only the Children's Advisory Committee recommendation, but also the Clean Air Advisory Committee. So they consider them along with public comments like everyone else, but I am not sure that they took the science specifically attributable to children into account.

Senator LAUTENBERG. Madam Chairman, thank you very much.

One thing is obvious that we have learned here in this Committee, that the primary gesture that you get from EPA when questions of significance are put to them or recommendations made that it is kind of thumbing their nose. Forget about the Congress. I mean, we can take the insults. But the abuse of children's health is an unacceptable condition and we have got to make it change here.

I thank you very much.

Dr. Gray, I wouldn't want to be at your spot at the table right now.

Thank you very much.

Senator BOXER. Senator, you speak for me.

Senator Whitehouse.

Senator WHITEHOUSE. Thank you, Chairman.

The suggestion in Senator Lautenberg's question is that it actually matters to the leadership of EPA how well the decisions turn out for children. There isn't actually a very good case for that proposition. The proposition that is supported by the evidence is that EPA cares about how this works out for industry and for the big donors to the Bush White House. It is very hard to reconcile their decisions with any other motivation.

I would like to focus particular on this ozone question that you looked at, Mr. Stephenson. As I understand it, the standard for ozone pollution had been set at 0.08 parts per million, and then the EPA's own clean air scientific advisory commission came back and said that is not safe. The safe range is between 0.07 and .06 parts per million, a range, .06 to .07. Then the Children's Health Advisory Committee chimed in on the Clean Air Advisory Committee, so now you have two scientific committees speaking, and the children's one says, Look, because the way you calculate the risk doesn't take into account the risk to children adequately, you should go to the low end of that range, and they recommended the 0.06.

Mr. STEPHENSON. Correct.

Senator WHITEHOUSE. So the Administrator is faced with two recommendations: one, a range that is the safe range from .06 to .07; within that a recommendation protective of children because of the specifics of the way this was done that said if you want to protect children you have got to go all the way to .006 [sic]. Straight out of the range, he sat, as your chart shows, a standard outside the safe range and quite distant from the range that had been recommended for children.

Mr. Gray tells us that we take extra precaution to protect those who are most vulnerable to contaminants in the environment, especially children. Can you reconcile Mr. Gray's statement with what was decided in this particular case? And could you elaborate at all? Well, let me ask you that first and then I will go to my second question.

Mr. STEPHENSON. Well, as with any rule or regulation you have to do a cost/benefit study and show the benefits, and you heard Dr. Gray talk about the benefits of this particular standard of .075. Just imagine how much greater the benefits would have been had they adopted the Children's Advisory Committee recommendations.

We did not do a cost/benefit analysis to show how much more expensive that would have been to the polluting entities, but EPA does have to take that into consideration.

These are small numbers we are talking about, .06 to .075, but percentage-wise that is huge.

Senator WHITEHOUSE. Yes. It is huge, and it matters a great deal to little lungs.

The question that I have, you see this going on. You have a clean air scientific advisory committee that is appointed by EPA, itself, with the best scientists in the Country. You have a children's Health and Protection Committee that Mr. Gray here in his own

testimony says is comprised of leading researchers, academics, health care providers, NGO's, industry representatives, and State and local government representatives. They get recommendations. They got recommendations specifically from the Children's Health Science Advisory Council. Then they ignore it.

You have pointed out how the final standards over and over again fall outside the safe range and in favor of industry. Did you try to explore why it is that this is happening?

Mr. STEPHENSON. No, not as part of this study. We haven't examined these specific clean air rules. We were more looking at just how EPA responded to specific recommendations from the Advisory Committee. We just pointed this out as an example of where the Advisory Committee had made very specific recommendations, 27 of them, in fact, and the ultimate result of those recommendations.

Senator WHITEHOUSE. Well, we can follow this up later, but I do think it is important outstanding understand, when Government goes off the rails like this, why, in part so that we can be more alert and not allow it to be repeated.

I would suggest that it is a combination of a very significant industry investment in phony science and in phony doubt about science corresponding with an Agency that is captured by political interests and basically instructed to disregard its mission. When you have that instruction coming from the top and the phony science to work with, given that motivation at the bottom, you connect those two dots and you get these results.

I think it is a matter of real concern and we will talk later on about maybe pursuing this and getting into the why question.

I appreciate the time to question. Thank you, Chairman.

Senator BOXER. Thank you.

Senator Barrasso.

Senator BARRASSO. Thank you, Madam Chairman.

If I could, Mr. Gray, when the EPA sets health standards, reference doses, what do you take into account in terms of maybe differential sensitivities when it comes to children and how you are trying to figure things out and what is safe and what is not?

Mr. GRAY. Well, the EPA always looks very closely at any potential adverse effects that a material might have, and those certainly include things that we might have concerns with children. We look at potential developmental effects, potential neurotoxic effects, and we consider those very, very seriously.

Just to give a feel for how much this is done, in the Office of Pesticides, the Food Quality Protection Act told EPA to go back and look at the assessments that they had done of pesticides to consider the special sensitivity that children might have. To this point, with a terrific amount of effort, EPA has reviewed and re-assessed over 9,700 pesticide tolerances—that is, the levels that can be on food—to take into account things about children—their consumption patterns that might be different. As a father, I know that your kids don't always eat what you want them to eat; they eat what they eat, and we have to make sure that we keep track of their consumption patterns, and also potential increase of susceptibility because of developmental issues.

So this is something that the Agency takes very, very seriously. We look at the science. We use a science-based approach to understand the right steps to take to prevent any harm to children.

Senator BARRASSO. So we looked at both existing chemicals and then potential new chemicals coming on the market? If we could talk about both of those separately, one is in terms of existing chemicals, what are the things you can do under the Toxic Substance Control Act to address the children's health concerns about existing chemicals. And then I want to ask a second question to followup in terms of new chemicals coming on the market.

Mr. GRAY. Well, for existing chemicals there are two things that we can point to. One is our VCCEP program that was launched in the late 1990's. This is the Voluntary Children's Chemical Evaluation Program. It was our attempt to learn how we can take in and develop special information about potential risks to children and to use that in our assessment process.

This is something that we have worked hard on. This has been a volunteer program that has involved the development of a great deal of data.

We have recently taken a look at that pilot to say what can we learn about the way we can get more information, that we can better use information to look at potential risks to children. We, in fact, have gone to our Children's Health Advisory Committee. We are going to them again in October with questions about this project. We are going to them very specifically. We are using them proactively to help us understand what we have learned from this process.

We have also had public meetings on this where we have worked with a variety of stakeholders. Because of this, we are looking at modifications to the way that we are going to run this VCCEP program. That is very important.

One of the modifications has to do with working through the program chemicals that we choose to evaluate. What we wanted to do there is to link it up with what we call our Champ program, our chemical assessment program that is committed to reviewing about 3,000 existing chemicals for their hazard and exposure information so that we can set the appropriate priorities.

We want to use what we learn from that to set priorities for our children's efforts, as well. So we have efforts going on to look at those chemicals in a very, very careful way.

Senator BARRASSO. Are the IRIS health-based risk values applicable only to adults, or do you include children in that, too, when you go into all of the——

Mr. GRAY. That is another good question. Our IRIS program is the way in which we develop health values that are used by other parts of the Agency, by States, by localities, by folks around the world to assess risks. In the IRIS program we look very specifically at potential risks to children. In fact, you will see that there are places. We have a couple of our IRIS assessments out there now that use what we call in the Agency speak our age-dependent adjustment factors to those assessments that are there specifically to account for situations in which there might be greater-risk children. This is something that we take into account in those assessments, as well.

Senator BARRASSO. Thank you, Mr. Gray.

Thank you, Madam Chairman.

Senator BOXER. Thank you, Senator.

Senator Klobuchar.

Senator KLOBUCHAR. Assistant Director Gray, Director Stephenson, thank you very much for being here. I tell you my interest in this came out of what we have seen in our State where we had a little 4-year-old boy die when he swallowed a charm that was 99 percent lead. I know that is under the Consumer Product Safety Commission, but when we started looking at that from the Commerce Committee we found that the agency had been a shadow of its former self, that it was down on the job, and as a result these toxic products were allowed on our shores and in our stores.

And then, getting ready for this hearing, we looked at what was going on in our State where we have seen more and more children with asthma, $3 billion in treatment, according to the Center for Disease Control; 14 million days of school lost per year. Minnesota children, 4,339 days hospitalized because of asthma. That is where my concern comes from.

As I read what was going on with Director Stephenson talked about with nor responding to the Advisory Committee, it reminds me eerily of what we saw with the climate change issue, where recommendations were made by scientists and the only ones that could see the endangerment standard were a group of Senators in a back room. It is like the science doesn't exist. And I come from a State where we believe in science. We brought the world everything from the Post-It note to the pacemaker. But it seems as though the Administration continues to live, as Senator Clinton has so adeptly put it, in an evidence-free zone.

So I want to talk a little bit about the evidence and how we can get the evidence into our Government again.

One of the things that I got here was an article from the Milwaukee Journal Sentinel, Assistant Administrator, and it talks about this EPA voluntary children's chemical evaluation program, and this program was supposed to rely on companies to provide information about the dangers about the chemicals they produce. What is the status of that program?

Mr. GRAY. Thank you, Senator.

As I just mentioned, the VCCEP program was our attempt. It was started in the late 1990's. it was an attempt to learn how we can develop the information that we need to help address potential sensitivities of children.

Senator KLOBUCHAR. And is there still funding for that program?

Mr. GRAY. Yes, there is. In fact, the program has recently undergone a number of reviews to help us understand this. We have gotten reviews from our Children's Health Protection Advisory Committee. We have talked to other stakeholders. We have held public meetings to help us understand what we have learned and what we might do to make this even more effective.

Senator KLOBUCHAR. And when is the last time that committee met?

Mr. GRAY. It is not really a committee; it is an ongoing process that is involved with getting data together and bringing it in. We do have a meeting planned. We had a public meeting in July, and,

in fact, in October we are going to our Children's Health Advisory Committee for their advice on what we should do with this program, as well.

Senator KLOBUCHAR. But is it true the Committee hasn't met in nearly a year?

Mr. GRAY. I will have to get back to you. I don't quite understand.

Senator KLOBUCHAR. You just said that it was a thriving committee and that there was funding, and it appears to me, according to this article, it hasn't met. Key members of the program can't even say if it is alive.

Chairman, could I put this into the record, the Milwaukee Journal article.

Senator BOXER. Without objection, yes.

Senator KLOBUCHAR. March 29, 2008.

[The referenced information was not received at time of print.]

Senator KLOBUCHAR. Then I just had a few questions of you, Mr. Stephenson. You talked about how these 70 letters come in from the advisory group to the EPA, and you can only think of three instances where there was some kind of a response. Could you explain those to me and what happened with the information from the letters to the Administrator as they were recommendations regarding children's health?

Mr. STEPHENSON. No. This is over a 10-year period. We said there were seven instances where we could identify where the EPA program offices actually came to the Advisory Committee to ask them for input or questions. Nevertheless, the Children's Health Protection Advisory Committee wrote 70 letters over those 10 years. We worked very hard to pull 600-plus recommendations out of those, and we are in the process of analyzing EPA's response to those. The furthest we have got along is for these NAP standards that you see on the chart in front of me here.

Senator KLOBUCHAR. And you had examples of how the EPA has disregarded, rejected, or ignored recommendations to protect the health and well-being of our children? Do you know how many children we are talking about there?

Senator KLOBUCHAR. No. We said that in reference to these NAP standards, that we looked at the 27 recommendations from the Advisory Committee specifically concerning those, and the EPA response was kind of non-responsive to those particular standards.

Senator KLOBUCHAR. This last thing I wanted to mention for future use is in Minnesota because of our frustration with what is going on. Our citizens have taken matters into their own hands, and there is a group called Health Legacy, which is a broad public health coalition of 29 members of health professionals, health-affected groups, environmental groups, faith communities, and parent groups. They have actually taken on the job of educating people in their community. I think it is worth looking into this, but obviously I think it would be better to do on the Federal level.

Thank you very much.

Senator BOXER. Thank you.

I will conclude, because I deferred my questions until the end.

Mr. Gray, why did Mr. Johnson refuse to come to this hearing?

Mr. GRAY. He was not available. I do not know any other details.

Senator BOXER. When will he be available to come before this Committee?

Mr. GRAY. We can get back to you for that.

Senator BOXER. You will get back to me? Will you get back to me today? We have been trying to get Mr. Johnson here since March. He is violating a promise and a pledge he has made to this Committee. Will you please tell him that we want an answer and we want to see him up here.

I will come back in a lame duck session. He has got to come before this Committee. Will you please relay that to him? So you don't know why he couldn't make it? Just couldn't make it.

Do you know if Mr. Johnson is planning foreign travel between now and the end of his term?

Mr. GRAY. I am sorry, I don't know his schedule that far in advance. We have a process where we can answer those questions.

Senator BOXER. Do you know if anyone is planning foreign travel? I am not asking you when, I am just asking does he plan foreign travel between now and the end of his term?

Mr. GRAY. I just don't know.

Senator BOXER. You don't know. OK. But you will please, if you would, find out for me if he is planning foreign travel, because I will tell you right now our kids are in trouble. There are lots of problems out there. The GAO has just done a stupendous job and you say you are proud of your work there with children, and yet they said, "EPA has largely disregarded key recommendations from its Children's Health Protection Advisory Committee, particularly several recent letters advising EPA on proposed revisions to the clean air standards."

Now, air pollution is a serious threat to public health across the Country, including tens of millions of children who live in areas who don't meet Federal air quality standards. Don't the families and children in our Country deserve better than this?

Mr. GRAY. Well, Senator, I think it is very clear that we do value the advice that we get from our Children's Health Advisory Committee, and there are numerous examples of situations in which we have made real progress, made real changes in programs because of their advice, where we have taken our smart growth programs and focused them on children, where——

Senator BOXER. Well, why did GAO give you such a thumbs down? There is no equivocation. They don't have any dog in the fight. They are just taking a look. If you are doing such a great job, why don't they know about it?

Also, if children are such a priority, why is it that the Administrator failed to re-establish the Children's Health Protection Advisory Committee, the task force? Why was that allowed to expire, the Children's Environmental Health Risks and Safety Risks, that task force expired in 2005. If children are so important, why did the Administrator let that expire?

Well, let me ask Mr. Stephenson, since you have lost your ability to answer these questions.

Based on your review, do you have any information that indicates that task force that was allowed to expire was not being effective?

Mr. STEPHENSON. No. To the contrary. It was initially set up under President Clinton for 4 years. It was re-established for 2 years in 2001 and 2003 by President Bush and was simply not extended after 2005. It made very valuable contributions. It exhibited leadership. It wrote strategic plans, which now have no one to implement them. We do see a need for an inter-agency task force.

I am sure that agencies talk all the time, but the discipline and rigor that a task force gives to a subject like this is very important, we think. And it is even recognized, as I mentioned, in EPA's own Fiscal Year 2009 operating plan. They give credit to that Presidential task force for its progress on lead. That is 3 years after it expired.

Senator BOXER. So, Mr. Gray, just spare me all your words that just are not true. I am sorry. Two-and-a-half years ago on March 8, 2006, EPA's independent children's health advisors found that EPA's cleanup levels for perchlorate "is not protective of children." They didn't mince words. They recommended that it be substantially strengthened. EPA still has not acted on that recommendation.

How can you justify the Agency's failure to set a cleanup standard for this toxic chemical that, by the way, is present in more than 40 of our States? How can you justify the Agency's failure to set a clean-up standard for this chemical found in the water of millions of children, a standard that considers the vulnerability, body weight, and exposure patterns of infants and young children? Give me your rationale for that one if you love children so much in your work.

Mr. GRAY. I do love children very much.

Senator BOXER. I know you do. I know.

Mr. GRAY. I have two of my own.

Senator BOXER. I don't question your private life; I am questioning your work.

Mr. GRAY. I think you will be happy to know that we are working very hard on perchlorate. We have developed and had new data from the Food and Drug Administration that helps us understand much more about children's routes of exposure. We have done extensive physiologically based pharmacokinetics modeling to help us understand the potential vulnerabilities of children. Perchlorate and children is an issue we take very seriously.

Senator BOXER. Well, Mr. Grumbles, just so you know, your own Mr. Grumbles sat here in your chair and told us he doubted there would even be a standard for perchlorate, Mr. Stephenson.

Mr. STEPHENSON. I was just going to mention that you will recall we also did some work on the integrated risk information system, which is scientific assessment of chemicals, and we used perchlorate as one of our poster children for being stuck in the assessment process for over a decade. So until you do that scientific assessment, it is a forerunner to any standard or regulation. Dr. Gray is correct. They are doing a lot of things on perchlorate. But we still haven't concluded the basic scientific assessment needed to move forward on a regulation or a standard.

Senator BOXER. And Mr. Grumbles practically told me they weren't going to have a standard, practically sat there and said it. And the time has been wasted.

I have to say with Senator Clinton here, we have gone backward at a rapid pace since the Clinton years. That is not what America does. In America we make life better for our people. We use the tools we have. But when you have special interests sitting at the table you can talk to me about science. Of course that is what we want. But if the people who are translating the science have a special interest in it, nothing good can come of it.

I can only speak for my State. We are setting a standard for perchlorate. We are not standing around waiting for you, because our kids are worth a lot to us. I just think this has been a very sad, sad moment for this Committee to sit here and hear this.

I just want to say, Mr. Stephenson, thank you for this. Senator Clinton and I are so pleased, because when you did this work you didn't equivocate. You just said this is where it comes down. We are just simply not doing the right thing for our children. That is clear.

We will call on the next panel.

We want to welcome our next panel. We ask you to take your seats as quickly as possible because the clock does tick around here and we have got to move forward.

First we are going to hear from Susan West Marmagas, Director of Health Programs, Commonweal, and former member of EPA's Children's Health Protection Advisory Committee, to be followed by Dr. Leo Trasande, Co-Director, Mount Sinai's Center for Children's Health and the Environment, and Dr. Robert Brent, Distinguished Professor of Pediatrics at duPont Hospital for Children.

We will call on Ms. Marmagas first.

STATEMENT OF SUSAN WEST MARMAGAS, DIRECTOR OF HEALTH PROGRAMS, COMMONWEAL

Ms. MARMAGAS. Thank you very much.

Senator BOXER. Try to keep it to 5 minutes.

Ms. MARMAGAS. Thank you very much.

Dear Madam Chair and members of the Committee, good morning. It is my honor to speak before you today about the importance of children's health and the environment and the track record at the U.S. Environmental Protection Agency to address this vital issue.

My name is Susan West Marmagas and I am the Director of Health Programs with Commonweal.

Today I am speaking as a former member of, but not representing, the Children's Health Protection Advisory Committee, a Federal advisory committee that advises the Administrator of the Environmental Protection Agency by offering scientific review, guidance, and technical assistance on children's environmental health.

As defined by EPA, the CHPAC is "a body of researchers, academicians, health care providers, environmentalists, children's advocates, professionals, Government employees, and members of the public who advise EPA on regulations, research, and communications issues relevant to children."

The CHPAC is comprised of a broad swath of children's health experts, from a range of perspectives, who reach all decisions by consensus. Every member has been appointed or reappointed by

this Administration, myself included. I served on the Committee from 2001 to 2007, during which time we brought many issues to the Agency.

Today I will demonstrate a pattern of neglect by EPA leadership in the last years to address significant health threats to our Nation's children. I will briefly comment on the weakened stature of the CHPAC, offer three specific examples where EPA leadership did not heed our advice, discuss the steady decline of EPA leadership support within the Agency on this issue, and conclude with brief comments on two timely policy issues.

First, the use of the CHPAC by the Administrator of EPA has changed considerably over the last several years. At its inception, the Committee was seen as the go-to body of experts on children's environmental health for EPA, and the Administrator and key offices came to the Committee for review, comment, and advice on critical policy, regulatory, and scientific issues. Many of these issues were well received by the Agency, and many incorporated into Agency decisionmaking.

Over the last several years, however, the Committee has been seen less by EPA leadership as a critical advisory body and more solely as a public commenter. This has not stopped the CHPAC from seeking out critical issues, looking at the science, and making recommendations to EPA. We have looked at such issues as the national ambient air quality standards for ozone, particulate matter and lead; mercury; perchlorate; and other issues. However, they have increasingly ignored the recommendations of this Committee.

I would like to just briefly talk about three issues. The first is the Clean Air Mercury Rule. This was an issue that the CHPAC took up in 2004 and wrote not one but four letters to the Agency. We wrote four letters because our first three letters were ignored, and we continued to talk about the scientific issues and the importance of addressing this issue.

Even after these three additional letters to the Administrator, the Agency continued to downplay and ignore the significant threat of mercury to children's health, even in the face of persistent evidence-based concerns on this issue.

The second is the National Ambient Air Quality Standards. We wrote letters on particulate matter, ozone, and lead, laying out the scientific basis for protecting children, and we also specifically followed the recommendations of the Clean Air Science Advisory Committee. However, all of these recommendations were ignored by the Agency and they did not set the standard that our advisory committee recommended.

Third, perchlorate, which has also come up in this hearing today. The main health risk of perchlorate is its effect on brain function, namely through the impact of perchlorate on the thyroid.

In 2006 we wrote a letter with regards to the EPA preliminary remediation goal and we argued then that it was not sufficiently protective of children, most notably infants and breast-feeding infants. However, our extensive input has not been taken up by the Agency. Since that time, there is even additional study and analysis, especially from the Centers for Disease Control, which shows that nursing infants are at particular risk.

I now feel that it is important to take both our recommendations and this new science in considering this new standard.

Finally, I would like to just talk briefly about the decrease of leadership within the Agency. I think this has been addressed already by the GAO report. There has been no permanent director of the Office of Children's Environmental Health until very recently. We actually as a committee wrote comment letters to the Agency specifically saying they needed a director, they should not be adding aging and environmental education to the list, and they should add resources to this office. They have moved staff around to handle these three issues and they have also not increased the budget to address them.

Finally, in my last second, I would just like to comment that there are two policy issues that are outside my role as the CHPAC, but I think are important, and one is the kids Safe Chemical Act. We found as a committee that it was challenging to get EPA to do what it needed to do to protect children because the Toxic Substances Control Act is not sufficient and does not effectively protect children, and the Kid-Safe Chemical Act would address a number of the issues and put children at the center of regulatory decisionmaking.

The last comment I will make is on the observational study of children. As we know, the cheers study in 2005 did not follow the ethical standards that we have as a Nation. It was withdrawn; however, what has been currently proposed doesn't go far enough to address the recommendations of the Senate or has not addressed the issues that have been brought up in the courts. I would argue that until those issues get addressed it is prudent for this Agency to hold back on observational studies. They have canceled RFA, but I think it is important that they really address these issues thoroughly before they move forward with an observational study on children.

With that, I conclude my remarks. Thank you very much.

[The prepared statement of Ms. Marmagas follows:]

U.S. Senate Committee on Environment and Public Works

"Oversight Hearing on EPA'S Children's Health Protection Efforts"
September 16, 2008

Testimony by
Susan West Marmagas, MPH
Director of Health Programs, Commonweal

Dear Madam Chair and Members of the Committee. Good morning. It is an honor to speak before you today about the importance of children's health and the environment, and the track record of the US Environmental Protection Agency (EPA) to address this vital issue. My name is Susan West Marmagas and I am the Director of Health Programs with Commonweal.

Today I am speaking as a former member of, but not representing, the Children's Health Protection Advisory Committee (CHPAC), a federal advisory committee that advises the Administrator of the Environmental Protection Agency by offering scientific review, guidance and technical assistance on children's environmental health. As defined by EPA, the CHPAC is

> "a body of researchers, academicians, health care providers, environmentalists, children's advocates, professionals, government employees, and members of the public who advise EPA on regulations, research, and communications issues relevant to children."[1]

The CHPAC is comprised of a broad swath of children's health experts, all decisions are made by consensus, and every member was appointed or re-appointed by the current administration, myself included. The Committee meets on an average 3 times each year, deliberates on key children's health issues, reaches consensus on its recommendations, and sends letters to the Administrator with advice, comment and recommendations for consideration. I served on the Committee from 2001-2007 during which time we brought numerous children's health concerns to the Agency. Committee rules require that members serve for a maximum of 6 years, therefore in 2007 my term on the Committee ended.

---

[1] http://yosemite.epa.gov/ochp/ochpweb.nsf/content/whatwe_advisory.htm

Today I would like to touch on the following main points:

Weakened Stature of the CHPAC:
The use of the CHPAC by the Administrator of EPA has changed considerably over the last eight years. At its inception, the Committee was seen as the "go-to" body of experts on children's environmental health for EPA, and the Administrator and key offices sought out the Committee for review, comment and advice on critical policy, regulatory, and science issues. Many of the CHPAC's recommendations were well received by the Agency, and many of them were incorporated into Agency decision-making. Over the last several years, the attention of EPA leadership to children's health overall has waned and the Committee has been seen less as a critical advisory body, and more as just another public commentator. However, that has not stopped the CHPAC from seeking out critical issues and offering its expertise to EPA. The Agency has increasingly ignored CHPAC's recommendations. This shift, I believe, has significantly weakened EPA's attention to children in its rule-making, research and policy affairs.

CHPAC Advice Not Heeded
While the CHPAC serves at the discretion of the Administrator, it is its role to offer the Agency the best scientific and policy advice regarding critical issues that impact the health of children. The Committee role is not solely one of "public comment", but rather is one of a federal advisory committee, set up under the FACA standards, to offer advice. However, the track record from the last several years clearly shows that many of the CHPAC recommendation letters have been viewed by the Agency as just another form of public comment, and not as the result of deliberative review by a body of experts from a broad swath of children's health expertise. In the last few years, the CHPAC has weighed in on such critical issues as the National Ambient Air Quality Standards for particulate matter, ozone and lead, mercury from coal-fired power plants, children's cancer risk assessment, regulation of toxic chemicals including the Voluntary Children's Chemical Evaluation (VCEEP) and High Production Volume Programs, and perchlorate. In numerous instances, the response from the Agency to the CHPAC's extensive and scientifically sound recommendations has been one of form letters, recommendations not heeded, or input treated as solely additional public comment. The problem is not only that the Committee has been ignored, but more importantly that critical children health concerns remain unaddressed.

Case Study I: Mercury and Children's Health
I would like to briefly highlight an example of CHPAC advice not being heeded with the example of the Clean Air Mercury Rule, a rule that has interestingly enough since been struck down by the courts. The CHPAC evaluated the issue of mercury from coal-fired power plants thoroughly and wrote not one, but four, letters to the Administration from January 2004 through January 2005. The recommendations made by the CHPAC were ignored by the Agency.

Beginning in January 2004, the CHPAC took up consideration of the proposed mercury from power plant rule. We reviewed the science on the health effects to children from mercury exposure, extensively questioned lead staff in EPA's Office of Air and Radiation about the EPA's proposed regulations to control mercury emissions from power plants, and examined the EPA's proposed preamble to the rule.

In our initial January 26, 2004 letter to Administrator Michael Leavitt, we outlined the significant health implications of low-dose methylmercury exposure for children. Based on our review of the extensive scientific record of toxicological and medical research on this subject, including an authoritative report by the National Research Council of the National Academy of Sciences, the CHPAC determined the following:

- Exposure to methylmercury in the womb can cause adverse developmental and cognitive effects in children, even at low doses that do not result in effects in the mother[2];
- Prenatal exposure from maternal consumption of fish can also cause impairments later on in the developing child. Recent epidemiologic studies have found that children exposed to even low levels of mercury before birth experience subtle symptoms of neurologic damage. Specific effects include poor performance on neuro-behavioral tests, particularly on tests of attention, fine motor function, language, visual-spatial abilities (e.g., drawing) and memory.[3]
- Infants and children have on-going dietary exposures to methylmercury. Children and infants are sensitive to mercury's effects because their nervous systems continue to develop until about age 20.[4]
- According to CDC's second National Report on Human Exposure to Environmental Chemicals, almost 8 percent of women of child bearing ages (16- 49) have levels of mercury that exceed what is considered safe for a fetus.[5]

Since this letter was written, continuing research in this field suggests that the actual number of infants exposed to methylmercury in utero at levels exceeding the EPA's safe reference dose may be much higher when data on maternal cord blood levels are also considered.[6]

Based on the CHPAC's review of the health effects science and the proposed rule, the Committee raised a number of key findings in our first letter[7] that we would continue to raise unsatisfactorily with the Agency over the next year:

- "This proposed action does not go as far as is feasible to reduce mercury emissions from power plants, and thereby does not sufficiently protect children."
- "From our understanding, the unique vulnerabilities of children, infants and women of child-bearing age were not adequately considered in the development of the EPA's proposed rules...we strongly recommend that EPA, when finalizing the rule, take into greater

---

[2] U.S. EPA, America's Children and the Environment, 2003.
[3] Toxicologial Effects of Methylmercury. National Academy Press, Washington, DC 2000. http://www.nap.edu.
[4] U.S. EPA. 1997b. Mercury Study Report to Congress, Volume VII: Characterization of Human and Wildlife Risks from Methylmercury Exposure in the United States. EPA-452/R-97-009.
[5] Schober SE, et.al. Blood mercury levels in US children and women of childbearing age, 1999-2000. JAMA 2003:289(13):1667-1674.
[6] Mahaffey KR, Clickner RP, Bodurow CC., Environ Health Perspect. 2004 Apr;112(5):562-70. http://ehp.niehs.nih.gov/members/2003/6587/6587.html
[7] January 26, 2004 from the CHPAC to Administrator Michael Leavitt.

consideration the health impacts on children and women of child-bearing age in as practicable a manner as possible given existing information"

- "Should EPA decide to move mercury regulations to Section 111, thereby changing the definition of mercury from power plants as a hazardous air pollutant, we are concerned about the unintended consequences of this re-classification for regulating mercury at the state level."
- "We recommend that EPA evaluate the possibility that hot spots could result and that the proposed regulation should be written to ensure that existing hot spots are reduced and no new ones created."
- We seek an integrated analysis from EPA with respect to whether emissions reductions under either of these proposals are the most child-protective, timely and cost effective." (including available technologies, costs, health implications, economic benefits)
- "We would like EPA to share the results of this integrated analysis with CHPAC for further consideration so that we may better advise EPA on the most child-protective regulatory options."

In response, political appointees indicated that EPA's strategy was the "the most cost effective and environmental beneficial". The Agency did not respond to the CHPAC's request for additional modeling or other impact analysis assessing the effect of the rule on children's health, or for integrated analysis on technology, costs, children's health impacts, or economic benefits. Upon further reiteration of our concerns, and our request for meetings with senior agency leadership, in two subsequent letters in June 2004 and November 2004, we received little additional responsive action from the Agency, and in January 2005 we sent our final letter to the Agency. Despite our repeated requests, no integrated impact analysis was ever provided to the CHPAC.

Three weeks before the release of the final rule, OAR Director Holmstead agreed to meet with the CHPAC. In the meeting on February 24, 2005, he stated that the Agency did not need to do specific analysis on children's health because the entire rule is about and for children. When asked about an integrated analysis that included children's health impacts, Holmstead promised that this analysis would be in the final rule.

In conclusion, the concerns raised by the EPA's own child health advisors were largely dismissed by the Agency in completing its rule-making on mercury emissions from power plants. The Agency did not conduct a comprehensive analysis on children's health impacts, although they did include a health benefits analysis in the final rule that was never made available for public comment prior to finalization of the mercury rule. The Agency never undertook an integrated analysis to assess technologies, costs, health impacts and economic benefits of more stringent reductions. And, in conclusion, as indicated in Mr. Holmstead's comments to the CHPAC in February 2005, the Agency downplayed or ignored the significant threat of mercury to children's health even in the face of persistent, evidence-based concerns voiced repeatedly by the leading children's health experts in the country.

Two Other Relevant and Timely Examples

National Ambient Air Quality Standards

Similar instances of EPA not heeding the advice of the CHPAC have occurred repeatedly in the last three years that have mirrored the experience with the Clean Air Mercury Rule. I would like briefly touch on the experience with the National Ambient Air Quality Standards. The CHPAC, in its letters to the Agency on particulate matter, ozone and lead, presented the documented health effects on children from all three contaminants. The CHPAC also made recommendations to the Agency about the standards for all three contaminants that would be protective of children. The EPA has not followed the recommendations of the CHPAC, nor the recommendations of the Clean Air Science Advisory Committee (CASAC), the federal committee charged with evaluating EPA's assessment of the science behind the standards. The Agency ultimately set standards that do not provide an adequate margin of safety for infants and children. In his testimony[8] of May 7, 2008 for the Senate Environment and Public Works Committee, Dr. John Balbus outlined the concerns of the CHPAC regarding the NAAQS for particulate matter and ozone, and the inadequate response from EPA.

Perchlorate

The main health risk of perchlorate is its effect on brain function, namely through the impact of perchlorate on the thyroid. The CHPAC in 2006 offered comments and recommendations on EPA's Office of Solid Waste & Emergency Response (OSWER) preliminary remediation Goal (PRG) on perchlorate.[9] The CHPAC letter stated that:

> "Perchlorate is a well-recognized endocrine disruptor at sufficiently high doses, targeting the thyroid and thus creating risk of neurodevelopmental toxicity. A key concern is the nursing infant because of the potentially high exposure rate associated with this pathway, and the high susceptibility at this life stage."

The CHPAC letter specifically outlined the risk to breast feeding infants, a population not considered in the development of the PRG, and yet the population deemed by the CHPAC to be most at risk from perchlorate exposure in breast milk. The CHPAC's review of the published literature concluded that a "nursing infant exposure is approximately 5 to 10 times higher than the perchlorate RfD." The CHPAC also outlined how infants are not only more exposed, but more susceptible to the neurodevelopmental effects of perchlorate because the central nervous system is still developing.

The CHPAC, after reviewing the PRG, concluded that:

> "The OSWER PRG ignores the higher exposure and susceptibility of infants, and could lead to nursing and bottle-fed infants being exposed to daily doses that are well above the perchlorate RfD; the PRG needs to protect this susceptible population."

---

[8] Testimony of John M. Balbus, MD, MPH, Oversight Hearing on Science and Environmental Regulatory Decisions Public Sector Solutions to Global Warming, Oversight, and Children's Health Protection, Subcommittee of the U.S. Senate Environment and Public Works Committee (May 7, 2008)

[9] Letter from Melanie Marty to Administrator Stephen Johnson regarding perchlorate PRG and water contamination (March 8, 2006)

The extensive input from the CHPAC was not addressed by EPA, and the recommendations have yet to be incorporated into Agency action. Specifically, the OSWER did not consider the significant issue of transport of perchlorate into breast milk and the elevated exposure of a nursing infant.

Since that time, additional studies and analyses have been published that make an even more compelling case to protect infants by setting a stronger PRG, a more protective RfD, and an overall drinking water standard for perchlorate. Specifically, as outlined by Dr. Gary Ginsberg in his April 25, 2007 testimony for the House Subcommittee on Environment and Hazardous Materials of the Committee on Energy and Commerce[10], the following findings justify the need for protective policy on perchlorate.

Most notably from the 2006 CDC study, evidence has emerged that at low exposures common across our population, perchlorate appears to disrupt the thyroid gland in humans[11]. The CDC study found an association between perchlorate exposure in the general population and altered thyroid status, namely low thyroid hormone, high TSH. The effect was only seen in women and only in those women with low iodide intake. This increases the concern that pregnant women could be especially at risk. The CDC study is more powerful than the study used by NAS and EPA to set the RfD as it involved thousands of subjects, it divided the population based upon known risk factors including low iodide intake, and it included a reliable exposure measure, urinary levels of perchlorate.

The CDC study confirms concerns raised by Ginsberg and others about the RfD as the association between perchlorate exposure and impaired thyroid function occurred at background population exposures that are 10 fold below the RfD. Ginsberg, et.al[12] found that perchlorate effects in a key subgroup of the population (the 36% of women with low iodide intake) indicates that the concerns are greater than originally thought with perchlorate, The CDC study offers a compelling justification for an overhaul of the RfD so that it more fully reflects the human epidemiology and laboratory data.

In addition, recent publications also built an even more compelling case to recognize the special vulnerability of the nursing infant to perchlorate. In the Ginsberg, et.al[13], the authors also document the "double jeopardy for the nursing infant", both lower iodine intake and a substantial dose of perchlorate.

---

[10] http://energycommerce.house.gov/cmte_mtgs/110-ehm-hrg.042507.Ginsberg-testimony.pdf

[11] Blount BC, Pirkle JL, Osterloh JD, Valentin-Blasini L, Caldwell KL. 2006a. Urinary perchlorate and thyroid hormone levels in adolescent and adult men and women living in the United States. Environ Health Perspect 114:1865-1871.

[12] Ginsberg, G.L., Hattis, D.B., Zoeller, R.T. and Rice, D.C. (2007) Evaluation of the USEPA/OSWER Preliminary Remediation Goal for perchlorate in groundwater: focus on exposure to nursing infants. Environ Health Perspect 115: 361-369.

[13] Ginsberg, et.al

Taken together with the CHPAC recommendations, these latest publications demonstrate a compelling justification for setting a child-protective drinking water standard for perchlorate.

Significant Decrease in EPA Leadership on Children's Health

Over the last eight years, there are specific examples of how the priority on children's health has been steadily decreasing. After having a permanent director running the Office of Children's Health Protection from 1997-2001, the Office was without a permanent director until just recently. During this time, the CHPAC repeatedly called in its letters to the Administrator to address this leadership gap, however the position remained empty. The CHPAC's December 16, 2002 highlighted that:

> "the Advisory Committee is deeply concerned that the OCHP is currently without a permanent director and has been for seven months. Consistent with your dedication to children's environmental health, we urge you to promptly fill this position with an energetic and well-qualified staff member."

At the same time, additional issue areas were added to the Office's mission without additional financial or staffing resources to support them. First, an aging initiative was added and most recently environmental education. In the same December 16, 2002 letter[14] the CHPAC expressed concern that:

> "expanding the mission of OCHP to cover environmental health concerns of both children and the aging will do justice to neither effort, thus diminish the effectiveness of both. We believe that OCHP should retain its present name and mission."

EPA Administrator Christine Todd Whitman responded[15] assuring the CHPAC that "additional resources are needed for the Aging Initiative and.... that EPA does not intend to reduce funding for children's health initiatives to meet that need."

However, the commitment of EPA leadership to children's health continues to diminish. Since the aging initiative was added, the office was more recently expanded the office to also include environmental education. And, once again, reduction in the budget and staff dedicated to children's environmental health has occurred.

The CHPAC most recently addressed this issue in its April 10, 2007 letter[16] to the Administration – in honor of the 10th anniversary of the Executive Order 13045: Protection of

---

[14] Letter from Melanie Marty to Christine Todd Whitman supporting the Initiative on Aging, but suggesting that the aging initiative be established as an independent office or effort instead of expanding the name and mission of OCHP (December 16, 2002)

[15] Response from Christine Todd Whitman to Melanie Marty thanking the Committee for their input on the Aging Initiative and the need to select a permanent director for OCHP (May 2, 2003)

[16] Letter from Melanie Marty to Administrator Stephen Johnson regarding the ten year anniversary of the Children's Health Executive Order (April 10, 2007)

Children from Environmental Health Risks and Safety Risks. The letter called for EPA to make a renewed commitment, specifically stating that:

- We have a moral imperative to leave the world cleaner, healthier and safer for our children;
- EPA's focus on children's environmental health has diminished in recent years;
- Considerations of children are still not explicitly considered in all relevant and critical Agency decisions and policies;
- EPA has not capitalized on opportunity to tackle significant challenges.

The letter presented seven key elements for EPA's vision on children's environmental health, and called on EPA to work with other federal and state agencies to make these happen:

- Ensure healthy environments for our children, including the recommendation that all regulations should address the unique susceptibilities of children;
- Eliminate environmental health disparities in populations at risk;
- Expand critical research to address impacts on children, especially addressing multiple exposures at all life stages, and addressing ethnical considerations;
- Strengthen the national approach to regulating chemicals, address flaws in our chemical regulatory system and put children at the center of a comprehensive effort;
- Foster environmental preparedness and prevention by taking preventive steps to address the threat of climate change and impact on children from natural disasters and terrorism;
- Institute "environmental health literacy" through strong educational, right-to-know programs, and community programs;
- Commit necessary infrastructure, leadership and resources within EPA and help to lead inter-agency collaboration on pursuing this vision.

Even though the Administrator took issue with the CHPAC's conclusion that the EPA's focus on children's health had diminished, he did commit the Agency to convene key staff across the Agency to address the seven elements. What has happened to the efforts to move the recommendations forward? It seems that the initial effort has now stalled yet again within the Agency.

Turning now from the role of the CHPAC in advising EPA decision-making on children's environmental health, I believe that the 10th anniversary letter also offers a 'roap map" to other federal agencies and Congress.

In my role as a leader in the field of children's environmental health, I would like to briefly comment on an legislative opportunity to address critical gaps in protecting America's children from exposure to toxic chemicals.

Kid-Safe Chemicals Act

As has been significantly documented, the Toxic Substances Control Act is severely lacking in its ability to protect children, and our most vulnerable, from exposure to toxic chemicals. As a member of the CHPAC, it proved challenging to offer effective recommendations about EPA toxic chemicals program because it is so significantly limited by current law. Without a more comprehensive approach to regulating toxic chemicals, EPA and our nation cannot effectively address this critical children's health issue. I believe that the Kid-Safe Chemicals Act, by prioritizing children, will protect the public's health more broadly. The Act will ensure

publically available health and safety information for the vast majority of chemicals and will put the burden of proof on chemical manufacturers to demonstrate that their chemicals are safe for children. The Act also codifies inter-agency collaboration with the specific partnership between EPA and the Centers for Disease Control and Prevention in the collection of biomonitoring data. This Act offers a comprehensive solution to our current regulatory system and is supported by a broad swath of public health, health professional, environmental, and community-based organizations.

Observational Studies of Children

In 2005, EPA was in the process of quietly setting up an observational study of children's exposure to pesticides in Florida, when this effort came to the public's (and the US Senate's) attention. Significant ethical issues were evident in the study design, and questions were raised by ethics professionals, scientists and the public health community across the United States as to the validity and ethics of such a study. The study, known as CHEERS, was abandoned under pressure, and the Agency has since developed guidance for future observational studies. However the Agency has not thoroughly addressed the concerns expressed by the US Senate. In the interim, the EPA released new rules on human testing, and the rules are currently being challenged in court.

However, EPA this summer released a RFA for a new $2.5 million cooperative agreement on observational studies and children. While the RFA seemed to be addressing some of the concerns raised by the proposed CHEERS study, it left open the door for a similar study to be approved. The RFA was cancelled last week. It seems prudent to thoroughly address the concerns that have been raised about observational studies and to wait until the concerns about the human testing rule are resolved by the courts. Given the track record of this Administration, I believe it is important for the Administrator to thoroughly address the concerns raised before new efforts are undertaken.

In conclusion, I would like to thank you for addressing vital children's health issues facing EPA and the nation. It has been my honor to present testimony about issues facing our children. I am happy to provide more specific detail, or answer any specific questions that you may have.

Susan West Marmagas, MPH
Director of Health Programs, Commonweal

Susan West Marmagas, MPH is the Director of Health Programs with Commonweal where she co-leads the Women's Health and Environment Initiative – an emerging national network of health, women's and environment leaders and organizations undertaking collaborative projects to improve the health of women in the US and globally. Based in Blacksburg, VA, West Marmagas recently returned to her rural roots to also help improve local public health in southwestern Virginia and Appalachia. She currently advises the Appalachia Community Cancer Network to address potential environmental determinants of cancer in the region.

West Marmagas has over fifteen years of experience in the public health field, most notably in the area of children's and women's environmental health. She joined Commonweal after serving as the Director of Environment & Health Programs at Physicians for Social Responsibility (PSR) in its national office in Washington, DC. In this position, she led PSR's national environmental health program, focusing on toxics and children's health, clean air and climate change, environmental public health tracking, and the emerging links between the environment and chronic disease. She has also held senior positions with the Children's Environmental Health Network and the National Environmental Education Foundation.

She received her Master of Public Health with a concentration in Community Health Education from the University of California at Berkeley and her Bachelor of Arts in International Studies from Earlham College. Her career has focused on engaging health professionals and scientists in protective public policy, facilitating strategic planning discussions across the health and environment fields, and implementing evidence-based policy efforts. West Marmagas has testified before the US Congress and has served as media spokesperson on national issues such as fish consumption, mercury pollution, and children's health. She served on the U.S. Environmental Protection Agency's Children's Health Protection Advisory Committee and co-chaired its Regulatory Work Group. She is a Site Visitor for the Council on Education for Public Health and a Fellow with the National Public Health Leadership Institute. West Marmagas serves in leadership with the American Public Health Association, including as former Chair of its Environmental Health Section.

Environment and Public Works Committee Hearing
September 16, 2008
Follow-up Questions for Written Submission

Responses from Susan West Marmagas to Questions from Senator Barbara Boxer

1. **Please describe how you think EPA can more effectively use the Children's Health Protection Advisory Committee to better protect children's health?**

When the Children's Health Protection Advisory Committee (CHPAC) was first created, the Administrator of EPA asked the Committee to identify the top five regulations that needed to better address children. The CHPAC reviewed regulations across the board and then selected the five that represented the highest priority for children. I believe that EPA could task the CHPAC with such an exercise again as a way to re-engage the CHPAC in helping to guide the most pressing issues for EPA from a children's health perspective.

In addition, I would recommend that the new EPA Administrator seek guidance from the CHPAC on the top children's health priorities for the next 1-2 years. This, coupled with the CHPAC recommendations in its 10th anniversary letter, would offer a road map to the new Administrator. While it is important for the CHPAC to be pro-active in identifying timely issues for EPA, I believe that EPA should return to its use of the CHPAC as the "go-to" body of experts and seek the CHPAC's guidance on a wide swath of the policy, research and outreach decisions the Agency must address.

2. **The Children's Health Protection Advisory Committee wrote a letter on the 10th anniversary of President Clinton's Executive Order on Children's Health. Would you please explain why the Committee wrote this letter?**

The Committee wanted to honor this anniversary and take stock of what had happened over the last decade. There was concern expressed by the CHPAC that an attention to children's health in the leadership of EPA (specifically by the Administrator, not the Office of Children's Health Protection) had diminished significantly. In addition, the CHPAC wanted to note that inter-agency collaboration at the highest levels within the Administration had ceased with the disbanding of the Inter-Agency Task Force on Children's Health and Safety. The CHPAC wanted to compel the EPA Administrator to renew the Agency's commitment, and offered a set of seven key elements to guide EPA's progress forward.

3. **Please also describe what the Agency's reaction was to the letter while you were on the Committee, and include any new information that you have regarding this issue since you left the Committee.**

The EPA Administrator sent a response letter to the CHPAC indicating that he would work with the program offices to discuss the recommendations in the letter. Work groups were to have been set up across the Agency on the seven key elements. However, all indications are that these efforts have stalled within the Agency and that CHPAC recommendations in the 10th anniversary letter are not being addressed.

Senator BOXER. Thank you very much. That really was helpful. Dr. Trasande, welcome.

STATEMENT OF LEO TRASANDE, CO-DIRECTOR, CHILDREN'S ENVIRONMENTAL HEALTH CENTER, MOUNT SINAI MEDICAL CENTER

Dr. TRASANDE. Good morning, Madam Chairwoman and members of the Committee. I am Dr. Leo Trasande. I am a pediatrician and co-direct the Children's Environmental Health Center at the Mount Sinai School of Medicine, the Nation's first academic policy center devoted to the protection of children against environmental threats to health.

Children are uniquely vulnerable to many of the 90,000 chemicals that are released into the environment every day. Pound for pound, they eat more food, they drink more water, and breathe more air than adults, so they take proportionately more of the toxins into their little bodies.

They also do not metabolize, detoxify, and excrete chemicals in the same way as adults; thus, the chemicals can reside longer in children's bloodstreams and cause more damage.

A third reason is that children are undergoing rapid growth and development, and those very complex developmental processes are easily disrupted.

Over the past 30 years chronic diseases of environmental origin have become epidemic in American children. These include asthma, birth defects, brain cancer, developmental disabilities, obesity, preterm birth, leukemia, and testicular cancer. These rapidly rising rates of chronic disease threaten the health of our children and the future security of our Nation. It may create a situation that has not been witnessed since the Great Depression in which our current generation of children may be the first to enjoy a shorter life span than the generation before them.

Evidence is increasing that many environmental chemicals contribute to the causation of these diseases. Lead, mercury, PBCs, and certain pesticides have been shown to cause brain damage and to contribute to learning disabilities and disruption of children's behavior. Benzene, 1,3-butadiene, and pesticides have been etiologically associated with childhood malignancies. Ambient air pollutants also have been shown to increase incidence of asthma and to trigger asthmatic attacks.

These diseases of environmental origin are also extremely costly to our economy. Four of the leading diseases of environmental origin in American children, lead poisoning, asthma, developmental disabilities, and childhood cancer have been found to cost our Nation $54.9 billion annually. These additional costs are disproportionately borne by the American taxpayer, and thus the reduction of unnecessary toxic exposure to environmental chemicals can be an effective and wise investment in our children's health.

Federal regulation of environmental chemicals has proven successful in the reduction of childhood disease and disability. The elimination of lead from gasoline in the U.S. resulted in IQs among pre-school aged children in the 1990's that were 2.4 to 2.7 points higher than they would have been if those children had a distribution of blood lead levels found among children in the 1970's. Before

the EPA's phase-out of diazanon and chlorpyrifos, these two pesticides were frequently detected in the core blood of New York City children and associated with decrements in birth weight and length. After these phase-outs, the pesticides and their association with predictors of cognitive potential were no longer detected.

In the past, the U.S. has taken a more proactive approach to protecting children from hazardous chemical exposures. The Food Quality Protection Act requires that standards for agricultural pesticides be set at levels sufficiently strict to protect the health of infants and children, yet this is the only Federal environmental regulation that embraces scientific reality that children are uniquely vulnerable to many environmental chemicals.

Despite compelling evidence that further efforts are needed to prevent further increases in disease and disability of an environmental origin among American children, major gaps remain in the regulatory approach taken by the EPA to protect children.

Without enforcement of the Clean Air Act, mercury emissions from coal-burning power plants will continue to poison the next generation of America's children. Clean air standards that regulate pollutants known to cause or worsen childhood respiratory diseases have been weakened, and new research suggests the existing standards require their strengthening.

Despite the fact that ten million children live within four miles of Superfund sites containing high levels of known toxic chemicals, the Superfund program remains chronically under-funded.

As studies like the one published today in the Journal of the American Medical Association document the health effects of bisphenol A and other chemicals, families are forced to choose products with incomplete information about their safety and placed into panic when studies are released documenting their health effects.

Legislation like the Kid-Safe Chemicals act would empower EPA to ensure pre-market testing of chemicals that are used in consumer products, and broader reform of TSCA is needed to ensure that gaps do not remain in testing of chemicals in all products.

It can take 15 or even more years for epidemiologic studies to determine whether children are harmed by these exposures after the fact, and this approach represents an ongoing, unsafe, and unnatural experiment on American children.

Finally in this testimony I wish to point out the critical need for funding the national children's study, which will unearth so much information of the health effects of the many chemicals for which toxicity data exists.

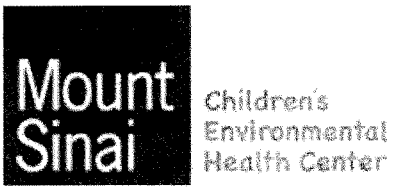
I would like to thank the chairwoman, as well as Senators Harkin, Specter, and Senator Clinton, as well, for their strong support of the National Children's Study. This study will take the extra steps to ensure that participation is completely voluntary, that environmental and health concerns are reported as soon as they are detected, and that families are empowered to protect themselves against known harmful exposures.

The National Children Study is an investment in our children and in America's future and will give our Nation the ability to understand the causes of chronic disease that cause so much suffering and death in our children. It will give us the information that we need on the environmental risk factors and the gene environment

interactions that are responsible for rising rates of morbidity and mortality. It will provide a blueprint for the prevention of disease and for the enhancement of the health in America's children today and in the future. It will be our legacy to the generations yet unborn.

Thank you. I shall be pleased to answer your questions.

[The prepared statement of Dr. Trasande follows:]



The Urgent Need for Federal Policy Interventions to Prevent Diseases of Environmental Origin in American Children

Testimony to U.S. Senate Environment and Public Works Committee

September 16, 2008

Prepared by:
Leonardo Trasande, MD, MPP
Co-Director
Children's Environmental Health Center
Department of Community and Preventive Medicine
Mount Sinai School of Medicine
One Gustave L. Levy Place Box 1057
New York, NY 10029
Leo.Trasande@mssm.edu
212-824-7023

Good morning, Madam Chairwoman and Members of the Committee.

I am Dr. Leonardo Trasande. I am a pediatrician and Assistant Professor of Community & Preventive Medicine and Pediatrics at the Mount Sinai School of Medicine. I co-direct the Children's Environmental Health Center, the nation's first academic policy center devoted to the protection of children against environmental threats to health.

Children are uniquely vulnerable to many of the 90,000 chemicals that are released into the environment every day:

* One important reason why children are so vulnerable to environmental chemicals is that they have disproportionately heavy exposures. Pound per pound of body weight, children drink more water, eat more food, and breathe more air than adults, and so they take proportionately more of the toxins in water, food and air into their little bodies. Small children's exposure is magnified further by their normal behaviors – their play close to the floor, and their hand-to-mouth activity, which we pediatricians call "normal oral exploratory behavior."

* A second reason for their great susceptibility to chemical toxins is that children do not metabolize, detoxify, and excrete many toxins in the same way as adults; thus the chemicals can reside much longer in children's bloodstreams and cause more damage.

* A third reason is that children are undergoing rapid growth and development, and those very complex developmental processes are easily disrupted.

* Finally, children have more future years of life than most adults and thus have more time to develop chronic diseases that may be triggered by early environmental exposures.

Over the past thirty years, chronic diseases of environmental origin have become epidemic in American children, and are the diseases of greatest current concern. These include:

* Asthma, which has more than doubled in frequency since 1980 and become the leading cause of pediatric hospitalization and school absenteeism;

* Birth defects, which are now the leading cause of infant death. Certain birth defects, such as hypospadias, have doubled in frequency;

* Neurodevelopmental disorders - autism, dyslexia, mental retardation, and attention deficit/ hyperactivity disorder (ADHD). These conditions affect 5-10% of the 4 million babies born each year in the United States. Reported rates of autism are increasing especially sharply - more than 20% per year.

* Leukemia and brain cancer in children and testicular cancer in adolescents. Incidence rates of these malignancies have increased since the 1970s, despite declining rates of mortality.

* Testicular cancer has risen by 55%, and primary brain cancer by 40%. Cancer is now the second leading cause of death in American children, surpassed only by traumatic injuries; and

* Preterm birth, which has increased in incidence by 27% since 1981.

These rapidly rising rates of chronic disease threaten the health of our children and the future security of our nation. Indeed, concern is strong among the pediatric community that rapidly rising rates of chronic disease may create a situation unprecedented in the 200 years of our nation's history, in which our current generation of children may be the first American children ever not to enjoy a longer life span than the generation before them.

Evidence is increasing that many environmental chemicals contribute to the causation of disease in children. Lead, mercury, polychlorinated biphenyls (PCBs) and certain pesticides have been shown to cause brain damage and to contribute to learning disabilities and to disruption of children's behavior. Benzene, 1,3-butadiene, and pesticides have been associated with childhood malignancies. Ambient pollutants - airborne fine particulates, ozone, oxides of nitrogen, and diesel exhaust also have been shown to increase incidence of asthma and to trigger asthmatic attacks. Although many of the causes of developmental problems in children are still not known, a recent National Academy of Sciences study suggests that at least twenty-eight percent of developmental disabilities in children -- dyslexia, attention deficit disorder and mental retardation -- are due to environmental causes.

Diseases of environmental origin in American children are also extremely costly to our nation. Four of the leading diseases of environmental origin in American children – lead poisoning, childhood asthma, neurodevelopmental disabilities and childhood cancer – have been found to cost our nation $54.9 billion annually. Mercury pollution has been found to cost our nation $8.7 billion annually as a result of lost economic productivity, and an additional 1566 cases of mental retardation have been associated with mercury pollution. Each of these cases is associated with additional special education and health care costs that are disproportionately borne by the American taxpayer.

Federal regulation of environmental chemicals has proven successful in the reduction of childhood disease and disability. Reductions in lead exposure associated with the elimination from lead in gasoline in the United States resulted in IQs among preschool aged children in the 1990s that were 2.2-4.7 points higher than they would have been if those children had a distribution of blood lead levels found among children in the 1970s. Before the US Environmental Protection Agency (USEPA)'s phase out of diazinon and chlorpyrifos, these two pesticides were frequently detected in the cord blood of New York City children and associated with decrements in birth weight and length. After these phaseouts, the pesticides and the association with predictors of cognitive potential were no longer detected.

In the past, the United States has taken a more proactive approach to protecting children from hazardous chemical exposures. The use of chlorofluorocarbons in aerosols was banned in 1977, several years before several European countries interceded. Manufacture of polychlorinated biphenyls was banned in 1977 in the federal Toxic Substances Control Act. Diethylstilbestrol was outlawed as a growth promoter in beef as early as 1972, well before the European Union banned its use in 1977. The Food Quality Protection Act of 1996, which was passed by unanimous vote of both houses of Congress, requires that standards for agricultural pesticides be set at levels sufficiently strict to protect the health of infants and children, and directs the EPA to use an additional tenfold safety factor in assessing the risks to infants and children to

take into account the potential for pre- and postnatal toxicity, particularly when the toxicology and exposure databases are judged to be incomplete.

Despite compelling evidence that further efforts are needed to prevent further increases in disease and disability of environmental origin among American children, major gaps remain in the regulatory approach taken by the Environmental Protection Agency to protect children. These include:

*** Enforcement of the Clean Air Act would prevent mercury emissions from coal-burning power plants from poisoning the next generation of America's children.** Mercury emissions from coal-fired power plants and other industrial sources leads to fish contamination with methylmercury. Nearly one-sixth of women are childbearing age have been documented to carry enough mercury in their bloodstream to affect the learning and development of their children. Under the Clean Air Act, coal-fired power plants were required to limit emissions to five tons per year by 2008. The Administration gutted those regulations in the Clean Air Mercury Rule, permitting twenty-six tons through 2010, needlessly exposing newborns to brain damage from this preventable exposure. Mercury pollution costs America $8.7 billion annually in lost economic productivity, and has been associated with 1,566 cases of mental retardation annually. The costs of placing filters on older coal-fired power plants do not necessarily outweigh the long-term benefits to our children and our economy.

*** The Toxic Substances Control Act (TSCA) still fails to reflect children's unique vulnerability and ensure that chemicals are safe before they are allowed to be introduced into our environment.** The current regulatory approval system for chemicals grandfathered in 62,000 chemicals, essentially approving them with little or no safety data. EPA has only 60 days to review new chemicals for their safety, and as a result between one and three thousand new chemicals are introduced each year with little or no safety data. Of the 3,000 most highly used chemicals, fewer than half have any toxicity testing data and fewer than one-fifth have been tested for their impact on developing children. The European Union recently instituted a more modern regulatory system for chemicals that ensures that safer alternatives are instituted as they become available. In the absence of such a system in the US, as studies document the health effects of bisphenol A and other toxins, families are forced to choose products with incomplete information about their safety, and placed into panic when studies are released documenting their health effects. Legislation like the Kids Safe Chemicals Act would empower EPA to ensure pre-market testing of chemicals that are used in consumer products, and broader reform of TSCA is needed to ensure that gaps do not remain in testing of chemicals in all products. It can take fifteen or even more years for epidemiologic studies to determine whether children are harmed by these exposures after the fact, and this approach represents an ongoing unsafe and unnatural experiment on America's children.

*** Failures of enforcement of existing environmental law have resulted in lost golden opportunities to prevent childhood disease.** The EPA has been failed to control some toxins in drinking water, such as arsenic and perchlorate, thereby exposing children to dangerous levels of these pollutants. Clean air standards that regulate pollutants known to cause or worsen

childhood respiratory diseases have been weakened, and new research suggest that the existing standards require further strengthening. Despite the fact that 10 million children live within four miles of Superfund sites containing high levels of known toxic chemicals, the Administration has consistently under-funded the Superfund program. As a result, the average number of Superfund sites cleaned up per year has dropped from 87 in the late 90's to 40. The Food Quality Protection Act represented Congress's explicit attempt to set food safety standards that account for children's unique exposures and vulnerabilities to pesticides. For many of the most dangerous pesticides, the EPA has failed to incorporate an additional child safety factor in setting the amount of pesticides that may remain in foods. In other cases, it has allowed some pesticide manufacturers to drag their feet in producing the health risk assessments necessary to protect children.

The National Children's Study -- Safeguarding the Health of Our Children

Finally in this testimony, I wish to point out the critical need for funding the National Children's Study, which will unearth so much information about the safety of chemicals widely used in the environment, and provide the foundation for appropriate and scientifically grounded policy.

The National Children's Study is a prospective multi-year epidemiological study that will follow 100,000 American children, a nationally representative sample of all children born in the United States, from conception to age 21. The study will assess and evaluate the environmental exposures these children experience in the womb, in their homes, in their schools and in their communities. It will seek associations between environmental exposures and disease in children. The diseases of interest include all those listed above. The principal goal of the Study is to identify the preventable environmental causes of pediatric disease and to translate those findings into preventive action and improved health care. The National Children's Study was mandated by Congress through the Children's Health Act of 2000. The lead federal agency principally responsible for the Study is the National Institute of Child Health and Human Development. Other participating agencies include the National Institute of Environmental Health Sciences, the Environmental Protection Agency, and the Centers for Disease Control and Prevention. By working with pregnant women and couples, the Study will gather an unprecedented volume of high-quality data on how environmental factors acting either alone, or in combination with genetic factors, affect the health of infants and children. Examining a wide range of environmental factors – from air, water, and dust to what children eat and how often they see a doctor – the Study will help develop prevention strategies and cures for a wide range of childhood diseases. By collecting data nationwide the study can test theories and generate hypotheses that will inform biomedical research and the care of young patients for years to come. Simply put, this seminal effort will provide the foundation for children's healthcare in the 21st Century.

Six aspects of the architecture of the National Children's Study make it a uniquely powerful tool for protecting the health of America's children:

1. *The National Children's Study is prospective in its design.* The great strength of the prospective study design is that it permits unbiased assessment of children's exposures in real time as they actually occur, months or years before the onset of disease or dysfunction. Most previous studies have been forced to rely on inherently inaccurate retrospective reconstructions of past exposures in children who were already affected with disease. The prospective design obviates the need for recall. It is especially crucial for studies that require assessments of fetal and infant exposures, because these early exposures are typically very transitory and will be missed unless they are captured as they occur. The National Children's Study will also adhere to the highest ethical standards to ensure that participation is completely voluntary, that environmental and health concerns are reported as soon as they are detected, and that families are empowered to protect themselves against known harmful exposures.

2. *The National Children's Study will employ the very latest tools of molecular epidemiology.* Molecular epidemiology is a cutting-edge approach to population studies that incorporates highly specific biological markers of exposure, of individual susceptibility and of the precursor states of disease. Especially when it is embedded in a prospective study, molecular epidemiology is an extremely powerful instrument for assessing interactions between exposures and disease at the level of the individual child.

3. *The National Children's Study will incorporate state-of-the-art analyses of gene-environment interactions.* Recognition is now widespread that gene-environment interactions are powerful determinants of disease in children. These interactions between the human genome and the environment start early in life, affect the health of our children, and set the stage for adult disorders. The heroic work of decoding the human genome has shown that only about 10-20% of disease in children is purely the result of genetic inheritance. The rest is the consequence of interplay between environmental exposures and genetically determined variations in individual susceptibility. Moreover, genetic inheritance by itself cannot account for the sharp recent increases that we have seen in incidence of pediatric disease.

4. *The National Children's Study will examine a nationally representative sample of American children.* Because the 100,000 children to be enrolled in the Study will be statistically representative of all babies born in the United States during the five years of recruitment, findings from the Study can be directly extrapolated to the entire American population. We will not need to contend with enrollment that is skewed by geography, by socioeconomic status, by the occurrence of disease or by other factors that could blunt our ability to assess the links between environment and disease.

5. *Environmental analyses in the National Children's Study will be conducted at the Centers for Disease Control and Prevention.* The CDC laboratories in Atlanta are the premier

laboratories in this nation and the world for environmental analysis. Because the testing will be done at CDC it will be the best available, and the results will be unimpeachable.

6. *Samples collected in the National Children's Study will be stored securely and will be available for analysis in the future.* New tests and new hypotheses will undoubtedly arise in the years ahead. Previously unsuspected connections will be discovered between the environment, the human genome and disease in children. The stored specimens so painstakingly collected in the National Children's Study will be available for these future analyses.

Congress has already laid a firm foundation for the National Children's Study. Between 2000 and 2008, the Congress invested more than $200 million to design the study and begin building the nationwide network necessary for its implementation. Seven Vanguard Centers and a Coordinating Center were designated in 2005 at sites across the nation – in Pennsylvania, New York, North Carolina, Wisconsin, Minnesota, South Dakota, Utah and California – to test the necessary research guidelines –and another twenty-six centers were announced in September 2007. Eventually, the Study will expand the program to 41 states and 105 communities nationwide. The tough job of designing and organizing is nearly complete. We appreciate the foresight of the House and Senate Labor/Health and Human Services Appropriations Committees for their full funding of the Study, at $192 million in their committee markups. Full funding for the Study this year will permit researchers to begin achieving the results that will make fundamental improvements in the health of America's children. To abandon the Study at this point would mean forgoing all of that dedication, all of that incredible effort, and all of the logistical preparation.

The National Children's Study will yield benefits that far outweigh its cost. It will be an extraordinarily worthwhile investment for our nation, and it can be justified even in a time of fiscal stress such as we face today. Six of the diseases that are the focus of the Study (obesity, injury, asthma, diabetes, autism and schizophrenia) cost America $642 billion each year. If the Study were to produce even a 1% reduction in the cost of these diseases, it would save $6.4 billion annually, 50 times the average yearly costs of the Study itself. But in actuality, the benefits of the National Children's study will likely be far greater than a mere 1% reduction in the incidence of disease in children. The Framingham Heart Study, upon which the National Children's Study is modeled, is the prototype for longitudinal medical studies and the benefits that it has yielded have been enormous. The Framingham Study was launched in 1948, at a time when rates of heart disease and stroke in American men were skyrocketing, and the causes of those increases were poorly understood. The Framingham Study used path-breaking methods to identify risk factors for heart disease. It identified cigarette smoking, hypertension, diabetes, elevated cholesterol and elevated triglyceride levels as powerful risk factors for cardiovascular disease. These findings contributed powerfully to the 42% reduction in mortality rates from cardiovascular disease that we have achieved in this country over the past 5 decades.

The data from Framingham have saved millions of lives – and billions of dollars in health care costs. The National Children's Study, which will focus on multiple childhood disorders, could be even more valuable. We do not need to wait 21 years for benefits to materialize from the national Children's Study. Valuable information will become available in a few years' time, as soon as the first babies in the Study are born.

Consider, for example, data on premature births. The rate of U.S. premature births in 2003 was 12.3%, far higher than the 7% rate in most western European countries. Hospital costs associated with a premature birth average $79,000, over 50 times more than the average $1,500 cost for a term birth. Just a 5% reduction in rates of prematurity would cut hospital costs by $1.6 billion annually. Within just two years, that savings would match the full cost of the Study.

The Study enjoys a broad group of supporters, including The American Academy of Pediatrics; Easter Seals; the March of Dimes; the National Hispanic Medical Association; the National Association of County and City Health Officials; the National Rural Health Association; the Association of Women's Health, Obstetric and Neonatal Nurses; United Cerebral Palsy; the Spina Bifida Association of America; and the United States Conference of Catholic Bishops, just to name a few. This broad and diverse group recognizes the overwhelming benefits this Study will produce for America's children.

The National Children's Study is an investment in our children – and in America's future, and will give our nation the ability to understand the causes of chronic disease that cause so much suffering and death in our children. It will give us the information that we need on the environmental risk factors and the gene-environment interactions that are responsible for rising rates of morbidity and mortality. It will provide a blueprint for the prevention of disease and for the enhancement of the health in America's children today and in the future. It will be our legacy to the generations yet unborn.

In summary, policy improvements are urgently needed to improve the health of our children and economic security of our nation. Efforts to reduce mercury emissions from coal-burning power plants are needed to ensure that future generations of children can achieve their fullest health and economic potential. The Toxic Substances Control Act (TSCA) should more accurately reflect children's unique vulnerability and ensure that chemicals are safe before they are allowed to be introduced into our environment. Enforcement of existing environmental law will go far to prevent costly diseases of environmental origin among American children. In addition to these policy actions, we also need sustained funding for the National Children's Study if we are to develop effective methods of preventing diseases of environmental exposure among American children.

Thank you. I look forward to the opportunity to answer any questions you might have.

ehp ENVIRONMENTAL HEALTH PERSPECTIVES
ehponline.org

Environment and Obesity in the National Children's Study

Leonardo Trasande, Chris Cronk, Maureen Durkin, Marianne Weiss, Dale A. Schoeller, Elizabeth A. Gall, Jeanne B. Hewitt , Aaron L. Carrel, Philip J. Landrigan, and Matthew W. Gillman

doi:10.1289/ehp.11839 (available at http://dx.doi.org/)
Online 12 September 2008

NIEHS
National Institute of Environmental Health Sciences
National Institutes of Health
U.S. Department of Health and Human Services

Environment and Obesity in the National Children's Study

Leonardo Trasande,[1,2] Chris Cronk,[3] Maureen Durkin,[4] Marianne Weiss,[5] Dale A. Schoeller,[6] Elizabeth A. Gall,[4] Jeanne B. Hewitt ,[7] Aaron L. Carrel,[8] Philip J. Landrigan,[1,2] Matthew W. Gillman[9]

[1]Department of Community and Preventive Medicine, Mount Sinai School of Medicine, New York, NY

[2]Department of Pediatrics, Mount Sinai School of Medicine, New York, NY

[3]Medical College of Wisconsin and Children's Hospital of Wisconsin, Milwaukee, WI

[4]Department of Population Health Sciences, University of Wisconsin, Madison, WI

[5]College of Nursing, Marquette University, Milwaukee, WI

[6]Interdepartmental Program in Nutritional Sciences, University of Wisconsin, Madison, WI

[7]Marine and Freshwater Biomedical Sciences Center, University of Wisconsin-Milwaukee, WI

[8]Department of Pediatrics, University of Wisconsin, Madison, WI

[9]Obesity Prevention Program, Department of Ambulatory Care and Prevention, Harvard Medical School and Harvard Pilgrim Health Care, Boston, MA

Corresponding Author: Leonardo Trasande, MD, MPP, Department of Community and Preventive Medicine, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1043, New York, NY 10029; telephone: 212-241-8029; fax: 212-996-0407; email: leo.trasande@mssm.edu

Running Title: Studying Obesity in the National Children's Study

Keywords: bisphenol A, built environment, endocrine disruptors, diet, National Children's Study, obesity, phthalates, physical activity,

Abbreviations:

ALSPAC: Avon Longitudinal Study of Parents and Children

BMI: Body Mass Index

BPA: bisphenol A

DES: Diethylstibestrol

EDs: Endocrine Disruptors

NCS: National Children's Study

NHANES: National Health and Nutrition Examination Survey

NICHD: National Institute of Child Health and Human Development

Acknowledgements: The authors are investigators in the Queens, New York and Waukesha County, Wisconsin Vanguard Centers and the Coordinating Center of the National Children's Study. This project has been funded in whole or in part with Federal funds from the National Institute of Child Health and Human Development, National Institutes of Health, under Contracts Number NICHD HHSN275200503411C/N01-HD-5-3411. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

Section Headers

Abstract

Introduction

Background

Progress of the National Children's Study

Obesity-Related Hypotheses of the National Children's Study

Impact of neighborhood environment on risk of obesity and insulin resistance

Chemical environmental agents and the endocrine system

Conclusion

References

Tables

Figure Legends

Figures

Abstract

Objective: To describe the approach taken by the National Children's Study (NCS), a 21-year prospective study of 100,000 American children, to understanding the role of environmental factors in the development of obesity.

Data Sources and Extraction: Review of the literature with regard to the two core hypotheses in the NCS that relate to environmental origins of obesity followed by descriptions of the strategies that will be used to test each hypothesis.

Data Synthesis: While it is clear that obesity in an individual results from an imbalance between energy intake and expenditure, control of the obesity epidemic will require understanding of factors in the modern built environment and chemical exposures that may have the capacity to disrupt the link between energy intake and expenditure. The NCS is the largest prospective birth cohort study ever undertaken in the US explicitly designed to seek information on the environmental causes of pediatric disease.

Conclusions: Through its embrace of the life-course approach to epidemiology, the NCS will be able to study the origins of obesity from preconception through late adolescence, including factors ranging from genetic inheritance to individual behaviors to the social, built and natural environment and chemical exposures. It will have sufficient statistical power to examine interactions among these multiple influences, including gene-environment and gene-obesity interactions. A major secondary benefit will derive from the banking of specimens for future analysis.

Introduction

Obesity is the consequence of a chronic net positive energy balance. The prevalence of obesity in American children has trebled in the past thirty years.(Ogden et al. 2006; Strauss and Pollack 2001; Troiano et al. 1995) In 2003-2006, 31.9% of 2-19 year olds had a Body Mass Index (BMI) ≥85th percentile for age and sex. (Ogden et al 2008) This great increase in obesity portends future increases in incidence of heart disease, (Bibbins-Domingo et al. 2007), diabetes, (Lee et al. 2007) stroke and possibly cancer (Bjorge et al. 2008), and is therefore projected to produce the first decline in US life expectancy since the Great Depression.(Olshansky et al. 2005) The recent explosive increase in prevalence of obesity reflects a complex interplay among: (1) changes in individual behaviors; (2) changes in community structure, lifestyle and the "built environment;" and (3) possibly exposures to certain synthetic chemicals, e.g. endocrine disruptors, that may have the capacity to disrupt energy balance.

Control of the obesity epidemic will require understanding of each of these factors and of the interplay among them. This understanding will guide development of multi-pronged evidence-based strategies for obesity control. The goal of this paper is to describe the approaches that the National Children's Study will employ to develop understanding of the causes of obesity, especially with regard to environmental factors.

Background

Behavioral change is critical to the prevention and treatment of childhood obesity. Yet interventions against obesity that focus solely on modifying individual behavior to increase energy expenditure and/or reduce caloric intake in individual children have had limited success in sustaining weight loss or preventing obesity.(Summerbell et al. 2005) A successful approach to reducing obesity and its comorbidities must also embrace understanding of community-level factors including the social, built and natural environment. These environmental influences interact with a child's diet, physical activity, genetic makeup and metabolism.(Meaney and Seckl 2004; Moll et al. 1991; Ong et al. 2007) An example of a multi-pronged approach that took careful cognizance of environmental influences is the success of the State of Arkansas in reducing obesity prevalence among school-age children. A thoughtful redesign of the school environment, with changes to school dietary options, implementation of universal physical education programs, and reduction of access to sugary soft drinks resulted in a decline in the prevalence of overweight children from 20.8% in the 2004-2005 school year to 20.4% in 2005-2006. (Anonymous 2007)

Access to safe play spaces may also influence activity patterns and thus reduce risk of obesity.(Ewing et al. 2003; Frumkin et al 2004) Direct marketing to children (for example, through television ads during child focused programming) encourages consumption of high-fat and high-sugar content foods, and is a negative environmental influence.(Gortmaker et al. 1996; Lobstein and Dibb 2005)

Unique windows of vulnerability have been identified for many of the environmental exposures linked to obesity. (Ong et al. 2007) Fetal stressors such as maternal nutritional deprivation and

smoking can result in intrauterine growth retardation and thereby influence hypothalamic-pituitary axis programming to increase future risk of obesity and diabetes. (Meaney and Seckl 2004) Infants born to women with insulin-dependent diabetes are known to be at higher risk of obesity, and milder, diet-controlled gestational diabetes may also increase risk.(Bo et al. 2004; Dabelea et al. 2000) Maternal smoking during pregnancy is an independent risk factor for the development of childhood obesity. (Bergmann et al. 2003; Oken et al. 2008) Excess gestational weight gain has been associated with increased child adiposity at age three in at least one prospective cohort. (Oken et al. 2007) Exposure to endocrine disrupting chemicals during pregnancy may enhance the risk for obesity in childhood. (Newbold et al. 2007) Rapid weight gain during the first year of life (Reilly et al. 2005) and fewer hours of sleep during infancy (Taveras et al. 2008) further enhance the risk for the development of childhood obesity.

While previous cohort studies have contributed greatly to identifying many individual-level factors that contribute to the development of obesity in children and its persistence into adulthood both in the US and other countries, (Berkey et al. 2000; Demerath et al. 2004; Freedman et al. 2005; Gordon-Larsen et al. 2006; Guo et al. 2002; Lake et al. 1997; Lauer et al. 1997; Moll et al. 1991; Nader et al. 2006; Nelson et al. 2006; Parsons 2001; Siervogel et al. 2000; Strauss and Knight 1999; Thompson et al. 2007) findings from those previous longitudinal studies have several limitations:

- First, previous studies have not fully capitalized on the life-course approach to chronic disease epidemiology,(Ben-Shlomo and Kuh 2002), an approach that embraces the concept that adult disease can have its origins in early life (or even fetal) exposures.

Barker promulgated this concept to account for an association between low birth weight and adult ischemic heart disease in Britain and Wales,(Barker and Osmond 1986). The concept has increasingly been adopted in the epidemiologic approach to understanding chronic conditions,(Lynch and Smith 2005) including obesity (Gillman MW 2004; James et al. 2006; Novak et al. 2006) and neurodegenerative conditions.(Landrigan et al. 2005) The application of the life course approach to identifying temporal relationships among risk factors for childhood obesity and their interaction is depicted graphically in Figure 1. Multiple studies have documented unique windows of vulnerability to environmental hazards that may contribute to the causation of chronic conditions such as obesity,(National Research Council 1993; Oken et al. 2008) yet few studies to date have collected the scope of data depicted in this figure at multiple points in the lifespan.

- Although the Centers for Children's Environmental Health and Disease Prevention have collected data on environmental exposures to pregnant women and young children, these research centers have rarely focused on child weight status as an outcome. (Wolff MS et al. 2008a) This weakness is especially relevant in light of new knowledge from animal studies which suggesting that endocrine-disrupting chemicals may modulate response to dietary intake,(Bhathena and Velasquez 2002; Enan et al. 1996) disrupt the hypothalamic-pituitary axis,(Rubin et al. 2001) and possibly increase risk for childhood obesity.(Newbold et al. 2007)
- Though some studies have collected genetic data on participants and been able to identify polymorphisms that increase risk for obesity, they have not simultaneously collected the data on environmental exposures that are necessary to examine carefully the interactions of genetic and environmental factors with diet and physical activity.

- Recent studies also suggest that obesity develops as a chronic condition much earlier than the school age years.(Kim et al. 2006) When many earlier cohort studies were first initiated, obesity in the preschool years was relatively infrequent, and thus they are unlikely to provide the data on exposures in early life that are essential to identify prenatal and early childhood risk factors for obesity.
- Many previous cohorts were limited in their capacity to identify risk factors for obesity that may be unique among Hispanics, a population for which obesity prevalence is increasing especially rapidly.(Freedman et al. 2006; Strauss and Pollack 2001)
- Previous cohorts are limited in that they have not included sufficient children to draw contrasts between risk factors specific to rural and urban environments. (Nelson et al. 2006)
- Past studies have been unable to allow accurate assessment of the role of access to parks and other places that encourage physical activity among children living in urban areas.(Kipke et al. 2007)
- Many previous cohort studies were begun before the tripling of childhood obesity prevalence occurred,(Kroke et al. 2006; Troiano et al. 1995; Wisemandle et al. 2000) trend that is increasingly attributed to the collective effect of community-level factors for which policy changes may be the only effective means for preventing further increases in obesity prevalence.(Summerbell et al. 2005) To assess the impact of these more recent community-level factors, new cohorts in which these risk factors exist are needed.
- While studies from other countries, such as the Avon Longitudinal Study of Parents and Children (ALSPAC),(Moll et al. 1991; Ong et al. 2007) and the Danish National Birth Cohort (Olsen et al. 2001) will provide important insights into the etiology of childhood

obesity, the environmental factors that contribute to obesity in American children are likely to be different, and the pool of genetic polymorphisms that modify risk may be much different from European children.

Progress of the National Children's Study

In response to increases in the prevalence of obesity and a number of other chronic conditions, the U.S. Congress through the Children's Health Act of 2000 authorized the National Institute of Child Health and Human Development (NICHD) "to conduct a national longitudinal study of environmental influences (including physical, chemical, biological and psychosocial) on children's health and development."(US Congress 2000.) The design of the National Children's Study has been extensively described elsewhere.(Branum et al. 2003; Landrigan et al. 2006; Trasande et al. 2006; Trasande and Landrigan 2004) With assistance from the staff of the National Center for Health Statistics at the Centers for Disease Control and Prevention, NCS staff developed a multistage clustered sampling approach to enroll a sample of 100,000 live births representative of all American children.(Strauss W) Families who are enrolled in the study will participate in a minimum of 13 data collection encounters: at least one visit before conception; 2 times during pregnancy; at birth; at 6, 12, and 18 months of age in early childhood; at 3, 5, 7, 9, and 12 years of age in childhood; and at 16 and 20 years of age in adolescence (Figure 2). Figure 2 graphically depicts the timeline of visits across the complete study, while Table 1 describes the measurements that are planned for preconception through age 3 for the seven Vanguard (pilot) locations. Enrollment of women will occur in 105 primary sampling

units (PSUs; counties or in the case of more sparsely populated areas clusters of counties), and is slated to begin in September 2008.

The mission of the National Children's Study is to provide the federal government with a scientifically robust guide to disease prevention, and to assure scientific rigor, the Study has always been hypothesis-driven. The topical working groups convened by the National Children's Study Advisory Committee developed initial core hypotheses for the Study, in consultation with thousands of scientists and representatives from community groups and professional organizations. A current list of hypotheses with supporting scientific rationale that were accepted and refined by the Interagency Coordinating Committee (composed of senior scientists from NICHD, the National Institute of Environmental Health Sciences, the Centers for Disease Control and Prevention and the Environmental Protection Agency) is available at www.nationalchildrensstudy.gov. (National Institute of Child Health and Human Development 2008)

Childhood obesity is a lead focus of the National Children's Study, and addressed in 6 of the 30 core hypotheses. Table 2 presents the gaps of knowledge that remain with respect to these core hypotheses: obesity and insulin resistance from impaired maternal glucose metabolism; obesity and insulin resistance associated with intrauterine growth restriction; breastfeeding associated with lower rates of obesity and lower risk of insulin resistance and fiber; whole grains, high glycemic index and obesity, insulin resistance; impact of neighborhood environment on risk of obesity and insulin resistance; and chemical environmental agents and the endocrine system. Table 2 also presents how the National Children's Study will address these gaps through its design. In this manuscript, we highlight how the Study will provide important new knowledge with regard to two core hypotheses that link factors in the chemical and built environments with childhood obesity.

Obesity-Related Hypotheses of the National Children's Study

Impact of neighborhood environment on risk of obesity and insulin resistance

Built environment features such as mixed land use, increased proximity to recreational activities and green space, as well as safety (e.g., low crime rates and perceived traffic safety for pedestrian and bicyclists) have been associated in cross-sectional studies with increased physical activity (Cervero and Duncan 2003; Ellaway et al. 2005; Li et al. 2005) and lower risk of obesity among adults. (Ewing et al. 2006; Frank et al. 2004; Lopez 2004) Few studies have examined the impact of the built environment on younger children, and those studies have focused upon circumscribed geographical areas and/or socio-economically advantaged and ethnically

homogeneous communities.(Papas et al. 2007) Decreased access to healthy eating choices in low socioeconomic status neighborhoods has been documented in at least two studies. (Galvez et al. 2007; Morland et al. 2006) Factors such as climate and topography have been taken into account infrequently. (Timperio et al. 2006) The effect of after-school and summer adult-organized programs on obesity and insulin resistance is unknown. In the absence of such programs, parents living in urban areas may instruct their children to go directly home from school where indoor activities are largely limited to watching television and playing computer games in the security of the home.

A systematic review of previous studies of the built environment and childhood obesity identified inconsistencies in measurements of the built environment across studies and cross-sectional design as major deficits of previous studies, and noted that these studies rarely studied both diet and physical activity.(Papas et al. 2007) Because of its focus on community characterization,(Landrigan et al. 2006) the National Children's Study will allow more careful identification of those features of neighborhoods that affect physical activity and diet, such as proximity to play spaces, availability of healthy food stores, and neighborhood walkability.

The National Children's Study represents a major opportunity to explore the role of specific aspects of the neighborhood environment at different periods in a child's development. Access to safe play spaces near a child's home, for example, may be especially protective against obesity during the early school years, but less so during adolescence. The design of the NCS capitalizes on the life-course approach and allows for separate analyses of the impact of certain factors on the development of obesity or increase in adiposity within certain time periods. Simultaneous

collection of socioeconomic and genetic data as well as measures of diet and physical activity (Table 1) will permit careful distinction of the role of certain environmental risk factors during each window of vulnerability.

Chemical environmental agents and the endocrine system

The impact of endocrine disruptors (EDs) on humans was first identified by Herbst and Bern, who observed eight cases of clear cell adenocarcinoma of the vagina in young women who had been exposed in utero to diethylstilbestrol (DES), a synthetic estrogen prescribed to pregnant women in the 1950s, 1960s and 1970s to prevent miscarriage.(Bern 1992) Prenatal exposure to DES has subsequently been found to induce obesity in an animal model.(Newbold et al. 2007) Identification of endocrine disrupting chemicals has been limited by the lack of toxicity testing data available for many chemicals in widespread use.(U.S. EPA 1998)

Because so few chemicals have been tested for their toxicity, the possibility exists that other chemicals besides DES to influence somatic growth and obesity.(Bhathena and Velasquez 2002; Rubin et al. 2001) One potential endocrine-disrupting chemical, bisphenol A (BPA), is used to manufacture polycarbonate resin in the coatings of food and beverage containers.(Brotons 1995) Exposure to BPA, phthalates and other endocrine disruptors is widespread in American children,(Centers for Disease Control and Prevention 2005) and animal studies increasingly suggest the potential for toxicity at current levels of exposure.(Vom Saal and Hughes 2005) In vitro studies have found BPA to induce fibroblast differentiation into adipocytes.(Masuno et al. 2002) Animal studies have found that BPA affects glucose transport in fat cells. (Sakurai et al.

2004) BPA has also been found to disrupt glucagon secretion in intact Langerhans cells at nanomolar levels.(Alonso-Magdalena et al. 2005) These studies raise the possibility that BPA could be a risk factor for the development of obesity, a question under ongoing examination in at least one Center for Children's Environmental Health and Disease Prevention.(Wolff et al. 2008)

Phthalates are used in a variety of personal care products such as shampoos, and in the synthesis of polyvinyl chloride.(Sathyanarayana 2008) Phthalates have been consistently documented in animal studies to have antiandrogenic effects.(Bell 1982; Fisher 2004; Parks et al. 2000) Cohort studies have begun to assess for potential affects in humans, and suggest susceptibility at lower levels of exposure than those documented to have effects in animals. It is hypothesized that the most severe effects may be associated with exposures in prenatal and early postnatl life. Decreases in anogenital distance among infant males have been associated with elevated urinary phthalate levels during pregnancy,(Swan et al. 2005) and breast milk levels of monoester phthalates have been associated with higher serum hormone binding globulin levels and luteinizing hormone to free testosterone ratios.(Main et al. 2006) Diminished sperm motility has been identified among exposed men,(Duty et al. 2003; Hauser 2006; Hauser et al. 2006) and low-molecular weight phthalates have been associated with increased birth weight and longer duration of gestation in at least one birth cohort.(Wolff MS et al. 2008b) While few studies have analyzed the impact of phthalate exposure on increased adiposity in children, analysis of the 1999-2002 National Health and Nutrition Examination Survey (NHANES) has identified increases in urinary phthalate levels among men with increased waist circumference and homeostatic model assessment, a measure of insulin resistance.(Stahlhut et al. 2007)

Lack of accurate information on the level and timing of past exposures to endocrine disruptors has been the principal limitation of most previous studies of the potential human impacts of endocrine disruptors. This limitation will be directly addressed by the prospective design of the National Children's Study. In the NCS, exposures to chemicals will be measured during pregnancy, in breast milk, and in the perinatal period before the appearance of health effects. The large sample size will have facilitate investigation of possible links between low-prevalence endocrine disruptor exposures and health outcomes, and state-of-the-art laboratory assessment of chemical exposures will further sharpen its ability to discern effects of exposures to endocrine disruptors. The large sample size will also permit study of genetic polymorphisms and gene-environment interactions, which will unearth individual differences in susceptibility to endocrine disruptors. As new endocrine disruptors are identified, specimens can be withdrawn from the NCS repository to analyze their content for appropriate biomarkers to assess whether these endocrine disruptors may be risk factors in the development of obesity.(Landrigan et al. 2003)

Conclusion

The National Children's Study presents previously unrealized opportunities for the identification of risk factors for childhood obesity, and for their subsequent elimination through prevention. Just as the Framingham Heart Study provided health care providers with hitherto novel information on risk factors for cardiovascular disease that enabled them to offer evidence-based advice to limit smoking, reduce the intake of fatty foods, and control hypertension, the National Children's Study will suggest interventions that can be used to prevent obesity by communities, policy makers and child health providers. A major strength of the Study is that it will be

representative of American children. It is anticipated, for example, that over 20,000 children in the cohort will be Hispanic, permitting examination of unique risk factors among a subgroup which has been disproportionately affected by the epidemic.

The hypotheses presented in this manuscript cover only a small percentage of the findings that are likely to emerge from the National Children's Study. The core NCS hypotheses are dynamic, and as the Study is implemented, new questions will emerge and result in modifications to the study protocol. Others may be clearly answered through the NCS or other studies, or become outdated as the whole body of knowledge adjusts the direction of inquiry. For some areas of inquiry whether the science is in relatively nascent stafes, the major benefits to be gained from the Study derive from its hypothesis-generating nature. The NCS will provide a major opportunity to confirm putative genetic links identified in other studies through the study of genetic sequences of children and their families. (Landrigan et al. 2008) As new putative endocrine disruptors are identified, subsamples of biospecimens stored at the NCS Specimen Repository can be rapidly analyzed to test for associations in a large-scale cohort that represents the population of US children.

Of course, no observational study by itself can demonstrate causality. The National Children's Study will identify risk factors for which causality may be suggested on the basis of strength, consistency, temporality, biological gradient, and plausibility. Findings from the NCS will prompt further interventions such as randomized controlled trials, policy interventions and other initiatives that will confirm or refute the role of identified risk factors in the development of obesity and its associated comorbidities.

The life-course approach underlying the design of the National Children's Study may very well lead to delineating the duration and impact of environmental, behavioral and social exposures on risk for obesity. No study will have followed women from preconception and subsequently followed their children at such frequent intervals early in childhood and then through adolescence and young adulthood. The National Children's Study will collect an array of biospecimens, dietary and physical activity data and social and chemical environmental factors on all 100,000 children for all proposed data collection timepoints, whereas other cohorts have collected more limited data at each timepoint or collected complete data on a smaller sample.

A major challenge of the National Children's Study will be to overcome the difficulties in measuring physical activity, diet and anthropometry in children that have bedeviled past studies. Limitations of reliability and validity do exist with food-frequency questionnaires (Coates and Monteilh 1997; Teufel 1997) and other instruments commonly used to measure dietary intake, though promising alternatives have been developed for populations in which past instruments have not proven reliable.(Yaroch et al. 2000). The vagaries of collecting physical activity by questionnaire are well documented, (Kohl et al. 2000) but accelerometry and other measuring techniques are increasingly promising in their precision and application. (Ekelund et al. 2001; Janz et al. 2002) BMI is not a perfect measure of adiposity,(Pietrobelli et al. 1998) and dual-absorption x-ray absorptiometry has been strongly correlated with cardiovascular disease factors in children.(Lindsay et al. 2001) Bioimpedance analysis and skinfold thickness are increasingly used to measure of adiposity. (Gutin et al. 1996; Kettaneh et al. 2005)

These challenges will not be easily dismissed, and the opportunity is ripe for contributions from the obesity research community to ensure that the best questionnaires and measurement approaches are utilized in a efficient and cost-effective way. At this time, the protocol has only been finalized for the seven Vanguard (pilot) locations, and even for those locations, only through birth. The National Children's Study also offers major opportunities to study the validity and reliability of alterative measurement approaches through adjunct studies in collaboration with existing Study Centers. These may use the full or a subsample of the study cohort, with the caveat that proposed new data collection not impose undue additional burden on Study participants or additional financial burden on the Study.

The National Children's Study will also trigger ancillary and follow-up studies and provide the next generation of obesity researchers opportunities to apply for funding. (Lyman et al. 2005) The National Children's Study will make public use, deidentified data sets available in accordance with federal privacy regulations.

Previous cohort studies of cardiovascular risk have plowed the terrain to identify major risk factors, and allow the National Children's Study to close in on solutions to the epidemic of childhood obesity. However, they have also demonstrated that these relationships are complex, and temporally dependent, making a large longitudinal cohort study beginning in the prenatal period essential. The National Children's Study thus offers us great hope in combating the obesity epidemic among America's children.

References

Alonso-Magdalena P, Laribi O, Ropero AB, Fuentes E, Ripoll C, Soria B, et al. 2005. Low Doses of Bisphenol A and Diethylstilbestrol Impair Ca 2 Signals in Pancreatic a-Cells through a Nonclassical Membrane Estrogen Receptor within Intact Islets of Langerhans. Environmental Health Perspectives 113(8): 969.

Anonymous. 2007. Improving Individual and Community Health through Health Promotion Strategies: Local Case Study -- Joseph Thompson and the Body Mass Index Assessment Project in Arkansas. In: Moments in Leadership: Case Studies in Public Health Policy and Practice (Barbara Debuono; Ana Rita Gonzalez; and Sara Rosenbaum, ed). 2007: Pfizer Inc., 127-132.

Barker DJ, Osmond C. 1986. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet 1(8489): 1077-1081.

Bell FP. 1982. Effects of phthalate esters on lipid metabolism in various tissues, cells and organelles in mammals. Environmental Health Perspectives 45: 41.

Ben-Shlomo Y, Kuh D. 2002. A life course approach to chronic disease epidemiology: conceptual models, empirical challenges and interdisciplinary perspectives. IEA, 285-293.

Bergmann KE, Bergmann RL, von Kries R, Böhm O, Richter R, Dudenhausen JW, et al. 2003. Early determinants of childhood overweight and adiposity in a birth cohort study: role of breast-feeding. International Journal of Obesity 27: 162-172.

Berkey CS, Rockett HRH, Field AE, Gillman MW, Frazier AL, Camargo CA, et al. 2000. Activity, Dietary Intake, and Weight Changes in a Longitudinal Study of Preadolescent and Adolescent Boys and Girls. Am Acad Pediatrics.

Bern H. 1992. The fragile fetus. In: Chemically-Induced Alteration in Sexual and Functional Development: The Wildlife/Human Connection (Colborn T CC, ed). Princeton, NJ: Princeton Scientific Publishing, 9-15.

Bhathena SJ, Velasquez MT. 2002. Beneficial role of dietary phytoestrogens in obesity and diabetes. American Journal of Clinical Nutrition 76(6): 1191.

Bibbins-Domingo K, Coxson P, Pletcher MJ, Lightwood J, Goldman L. 2007. Adolescent Overweight and Future Adult Coronary Heart Disease. New England Journal of Medicine 357(23): 2371.

Bjorge T, Engeland A, Tverdal A, Smith GD. 2008. Body Mass Index in Adolescence in Relation to Cause-specific Mortality: A Follow-up of 230,000 Norwegian Adolescents. Am J Epidemiol: kwn096.

Bo S, Menato G, Gallo ML, Bardelli C, Lezo A, Signorile A, et al. 2004. Mild gestational hyperglycemia, the metabolic syndrome and adverse neonatal outcomes. Acta Obstetricia et Gynecologica Scandinavica 83(4): 335-340.

Branum AM, Collman GW, Correa A, Keim SA, Kessel W, Kimmel CA, et al. 2003. The National Children's Study of environmental effects on child health and development. Environmental Health Perspectives 111(4): 642.

Brotons J. 1995. Xenoestrogens released from lacquer coatings in food cans. Environmental Health Perspectives 103(6): 608-612.

Centers for Disease Control and Prevention. 2005. Third National Report on Human Exposure to Environmental Chemicals. Atlanta: Centers for Disease Control and Prevention.

Cervero R, Duncan M. 2003. Walking, Bicycling, and Urban Landscapes: Evidence From the San Francisco Bay Area. Am Public Health Assoc, 1478-1483.

Coates RJ, Monteilh CP. 1997. Assessments of food-frequency questionnaires in minority populations. Am J Clin Nutr 65(4 Suppl): 1108S-1115S.

Dabelea D, Hanson RL, Lindsay RS, Pettitt DJ, Imperatore G, Gabir MM, et al. 2000. Intrauterine exposure to diabetes conveys risks for type 2 diabetes and obesity: a study of discordant sibships. Diabetes 49(12): 2208-2211.

Demerath EW, Li J, Sun SS, Chumlea WC, Remsberg KE, Czerwinski SA, et al. 2004. Fifty-year trends in serial body mass index during adolescence in girls: the Fels Longitudinal Study. American Journal of Clinical Nutrition 80(2): 441.

Duty SM, Silva MJ, Barr DB, Brock JW, Ryan L, Chen Z, et al. 2003. Phthalate Exposure and Human Semen Parameters. Epidemiology 14(3): 269.

Ekelund ULF, SjÖStrÖM M, Yngve A, Poortvliet E, Nilsson A, Froberg K, et al. 2001. Physical activity assessed by activity monitor and doubly labeled water in children. Medicine & Science in Sports & Exercise 33(2): 275.

Ellaway A, Macintyre S, Bonnefoy X. 2005. Graffiti, greenery, and obesity in adults: secondary analysis of European cross sectional survey. BMJ 331(7517): 611-612.

Enan E, Lasley B, Stewart D, Overstreet J, Vandevoort CA. 1996. 2, 3, 7, 8-Tetrachlorodibenzo-p-dioxin (TCDD) modulates function of human luteinizing granulosa cells via cAMP signaling and early reduction of glucose transporting activity. Reproductive Toxicology 10(3): 191-198.

Ewing R, Brownson RC, Berrigan D. 2006. Relationship Between Urban Sprawl and Weight of United States Youth. American Journal of Preventive Medicine 31(6): 464-474.

Ewing R, Schmid T, Killingsworth R, Zlot A, Raudenbush S. 2003. Relationship Between Urban Sprawl and Physical Activity, Obesity, and Morbidity. American Journal of Health Promotion 18(1): 47-57.

Fisher JS. 2004. Environmental anti-androgens and male reproductive health: focus on phthalates and testicular dysgenesis syndrome. Reproduction 127(3): 305.

Frank LD, Andresen MA, Schmid TL. 2004. Obesity relationships with community design, physical activity, and time spent in cars. American Journal of Preventive Medicine 27(2): 87-96.

Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. 2005. The Relation of Childhood BMI to Adult Adiposity: The Bogalusa Heart Study. Pediatrics 115(1): 22-27.

Freedman DS, Khan LK, Serdula MK, Ogden CL, Dietz WH. 2006. Racial and ethnic differences in secular trends for childhood BMI, weight, and height. Obesity (Silver Spring) 14(2): 301-308.

Frumkin H Frank L Jackson RJJ. Urban Sprawl and Public Health: Designing, Planning, and Building for Healthy Communities. . 2004 ed. Washington DC:: Island Press, 2004.

Galvez MP, Morland K, Raines C, Kobil J, Siskind J, Godbold J, et al. 2007. Race and food store availability in an inner-city neighbourhood. Public Health Nutrition: 1-8.

Gillman MW. 2004. A life course approach to overweight and obesity. In: A Life Course Approach to Chronic Diseases Epidemiology (Kuh D and Ben-Shlomo Y, ed). Oxford: : Oxford University Press.

Glass TA, McAtee MJ. 2006. Behavioral science at the crossroads in public health: Extending horizons, envisioning the future. Social Science and Medicine, 62(7), 1650-1671.

Gordon-Larsen P, Nelson MC, Page P, Popkin BM. 2006. Inequality in the Built Environment Underlies Key Health Disparities in Physical Activity and Obesity. Pediatrics 117(2): 417-424.

Gortmaker SL, Must A, Sobol AM, Peterson K, Colditz GA, Dietz WH. 1996. Television viewing as a cause of increasing obesity among children in the United States, 1986-1990. Archives of Pediatrics and Adolescent Medicine 150(4): 356-362.

Guo SS, Wu W, Chumlea WC, Roche AF. 2002. Predicting overweight and obesity in adulthood from body mass index values in childhood and adolescence. Am J Clin Nutr 76(3): 653-658.

Gutin B, Litaker M, Islam S, Manos T, Smith C, Treiber F. 1996. Body-composition measurement in 9-11-y-old children by dual-energy X-ray absorptiometry, skinfold-thickness measurements, and bioimpedance analysis. Am J Clin Nutr 63(3): 287-292.

Hauser R. 2006. The environment and male fertility: recent research on emerging chemicals and semen quality. Semin Reprod Med 24(3): 156-167.

Hauser R, Meeker JD, Duty S, Silva MJ, Calafat AM. 2006. Altered Semen Quality in Relation to Urinary Concentrations of Phthalate Monoester and Oxidative Metabolites. Epidemiology 17(6): 682.

James SA, Fowler-Brown A, Raghunathan TE, Van Hoewyk J. 2006. Life-Course Socioeconomic Position and Obesity in African American Women: The Pitt County Study. Am Public Health Assoc, 554-560.

Janz KF, Levy SM, Burns TL, Torner JC, Willing MC, Warren JJ. 2002. Fatness, Physical Activity, and Television Viewing in Children during the Adiposity Rebound Period: The Iowa Bone Development Study. Preventive Medicine 35(6): 563-571.

Kettaneh A, Heude B, Lommez A, Borys JM, Ducimeticre P, Charles MA. 2005. Reliability of bioimpedance analysis compared with other adiposity measurements in children: The FLVS II Study. Diabetes and Metabolism 31(6): 534-541.

Kim J, Peterson KE, Scanlon KS, Fitzmaurice GM, Must A, Oken E, et al. 2006. Trends in overweight from 1980 through 2001 among preschool-aged children enrolled in a health maintenance organization. Obesity (Silver Spring) 14(7): 1107-1112.

Kipke MD, Iverson E, Moore D, Booker C, Ruelas V, Peters AL, et al. 2007. Food and Park Environments: Neighborhood-level Risks for Childhood Obesity in East Los Angeles. Journal of Adolescent Health 40(4): 325-333.

Kohl HW, Fulton JE, Caspersen CJ. 2000. Assessment of Physical Activity among Children and Adolescents: A Review and Synthesis. Preventive Medicine 31(2): 54-76.

Kroke A, Hahn S, Buyken AE, Liese AD. 2006. A comparative evaluation of two different approaches to estimating age at adiposity rebound. International Journal of Obesity 30: 261-266.

Lake JK, Power C, Cole TJ. 1997. Child to adult body mass index in the 1958 British birth cohort: associations with parental obesity. Archives of Disease in Childhood 77(5): 376.

Landrigan P, Garg A, Droller DBJ. 2003. Assessing the effects of endocrine disruptors in the National Children's Study. Environmental Health Perspectives 111(13): 1678.

Landrigan PJ, Sonawane B, Butler RN, Trasande L, Callan R, Droller D. 2005. Early environmental origins of neurodegenerative disease in later life. Environ Health Perspect 113(9): 1230-1233.

Landrigan PJ, Trasande L, Swanson JM. 2008. Genetics, altruism, and the National Children's Study. Am J Med Genet A 146(3): 294-296.

Landrigan PJ, Trasande L, Thorpe LE, Gwynn C, Lioy PJ, D'Alton ME, et al. 2006. The National Children's Study: a 21-year prospective study of 100,000 American children. Pediatrics 118(5): 2173-2186.

Lauer RM, Clarke WR, Burns TL. 1997. Obesity in childhood: the Muscatine Study. Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi 38(6): 432-437.

Lee JM, Okumura MJ, Freed GL, Menon RK, Davis MM. 2007. Trends in hospitalizations for diabetes among children and young adults: United States, 1993 2004. Diabetes Care 30(12): 3035-3039.

Li F, Fisher KJ, Brownson RC, Bosworth M. 2005. Multilevel modelling of built environment characteristics related to neighbourhood walking activity in older adults. British Medical Journal 59(7): 558.

Lindsay RS, Hanson RL, Roumain J, Ravussin E, Knowler WC, Tataranni PA. 2001. Body Mass Index as a Measure of Adiposity in Children and Adolescents: Relationship to Adiposity by Dual Energy X-Ray Absorptiometry and to Cardiovascular Risk Factors. Endocrine Soc, 4061-4067.

Lobstein T, Dibb S. 2005. Evidence of a possible link between obesogenic food advertising and child overweight. Obesity Reviews 6(3): 203-208.

Lopez R. 2004. Urban Sprawl and Risk for Being Overweight or Obese. Am Public Health Assoc, 1574-1579.

Lyman WD, Barone C, Castle V, Davies HD, Stanton B, Paneth N. 2005. Making the National Children's Study a Real Partnership with Academic Pediatrics. The Journal of Pediatrics 147(5): 563-564.

Lynch J, Smith GD. 2005. A LIFE COURSE APPROACH TO CHRONIC DISEASE EPIDEMIOLOGY. Annual Review of Public Health 26(1): 1-35.

Main KM, Mortensen GK, Kaleva MM, Boisen KA, Damgaard IN, Chellakooty M, et al. 2006. Human Breast Milk Contamination with Phthalates and Alterations of Endogenous Reproductive Hormones in Infants Three Months of Age. Environmental Health Perspectives 114(2): 270.

Masuno H, Kidani T, Sekiya K, Sakayama K, Shiosaka T, Yamamoto H, et al. 2002. Bisphenol A in combination with insulin can accelerate the conversion of 3T3-L1 fibroblasts to adipocytes. The Journal of Lipid Research 43(5): 676-684.

Meaney MJ, Seckl JR. 2004. Glucocorticoid programming. Ann NY Acad Sci 1032: 63-84.

Moll PP, Burns TL, Lauer RM. 1991. The genetic and environmental sources of body mass index variability: the Muscatine Ponderosity Family Study. Am J Hum Genet 49(^ s1243-50).

Morland K, Diez Roux AV, Wing S. 2006. Supermarkets, Other Food Stores, and Obesity The Atherosclerosis Risk in Communities Study. American Journal of Preventive Medicine 30(4): 333-339.

Nader PR, O'Brien M, Houts R, Bradley R, Belsky J, Crosnoe R, et al. 2006. Identifying Risk for Obesity in Early Childhood. Pediatrics 118(3): e594.

National Institute of Child Health and Human Development. 2008. National Children's Study. Accessed at www.nationalchildrensstudy.gov 1 July 2008.

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

Nelson MC, Gordon-Larsen P, Song Y, Popkin BM. 2006. Built and Social Environments Associations with Adolescent Overweight and Activity. American Journal of Preventive Medicine 31(2): 109-117.

Newbold RR, Padilla-Banks E, Snyder RJ, Phillips TM, Jefferson WN. 2007. Developmental exposure to endocrine disruptors and the obesity epidemic. Reproductive Toxicology 23(3): 290-296.

Novak M, Ahlgren C, Hammarström A. 2006. A life-course approach in explaining social inequity in obesity among young adult men and women. International Journal of Obesity 30: 191-200.

Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. 2006. Prevalence of overweight and obesity in the United States, 1999-2004. JAMA 295(13): 1549-1555.

Ogden CL, Carroll MD, Flegal KM. 2008. High body mass index for age among US children and adolescents, 2003-2006. JAMA 299(20): 2401-2405.

Oken E, Levitan EB, Gillman MW. 2008. Maternal smoking during pregnancy and child overweight: systematic review and meta-analysis. International Journal of Obesity 32: 201-210.

Oken E, Taveras EM, Kleinman KP, Rich-Edwards JW, Gillman MW. 2007. Gestational weight gain and child adiposity at age 3 years. American Journal of Obstetrics and Gynecology 196(4): 322-322.

Olsen J, Melbye M, Olsen SF, Sorensen TIA, Aaby P, Nybo Andersen AM, et al. 2001. The Danish National Birth Cohort-its background, structure and aim. Scandinavian Journal of Public Health 29(4): 300.

Olshansky SJ, Passaro D, Hershow R, Layden J, Carnes BA, Brody J, et al. 2005. A Possible Decline in Life Expectancy in the United States in the 21st Century ". New England Journal of Medicine: 1103-1110.

Ong KK, Northstone K, Wells JC, Rubin C, Ness AR, Golding J, et al. 2007. Earlier Mother's Age at Menarche Predicts Rapid Infancy Growth and Childhood Obesity. PLoS Med 4(4): e132.

Papas MA, Alberg AJ, Ewing R, Helzlsouer KJ, Gary TL, Klassen AC. 2007. The Built Environment and Obesity. Epidemiologic Reviews 29(1): 129.

Parks LG, Ostby JS, Lambright CR, Abbott BD, Klinefelter GR, Barlow NJ, et al. 2000. The Plasticizer Diethylhexyl Phthalate Induces Malformations by Decreasing Fetal Testosterone Synthesis during Sexual Differentiation in the Male Rat. Soc Toxicology, 339-349.

Parsons TJ. 2001. Fetal and early life growth and body mass index from birth to early adulthood in 1958 British cohort: longitudinal study. BMJ 323(7325): 1331-1335.

Pietrobelli A, Faith MS, Allison DB, Gallagher D, Chiumello G, Heymsfield SB. 1998. Body mass index as a measure of adiposity among children and adolescents: a validation study. J Pediatr 132(2): 204-210.

Reilly JJ, Armstrong J, Dorosty AR, Emmett PM, Ness A, Rogers I, et al. 2005. Early life risk factors for obesity in childhood: cohort study. BMJ 330(7504): 1357.

Rubin BS, Murray MK, Damassa DA, King JC, Soto AM. 2001. Perinatal exposure to low doses of bisphenol A affects body weight, patterns of estrous cyclicity, and plasma LH levels. Environmental Health Perspectives 109(7): 675.

Sakurai K, Kawazuma M, Adachi T, Harigaya T, Saito Y, Hashimoto N, et al. 2004. Bisphenol A affects glucose transport in mouse 3T3-F442A adipocytes. British Journal of Pharmacology 141: 209-214.

Sathyanarayana S. 2008. Phthalates and children's health. Curr Probl Pediatr Adolesc Health Care 38(2): 34-49.

Siervogel RM, Wisemandle W, Maynard LM, Guo SS, Chumlea WC, Towne B. 2000. Lifetime Overweight Status in Relation to Serial Changes in Body Composition and Risk Factors for Cardiovascular Disease: The Fels Longitudinal Study. NAASO, 422-430.

Stahlhut RW, van Wijngaarden E, Dye TD, Cook S, Swan SH. 2007. Concentrations of Urinary Phthalate Metabolites Are Associated with Increased Waist Circumference and Insulin Resistance in Adult US Males. Environmental Health Perspectives 115(6): 876.

Strauss RS, Knight J. 1999. Influence of the Home Environment on the Development of Obesity in Children. Am Acad Pediatrics.

Strauss RS, Pollack HA. 2001. Epidemic increase in childhood overweight, 1986-1998. JAMA 286(22): 2845-2848.

Strauss W LJ, Menkedick J, Ryan L, Pivetz T, McMillan N, Pierce B, Rust S,. White Paper on Evaluation of Sampling Design Options for the National Children's Study. Available at. Available: http://www.nationalchildrensstudy.gov/research/analytic_reports/upload/Executive-Summary-for-the-White-Paper-on-Evaluation-of-Sampling-Design-Options-for-the-National-Children-s-Study.pdf [accessed May 1 2007].

Summerbell CD, Waters E, Edmunds LD, Kelly S, Brown T, Campbell KJ. 2005. Interventions for preventing obesity in children (Review). The Cochrane Database Syst Rev 3.

Swan SH, Main KM, Liu F, Stewart SL, Kruse RL, Calafat AM, et al. 2005. Decrease in Anogenital Distance among Male Infants with Prenatal Phthalate Exposure. Environmental Health Perspectives 113(8): 1056.

Taveras EM, Rifas-Shiman SL, Oken E, Gunderson EP, Gillman MW. 2008. Short Sleep Duration in Infancy and Risk of Childhood Overweight. Archives of Pediatrics and Adolescent Medicine 162(4): 305.

Teufel NI. 1997. Development of culturally competent food-frequency questionnaires. Am J Clin Nutr 65(4 Suppl): 1173S-1178S.

Thompson DR, Obarzanek E, Franko DL, Barton BA, Morrison J, Biro FM, et al. 2007. Childhood Overweight and Cardiovascular Disease Risk Factors: The National Heart, Lung, and Blood Institute Growth and Health Study. The Journal of Pediatrics 150(1): 18-25.

Timperio A, Ball K, Salmon J, Roberts R, Giles-Corti B, Simmons D, et al. 2006. Personal, Family, Social, and Environmental Correlates of Active Commuting to School. American Journal of Preventive Medicine 30(1): 45-51.

Trasande L, Cronk CE, Leuthner SR, Hewitt JB, Durkin MS, McElroy JA, et al. 2006. The National Children's Study and the children of Wisconsin. WMJ 105(2): 50-54.

Trasande L, Landrigan PJ. 2004. The National Children's Study: a critical national investment. Environ Health Perspect 112(14): A789-790.

Troiano RP, Flegal KM, Kuczmarski RJ, Campbell SM, Johnson CL. 1995. Overweight prevalence and trends for children and adolescents. The National Health and Nutrition Examination Surveys, 1963 to 1991. Archives of Pediatrics and Adolescent Medicine 149(10): 1085-1091.

U.S. EPA. 1998. Chemical hazard data availability study: what do we really know about the safety of high production volume chemicals? . Washington, DC.

US Congress. 2000. Children's Health Act of 2000. In: Public Law 106-310.

Vom Saal FS, Hughes C. 2005. An Extensive New Literature concerning Low-Dose Effects of Bisphenol A Shows the Need for a New Risk Assessment. Environmental Health Perspectives 113(8): 926-934.

Wisemandle W, Maynard LM, Guo SS, Siervogel RM. 2000. Childhood Weight, Stature, and Body Mass Index Among Never Overweight, Early-Onset Overweight, and Late-Onset Overweight Groups. Am Acad Pediatrics.

Wolff MS, Britton JA, Boguski L, Hochman S, Maloney N, Serra N, et al. 2008a. Environmental exposures and puberty in inner-city girls. Environmental Research 107(3): 393-400.

Wolff MS, Engel SM, Berkowitz GS, Ye X, Silva MJ, Zhu C, et al. 2008b. Prenatal Phenol and Phthalate Exposures and Birth Outcomes : . Environ Health Perspect doi:10.1289/ehp.11007. [Online 20 March 2008]

Yaroch A, Resnicow KEN, Davis M, Davis A, Smith M, Khan LK. 2000. Development of a Modified Picture-Sort Food Frequency Questionnaire Administered to Low-income, Overweight, African-American Adolescent Girls. Journal of the American Dietetic Association 100(9): 1050-1056.

Table 1. National Children's Study Proposed Measurements Through Age 3

	Preconception					Pregnancy							
	Initial	Initial follow-up	First month	Second month	Fourth month	1st trimester (<14 wks)	1st trimester follow-up (<14 wks)	1st trimester ultrasound*	16-17 wks	2nd trimester (22-24 wks)	3rd trimester (28-32 wks)	3rd trimester follow-up	36 wks
Location/Type	Home	Mail	Phone	Phone	Phone	Home	Mail	Clinic	Phone	Clinic	Clinic	Mail back	Phone
Body composition													
Gestational Age													
Length/Height													
Weight	M					M, F				M	M		
Head circumference													
Arm circumference	M					M, F				M	M		
Waist circumference	M					M, F				M	M		
Hip circumference	M					M, F				M	M		
Leg Length													
Skin folds	M					M, F				M	M		
Ultrasound						M*		M*		M	M		
Blood pressure	M					M, F				M	M		
Bioimpedance analysis													
Diet													
Community-Based Food Collection						M, N							
Food Frequency Questionnaire							M					M	
Self-Completion Diary	M	M	M	M	M	M	M	M	M	M	M	M	M
Activity measures													
Activity questionnaire													
TV viewing													
Time outdoors													
Activity diary													
Biological Specimens													
Vaginal Swabs	M					M					M		
Blood	M					M, F					M		
Urine (self-collected)		M					M, F				M		
Saliva (self-collected)							M					M	
Hair	M					M, F					M		
Cord Blood													
Umbilical Cord and Placenta													
Meconium													
Breast Milk													
Socioeconomic/Environmental Data													
Mother/Father Education/SES/Housing	M	M	M	M	M	M, F	M	M	M	M	M	M	M
Medical Provider Visit Log	M	M	M	M	M	M	M	M	M	M	M	M	M
Medical Record/Chart Abstraction													

* Data to be abstracted from clinical ultrasound if available; otherwise ultrasound to be performed on mother in clinic setting as part of NCS

M = Mother; F = Father; C = Child; N = Neighborhood

Table 1. National Children's Study Proposed Measurements Through Age 3 (Continued)

	Birth	Neonate	Childhood									
	Delivery	Pre-Discharge Visit	3 m	6 m	6 m follow-up	9 m	12 m	12 m follow-up	18 m	24 m	30 m	36 m
Location/Type	Hospital	Hospital	Phone	Home	Mailback	Phone	Home	Mail back	Phone	Phone	Phone	Clinic
Body composition												
Gestational Age		C										C
Length/Height		C		C			C					C
Weight		C		C			C					C
Head circumference		C		C			C					C
Arm circumference		C		C			C					C
Waist circumference		C		C			C					C
Hip circumference		C		C			C					C
Leg Length												C
Skin folds		C		C			C					C
Ultrasound												
Blood pressure							C					C
Bioimpedance analysis												C
Diet												
Community-Based Food Collection									C, N			C, N
Food Frequency Questionnaire				M				M				C
Self-Completion Diary												C
Activity measures												
Activity questionnaire												C
TV viewing												C
Time outdoors												C
Activity diary												C
Biological Specimens												
Vaginal Swabs												
Blood	M, C						C					C
Urine (self-collected)	M			C			C					C
Saliva (self-collected)					M, F			C				C
Hair				C			C					C
Cord Blood	C											
Umbilical Cord and Placenta	M											
Meconium		C										
Breast Milk			M		M				M			C
Socioeconomic/Environmental Data												
Mother/Father Education/SES/Housing			M	M, F	M	F	M	M	F	M	M	M, F
Medical Provider Visit Log			M	M	M	M	M	M	M	M	M	C
Medical Record/Chart Abstraction		M, C										C

* Data to be abstracted from clinical ultrasound if available; otherwise ultrasound to be performed on mother in clinic setting as part of NCS

M = Mother; F = Father; C = Child; N = Neighborhood

Table 2. Core Hypotheses of the National Children's Study Relating to Obesity

Hypothesis domain	*Obesity and insulin resistance from impaired maternal glucose metabolism*	*Obesity and insulin resistance associated with intrauterine growth restriction*	*Breastfeeding associated with lower rates of obesity and lower risk of insulin resistance*
Relevance	If gestational diabetes (or excessive gestational weight gain) is conclusively demonstrated to increase risk of childhood obesity/insulin resistance, then prevention of overweight among women of childbearing age may be especially useful in the prevention of childhood obesity.	If IUGR is identified as a preventable cause of obesity, then prevention of IUGR could form a major component of obesity prevention in the United States.	In the absence of proven alternatives, breastfeeding could serve as a lead component of obesity prevention in the United States. Because breastfeeding initiation, exclusivity, and continuation vary greatly by race and ethnic group, breastfeeding could also be a major causative factor for existing and widening disparities in prevalence of childhood obesity and its comorbidities, and targeted interventions among populations where breastfeeding is less frequent would be urgently indicated.
Gaps in state of knowledge	Most studies have had small sizes, and have not completely differentiated severe, insulin dependent and mild diet-controlled gestational diabetes. Follow-up has typically been limited to the offspring preschool years, thus precluded documentation of longer terms effect on child body composition and metabolic status.	Most studies of IUGR and adult insulin resistance are based on historical data, and limited to information about size at birth and adult outcomes, with no information available about different periods during prenatal development. Results have been contradictory because of differing definitions of key dependent and independent variables, use of different measurements, and limitation on the period of follow up. Many apparent confounders for this phenomenon (e.g. levels of such hormones as cortisol and insulin-like growth factors) are likely embedded in the same causal framework with IUGR that underlies the fetal origins of later life phenomena. Few studies have serially measured fetal size and growth using ultrasound.	If breastfeeding is protective for childhood obesity, it is unclear whether this is due to constituents of breast milk, metabolic programming, regulation/control of intake by mother and/or infant, or aspects of family lifestyle/home environment that are different for breast and formula-fed infants. Measurement of family-level confounders appears to be extremely important, and has been lacking in previous studies of breastfeeding and obesity. Studies do suggest that breastfeeding may only proffer protection from future risk of obesity in certain subpopulations.
Unique Capacity of the National Children's Study	A cohort of 100,000 is adequate for assessment of main effects for exposures at least as prevalent as maternal gestational diabetes, and outcomes at least as prevalent as adolescent type 2 diabetes. It is certainly not too large, as power becomes marginal for main effects within sex and race/ethnicity-specific strata, when exposures are as uncommon as gestational diabetes, even for relatively common outcomes such as obesity, for odds ratios below 1.5.	The National Children's Study design will provide prospective measurements of maternal nutritional status and potential fetal stressors at different periods during prenatal development; fetal growth throughout gestation measured with serial ultrasounds; serial fetal body composition including regional adiposity; size and body composition at birth and then throughout childhood, adolescence and early adulthood; dietary intake of mother during pregnancy and the offspring postnatally; and key hormonal levels in the mother during pregnancy as well as the child. Information about family factors (e.g. sibling birth size, body composition of other family members, maternal history of birth size will better control confounding.	Prospective report of breastfeeding, and use of a metric that incorporates duration of breastfeeding with the percentage of intake derived from breastmilk will settle existing debates about the protective benefit offered by breastfeeding. Collection of genetic data will provide an opportunity to identify whether genetic or other factors influence the relationship between breastfeeding and obesity/insulin resistance among whites and non-whites. The NCS will follow a large multiethnic population and have the power to assess comprehensively the influence cultural factors may have on breastfeeding, and supplementation of breastfeeding with formula.

Table 2. Core Hypotheses of the National Children's Study Relating to Obesity (continued)

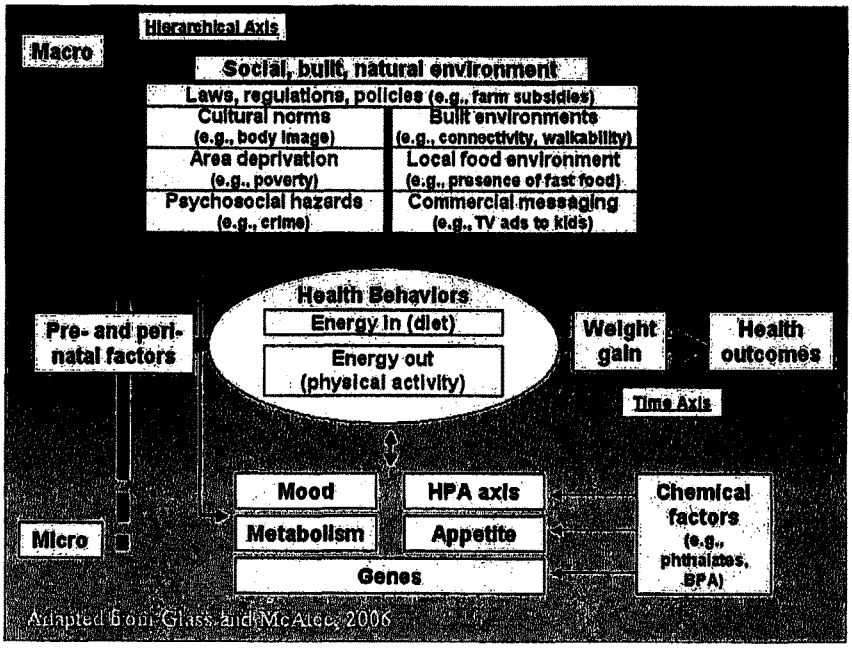
Hypothesis domain	*Impact of neighborhood environment on risk of obesity and insulin resistance*	*Chemical environmental agents and the endocrine system*	*Fiber, whole grains, high glycemic index and obesity, insulin resistance*
Relevance	As features of the neighborhood environment are identified as protective for childhood obesity, design of communities can be planned to optimize the health of children.	Based upon laboratory studies and limited human data, exposure to bisphenol A and phthalates may increase risk for childhood obesity through disruption of the endocrine system. It is possible that many more chemicals possess the capacity to disrupt the endocrine system.	The role of glycemic content in modulating response to an energy load is of tremendous interest in the policy community. Soft drink consumption by children is on the rise, and easy access in some schools is cited as a possible exacerbating factor to the obesity epidemic. The most recent US Department of Agriculture Dietary Guidelines for Americans now encourages three ounces/day whole grain intake, but this amount of intake may not be sufficient to reduce risk.
Gaps in state of knowledge	Few studies have assessed the impact on the built environment on children, and inconsistencies in measurements of the built environment across studies and cross-sectional design are major deficits of those studies. Past studies rarely studied both diet and physical activity, and have focused on homogeneous communities within a certain geographic area.	Lack of accurate information on the level and timing of past exposures to endocrine disruptors has been the principal limitation of previous studies.	Studies of the role of glycemic index to date have been limited to small samples, and because the duration of follow-up has typically been brief, the applicability of these findings to broad populations of children has been limited. The contribution of sugary snacks and drinks to current prevalence is unknown, and studies to date have not had the statistical power to isolate for confounding with caloric intake, genetics, physical activity among other factors, or to examine the possibility of specific windows of vulnerability with regard to high glycemic content. Few studies have assessed the impact of whole grains on risk of obesity and insulin resistance in younger children.
Unique Capacity of the National Children's Study	The National Children's Study will allow more careful identification of those features of neighborhoods that affect physical activity and diet, such as proximity to play spaces, availability of healthy food stores, and neighborhood walkability, and capitalizes on the life-course approach to determine impact of certain factors on the development of obesity or increase in adiposity within certain time periods.	The large sample size will facilitate investigation of possible links between low prevalence endocrine disruptor exposures and health outcomes. State-of-the-art laboratory assessment of chemical exposures will further sharpen its ability to discern endocrine effects of endocrine disruptor exposures. The large sample size will also permit study of genetic polymorphisms and gene-environment interactions, which will unearth individual differences in susceptibility to endocrine disruptors. As new endocrine disruptors are identified, the existence of a specimen repository will allow to assess whether they may be risk factors in the development of obesity or increase in adiposity	The National Children's Study offers strong statistical power to examine the role of factors in the dietary environment of children, and is the first large cohort study with the potential to use the knowledge produced by the Human Genome Project to examine the role of genetic vulnerability in modifying the risk posed by factors such as glycemic index.

Figure Legends

Figure 1. The lifespan is depicted horizontally, while factors are depicted at various levels hierarchically, from the individual level factors in the lower part of the figure to the community level factors in the upper part.

Figure 2. Stars denote ultrasound assessment, while I on the timeline represent home/clinical assessments (denoted by H/C). Circles denote telephone follow-ups, and asterisks denote components of the timeline for telephone and mail questionnaires that are still under development.

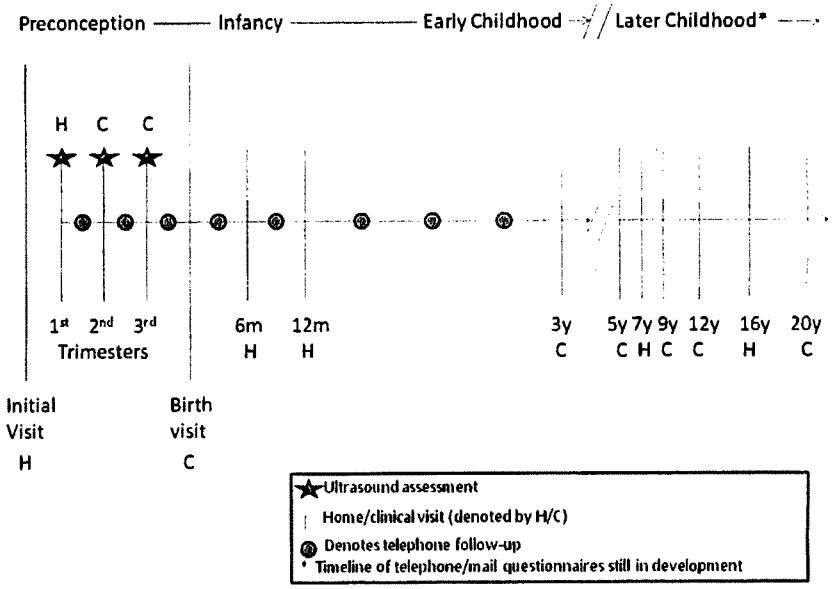
Figure 1. A Life-Course Approach to Childhood Obesity



The lifespan is depicted horizontally, while factors are depicted at various levels hierarchically, from the individual level factors in the lower part of the figure to the community level factors in the upper part.

Adapted from Glass TA, McAtee MJ. Behavioral science at the crossroads in public health: Extending horizons, envisioning the future. Social Science and Medicine, 62(7), 1650-1671, 2006 with permission from Elsevier. http://www.sciencedirect.com/science/journal/02779536

Figure 2. Schedule of Visits, National Children's Study



PEDIATRICS®
OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

The National Children's Study: A 21-Year Prospective Study of 100 000 American Children

Philip J. Landrigan, Leonardo Trasande, Lorna E. Thorpe, Charon Gwynn, Paul J. Lioy, Mary E. D'Alton, Heather S. Lipkind, James Swanson, Pathik D. Wadhwa, Edward B. Clark, Virginia A. Rauh, Frederica P. Perera and Ezra Susser

Pediatrics 2006;118;2173-2186
DOI: 10.1542/peds.2006-0360

American Academy of Pediatrics
DEDICATED TO THE HEALTH OF ALL CHILDREN™

SPECIAL ARTICLE

The National Children's Study: A 21-Year Prospective Study of 100 000 American Children

Philip J. Landrigan, MD, MSc[a,b], Leonardo Trasande, MD, MPP[a,b], Lorna E. Thorpe, PhD[c], Charon Gwynn, PhD[c], Paul J. Lioy, PhD[d], Mary E. D'Alton, MD[e], Heather S. Lipkind, MD[e], James Swanson, PhD[f], Pathik D. Wadhwa, MD, PhD[g], Edward B. Clark, MD[h], Virginia A. Rauh, ScD[i], Frederica P. Perera, DrPH[j], Ezra Susser, MD, DrPH[k]

[a]Center for Children's Health and the Environment, Department of Community and Preventive Medicine, New York, New York; [b]Department of Pediatrics, Mount Sinai School of Medicine, New York, New York; [c]Division of Epidemiology, New York City Department of Health and Mental Hygiene, New York, New York; [d]Environmental and Occupational Health and Safety Institute, University of Medicine and Dentistry of New Jersey, Piscataway, New Jersey; [e]Division of Maternal Fetal Medicine, Columbia University Medical Center, New York, New York; Departments of [f]Pediatrics and [g]Psychiatry and Human Behavior, University of California, Irvine, California; [h]Department of Pediatrics, University of Utah, Salt Lake City, Utah; [i]Heilbrunn Department of Population and Family Health, Departments of [j]Environmental Health Sciences, and [k]Epidemiology, Mailman School of Public Health, New York, New York

Financial Disclosure: The authors have indicated they have no financial relationships relevant to this article to disclose.

ABSTRACT

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

www.pediatrics.org/cgi/doi/10.1542/peds.2006-0360

doi:10.1542/peds.2006-0360

With the exception of Dr Berkowitz, the authors are investigators in the Queens, NY, Orange County, CA, and Salt Lake City, UT, Vanguard Centers of the National Children's Study. This project was funded in whole or in part with Federal funds from the National Institute of Child Health and Human Development, National Institutes of Health, under NICHD grant HHSN275200503411C/N01-HD-5-3411. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the US Government.

Key Words
National Children's Study, epidemiology, asthma, attention-deficit/hyperactivity disorder, autism, schizophrenia, obesity

Abbreviations
CVD—cardiovascular disease
NICHD—National Institute of Child Health and Human Development
CDC—Centers for Disease Control and Prevention
NCS—National Children's Study
HPV—high production volume
NCPP—National Collaborative Perinatal Project
CHDS—Child Health Development Study
NIH—National Institutes of Health

Accepted for publication Jun 27, 2006

Address correspondence to Philip J. Landrigan, MD, Department of Community and Preventive Medicine, Mount Sinai School of Medicine, One Gustave L. Levy Place, PO Box 1057, New York, NY 10029. E-mail: phil.landrigan@mssm.edu

PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

ENVIRONMENTAL EXPOSURES IN early life can influence development, impair health, and increase risk of disease and dysfunction.[1-3] Chemical, physical, and psychosocial factors have all been shown to exert great influence. Among potentially harmful chemical and physical exposures are cigarette smoking during pregnancy,[4,5] thalidomide,[6,7] diethylstilbestrol,[8] lead,[9-15] ethyl alcohol,[16] ionizing radiation,[17,18] polychlorinated biphenyls and other organochlorine compounds,[19] methylmercury,[20-26] outdoor air pollutants,[27] benzene,[28] and certain pesticides.[29]

Evidence is mounting that prenatal factors and early childhood experiences may play a role in disease development in later life.[30] Altered fetal growth has been related to increased risk of cardiovascular disease (CVD), hypertension, and diabetes in adulthood,[31-34] and accelerated childhood growth is related to subsequent risk of breast cancer in women,[35] as well as to impaired glucose tolerance in adulthood.[36] There almost certainly exist additional etiologic associations between environmental exposures and disease in children that have not yet been discovered.

Progress in elucidating the role of the environment in causation of disease has for the most part been slow and incremental. Nearly all previous studies have examined relatively small populations of pregnant women and their offspring[37]; have considered only one chemical at a time[38]; have had little statistical power to examine interactions among chemical, social, and behavioral factors in the environment[39]; have had limited ability to examine gene–environment interactions[40]; and have suffered from brief duration of follow-up.[41] Almost nothing is known regarding the interrelationships between chemicals and other environmental hazards and between the chemical and physical environment and social environments.[42]

Large, prospective, multiyear epidemiologic studies can overcome the limitations of previous investigations. A great strength of the prospective study design is that it permits unbiased assessment of exposures as they occur, before the onset of disease or dysfunction. This is crucial for studies of fetal and infant exposures, because attempts to reconstruct past exposures months or years after their occurrence are inherently limited and subject to the vagaries of human memory, as well as of recall bias. These limitations constrain the ability of retrospective or case-control studies to obtain unbiased and precise data on the nature and timing of exposures in early life. Prospective studies have the additional advantage that they permit exploration of exposures within a multilevel framework, which considers exposures at the individual, family, neighborhood, and societal levels.[43,44] They are especially powerful when they incorporate biomarkers of exposure and of genetically mediated susceptibility.

To take advantage of new developments in study design, exposure assessment, and information technology, and to overcome the shortcomings of previous studies, the President's Task Force on Environmental Health and Safety Risks to Children recommended in 1998 that a large prospective, multiyear epidemiologic study of American children be undertaken.[45] In response to that recommendation, the US Congress, through the Children's Health Act of 2000, authorized the National Institute of Child Health and Human Development (NICHD) "to conduct a national longitudinal study of environmental influences (including physical, chemical, biological and psychosocial) on children's health and development."[46] The National Institute of Environmental Health Sciences, the Centers for Disease Control and Prevention (CDC), and the US Environmental Protection Agency have joined the NICHD in planning this study, now named the National Children's Study (NCS).

RATIONALE FOR THE NCS

Patterns of illness among children in the United States and in other industrially developed nations have changed substantially in the past 100 years.[47] Today the major illnesses confronting children are a group of chronic conditions termed the "new pediatric morbidity."[48] These include premature birth[49]; asthma[50]; childhood and young adult cancers, such as acute lymphocytic leukemias,[51] brain cancer,[52] and testicular cancer[53]; neurodevelopmental disorders such as learning disabilities, dyslexia, mental retardation, attention deficit/hyperactivity disorder, and autism[54-59]; obesity and type 2 diabetes[60-62]; and some birth defects, such as gastroschisis.[63-70]

The environment in which children live has also changed.[71,72] Today there are >80 000 synthetic chemicals, most of them developed since the 1950s.[73] These include plastics, pesticides, fuels, building materials, antibiotics, chemotherapeutic agents, flame retardants, and synthetic hormones. Children are at especially high risk of exposure to the 2800 synthetic chemicals that are produced in quantities of ≥1 million tons per year.[2] These high production volume (HPV) chemicals are the synthetic materials dispersed most widely in the environment in air, food, water, and consumer products in homes, schools, and communities.[74] In recent national surveys, quantifiable levels of a number of HPV chemicals have been detected in the bodies of most Americans, as well as in the milk of nursing mothers.[75]

A National Academy of Sciences committee on pesticides in the diets of infants and children identified 4 fundamental differences between children and adults that contribute to children's heightened susceptibility to toxic chemicals[76]:

- Children have disproportionately heavy exposures to environmental toxicants as a consequence of their

greater intake kilogram-for-kilogram of food, water, and air coupled with their unique behaviors, in particular their oral exploratory behavior.

- Children's metabolic pathways, especially in the first months after birth, are immature. In many instances, children are less able than adults to excrete and/or detoxify toxic compounds.
- Children are undergoing rapid growth and development. These developmental processes create windows of great vulnerability in which the course of development can be permanently disrupted by environmental toxins.
- Because children have more future years of life than most adults, they have more time to develop chronic diseases that may be initiated by early exposures.

Although much remains to be learned about associations between the environment and disease in children, evidence is accumulating that environmental factors make important contributions to disease causation. Numerous pollutants in the indoor environment have been shown to be triggers for childhood asthma, such as second-hand tobacco smoke, mold and mites, cockroach droppings, animal dander, and certain pesticides.[77,78] Reduction in children's exposures to these indoor pollutants was shown to reduce frequency of asthma.[79] Ambient air pollutants (fine particulates, ozone, oxides of nitrogen, and diesel exhaust) also were shown to increase incidence of asthma and to trigger asthmatic attacks.[26,80,81] Reduction in levels of ambient air pollution was associated with reduction in the number of hospitalizations resulting from asthma and other respiratory diseases.[82-84] Childhood cancer has long been linked to ionizing radiation. More recently, benzene, 1,3-butadiene, and pesticides were etiologically associated with childhood malignancies.[85,86] A recent National Academy of Sciences study suggests that ≥28% of developmental disabilities in children may be caused by environmental factors acting alone or in combination with genetic factors.[87]

A higher proportion of children in America today live in cities and suburbs than ever before, and the built environment has been shown to be capable of influencing children's health and risk of disease.[88-92] The adverse effects of the modern built environment are especially magnified in low-income, predominantly minority urban communities where crowded streets, lack of outdoor play-spaces, limited access to fresh and healthy food, and substandard housing all contribute to substantial and well-documented disparities in health care.[93-97] Recognition is increasing that characteristics of the built environment may influence diet and activity patterns and, as a result, increase the risk of obesity.[98,99]

PREVIOUS LONGITUDINAL STUDIES

Adult Longitudinal Studies

Previous major prospective epidemiologic studies of adults have yielded invaluable gains in knowledge of disease causation and have provided critical tools for prevention and treatment. A classic example is the Framingham Heart Study (Framingham, MA), established in 1948. At that time immediately after World War II, heart disease and stroke were epidemic in the United States. The causes were poorly understood. The goal of the Framingham Heart Study was to identify preventable risk factors for CVD. Data from Framingham identified cigarette smoking[100] and elevated cholesterol and hypertension as preventable causes of CVD[101,102]; later analyses elucidated the role of elevated triglycerides, sedentary lifestyle, and diabetes. This information provided the blueprint for highly successful programs of prevention that have reduced incidence of CVD in adult males in the United States by >50% over the past 4 decades (Fig 1).[103]

The Nurses' Health Study, established in 1976, and the Nurses' Health Study II, established in 1989, are 2 major prospective investigations in the United States into the risk factors for chronic disease in women. The initial goal was to study the health consequences of oral contraceptive use. Invitations were mailed to 170 000

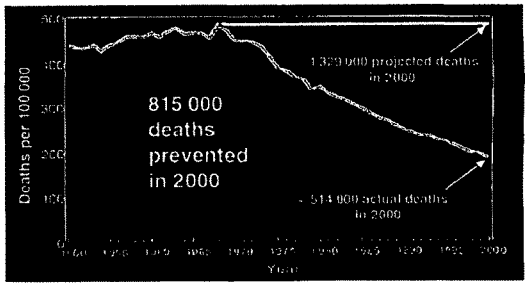


FIGURE 1
Incidence of coronary heart disease: United States, 1950–2000 (age-adjusted death rates, actual and expected). A striking reduction in incidence of heart disease and stroke was achieved over the past half century in US men and women. This decline resulted from discoveries made in prospective epidemiologic studies such as the Framingham Heart Study showing that elevated cholesterol, cigarette smoking, hypertension, obesity, diabetes, and sedentary lifestyle are powerful risk factors for CVD. (Reproduced with permission from a presentation by NIH director Elias Zerhouni, MD, at National Prevention Summit, Washington, DC, October 24–25, 2005. The full presentation is available at www.healthierus.gov/steps/summit/day1//zerhouni-1030am.ppt.)

registered nurses in 11 states, and >120 000 enrolled. The Nurses Health Study II enrolled a younger cohort (25–42 years of age) of 116 686 women.[104] A third major study of women's health, the Women's Health Initiative sponsored by the National Heart, Lung, and Blood Institute has enrolled >161 000 women aged 50 to 79 years. Its goal is to study the risks and benefits of hormone replacement therapy in postmenopausal women, as well as the benefits of dietary supplementation to prevent osteoporosis, fractures, and breast and colorectal cancer.[105] These large population studies have also pioneered and tested a series of logistic and methodologic advances that provide the basis for future prospective studies.

PEDIATRIC LONGITUDINAL STUDIES

A number of prospective, longitudinal studies of children were previously conducted, and experience gained in these studies has helped to guide the NCS. A cohort study of 16 000 children in Bogalusa, Louisiana[106] showed that obese children frequently remain obese through adulthood[107] and identified a number of significant long-term consequences of childhood obesity for cardiovascular health.[108] Since 1970, 20 000 children have participated in the Muscatine (Iowa) study of childhood predictors of adult CVD,[109] which has identified genetic and environmental predictors of childhood obesity.[110]

Birth cohorts have also identified many of the important pharmaceutical, obstetric, socioeconomic, and genetic factors that are currently known to affect neurologic and behavioral development in utero and in childhood. The first such longitudinal study was the British National Survey of Health and Development, initiated in 1946, and based on a national sample of births in England during a 1-week period. The cohort has since been followed up 23 times, providing the most detailed data available anywhere on the evolution of health and disease over the life course. Later, British birth cohorts of 1958 and 1970 were constructed along similar lines.

In the 1950s, 2 very important studies were launched in the United States, the National Collaborative Perinatal Project (NCPP)[111] and the California Child Health and Development Study (CHDS).[112,113] These studies differed from the British studies in that they began follow-up before birth at the first prenatal visit, collected and archived biological specimens such as serum samples, and were of a much larger size. The NCPP was established by the National Institute of Neurologic Disorders and Blindness in the 1950s as a prospective epidemiologic study to investigate the relationships between pregnancy, labor, and delivery and subsequent neurodevelopmental outcomes in infants and children.[114] Fourteen medical centers within 12 universities collected data on >58 000 pregnancies and followed the health of surviving children through age 7 or 8. Similarly, the CHDS examined ~20 000 pregnancies, birth outcomes, and health in surviving children.[112] Additional pregnancy/birth cohorts were also established in Australia,[115] New Zealand,[116] Israel, and the Scandinavian countries. The NCPP still provides important knowledge about the causation of childhood disease decades later. Recent findings include the identification of in utero tobacco exposure as an important predictor of adolescent smoking behavior[117] and confirmation of the positive relationship between birth weight and childhood cognitive potential.[118]

More recently initiated pregnancy/birth cohorts provide an additional foundation of experience and knowledge for the NCS. The Avon Longitudinal Study of Pregnancy and Childhood in England[119] has collected genetic as well as detailed phenotypic information on ~15 000 children and their parents; the children are now in their teens. The Danish National Birth Cohort[120] and the Norwegian study of mothers, fathers, and infants[121] have collected data from the prenatal period to date on ~100 000 live births in each study. Examples of findings from the Avon study include identification of paternal depression as an important factor in a child's emotional and psychological development[122] and confirmation of the frequency and potential psychological basis for recurrent abdominal pain in children.[123] The Danish study has provided important insights into the health of the offspring of pregnancies begun through in vitro fertilization.[124]

Although follow-up of birth cohorts into adult life is always a challenge, especially among relatively mobile US populations, investigators at several sites have proven that long-term follow-up and cohort retention are feasible. For example, a subset of the Providence CPP cohort was recontacted at ages 18 to 27 years to examine the relationship between prenatal and delivery complications and psychiatric disorders in adult life.[113] The CHDS cohorts are currently being followed for nested case-control studies of prenatal determinants of schizophrenia, male reproduction, and neurodevelopment.[126–130]

These cohorts constitute national treasures, especially because of the availability through them of stored sera and carefully collected exposure and health outcome data. However, a shortcoming is that none of these previous longitudinal studies of children have obtained data on environmental exposures, nor did any of them incorporate newer technologies for the collection of biological and environmental samples or of genetic material. Pilot studies to explore the feasibility of obtaining environmental data in the context of prospective birth cohort studies have been conducted during the past 5 years within the initial network of federally funded Centers for Children's Environmental Health and Disease Prevention Research.

Smaller-scale prospective cohort studies were successfully launched by 3 of these federally funded centers

at Columbia University, Mount Sinai Medical School, and the University of California at Berkeley. These studies showed the feasibility of conducting epidemiologic studies in the United States that examine the health consequences of early environmental exposures.[29] They used a combination of exposure biomarkers and monitoring strategies to characterize in utero and postnatal exposures to environmental contaminants, and they incorporated molecular genetic assessments of individual susceptibility factors to examine the interplay between environmental exposures and the human genome. Although involving sample sizes of <1000 children, these studies yielded valuable data and experience that support and foreshadow the NCS initiative, and they provided practical lessons that can inform its conduct.

HYPOTHESES TO BE ADDRESSED BY THE NCS

The NCS is hypothesis-driven and will address a series of specified questions pertaining to the influence of the environment (chemical, biological, physical and psychosocial) on children's health, growth, development, and risk of disease. It will also seek to discover etiologically important gene-environment interactions, as well as the factors that modulate individual susceptibility to environmental exposures. Working groups convened by the NICHD and the NCS Advisory Committee developed the core hypotheses for the NCS, in consultation with hundreds of scientists, community groups, and professional organizations from across the United States and worldwide.

A current list of hypotheses with supporting scientific rationale that were accepted and refined by the Interagency Coordinating Committee (composed of senior scientists from the NICHD, National Institute of Environmental Health Sciences, CDC and US Environmental Protection Agency) is available at www.nationalchildrensstudy.gov.[131] As the NCS is implemented, new questions will emerge and be added, and some may become outdated. A key criterion for the selection of these hypotheses is that they cannot be reasonably studied with fewer children or a different study design.

A representative sample of the questions that NCS will address is provided below:

- What is the role of bioaerosols in the causation of asthma? Multiple studies have shown strong associations between exposures to bioaerosols and the exacerbation of asthma in children with preexisting disease. The NCS is perhaps the only opportunity to differentiate the complex interrelationships of allergens, endotoxins, mold, and indoor and outdoor air pollution in inducing asthma.[26]
- What is the role of the built environment in increasing risk for obesity and insulin resistance? Being overweight as a child is a risk factor for being overweight in adulthood[132] and is associated with increased risk of type 2 diabetes, hypertension, and coronary artery disease.[133] Overweight children have also been found to have a higher risk of developing diabetes at age 21 years.[134] Research in urban planning and public health finds that pedestrian-oriented environments are associated with increased walking,[135,136] and a small but growing literature is beginning to confirm that pedestrian-oriented environments are associated also with lower rates of obesity than car-dependent environments.[98,137] A study with the large sample size and prospective design of the NCS is needed if we are to carefully unravel the complex relationships among genetics, diet, physical activity, and risk for obesity and its comorbidities and develop effective prevention approaches to the obesity epidemic.
- What is the etiologic role of impaired glucose metabolism in birth defects? Women with type 1 or type 2 diabetes before pregnancy have an increased risk of congenital anomalies in offspring, and animal models confirm the teratogenicity of impaired glucose metabolism.[138–141] Limited data also suggest an association in women with gestational diabetes or those with lesser degrees of impaired glucose metabolism during pregnancy.[142,143] Because obesity and gestational diabetes are important risk factors for insulin resistance and have reached epidemic levels in the United States, evaluation of the impact of impaired glucose tolerance on certain birth defects becomes an important priority for efforts to reduce the burden of such conditions in the population.
- What is the role of psychosocial stressors in causing adverse neurobehavioral outcomes? Do these stressors act through altered gene expression? Efforts to find a cure for depression have been confounded by lack of a clear understanding of its complex etiology. One obstacle to understanding depression may be genetic variability in the influence of the environment on gene expression.[144] Research on nonhuman primates has also shown that genotype alone does not sufficiently predict aggression or antisocial behaviors.[145]
- Does increasing exposure to endocrine-disrupting chemicals such as phthalates explain the rise in hypospadias? Animal studies have suggested a pathway through which these synthetic chemicals may disrupt reproductive organogenesis,[146,147] but the relatively low rates of this particular birth defect make it difficult to detect an association without a cohort study of this size.
- How do factors in the chemical, psychosocial, and physical environment interact in the causation of disease and disability? Studies have documented variations in children's health outcomes across geographic areas, but they have not achieved the statistical power or interdisciplinary complexity necessary to estimate

impacts of community and neighborhood factors on children's health.[148]

- What are the interactions between environmental factors and individual, genetically determined susceptibility in the genesis of disease? The Human Genome Project is beginning to elucidate the complexity of the molecular genetic factors that influence individual susceptibility to environmental exposures. The NCS will apply the powerful findings of the Human Genome Project to definition of a wide array of gene–environment interactions that could not be delineated except through a large, prospective NCS that began at conception.[149] Previously, gene–environment interactions have been ascertained only in piecemeal fashion, mostly one at a time because of small sample sizes, but well-designed studies have confirmed the existence of such interactions and have reinforced the need for a large, prospective study like the NCS. One recent study found, for example, a fourfold increased risk of orofacial clefts among infants with the NAT1 and NAT2 genetic polymorphisms born to mothers who smoked.[150] Data from the Children's Environmental Health Center at Mount Sinai found an association between maternal exposure to the pesticide chlorpyrifos during pregnancy, low expression levels of the pesticide-metabolizing enzyme PON1, and increased risk of small head circumference at birth.[151]

DEVELOPMENT AND IMPLEMENTATION OF THE NCS

Since the legislation authorizing the NCS was enacted in 2000, working groups have been convened by the NICHD to develop hypotheses and propose research protocols to test them. For the past 4 years, these working groups convened and have been developing and delineating research protocols and planning logistics, such as specifying methods for collecting data to characterize environmental exposures that may cause or increase risk of asthma, CVDs, neurobehavioral disorders, diabetes, obesity, and osteoporosis, just to name a few.

The NCS will use a national probability sampling approach. The primary sampling units were based on counties in the United States, and 105 of 3400 US counties were selected to represent geography and population density. This sampling design uses a multistage clustered approach, with oversampling of certain subpopulations to ensure adequate numbers of participants in target groups and to allow valid inferences on exposure-outcome relations in these subpopulations. Women of childbearing age will comprise the population for enrollment, and household surveys of neighborhoods randomly selected within the 105 counties will be used to recruit a representative sample. Because the focus of the NCS is the assessment of the impact of exposures that occur early in pregnancy, pregnant women beyond the first trimester of pregnancy will not be enrolled. After recruitment, 3 subgroups of women and their partners will be followed according to the likelihood of pregnancy: pregnant women already in the first trimester, women planning pregnancy, and women of childbearing age but not planning a pregnancy. At enrollment, participants will be asked to provide written consent for participation in the study and will complete a short interview.

Families who are enrolled in the study will participate in a minimum of 15 in-person visits with research teams across stages of development (ie, before conception; 3 times during pregnancy; at birth; at 1, 6, 12, and 18 months of age in early childhood; at 3, 5, 7, 9, and 12 years of age in childhood; and at 16 and 20 years of age in adolescence). Seven of these visits will be in the participants' homes and 8 will be in clinical settings, including the infants' place of delivery. Data will be remotely collected via telephone, computer, or mail-in questionnaires every 3 months through the age of 5 and annually thereafter. Biological samples from the mother and child to measure body burdens of environmental chemicals and environmental samples such as air, water, dirt, and dust from the child's home environment will be collected over the course of the study. Individual parent, child, and family psychosocial domains to be assessed include family composition (including absentee parents and children not living at home and disruptions), family conflict (including domestic violence and abuse), mother and/or father's physical and mental health history, mother and/or father's current emotional and cognitive adjustment (eg, depressive symptoms, anxiety, cognitive functioning, literacy, coping style, parenting skills, and knowledge of child development), parent–child interaction, and quality of the caretaking environment.

The NCS has already awarded contracts to 7 academic institutions to establish Vanguard Centers for the study, sites where the NCS would start to recruit participants and test protocols to ensure that the study goes smoothly before it is brought to scale (recruiting and assessing 100 000 children from birth to age 21). The 7 Vanguard locations represent a broad array of rural and urban areas with a broad diversity of social, ethnic, and other demographic factors.[152] A map of study locations is provided in Fig 2, and a list of study sites is provided in the Appendix. Recruitment is scheduled to begin in 2007.

DISCUSSION

The NCS is the largest prospective study of American children ever to be undertaken. It is the first national cohort study of children in the United States since the Collaborative Perinatal Project of ~40 years ago. It is the first large birth cohort study in any nation to specifically examine the influence of environmental factors on birth outcomes, child health, and human development, and the first designed to systematically examine the influ-

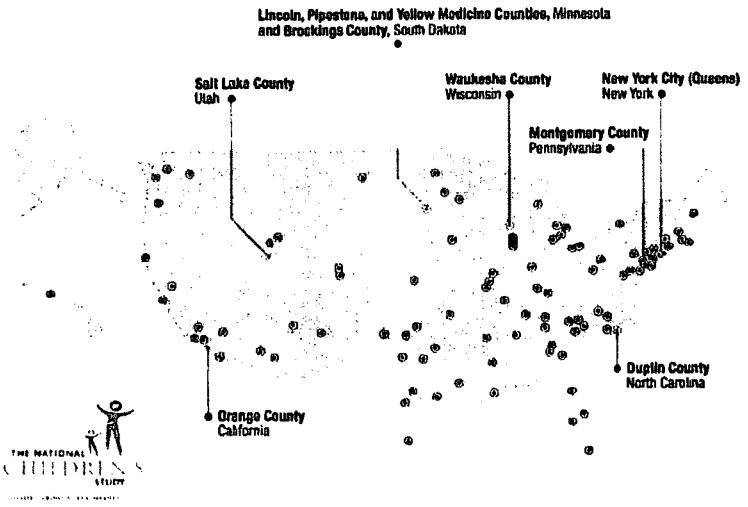


FIGURE 2
Map of study locations for the NCS (Vanguard sites named). (Adapted with permission from data at www.nationalchildrensstudy.gov.)

ence of gene-environment interactions on children's health.

We anticipate that the NCS will provide pediatricians and other child health providers with powerful information on preventable, environmental risk factors for disease in children. This information is available from no other source and will help practitioners to improve birth outcomes such as premature birth and to prevent such chronic diseases in children as asthma, certain birth defects, dyslexia, attention-deficit/hyperactivity disorder, autism and schizophrenia, and obesity. Just as data from the Bogalusa and Muscatine Heart Studies described the predictive power of childhood BMI with adult adiposity,[108,153] and as findings from the Framingham Heart Study provided critically important information on preventable risk factors for CVD in adults (information that has saved millions of lives), findings from the NCS promise to provide the evidentiary basis for a comprehensive blueprint for the prevention of chronic disease in America's children.

The NCS will also provide information on a wide range of other issues relevant to child health in the United States. The study will, for example, abstract medical records and unite these abstracts with data from other sources, such as hospital and school records, to create public access databases that will be available to properly qualified researchers for secondary analyses. Thus, health services researchers will be able to use the data from the NCS to conduct analyses of the impact of early treatment of childhood asthma with medications. Social psychologists could use these data to analyze the impacts of family structure and parental education on cognitive function. Pediatric emergency department physicians could use these data to assess the relationship of socioeconomic factors to use of emergency care and hospitalization and other adverse outcomes.

A major strength of the NCS is its prospective design. This design permits assessment of environmental exposures in real time as they actually occur, which is especially important for monitoring prenatal exposures where precise ascertainment of the nature, exact level, and timing of exposures is critical. The prospective design obviates the need to reconstruct past exposures from memory months or years after their occurrence, an inherently imperfect approach to exposure assessment. Although it is true that the level of detailed environmental sampling to be undertaken in the main cohort of the NCS is less than might be attained in smaller, more focused studies, nested, highly detailed environmental sampling will be undertaken in subsamples of the national cohort through the mechanism of satellite studies (eg, personal monitors will be used to measure air pollution at the level of the individual child's breathing zone, and robots will be used to assess exposures at floor level where young children play). Another strength of the NCS is that analyses of environmental samples will

be conducted at the laboratories of the CDC, the world's premier laboratory for the quantitative analysis of multiple exogenous chemicals in biological and environmental samples down to extremely low levels. Moreover, aliquots of environmental and biological samples will be archived under highly secure conditions and will be available for future analyses.

Some scientists have suggested that a large cohort study representing the age distribution of the current US population might provide a better design for the investigation of gene–environment interactions related to the major diseases of adult life. However, such an approach ignores the growing evidence that a number of important environmental contributions to disease in adult life have their origins early in development. Such early environmental exposures would be missed by a study that looked principally at adults. Only a longitudinal assessment of lifetime environmental exposures that follows individuals from conception onward can capture the consequences of early exposures and unravel the interactions between these exposures and individual susceptibility factors that underlie vulnerability to diseases of adulthood. It is now clear that vulnerability to a particular risk factor is often determined not only by the genome acquired at conception, but also by dynamic modifications to the genome over the life span. Therefore, to adequately assess gene–environment interactions, not only will the stable DNA sequence be essential but also epigenetic modifications to nuclear and mitochondrial DNA will have to be identified.

A multigenerational sample would represent another approach to the assessment of gene–environment interactions in the genesis of chronic disease. However, the cost to collect, store, process, and analyze material for genetic investigations across multiple generations would be enormous. Moreover, the opportunity exists within the prospective birth-cohort design of the NCS to acquire biological samples from family members across multiple generations, and the design of the study would provide the added benefit of linkage to environmental measures that will apply across the generations. As new genetic tests and methods are developed through efforts by many institutes, including the National Human Genome Research Institute, they can be applied immediately to environmental as well as genetic samples that will be stored in the NCS Data Repository, thus providing opportunities for rapid application of up-to-date knowledge initially on behalf of our nation's children.

Some have argued that a study of the magnitude of the NCS should be postponed until the most recent technologic advancements can be applied. Similar arguments were raised >50 years ago about large cohort studies such as the Framingham Heart Study, and to be sure none of those studies was perfect. But each of those studies was incredibly productive and has enormously benefited public health in the United States. Moreover, the methodologies used in each of those large study platforms have periodically been updated to take advantage of new developments in biomedical methodology; none have been methodologically static.

More than ever, pediatricians are yearning for guidance in the prevention and treatment of diseases of environmental origin in children.[154,155] Although the public is concerned about environmental threats to children's health[156] and patients frequently ask their physicians about the health effects of environmental exposures,[157] most pediatricians report that they have received little specific training in environmental pediatrics, and few report that they feel comfortable in diagnosing and managing disease of possible environmental origin.[158] As researchers better delineate the role of environmental exposures in childhood disease, findings from the study will inform pediatric practice. It may reasonably be anticipated that the study will provide the impetus for the training of a generation of pediatricians in environmental pediatrics, much as the Collaborative Perinatal Study provided the impetus for creation of the specialty of pediatric neurology.

Some scientists have argued the projected $2.7 billion cost of the 25-year NCS is too high and that the National Institutes of Health (NIH) should invest its funds in more focused research to investigate individual diseases. However, countering that argument is the expectation that the savings that will derive from the NCS will enable the study to pay for itself many times over. Six of the chronic diseases that the NCS plans to examine (obesity, injury, asthma, diabetes, schizophrenia, and autism) cost America $642 billion per year. Even if the NCS were to produce only a 1% reduction in the cost of these chronic diseases, it would yield savings of $6.4 billion per year, far more than the $2.7 billion that the study is projected to cost over 25 years.[38] Using conservative estimates of the impact of the NCS on 10 major adverse health outcomes, the Battelle Memorial Institute has projected that the NCS is poised to achieve an estimated 8-to-1 net benefit-to-cost ratio by 2020, 30-to-1 ratio by 2030, and 50-to-1 ratio by 2040 (Table 1) (Tim Pivetz, MS, and Warren Strauss, ScM, Battelle Memorial Institute, verbal communication, 2006).

Although some critics have also expressed concern that the NCS will threaten the viability of existing research projects funded by the NICHD and other institutes of the NIH, the effect is more likely to be the opposite. Findings from the NCS are likely to increase interest generally in prevention-oriented research that focuses on the diseases of children and to generate innumerable hypotheses for additional investigation. In previous large-scale projects, the bolus of findings triggered follow-up studies and provided investigators and trainees a framework to propose new studies. We expect the same effect from the use of data from the NCS.[159] Because the decoding of the human genome makes pos-

TABLE 1 Potential Economic Savings From NCS: Median Estimated Reductions

Health Outcome	Estimated Cost (2003), Billion $	Age at Diagnosis, y	Results Published	Projected Costs, Billion $ (2006)	Median Estimated Reductions, %	Cost Savings From NCS, Billion $ (2006)			
						2020	2025	2030	2040
Diabetes	136.6	10	2025	149.27	1.00	0.00	0.00	7.46	22.39
Asthma	14.5	3	2018	15.84	5.00	1.58	5.55	9.51	17.43
Obesity (excluding diabetes)	46.3	10	2025	50.59	3.00	0.00	0.00	7.59	22.77
Low birth weight	13.1	0	2015	14.31	5.50	3.94	7.87	11.81	19.68
Mental retardation	51.7	6	2021	55.95	3.50	0.00	7.83	17.62	37.21
Motor vehicle accidents	19	18	2033	20.76	0.25	0.00	0.00	0.00	0.36
Violence	24.3	18	2033	26.55	0.25	0.00	0.00	0.00	0.46
Mercury exposure	0.8	6	2021	0.87	0.12	0.00	0.00	0.01	0.02
Nonpersistent pesticide exposure	49	6	2021	53.54	0.50	0.00	1.07	2.68	5.35
Autism	40.6	3	2018	44.16	1.00	0.89	3.11	5.32	9.76
Total	395.4			432.06		6.41	25.43	62.00	135.44
Study implementation costs						1.24	1.66	1.93	2.0
Net cost savings (excluding medical cost of implementing findings)						5.17	23.83	60.09	133.41
Estimated cost of implementing prevention strategies (20% of net cost savings)						1.03	4.77	12.02	26.68
Net cost savings						4.14	19.06	48.07	106.73
Ratio of net cost savings from improved health outcomes to NCS implementation costs						3.3	11.9	25.1	52.6

Obtained from Tim Pivetz and Warren Strauss, Battelle Memorial Institute. Published with permission.

sible elucidation of the interplay between genetically determined individual differences in susceptibility to environmental exposures and risk of disease, a new generation of investigators armed with this knowledge should be able to make additional scientific advances well beyond those produced by earlier cohort studies.

We have described some of the weaknesses and criticisms of the NCS, and we recognize the proposed study is not perfect (no study is). Although the NCS will never be perfect, its time has come.

APPENDIX: LIST OF NCS SITES (ADAPTED FROM www.nationalchildrensstudy.gov)

Vanguard Locations (7 Total)

Orange County, California
Duplin County, North Carolina
New York City (Queens), New York
Montgomery County, Pennsylvania
Salt Lake County, Utah
Waukesha County, Wisconsin
Lincoln, Pipestone, and Yellow Medicine Counties, Minnesota, and Brookings County, South Dakota

Study Locations (98 Total)

Colbert County, Alabama
Benton County, Arkansas
Apache County, Arizona
Maricopa County, Arizona
Pinal County, Arizona
Humboldt County, California
Kern County, California
Los Angeles County, California
Sacramento County, California
San Bernardino County, California
San Diego County, California
San Mateo County, California
Ventura County, California
Denver, Colorado
Douglas County, Colorado
Litchfield County, Connecticut
New Haven County, Connecticut
New Castle County, Delaware
Baker County, Florida
Hillsborough County, Florida
Miami-Dade County, Florida
Orange County, Florida
Baldwin County, Georgia
DeKalb County, Georgia
Fayette County, Georgia
Honolulu County, Hawaii
Polk County, Iowa
Bear Lake County, Idaho and Lincoln and Uinta Counties, Wyoming
Cook County, Illinois
DuPage County, Illinois
Johnson, Union, and Williamson Counties, Illinois
Macoupin County, Illinois
Will County, Illinois

Marion County, Indiana
Saline County, Kansas
Jefferson County, Kentucky
Jessamine County, Kentucky
Beauregard and Vernon Parishes, Louisiana
New Orleans, Louisiana
Bristol County, Massachusetts
Worcester County, Massachusetts
Baltimore County, Maryland
Montgomery County, Maryland
Cumberland County, Michigan
Genesee County, Michigan
Grand Traverse County, Michigan
Lenawee County, Michigan
Macomb County, Michigan
Wayne County, Michigan
Becker, Clearwater, and Mahnomen Counties, Minnesota
Ramsey County, Minnesota
Stearns County, Minnesota
Jefferson County, Missouri
St Louis, Missouri
Coahoma County, Mississippi
Hinds County, Mississippi
Buncombe County, North Carolina
Burke County, North Carolina
Cumberland County, North Carolina
Durham County, North Carolina
Gaston County, North Carolina
Rockingham County, North Carolina
Stark County, North Dakota
Burlington County, New Jersey
Middlesex County, New Jersey
Passaic County, New Jersey
Warren County, New Jersey
Valencia County, New Mexico
Monroe County, New York
Nassau County, New York
New York City (Brooklyn), New York
New York City (Manhattan), New York
Cuyahoga County, Ohio
Lorain County, Ohio
Cleveland County, Oklahoma
Comanche County, Oklahoma
Marion County, Oregon
Philadelphia County, Pennsylvania
Schuylkill County, Pennsylvania
Westmoreland County, Pennsylvania
Providence County, Rhode Island
Spartanburg County, South Carolina
Bradley County, Tennessee
Cumberland and Morgan Counties, Tennessee
Davidson County, Tennessee
Bexar County, Texas
Childress, Collingsworth, Donley, and Hall Counties, Texas
Dallas County, Texas
Harris County, Texas
Hidalgo County, Texas
Lamar County, Texas
Stephens and Young Counties, Texas
Travis County, Texas
Cache County, Utah
Grant County, Washington
King County, Washington
Thurston County, Washington
Marion County, West Virginia

ACKNOWLEDGMENTS

We acknowledge the advice and input of Joseph Boscarino, Barbara Brenner, Paul Contino, Anne Golden, Jack Gorman, Jessica Moise, Larry Siever, Robert Southwick, and Ilene Wilets of Mount Sinai School of Medicine; Panos Georgopoulos and Cliff Weisel of the University of Medicine and Dentistry of New Jersey; and Howard Andrews, David Alge, Michaeline Bresnahan, Pam Factor-Litvak, William Fifer, Jeffrey Halperin, Steve Kahn, Eugene Mattes, Mary Mckay, Virginia Rauh, Deliang Tang, and Robin Whyatt of the Columbia University Mailman School of Public Health.

REFERENCES

1. National Research Council. *Toxicity Testing: Needs and Priorities*. Washington, DC: National Academy Press; 1984
2. US Environmental Protection Agency. *Chemical Hazard Data Availability Study: What Do We Really Know About the Safety of High Production Volume Chemicals?* Washington, DC: US Environmental Protection Agency, Office of Pollution Prevention and Toxic Substances; 1998
3. Berkowitz GS, Wolff MS, Matte T, Susser E, Landrigan PJ. The rationale for a national prospective cohort study of environmental exposure and childhood development. *Environ Res*. 2001;85:59–68
4. Haddow JE, Knight GJ, Palomaki GE, McCarthy JE. Second trimester serum cotinine levels in nonsmokers in relation to birth weight. *Am J Obstet Gynecol*. 1988;159:481–484
5. World Health Organization. 1999 International Consultation on Environmental Tobacco Smoke (ETS) and Child Health: consultation report. Geneva, Switzerland: World Health Organization. Available at: www.who.int/toh. Accessed February 22, 2004
6. Schardein JL. *Chemically Induced Birth Defects*. 2nd ed, Revised. New York, NY: Marcel Dekker; 1993
7. Lenz W, Knapp K. Thalidomide embryopathy [in German]. *Dtsch Med Wochenschr*. 1962;87:1232–1242
8. Herbst AL, Scully RE. Adenocarcinoma of the vagina in adolescence: a report of 7 cases including 6 clear-cell carcinomas. *Cancer*. 1970;25:745–757
9. Needleman HL, Riess JA, Tobin MJ, Biesecker GE, Greenhouse JB. Bone lead levels and delinquent behavior. *JAMA*. 1996;275:363–369
10. Laraque D, Trasande L. Lead poisoning: successes and 21st century challenges. *Pediatr Rev*. 2005;26:435–443
11. Needleman HL, McFarland C, Ness RB, Fienberg SE, Tobin MJ. Bone lead levels in adjudicated delinquency: a case-control study. *Neurotoxicol Teratol*. 2002;24:711–717
12. Bellinger DC. Lead. *Pediatrics*. 2004;113(4 suppl):1016–1022
13. Baghurst PA, Robertson EF, McMichael AJ, Vimpani GV, Wigg NR, Roberts RR. The Port Pirie Cohort Study: lead effects

on pregnancy outcome and early childhood development. *Neurotoxicology*. 1987;8:395–401
14. Dietrich KN, Krafft KM, Bornschein RL, et al. Low-level fetal lead exposure effect on neurobehavioral development in early infancy. *Pediatrics*. 1987;80:721–730
15. Dietrich KN, Ris MD, Succop PA, Berger OG, Bornschein RL. Early exposure to lead and juvenile delinquency. *Neurotoxicol Teratol*. 2001;23:511–518
16. Lupton C, Burd L, Harwood R. Cost of fetal alcohol spectrum disorders. *Am J Med Genet C Semin Med Genet*. 2004;127:42–50
17. Newcombe HB, McGregor JF. Childhood cancer following obstetric radiography. *Lancet*. 1971;2(7734):1151–1152
18. Stewart A, Kneale GW. Radiation dose effects in relation to obstetric x-rays and childhood cancers. *Lancet*. 1970;1(7658):1185–1188
19. Jacobson JL, Jacobson SW. Intellectual impairment in children exposed to polychlorinated biphenyls in utero. *N Engl J Med*. 1996;335:783–789
20. Jorgensen EB, Weihe P, Grandjean P. Adverse mercury effects in seven year old children as expressed as loss in IQ. Available at: www.chef-project.dk. Accessed May 15, 2004
21. Trasande L, Schechter C, Landrigan PJ. Public health and economic consequences of environmental methylmercury toxicity to the developing brain. *Environ Health Perspect*. 2005;113:590–596
22. National Research Council. *Toxicological Effects of Methylmercury*. Washington, DC: National Academy Press; 2000
23. Murata K, Weihe P, Budtz-Jorgensen E, Jorgensen PJ, Grandjean P. Delayed brainstem auditory evoked potential latencies in 14-year-old children exposed to methylmercury. *J Pediatr*. 2004;144:177–183
24. Kjellstrom T, Kennedy P, Wallis S, Mantell C. *Physical and Mental Development of Children With Prenatal Exposure to Mercury From Fish. Stage I: Preliminary Tests at Age 4*. Report 3080. Solna, Sweden: National Swedish Environmental Protection Board; 1986
25. Kjellstrom T, Kennedy P, Wallis S, et al. *Physical and Mental Development of Children With Prenatal Exposure to Mercury From Fish. Stage II: Interviews and Psychological Tests at Age 6*. Report 3642. Solna, Sweden: National Swedish Environmental Protection Board; 1989
26. Trasande L, Schechter CB, Haynes KA, Landrigan PJ. Mental retardation and prenatal methylmercury toxicity. *Am J Ind Med*. 2006;49:153–158
27. Trasande L, Thurston GD. The role of air pollution in asthma and other pediatric morbidities. *J Allergy Clin Immunol*. 2005;115:689–699
28. Raaschou-Nielsen O, Hertel O, Thomsen BL, Olsen JH. Air pollution from traffic at the residence of children with cancer. *Am J Epidemiol*. 2001;153:433–443
29. Berkowitz GS, Wetmur JG, Birman-Deych E, et al. In utero pesticide exposure, maternal paraoxonase activity, and head circumference. *Environ Health Perspect*. 2004;112:388–391
30. Barker DJP, ed. *Fetal and Infant Origins of Adult Disease*. London, United Kingdom: BMJ Publishing; 1992
31. Barker DJ, Osmond C. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. *Lancet*. 1986;1(8489):1077–1081
32. Barker DJ, Winter PD, Osmond C, Margetts B, Simmonds SJ. Weight in infancy and death from ischaemic heart disease. *Lancet*. 1989;2(8663):577–580
33. Poulter NR, Chang CL, MacGregor AJ, Snieder H, Spector TD. Association between birth weight and adult blood pressure in twins: historical cohort study. *BMJ*. 1999;319:1330–1333
34. Barker DJ. Fetal origins of coronary heart disease. *BMJ*. 1995;311:171–174
35. Ahlgren M, Melbye M, Wohlfahrt J, Sorensen TI. Growth patterns and the risk of breast cancer in women. *N Engl J Med*. 2004;351:1619–1626
36. Hales CN, Barker DJ, Clark PM, Cox LJ, Fall C, Osmond C, Winter PD. Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ*. 1991;303:1019–1022
37. Dietrich KN, Eskenazi B, Schantz S, et al. Principles and practices of neurodevelopmental assessment in children: lessons learned from the Centers for Children's Environmental Health and Disease Prevention Research. *Environ Health Perspect*. 2005;113:1437–1446
38. Trasande L, Landrigan PJ. The National Children's Study: a critical national investment. *Environ Health Perspect*. 2004;112:A789–A790
39. Srinivasan S, O'Fallon LR, Dearry A. Creating healthy communities, healthy homes, healthy people: initiating a research agenda on the built environment and public health. *Am J Public Health*. 2003;93:1446–1450
40. Olden K. Genomics in environmental health research: opportunities and challenges. *Toxicology*. 2004;198:19–24
41. Eskenazi B, Gladstone EA, Berkowitz GS, et al. Methodologic and logistic issues in conducting longitudinal birth cohort studies: lessons learned from the Centers for Children's Environmental Health and Disease Prevention Research. *Environ Health Perspect*. 2005;113:1419–1429
42. Freeman NCG, Jimenez M, Reed KJ, et al. Quantitative analysis of children's microactivity patterns: the Minnesota children's pesticide exposure study. *J Exp Anal Environ Epidemiol*. 2001;11:501–509
43. Caspi A, Taylor A, Moffitt TE, Plomin R. Neighborhood deprivation affects children's mental health: environmental risks identified in a genetic design. *Psychol Sci*. 2000;11:338–342
44. Wadhwa PD, Culhane JF, Rauh V, et al. Stress, infection and preterm birth: a biobehavioural perspective. *Paediatr Perinat Epidemiol*. 2001;15(suppl 2):17–29
45. US Department of Health and Human Services. The President's Task Force on Environmental Health Risks and Safety Risks to Children. Available at: http://nationalchildrensstudy.gov/about/task_force.cfm. Accessed September 13, 2004
46. Children's Health Act of 2000. Pub L. No. 106–310
47. Centers for Disease Control and Prevention, National Center for Health Statistics. Health, United States, 2004. Available at: www.cdc.gov/nchs/hus.htm. Accessed January 20, 2004
48. Haggerty R, Rothman J. *Child Health and the Community*. New York, NY: John Wiley & Sons; 1975
49. Ananth CV, Joseph KS, Demissie K, Vintzileos AM. Trends in twin preterm birth subtypes in the United States, 1989 through 2000: impact on perinatal mortality. *Am J Obstet Gynecol*. 2005;193(3 pt 2):1076–1082
50. Mannino DM, Homa DM, Pertowski CA, et al. Surveillance for asthma: United States, 1960–1995. *MMWR CDC Surveill Summ*. 1998;47(SS-1):1–28
51. Robison LL, Buckley JD, Bunin G. Assessment of environmental and genetic factors in the etiology of childhood cancers: the Childrens Cancer Group epidemiology program. *Environ Health Perspect*. 1995;103(suppl 6):111–116
52. Schechter CB. Re: Brain and other central nervous system cancers: recent trends in incidence and mortality. *J Natl Cancer Inst*. 1999;91:2050–2051
53. Devesa SS, Blot WJ, Stone BJ, Miller BA, Tarone RE, Fraumeni JF Jr. Recent cancer trends in the United States. *J Nat Cancer Inst*. 1995;87:175–182
54. Bertrand J, Mars A, Boyle C, Bove F, Yeargin-Allsopp M, Decouflé P. Prevalence of autism in a United States population: the Brick Township, New Jersey, investigation. *Pediatrics*. 2001;108:1155–1161
55. Centers for Disease Control and Prevention. Developmental

disabilities. 2004. Available at: www.cdc.gov/ncbddd/dd/default.htm. Accessed June 21, 2004
56. Centers for Disease Control and Prevention. Economic costs associated with mental retardation, cerebral palsy, hearing loss, and vision impairment: United States, 2003. *MMWR Morb Mortal Wkly Rep*. 2004;53:57–59
57. LeFever GB, Dawson KV, Morrow AL. The extent of drug therapy for attention deficit hyperactivity disorder among children in public schools. *Am J Public Health*. 1999;89:1359–1364
58. Safer DJ, Zito JM, Fine EM. Increased methylphenidate usage for attention deficit disorder in the 1990s. *Pediatrics*. 1996;98:1084–1088
59. Zito JM, Safer DJ, dosReis S, Gardner JF, Boles M, Lynch F. Trends in the prescribing of psychotropic medications to preschoolers. *JAMA*. 2000;283:1025–1030
60. Ogden CL, Flegal KM, Carroll MD, Johnson CL. Prevalence and trends in overweight among US children and adolescents, 1999–2000. *JAMA*. 2002;288:1728–1732
61. Centers for Disease Control and Prevention, National Center for Health Statistics. Prevalence of overweight among children and adolescents: United States, 1999–2002. Available at: www.cdc.gov/nchs/products/pubs/pubd/hestats/overwght99.htm. Accessed July 18, 2006
62. Thorpe LE, List DG, Marx T, May L, Helgerson SD, Frieden TR. Childhood obesity in New York City elementary school students. *Am J Public Health*. 2004;94:1496–1500
63. Williams LJ, Kucik JE, Alverson CJ, Olney RS, Correa A. Epidemiology of gastroschisis in metropolitan Atlanta, 1968 through 2000. *Birth Defects Res A Clin Mol Teratol*. 2005;73:177–183
64. Penman DG, Fisher RM, Noblett HR, Soothill PW. Increase in incidence of gastroschisis in the South West of England in 1995. *Br J Obstet Gynaecol*. 1998;105:328–331
65. McDonnell R, Delany V, Dack P, Johnson H. Changing trend in congenital abdominal wall defects in eastern region of Ireland. *Ir Med J*. 2002;95:236–238
66. Stoll C, Alembik Y, Roth MP. Risk factors in congenital wall defects (omphalocele and gastroschisis): a study in a series of 265 858 consecutive births. *Ann Genet*. 2001;44:201–208
67. Curry JI, McKinney P, Thornton JG, Stringer MD. The aetiology of gastroschisis. *Br J Obstet Gynaecol*. 2000;107:1339–1346
68. Suita S, Okamatsu T, Yamamoto T, et al. Changing profile of abdominal wall defects in Japan: results of a national survey. *J Pediatr Surg*. 2000;35:66–72
69. Nichols CR, Dickinson JE, Pemberton PJ. Rising incidence of gastroschisis in teenage pregnancies. *J Matern Fetal Med*. 1997;6:225–229
70. Kilby MD, Lander A, Usher-Somers M. Exomphalos (omphalocele). *Prenat Diagn*. 1998;18:1283–1288
71. National Research Council. *Human Exposure Assessment for Airborne Pollutants: Advances and Opportunities*. Washington, DC: National Academies Press; 1991:1–321
72. Lioy PJ. The 1998 ISEA Wesolowski Award Lecture. Exposure analysis: reflections on its growth and aspirations for its future. *J Expo Anal Environ Epidemiol*. 1999;9:273–281
73. Chemicals-in-Commerce Information System. *Chemical Update System* [database online]. Washington, DC: US Environmental Protection Agency; 1998
74. US Environmental Protection Agency, Office of Pesticide Programs. Principles for performing aggregate exposure and risk assessments. In: *Framework for Cumulative Risk Assessment*. Washington, DC: US Environmental Protection Agency; 2003:1–29
75. Centers for Disease Control and Prevention. Third national report on human exposure to environmental chemicals. Available at: www.cdc.gov/exposurereport. Accessed August 19, 2005
76. National Research Council. *Pesticides in the Diets of Infants and Children*. Washington, DC: National Academy Press; 1993
77. Gergen PJ, Mortimer KM, Eggleston PA, et al. Results of the National Cooperative Inner-City Asthma Study (NCICAS) environmental intervention to reduce cockroach allergen exposure in inner-city homes. *J Allergy Clin Immunol*. 1999;103:501–506
78. Lioy PJ, Freeman NC, Millette JR. Dust: a metric for use in residential and building exposure assessment and source characterization. *Environ Health Perspect*. 2002;110:969–983
79. Kattan M, Stearns SC, Crain EF, et al. Cost-effectiveness of a home-based environmental intervention for inner-city children with asthma. *J Allergy Clin Immunol*. 2005;116:1058–1063
80. Salam MT, Li YF, Langholz B, Gilliland FD; Children's Health Study. Early-life environmental risk factors for asthma: findings from the Children's Health Study. *Environ Health Perspect*. 2004;112:760–765
81. Gauderman WJ, Avol E, Gilliland F, et al. The effect of air pollution on lung development from 10 to 18 years of age. *N Engl J Med*. 351:1057–1067
82. Friedman MS, Powell KE, Hutwagner L, Graham LM, Teague WG. Impact of changes in transportation and commuting behaviors during the 1996 Summer Olympic Games in Atlanta on air quality and childhood asthma. *JAMA*. 2001;285:897–905
83. Suh HH, Bahadori T, Vallarino J, Spengler JD. Criteria air pollutants and toxic air pollutants. *Environ Health Perspect*. 2000;108(suppl 4):625–633
84. Wallace LA, Mitchell H, O'Connor GT, et al. Particle concentrations in inner-city homes of children with asthma: the effect of smoking, cooking, and outdoor pollution. *Environ Health Perspect*. 2003;111:1265–1272
85. Daniels JL, Olshan AF, Teschke K, et al. Residential pesticide exposure and neuroblastoma. *Epidemiology*. 2001;12:20–27
86. Lee WJ, Cantor KP, Berzolsky JA, Zahm SH, Blair A. Non-Hodgkin's lymphoma among asthmatics exposed to pesticides. *Int J Cancer*. 2004;111:298–302
87. National Academy of Sciences, Committee on Developmental Toxicology. *Scientific Frontiers in Developmental Toxicology and Risk Assessment*. Washington, DC: National Academies Press; 2000
88. Frumkin H. Urban sprawl and public health. *Public Health Rep*. 2002;117:201–217
89. US Department of Agriculture, Natural Resources Conservation Services. National resources inventory, 2001 annual NRI: urbanization and development of rural lands. Available at: www.nrcs.usda.gov/technical/land/nri01/urban.pdf. Accessed September 10, 2003
90. Jackson RJ. The impact of the built environment on health: an emerging field. *Am J Public Health*. 2003;93:1382–1384
91. Galvez MP, Frieden TR, Landrigan PJ. Obesity in the 21st century. *Environ Health Perspect*. 2003;111:A684–A685
92. Horowitz CR, Colson KA, Hebert PL, Lancaster, K. Barriers to buying healthy foods for people with diabetes: evidence of environmental disparities. *Am J Public Health*. 2004;94:1549–1554
93. Morland K, Wing S, Diez Roux A. The contextual effect of the local food environment on residents' diets: the atherosclerosis risk in communities study. *Am J Public Health*. 2002;92:1761–1767
94. Morland K, Wing S, Diez Roux A, Poole C. Neighborhood characteristics associated with the location of food stores and food service places. *Am J Prev Med*. 2002;22:23–29
95. Sallis JF, Bauman A, Pratt M. Environmental and policy in-

terventions to promote physical activity. *Am J Prev Med*. 1998; 15:379–397
96. Sallis JF, Hovell MF, Hofstetter CR, et al. Distance between homes and exercise facilities related to frequency of exercise among San Diego residents. *Public Health Rep*. 1990;105: 179–185
97. Sallis JF, Kraft K, Linton LS. How the environment shapes physical activity: a transdisciplinary research agenda [commentary]. *Am J Prev Med*. 2002;22:208
98. Ewing R, Schmid T, Killingsworth R, Zlot A, Raudenbush S. Relationship between urban sprawl and physical activity, obesity, and morbidity. *Am J Health Promot*. 2003;18:47–57
99. Frank L, Andressen M, Schmid T. Obesity relationships with community design, physical activity, and time spent in cars. *Am J Prev Med*. 2004;27:87–96
100. Dawber TR. Summary of recent literature regarding cigarette smoking and coronary heart disease. *Circulation*. 1960;22: 164–166
101. Kannel WB, Dawber TR, Kagan A, Revotskie N, Stokes JI. Factors of risk in the development of coronary heart disease: six year follow-up experience—the Framingham Study. *Ann Intern Med*. 1961;55:33–50
102. Kannel WB, Wolf PA, Dawber TR. Hypertension and cardiac impairments increase stroke risk. *Geriatrics*. 1978;33:71–83
103. Centers for Disease Control and Prevention, National Center for Vital Statistics. Health, United States, 2004. Available at: www.cdc.gov/nchs/hus.htm. Accessed January 20, 2004
104. Channing Laboratory. The Nurses Health Study. Available at: www.channing.harvard.edu/nhs/index.html. Accessed December 9, 2005
105. National Heart Lung and Blood Institute. Women's health initiative. Available at: www.nhlbi.nih.gov/whi/index.html. Accessed December 9, 2005
106. National Heart Lung and Blood Institute. The Bogalusa Heart Study. Available at: www.nhlbi.nih.gov/resources/deca/descriptions/bhs.htm. Accessed November 21, 2005
107. Freedman DS, Khan LK, Serdula MK, Dietz WH, Srinivasan SR, Berenson GS. The relation of childhood BMI to adult adiposity: the Bogalusa Heart Study. *Pediatrics*. 2005;115: 22–27
108. Freedman DS, Dietz WH, Srinivasan SR, Berenson GS. The relation of overweight to cardiovascular risk factors among children and adolescents: the Bogalusa Heart Study. *Pediatrics*. 1999;103:1175–1182
109. Lauer RM, Clarke WR, Mahoney LT, Witt J. Childhood predictors for high adult blood pressure: the Muscatine Study. *Pediatr Clin North Am*. 1993;40:23–40
110. Moll PP, Burns TL, Lauer RM. The genetic and environmental sources of body mass index variability: the Muscatine Ponderosity Family Study. *Am J Hum Genet*. 1991;49:1243–1255
111. Broman SH. The Collaborative Perinatal Project: an overview. In: Mednick, SA, Harway M, Finello K, eds. *Handbook of Longitudinal Research*. NY: Praeger; 1984:166–179Vol 1. New York
112. van den Berg BJ, Christianson RE, Oechsli FW. The California Child Health and Development Studies of the School of Public Health, University of California at Berkeley. *Paediatr Perinat Epidemiol*. 1988;2:265–282
113. Buka SL, Tsuang MT, Lipsitt LP. Pregnancy/delivery complications and psychiatric diagnosis: a prospective study. *Arch Gen Psychiatry*. 1993;50:151–156
114. Hardy JB, Shapiro S, Mellits ED, et al. Self-sufficiency at ages 27 to 33 years: factors present between birth and 18 years that predict educational attainment among children born to inner-city families. *Pediatrics*. 1997;99:80–87
115. Australian Institute of Family Studies. Growing up in Australia. Available at: www.aifs.gov.au/growingup/about.html. Accessed April 3, 2006
116. Nicholson JM, Rempel LA. Australian and New Zealand birth cohort studies: breadth, quality and contributions. *J Paediatr Child Health*. 2004;40:87–95
117. Buka SL, Shenassa ED, Niaura R. Elevated risk of tobacco dependence among offspring of mothers who smoked during pregnancy: a 30-year prospective study. *Am J Psychiatry*. 2003; 160:1978–1984
118. Matte TD, Bresnahan M, Begg MD, Susser ES. Influence of variation in birth weight within normal range and within sibships on IQ at age 7 years: cohort study. *BMJ*. 2001;323: 310–314
119. Farrow A, Farrow SC, Little R, Golding J. The repeatability of self-reported exposure after miscarriage. ALSPAC Study Team. *Avon Longitudinal Study of Pregnancy and Childhood. Int J Epidemiol*. 1996;25:797–806
120. The Norwegian Institute of Public Health. Available at: www.fhi.no/eway/default0.asp?pid=225&oid=06&e=0&trg=MainArea_4807&MainArea_4807=4828:0:15,3046:1:0:0:4807,4809;::0:0:0. Accessed July 16, 2006
121. Olsen J, Melbye M, Olsen SF, et al. The Danish National Birth Cohort: its background, structure and aim. *Scand J Public Health*. 2001;29:300–307
122. Solantaus T, Salo S. Paternal postnatal depression: fathers emerge from the wings. *Lancet*. 2005;365(9478):2158–2159, 2201–2205
123. Ramchandani PG, Hotopf M, Sandhu B, Stein A; ALSPAC Study Team. The epidemiology of recurrent abdominal pain from 2 to 6 years of age: results of a large, population-based study. *Pediatrics*. 2005;116:46–50
124. Lidegaard O, Pinborg A, Andersen AN. Imprinting diseases and IVF: Danish National IVF cohort study. *Hum Reprod*. 2005;20:950–954
125. Susser E, Factor-Litvak P. A life course approach to neuropsychiatric disorders. In: Kuh D, Ben-Shlomo Y, eds. *A Life Course Approach to Chronic Disease Epidemiology*. 2nd ed. Oxford, United Kingdom: Oxford University Press; 2004:306–324
126. Susser E, Terry MB. A conception-to-death cohort. *Lancet*. 2003;361(9360):797–798
127. Susser E, Schaefer C, Brown A, Begg M, Wyatt RJ. The design of the prenatal determinants of schizophrenia (PDS). *Schizophr Bull*. 2000;26:257–273
128. Susser E, Terry MB, Matte T. The birth cohort grow up: new opportunities for Epidemiology. *Paediatr Perinat Epidemiol*. 2000;14:98–100
129. Matte T, Wolff M, Godbold J, Schonfeld J, Stern Y, Susser E. Prenatal exposure to polychlorinated biphenyls (PCBs) and measured intelligence in urban African-American cohort. *Environ Health Perspect*. 2006: In press
130. Brown AS, Begg MD, Gravenstein S, et al. Serologic evidence of prenatal influenza in the etiology of schizophrenia. *Arch Gen Psychiatry*. 2004;61:774–780
131. National Institute of Child Health and Human Development. National Children's Study Hypotheses. Available at: http://nationalchildrensstudy.gov/research/hypotheses/hypotheses_list.cfm. Accessed August 22, 2005
132. Serdula MK, Ivery D, Coates RJ, Freedman DS, Williamson DF, Byers T. Do obese children become obese adults? A review of the literature. *Prev Med*. 1993;22:167–177
133. Freedman DS, Khan LK, Dietz WH, Srinivasan SR, Berenson GS. Relationship of childhood obesity to coronary heart disease risk factors in adulthood: the Bogalusa Heart Study. *Pediatrics*. 2001;108:712–718
134. Sinha R, Fisch G, Teague B, et al. Prevalence of impaired glucose tolerance among children and adolescents with marked obesity. *N Engl J Med*. 2002;346:802–810

The National Children's Study: A 21-Year Prospective Study of 100 000 American Children

Philip J. Landrigan, Leonardo Trasande, Lorna E. Thorpe, Charon Gwynn, Paul J. Lioy, Mary E. D'Alton, Heather S. Lipkind, James Swanson, Pathik D. Wadhwa, Edward B. Clark, Virginia A. Rauh, Frederica P. Perera and Ezra Susser

Pediatrics 2006;118;2173-2186
DOI: 10.1542/peds.2006-0360

135. Saelens BE, Sallis JF, Black JB, Chen D. Neighborhood-based differences in physical activity: an environment scale evaluation. *Am J Public Health*. 2003;93:1552–1557
136. Berrigan D, Troiano RP. The association between urban form and physical activity in US adults. *Am J Prev Med*. 2002;23:74–79
137. Lopez R. Urban sprawl and risk for being overweight or obese. *Am J Public Health*. 2004;94:1574–1579
138. Schaefer-Graf UM, Buchanan TA, Xiang A, Songster G, Montor M, Kjos SL. Patterns of congenital anomalies and relationship to initial maternal fasting glucose levels in pregnancies complicated by type 2 and gestational diabetes. *Am J Obstet Gynecol*. 2000;182:313–320
139. Becerra JE, Khoury MJ, Cordero JF, Erickson JD. Diabetes mellitus during pregnancy and the risks for specific birth defects: a population-based case-control study. *Pediatrics*. 1990;85:1–9
140. Sheffield JS, Butler-Koster JL, Casey BM, Donald D, McIntire DD, Leveno KJ. Maternal diabetes mellitus and infant malformations. *Obstet Gynecol*. 2002;100:925–930
141. Sharpe PB, Chan A, Haan EA, Hiller JE. Maternal diabetes and congenital anomalies in south Australia 1986–2000: a population-based cohort study. *Birth Defects Research (Part A)*. 2005;73:605–611
142. Farrell T, Neale L, Cundy T. Congenital anomalies in the offspring of women with type 1, type 2 and gestational diabetes. *Diabet Med*. 2002;19:322–326
143. Schaefer UM, Songster G, Xiang A, Berkowitz K, Buchanan TA, Kjos SL. Congenital malformations in offspring of women with hyperglycemia first detected during pregnancy. *Am J Obstet Gynecol*. 1997;177:1165–1171
144. Caspi A, McClay J, Moffitt TE, et al. Role of genotype in the cycle of violence in maltreated children. *Science*. 2002;297:851–854
145. Meyer H, Palchaudhuri M, Scheinin M, Flugge G. Regulation of alpha(2a)-adrenoceptor expression by chronic stress in neurons of the brain stem. *Brain Res*. 2000;880:147–158
146. Fisher JS. Environmental anti-androgens and male reproductive health: focus on phthalates and testicular dysgenesis syndrome. *Reproduction*. 2004;127:305–315
147. Skakkebaek NE, Rajpert-De Meyts E, Main KM. Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. *Hum Reprod*. 2001;16:972–978
148. National Institutes of Health, Office of Behavioral and Social Sciences Research. *Toward Higher Levels of Analysis: Progress and Promise in Research on Social and Cultural Dimensions of Health, June 27–28, 2000*. Bethesda, MD: National Institutes of Health; 2001. NIH Publication 01–5020
149. Kelada SN, Eaton DL, Wang SS, Rothman NR, Khoury MJ. The role of genetic polymorphisms in environmental health. *Environ Health Perspect*. 2003;111:1055–1064
150. Lammer EJ, Shaw GM, Iovannisci DM, Van Waes J, Finnell RH. Maternal smoking and the risk of orofacial clefts: susceptibility with NAT1 and NAT2 polymorphisms. *Epidemiology*. 2004;15:150–156
151. Chen J, Kumar M, Chen W, Berkowitz G, Wetmur JG. Increased influence of genetic variation on PON1 activity in neonates. *Environ Health Perspect*. 2003;111:1403–1409
152. Trasande L, Cronk CE, Leuthner SR, et al. The National Children's Study and the children of Wisconsin. *WMJ*. 2006;105:50–54
153. Lauer RM, Clarke WR, Burns TL. Obesity in childhood: the Muscatine Study. *Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi*. 1997;38:432–437
154. Trasande L, Boscarino J, Graber N, et al. The environment in pediatric practice: a study of New York pediatricians' attitudes, beliefs, and practices towards children's environmental health. *J Urban Health*. 2006;83:760–762
155. Trasande L, Schapiro ML, Falk R, et al. Pediatrician attitudes and knowledge of environmental health in Wisconsin. *WMJ*. 2006;105(2):45–49
156. Pew Charitable Trusts. *Public Opinion Research on Public Health, Environmental Health and the Country's Public Health Capacity to Adequately Address Environmental Health Problems*. Philadelphia, PA: Pew Charitable Trusts; 1999
157. Szneke P, Nielsen C, Tolentino N. Connecticut physicians' knowledge and needs assessment of environmentally related health hazards: a survey. *Conn Med*. 1994;58:131–135
158. Kilpatrick N, Frumkin H, Trowbridge J, et al. *Environ Health Perspect*. 2002;110:823–827
159. Lyman WL, Barone C, Castle V, Davies HD, Stanton B, Paneth N for the Michigan Alliance for the National Children's Study. Making the National Children's Study a real partnership with academic pediatrics. *J Pediatr*. 2005;147:563–564

Questions from:
Senator James M. Inhofe

1) In your statement, you said that chronic diseases of environmental origins were increasing. How do you define "environmental origins"? Does that definition include everything except genetics, e.g. physical, chemical, biological and social factors?

Chronic diseases of environmental origin have become epidemic in American children, and are the diseases of greatest current concern. Chemical factors that contribute to these conditions include and are not limited to lead, mercury, polychlorinated biphenyls (PCBs), certain pesticides and outdoor air pollutants. Physical, biological and social factors do also contribute to the development and exacerbation of these conditions, and studies such as the National Children's Study endeavor to have the statistical power to accurately quantify the various role these factors in addition to chemical factors contribute to the conditions. The study of obesity, as documented in a manuscript now electronically published in Environmental Health Perspectives, requires simultaneous examination of all of these factors to guide thoughtful prevention.

2) Does the National Children's Study broadly address environmental factors - e.g. the Study includes physical, chemical, biological and social factors, are other factors not included?

The National Children's Study endeavors to examine the role of physical, biological and social factors as well as chemical factors in contributing to disease and disability in children. Attached please find a manuscript published in Pediatrics in 2004 that answers your question in greater detail. It also provides extensive references to support every one of the statements provided in my testimony, and I submit it to the record in response to comments made by Senator Barrasso and Dr. Brent regarding my testimony.

3) With respect to childhood cancer, please comment on the National Cancer Institute (NCI) contention that rates of childhood leukemia in the years from 1985 to the present "have shown no consistent upward or downward trend and have ranged from 3.7 to 4.9 cases per 100,000." And that, with respect to childhood brain tumors, NCI states, " ...childhood brain tumor incidence has been essentially stable since the mid-1980s." NCI Reference: http://www.cancer.gov/cancertopics/factsheet/Sites-Tvpes/childhood . Given that NCI is widely recognized as one of the nation's leading cancer research institutions, if you were aware of the National Cancer Institute's facts and figures at the time of the hearing, is there any particular reason(s) why this data was not cited in your testimony?

The website to which the Senator refers also states that, "For childhood brain tumors, the overall incidence rose from 1975 through 2004, from 2.3 to 3.2 cases per 100,000, with the greatest increase occurring from 1983 through 1986." While rates may have remained stable since the mid-1980s, a temporal increase in pediatric cancers raises major concerns about their origins, as changes in genetics cannot alone explain the rapidity of such an increase. Chemical factors such as benzene, 1,3-butadiene, and pesticides have been etiologically associated with

childhood malignancies. More research is needed, and diagnostic certainty is a major consideration in analyzing cases for comparison with controls in large-scale studies.

While time trend analyses must be interpreted with caution, studies of case clusters of leukemias have identified hazardous waste sites as a possible etiologic contributor. The Toms River, NJ case cluster identified prenatal well water ingestion as a risk factors for females with leukemia. Because cancers are such rare events at baseline in children, linkage of the National Children's Study with other international child cohorts will go be necessary to achieving the statistical power to identify most effectively the preventable causes of childhood cancer.

Senator BOXER. Thank you very much.
Dr. Brent.

STATEMENT OF ROBERT BRENT, DISTINGUISHED PROFESSOR OF PEDIATRICS, RADIOLOGY AND PATHOLOGY, THOMAS JEFFERSON UNIVERSITY, A.I. DUPONT HOSPITAL FOR CHILDREN

Dr. BRENT. Good morning. Good morning, Senators.

My name is Robert Brent. I am a Distinguished Professor of Pediatrics, Radiology, and Pathology at the Jefferson Medical College, and at the duPont Hospital for Children. I have been there 51 years, and I have a great-grandchild, Senator Boxer.

Senator BOXER. That is great.

Dr. BRENT. Besides 11 grandchildren.

Senator BOXER. Well, I am catching up to you slowly, seriously.

Dr. BRENT. I am here as a scientist. I have had no interaction with the Children's Health Protection Advisory Committee's relationship with the EPA at all. I learned about it here today. But I have had an interaction with the EPA. I have been funded by the NIH and the Department of Energy my entire scientific life. I have never had a grant from a chemical company or pharmaceutical company, and so I am a scientist.

The most important thing a scientist has to do with regard to environmental exposures is risk analysis, and in order to do risk analysis you have to know the exposure that the population receives. That is the tremendous value of the National Children's Study, because we are going to get exposures.

Not only that, I can tell you most of you weren't even born when the collaborative perinatal project was done in 1957 to 1965. They saved that serum. We were able to go back and take that serum and find out whether AIDS was present in 1957. it wasn't. They looked at 500 prostitutes in 1960 to see whether the AIDS virus was there. It wasn't. We did the same thing with caffeine. So we are going to save these serum samples, and not only will it be prospectively helpful, but it will be retrospectively. Ten years later you can go back and look at the samples.

So we need to obtain information where we can do risk analysis, and that means serum levels, urine levels of the constituents, and we need to be able to relate that to some type of risk analysis.

Well, to do, for instance, a bisphenol study, Rochelle Till did a bisphenol study. It cost $2.5 million to do one animal study on one chemical. We can't afford that.

So what has my interaction been with the EPA? In 2003 Michael Weitzman and I got a grant from the EPA to write a supplement to pediatrics on environmental risks. The title of the book was, The Vulnerability, Sensitivity, and Resiliency of the Developing Embryo, Infant Child, and Adolescent to the Effects of Chemicals, Drugs, and Physical Agents.

In the second chapter we then reviewed all the toxicants that are known to find out how sensitive children are. The first thing that we found is that about 20 percent of chemicals, adult is more vulnerable than a child. That was very surprising. Well, it is because

very frequently the infant hasn't developed the metabolic ability to convert the toxic substance to a toxic agent.

So you can't say that just because the child or an infant is a child that they are going to be more sensitive to a toxicant. You have got to do the studies.

So my next interaction was I was put on the Developmental Toxicology Committee of the National Academy of Scientists. I happen to be a member of the National Academy of Scientists. We spent 3 years developing a program, and the book was published in 2007. It was called, Toxicology in the 21st Century. In there we proposed high throughput toxicity testing where we could do thousands of chemicals a year testing. You can't do all those chemicals with an animal study.

I am telling you my good interactions with the EPA. The EPA adopted our recommendations before we even finished our committee report, and Robert Cadlock, the Ph.D., got a $50 million grant from the EPA. They have initiated these high throughput tests, and they are completing the first phase of the study. I don't know whether it will be successful, but it is worth pursuing that.

So these are two areas that we have to pursue. The scientists at EPA—I can't tell you about the administrators, but the scientists at EPA are working hard to try to solve our problem with determining reproductive toxicity. And that is the answer—science. That is where I spend my time. I don't get involved in these political things.

I would point out to you, Senator Boxer, you mentioned the fact that there is an epidemic of birth defects. I spent my whole life studying birth defects. It is not an epidemic of birth defects. What happened is it tells you we solve problems. In 1908 8 percent of children died from birth defects. In 1988 25 percent of children died from birth defects in the first year of life. Why? Because we got rid of scarlet fever, dyptheria, whooping cough, all the diseases, infantile diarrhea. So what happens is birth defects make up a higher proportion of deaths. It is not because they are increasing. See, you have to be careful that you misinterpret the information erroneously. You say we have an epidemic of birth defects; we don't have an epidemic of birth defects. I wish we could prevent all birth defects, but we can't.

Anyway, my recommendation is science. We have got to support the EPA to do the scientific studies. We have got to develop risk analysis procedures. When we can't do it with the chemical high throughput test, we then take an animal study and try to do it. That is our answer. We have got to support science. We need more science. We need pharmacokinetics, we need tahokinetics, and we have got to use that data to determine which of those chemicals out there are at most risk. So you have got to depend on science here.

Senator BOXER. Thank you, Doctor.

Dr. BRENT. By the way, Senator Lautenberg, I hope your child is on inhalation steroids, because if he is not in inhalation steroids he is going to keep having asthma attacks.

[The prepared statement of Dr. Brent follows:]

Oncogenic sensitivity of children to environmental toxicants (Brent), 6-18-08

Robert L. Brent MD. Ph.D

The topic of oncogenic risks from exposures to mutagenic and other environmental toxicants is the relatively complex for several reasons. There are multiple causes of cancer and many of the animal and human studies only focus on one of the causes or one of the mechanisms. In humans, both in adults and children, cancer can be caused by the following etiologies or mechanisms of action (MOA) and these mechanisms may interact to increase or decrease the risks.

1. Spontaneous mutations (Chromosomal abnormalities, point mutations at the molecular level.)
2. Genetic predisposition. Inherited "cancer" genes. Polymorphism
3. Increased accumulation of mutations in populations of cells with increased rate of proliferation as the result of inflammatory processes (**Cohen et al 1995, 1998**) or in the aged population.
4. Genotoxic and mutagenic drugs, chemicals and physical agents
5. Endocrine receptor agonists and antagonists. Other receptor agonists and antagonists.
6. Increased mutations in harmartomas and other forms of displaced tissues (i.e. columnar epithelium in the lining of the vagina from intrauterine DES exposure).
7. Immunological suppression from genetic diseases, or environmental exposures to immunosuppressive toxicants.

Cancer is a leading cause of death in childhood and adolescence **(Napier, 2003)**. In the age group of 1 to 4 years, cancer is the third highest cause of death. From ages of 5 to 9 and 10 to 14, cancer is the second highest cause of death and from age 15 to 19, cancer is the fourth

highest cause of death and during adulthood, cancer is the second highest cost of death. Environmental oncogenic exposures can occur during preconception gametocyte development, pregnancy, childhood, adolescence and adulthood. While here are many causes of cancer, including environmental toxicants, there is uncertainty with regard to the magnitude of the contribution of environmental toxicant exposure (chemicals and drugs) to the overall incidence of cancer in children and adults. It is common knowledge that tobacco smoking and the ingestion of alcohol significantly increased the risk of certain cancers.

What is the impact of chemicals and drugs on the prevalence of cancer in these age groups? There is a truism in toxicology that indicates that children are at greater risk from exposure to environmental toxicants. If the toxicant's effect is deterministic and therefore has a threshold, then the threshold for children may be lower. Investigators as a group, are not supportive of this generalization that infants and children may be more sensitive, since there is data that indicates that developing organisms may be less sensitive or equally sensitive to a many environmental toxicants **(Done, 1964; Brent et al., 2004, Brent and Weitzman, 2004. Sheuplein et al., 2002).** stated, "The newborns metabolic activity rapidly matures, and by about 6 months of age, children are usually not more sensitive to chemical toxicity than adults. By then most metabolic systems are relatively mature, becoming almost completely capable by one year of age. In many instances children are less sensitive than adults. Whether children are at greater risk from chemical exposures is another question".

If the toxicant has a mutagenic effect and has the potential for the induction of cancer, then the effect is considered to be stochastic and theoretically there may not be a threshold. However, there is not unanimity of opinion concerning the universal application of the linear-no-threshold hypothesis for risk assessment of mutagenic oncogenic agents. There is a significant

group of scientists that support the concept of "hormesis" which subscribes to the concept that toxicants, that are harmful at high exposures, may be without effects or even beneficial at very low exposures (Luckye 1980, 1994). This concept has not been generally accepted by the scientific community.

Children are believed to be more sensitive to the oncogenic effects of mutagenic agents. The magnitude of the increased risk varies considerably with the oncogenic agent and the life-stage when the exposure occurs. The following life stages have to be considered.

1. Preconception exposure to environmental toxicants

The risk of mutagenic exposures to the gametocytes of adults and the risk of mutations in the ova or sperm that would increase the risk of cancer in the F-1 offspring has been studied in animal models and large human populations exposed to environmental toxicants. High exposures of some cytotoxic drugs and chemicals can produce sterility in animal models as well as an increase in the incidence of pregnancy loss from unbalanced chromosome abnormalities. However, the frequency of chromosome abnormalities in the offspring that are viable is very low. The incidence of cancer in the viable offspring is not measurably increased in these human population studies. In humans this is a low risk phenomenon as indicated by numerous human epidemiology studies. (**Ames and Gold, 1990; Boice JD et al., 2003; Brent 1994, 1999, 2007, Brent et al., 2004; Byrne, 1999; Mulvihill et al 1987, Neel, 1999; Neel and Lewis, 1990; Nygaard et al., 1991a and b; Winther et al., 2004**). There are some researchers who are of the opinion that methylation mutations produced by preconception pesticide exposures in animal models has been demonstrated to be inherited and these investigations are ongoing in some laboratories (**Anway.et al 2005**).

What questions have been raised with regard to preconception exposures of children that may or may not be applicable to other populations? In Nygaard's studies of almost 1000 leukemic children who were successfully treated for leukemia there was a much higher incidence of infertility in the males than in the females; a significant gender difference in infertility. If the surviving patients became pregnant or fathered a child successfully, the incidence of developmental problems in the offspring was not increased (Nygaard et al 1991 a and b). Whether this gender difference in susceptibility can be applied to adult populations has not been definitively answered. While infertility has been observed in the offspring of adults who were treated for cancer as children or adolescents, there does not appear to be an increase in cancer in the F-1 generation, but the numbers of F-1 children in these studies are small.

2. Oncogenic risks from *in utero* exposures to environmental toxicants

There are publications that indicate that *in utero* embryonic or fetal exposures to environmental toxicants can increase the risk of cancer in the offspring. Two widely studied intrauterine toxicants are diethylstilbestrol (DES) and ionizing radiation. A research group at the "Boston Lying-in Hospital" published their report on the benefits of DES administration during problem pregnancies for "preventing late pregnancy accidents" (**Smith 1948; Smith et al. 1946; Smith and Van S. Smith 1949**). The alleged benefits of DES were accepted by a large group of practitioners for the treatment of recurrent abortion, pregnant diabetics, threatened abortion, pregnancy bleeding, hypertension and other pregnancy problems (**Marselos and Tomatis 1993; Noller and Fish 1974**).

In 1971 the FDA removed its approval of the use of DES for use in pregnant women (**FDA Drug Bulletin 1971**). This was the same year that **Herbst et al. (1971)** reported the cluster of cases of clear-cell adenocarcinoma of the vagina (CCACV) in young women whose

mothers had been administered DES during pregnancy. It was Herbst's effort to create the registry that permitted the accumulation of cases of clear cell adenocarcinoma of the vagina (CCAV) and to estimate the incidence between 1:1000 and 1:10,000 exposures of DES during pregnancy.

Studies of the exposure of ionizing radiation to pregnant animals and to pregnant women have **not** resulted in consistent results with regard to the risk of cancer in the offspring. Stewart and colleagues reported that the embryo was much more sensitive to the oncogenic effects of ionizing radiation than the child or adult **(Stewart, 1970; Stewart et al., 1958; Stewart and Kneale, 1973).** In 1999 Boice and Miller published their interpretation of the data pertaining to the oncogenic risks of intrauterine radiation. They noted, "Evidence for a causal association derives almost exclusively from case-control studies, whereas practically all cohort studies find no association, most notably the series of atomic bomb survivors exposed in utero." The most recent report from Radiation Effects Research Foundation (RERF) supports the conclusions of **Boice and Miller (1999). Preston et al (2008)** compared the oncogenic effect of in utero and childhood radiation exposure and concluded that "the lifetime risks following in utero exposure may be considerably lower than following childhood exposure", which is in marked disagreement with Stewart's conclusions about the marked increase in risk following in utero radiation.

During the final preparation of this manuscript the long-awaited results of the in-utero radiation carcinogenic effects were published in March 2008 in the Journal of the National Cancer Institute by Preston et al (2008). The data is summarized in Tables 1 and 2
The authors concluded,

> "Lifetime risks following in utero exposure may be considerably lower than for early childhood exposure, but further follow-up is needed. There was no statistical increase in the oncogenic risks of in utero exposed individuals with exposures <0.2 Sv (,20 rads) (Table 1). The in utero exposed population was much less sensitive to the oncogenic effects of radiation than the children that were exposed to the A-bomb[144] (Tables 2 and 3).

It is interesting that the research of Rugh et al. (1966) and Brent and Bolden (1961) indicated that the embryonic mouse was less sensitive to the oncogenic effects of ionizing radiation than the postnatal mouse. However, both Rugh and Brent were reluctant to refute Stewart's conclusion that the radiation induced oncogenic risk of the human embryo was two orders of magnitude greater than the postnatal human based on the mouse radiation studies alone.

Preston et al. (2008) concluded that the embryo is actually less sensitive to the oncogenic effects of ionizing radiation than the young child (Tables 1 and 2). In fact these authors concluded that below 0.2 Sv (20 rad) there was no statistically increased incidence of cancer in the in utero population. This is in marked contradiction to the studies of Stewart in the 1950's to the 1970's that copncluded that the fetus was markedly more sensitive to the oncogenic effects of ionizing radiation that the child or adult.

Table 1				
Number of patients with solid cancers				
In utero exposure from the Atomic bomb				
Dose in Sv (rads)	No. of patients	No. of Cancers	Person years	% of Cancers
<0.005 (<0.5)	1547	54	49,326	3.5
0.005-<0.1 (0.5 to 10)	435	16	14,005	**3.7**
0.1 to <0.2 (10 to <20)	168	6	5041	**3.6**
0.2 to <0.5 (20 to <50)	172	8	5496	**4.6**
0.5 to <1.0 (50 to <100)	92	7	2771	**7.6**
>1.o	48	3	1404	**6.2**
Total	2452	94	94	**3.5**

Table 2				
Number of patients with solid cancers				
Early childhood exposure from the Atomic bomb				
Dose in Sv (rads)	No. of patients	No. of Cancers	Person years	% of Cancers
<0.005 (<0.5)	8549	318	247,744	**3.7**
0.005-<0.1 (0.5 to 10)	4528	173	134,621	**3.8**
0.1 to <0.2 (10 to <20)	853	38	25,802	**4.4**
0.2 to <0.5 (20 to <50)	859	51	25,722	**5.9**
0.5 to <1.0 (50 to <100)	325	21	9522	**6.5**
>1.o	274	48	7620	**17.5**

Total	15388	649	451,031	4.2

One of the mechanisms hypothesized to explain the increased risk of cancer in offspring that were irradiated in utero is the increased prevalence of chromosome abnormalities in the cells of the in utero irradiated offspring. Nakano et al, (2007) irradiated mice in utero with 1 or 2 Gy of x-rays and 6 week-old mice with the same exposures. The mice irradiated at 6 weeks of age had a 5% incidence of translocations while the mice that were irradiated in utero had a 0.8% incidence of translocations. The authors found that the embryos were sensitive to the induction of chromosome aberrations, but that the aberrant cells do not persist because fetal stem cells tend to be free of aberrations and their progeny replace the pre-existing cell populations during the postnatal growth of the animals.

For 50 years the predominant view has been that the embryo is much more sensitive to the oncogenic risk of ionizing radiation than the child or the adult. This view prevailed in spite of the fact that many cohort studies were negative and the case control studies were not consistent. The most recent data provided by outstanding and objective scholars is that the embryo is less sensitive to the oncogenic effects of ionizing radiation and that there may even be a threshold for the oncogenic effects.

These results raise a number of issues.

1. Is there a threshold or no effect exposure for the oncogenic effects of some chemicals or drugs, not only for the embryo, but for the child and adult as well?
2. Because there are multiple mechanisms and exposures that increase oncogenic risks it is difficult to establish generalizations regarding exposures and oncogenic risks. In fact oncogenic risks that result from the production of congenital malformations or displaced tissues (DES) have less of a role in increasing cancer risks from exposures to children and adults.

3. Oncogenic risks from environmental toxicant exposures in children and adolescents

An increase in carcinogenic risks has been demonstrated for children exposed to high doses of ionizing radiation, and for exposures to radioactive ^{131}. A number of authors and agencies have suggested that children may be 10 times more sensitive to the oncogenic effects of ionizing radiation. In Hall's 2002 publication he writes, "It is clear that children are ten times

more sensitive than adults to the induction of cancer" **(Hall, 2002) (Figure 1)**. Figure 1 is a simplification of Figure 3 in Hall's 2002 publication. This graph is not a chart of the relative sensitivity of different aged individuals to the oncogenic effect of radiation, but a chart of the decreasing ability of older individuals to manifest the full extent of the oncogenic risks and the greater risk that the older population will die from non-radiation causes. It takes 40 to 50 years to manifest the full extent of the risk of whole-body ionizing **radiation.** There are reports that indicate that low exposures to radiation, below 0.2 Gy (20 rad) do not increase the risk of cancer. The scientists from the Hospital for Sick Children reported on the incidence of cancer in infants who had cardiac catheterization from 1946 to 1968 at a time when image amplification was not utilized and therefore exposures could be as high as 0.3 Gy (30 rad). Yet, there was no increase in any type of cancer in this population (almost 5000 patients in the original exposed population involved in the study) reported in 1983 and 1993. **(Spengler et al., 1983, McLaughlan et al., 1993)**.

Most agents that have been demonstrated to be carcinogenic in humans will produce cancer in some laboratory animals, but not all laboratory animals. But the converse is not true; namely, that all agents that have been demonstrated to be carcinogenic in animals are carcinogenic in humans. Animal studies have revealed marked differences among species with regard to the oncogenic susceptibility to environmental chemicals and drugs as exemplified by the phthalates. Animal carcinogenicity studies utilizing the phthalates and other chemicals that stimulate the peroxisome proliferation response may not be appropriate models to determine human cancer risks (**Koop et al., 1999**).

The second agent that received much attention is saccharin, which produced bladder cancer when high doses of saccharin were administered to rodents. At high doses, precipitates of

saccharin accumulate in the rodent bladder producing inflammation and proliferation that ultimately results in bladder tumors. Other experiments indicated that human exposures of saccharin would never result in the situation that occurred in the rodent (**Cohen et al., 1995; 1998, 2006; Dominick et al., 2006; Wei et al., 2005**)

We really do not have enough data pertaining to each mutagenic agent to be able to estimate the risk of its mutagenic effect. Many of these studies are ecological studies, in which the exposure is estimated or even hypothesized. No measurements are made on the exposed populations. The exposure is assumed because of the location of the population being studied. That risk estimates based on an assumption of the exposure, may be erroneous. Many of these exposures are mixtures and we are still attempting to solve the problem of estimating the toxic effect of mixtures.

While there is no question that the developing embryo, child and adolescent are more susceptible to oncogenic effects of mutagens there is very little discussion in the available publications about the dose response curve of the mutagenic agents and whether there is a threshold for mutagenic effects at low exposures which frequently occur with exposures to environmental chemical agents and whether the NOAEL is the same or lower for developing humans.

Many of the animal studies utilized very large doses of the mutagens and most investigators did not determine a NOAEL. In many of the human industrial exposure studies or air pollution studies the content of the contaminated environment is not quantitatively determined. None of the studies evaluated the immunological status of the animals to determine whether the immune system was suppressed by the genotoxic agent. We know that when the immune system is suppressed the risk of cancer is increased. This happens clinically when

patients are administered large doses of cortisone, are treated with chemotherapeutic drugs or develop immune deficiency diseases. Genetic effects in the F-1 generation cannot be determined in preliminary one-generation or multigenerational studies, because you would need very large populations of animals to perform studies that would estimate human risks for genetic disease in the offspring of exposed adult animals prior to conception, except for the Rodent Dominant Lethal Assay (**Environmental Protection Agency, EPA 1998 a-d**)

Most publications refer to the variable risk of cancer in the fetus, child and adolescence as the result of variable sensitivity. In other words, the infant is more sensitive to a mutagenic agent and therefore has an increased risk of cancer following an exposure. Actually there are two other explanations for the increased life-long cancer risk that infants may manifest. A developing organism has a greater proportion of its cells undergoing division and therefore the cells may not be more sensitive, but the proportion of susceptible cells is greater. More important is the fact that the child that is exposed has a lifetime to manifest the genotoxic effect in a clinical malignancy (waiting for that second mutation to occur).

The difficulties that we face in determining the oncogenic risk of environmental toxicants are that most of the animal studies utilize exposures above the typical population exposures. We do not know whether there is a NOAEL for the induction of cancer from chemicals, drugs or even physical agents... We do not know whether the NOAEL is lower or higher in developing organisms. Many of the publications that estimate oncogenic risks are in disagreement and we do not know which is correct or whether any of the risk estimates are correct. Even the concept that the developing organism is more "sensitive" has to be evaluated. Are the cells more sensitive; are there more cells in the sensitive stage (proliferating) or is the organism more "sensitive" because it has a longer period of time to manifest the toxic effects? Obviously, there are important

problems to solve for the scientists working in the field of the oncogenic effects of environmental toxicants.

Conclusions:

1. Since children are still developing during childhood and adolescence it is believed that children are more sensitive to the effects of environmental toxicants and that they may be more susceptible to the oncogenic and mutagenic effects of oncogenic exposures. What we do not know is whether there is a threshold for chemically induced oncogenensis and if there is a threshold, is the threshold lower, higher for children than adults or the same.

2. The studies dealing with the survivors of childhood leukemia indicate that boys who receive chemotherapy are four times more likely to be infertile than the girl survivors. We do not know the extent of infertility of males in adult populations treated with chemotherapy when compared to females similarly exposed..

3. In the past it was believed that the embryo was the most sensitive to the oncogenic effects of environmental toxicant, but the recent publication of Preston et al (2008) indicated that the embryo was less sensitive than children and that there was a threshold below which the risk was not increased.

4. Immunological suppression is a mechanism responsible for an increased risk of cancer. This phenomenon occurs in both children and adults. It is not known whether the increased incidence in these immunosuppressed populations is due to the inability to monitor spontaneously occurring new cancer clusters or because the oncogenic mutations are increased in the population exposed to immunosuppressants.

5. While animal studies are useful for studying the toxic effect of chemicals, the problem with the risk of cancer in humans from oncogenic exposures is the long latency period. The long

latency period differentiates human cancer development and animal cancer development following oncogenic exposures.

All these factors make it extremely difficult to transpose investigations in animals and humans at one stage to other human stages for determining both qualitative and quantitative risks for cancer.

PEDIATRICS

Preface

Robert L. Brent and Michael Weitzman

Pediatrics 2004;113;933-934
DOI: 10.1542/peds.113.4.S1.933

Preface

Robert L. Brent, MD, PhD*, and Michael Weitzman, MD‡

ABBREVIATIONS. NOAEL, no observable adverse effect level; MPL, maximum permissible level.

We are very appreciative for the support of the Environmental Protection Agency to permit this project to go forward and to all of the authors and reviewers of the many chapters in this supplement to *Pediatrics*. We especially thank Ramona Trovato and Martha Berger of the Environmental Protection Agency's Office of Children's Health Protection for their encouragement and assistance.

We have dedicated this supplement to practicing pediatricians in the hope that the articles in this supplement will stimulate their interest in reading and understanding the rapidly enlarging literature dealing with pediatric environmental toxicology. A better understanding of epidemiology and toxicology publications will permit the physician to be able to read the literature more critically. This should enable pediatricians to better counsel their patients about the risk or lack of risk of environmental exposures. The readership of this supplement will also realize that some scientists have taken positions that many environmental toxicants are a major child health problem whereas others have minimized the risks of children's environmental exposures. Objectively, there are environmental toxicant exposures for which we have substantial evidence of serious effects at levels frequently experienced by children, and there are others for which there are either inadequate data or the data do not support danger to children. For some, there is clear evidence that the fetus and the child has increased sensitivity and vulnerability; for other toxicants, there is evidence of increased resilience and decreased vulnerability. For most chemicals, however, we do not yet have the actual exposure level of the nation's children or adequate data concerning the no observable adverse effect level (NOAEL). This is why the most important conclusion of this supplement is the request for significantly increased and improved pediatric environmental toxicology research.

Important terms used in this monograph include the NOAEL, which is the highest exposure at which no adverse effect is seen. The threshold exposure is the lowest exposure at which deleterious effects can be produced or observed. These 2 exposures are very similar, with the threshold exposure being slightly higher. Another term is the maximum permissible exposure or maximum permissible level (MPL), which refers to a level of exposure that is established by regulatory agencies to protect the public. Clinicians frequently confuse this term with the NOAEL. This means that 2- to 10-fold increases above the MPL or even higher exposures may still not have any demonstrable adverse effect on the embryo, child, adolescent, or adult. However, to be cautious so that the public is not at increased risk, MPLs are usually set very low. There frequently is honest debate about the level at which the MPL should be set, with the need to regulate exposure despite limited data.

Throughout this supplement, pediatricians have been complimented for their contributions to discoveries of environmental risks and for educating their patients about these risks. Perhaps their greatest contribution has been the recognition of clusters of patients with relatively acute, or "toxic," exposures, usually those that have led to overt signs and symptoms and often distinct clinical problems. This supplement illustrates that illnesses, diseases, and subtle but serious alterations or decrements in functioning that occur at low exposure levels of environmental toxicants are more difficult to identify when observing small clusters of patients with illness or disease or those with no readily apparent signs or symptoms but with low-level exposure. With low exposures, sophisticated epidemiology and toxicology tools must be introduced. It is difficult to conclude definitively a causal association from low exposures of environmental toxicants without appropriate studies, many of which require large numbers of children followed over extended periods of time. Several such studies are discussed in detail in this supplement. A serious problem occurs when physicians or scientists are willing to conclude a causal association when adequate data are not available or not to conclude a causal relationship in the face of extensive data supporting such a relationship. Although most pediatricians have been responsible in this area of medicine, there have been those who have taken positions that were not in the best interest of children. For example, the few physicians who mounted campaigns against immunization in the media and in the courts, or, more recently, the decision to remove ethyl mercury (in the preservative thimerosal) from vaccines that was not based on scientific evidence of adverse effects. In 2001 the Centers for Disease Control and Prevention convened a panel of >100 scientists, who

From the *Thomas Jefferson University, Alfred I. duPont Hospital for Children, Laboratory of Clinical and Environmental Teratology, Wilmington, Delaware; and the ‡American Academy of Pediatrics, Center for Child Health Research and Department of Pediatrics, University of Rochester School of Medicine and Dentistry, Rochester, New York.

reviewed the epidemiologic data, animal studies, and the pharmacokinetics of ethyl mercury and concluded that the vaccines with ethyl mercury, at the levels being used, were without risk to children, yet the ethyl mercury was removed, resulting in a period of vaccine shortage, and the necessity to handle the vaccines differently, thus raising their costs.

The most important message of this supplement is this: you cannot reach definitive conclusions about cause and effect of environmental toxicants without quality epidemiology, toxicology, and basic science research studies.

To make certain that the pediatrician maintains his or her global view of environmental risks, we have added an appendix entitled "Prioritizing Environmental Risks." It is something that pediatricians do every day in their office when they interact with patients and their families. We hope that this supplement will be of interest and use to pediatricians as the field of pediatric environmental health continues to grow and to provide vitally important new information about the effects of environmental exposures on our nation's children and ways to protect them from these exposures.

Preface

Robert L. Brent and Michael Weitzman

Pediatrics 2004;113;933-934
DOI: 10.1542/peds.113.4.S1.933

PEDIATRICS®

A Pediatric Perspective on the Unique Vulnerability and Resilience of the Embryo and the Child to Environmental Toxicants: The Importance of Rigorous Research Concerning Age and Agent

Robert L. Brent, Susanne Tanski and Michael Weitzman

Pediatrics 2004;113;935-944
DOI: 10.1542/peds.113.4.S1.935

A Pediatric Perspective on the Unique Vulnerability and Resilience of the Embryo and the Child to Environmental Toxicants: The Importance of Rigorous Research Concerning Age and Agent

Robert L. Brent, MD, PhD*; Susanne Tanski, MD‡; and Michael Weitzman, MD‡

ABBREVIATIONS. PCB, polychlorinated biphenyl; MPE, maximal permissible exposure; NOAEL, no observable adverse effect level.

There is realistic concern about the impact of environmental influences on the health of human populations. First, exposure to environmental agents continues despite successes in reducing exposures to known toxicants such as lead, polychlorinated biphenyls (PCBs) and tobacco smoke. Second, there has been increasing concern about the cause of autism and other neurodevelopmental problems and hypotheses that environmental influences may play a role in the prevalence of these and other such childhood and adult conditions as asthma and obesity. Third, many other conditions are directly or indirectly related to environmental influences and are preventable, such as injuries, untoward consequences of alcohol, suicide, drug addiction, and gun-related deaths. There have been numerous publications since the 1970s of symposia, proceedings, monographs, and articles dealing with the increased susceptibility of the embryo, infant, and child to environmental toxicants,[1–17] reflecting a greater level of concern about embryonic and childhood exposures. Indeed, great deal of attention has been paid to the vulnerability of the embryo and the fetus to environmental chemicals, drugs, and physical agents. In fact, the publication edited by Miller[1] was primarily devoted to exposures to the embryo and the fetus. Because the embryo and the child are growing and their tissues and organs are differentiating, deleterious effects may occur at lower exposures to some chemicals, drugs, and physical agents and produce more severe effects than those seen in adults. In fact, some effects may not occur in adults. Thus, maximal permissible exposures (MPEs) for some environmental chemicals should be lower for the embryo and the child.

It is important to note that children and adolescents have better recuperative capacities than adults for many toxic agents, and, similarly, appropriate drug dosages may be lower or higher on a mg/kg or surface area basis in children than in adults to attain effective therapeutic blood levels or to avoid toxicity. In addition, effects produced by drugs, chemicals, and physical agents are not always deleterious or always irreversible. This means that for some exposures, the young can recover from some effects more rapidly and completely than adults (Table 1). If the exposure does result in irreversible effects by exceeding the threshold exposure, then the impact on a developing organism can be more severe than in the adult.

Much of the discussion and publications that deal with the vulnerability of the developing embryo, infant, child, and adolescent to environmental agents have focused on particular environmental toxicants or agents, summarizing the spectrum of pathology that results from exposures to these agents. There is nothing wrong with this approach from the toxicologist's point of view, because it is obvious that the developing child and adolescent can be more severely or differently affected by some environmental toxicants.

GOALS

This supplement to *Pediatrics* is being directed toward pediatric clinicians; thus, there are goals that are different from previous conferences, workshops, and publications.

1. To bolster the enthusiasm of practicing pediatricians for diagnosing, treating, and preventing illnesses and subtle but serious long-term negative effects caused by toxic environmental exposures. This supplement contains an article by Dr Robert Miller that provides a historical perspective on the

From the *Thomas Jefferson University, Alfred I. duPont Hospital for Children, Laboratory of Clinical and Environmental Teratology, Wilmington, Delaware; and the ‡American Academy of Pediatrics, Center for Child Health Research and Department of Pediatrics, University of Rochester School of Medicine and Dentistry, Rochester, New York.

Received for publication Oct 7, 2003; accepted Oct 20, 2003.

Dr Brent's research support has been derived from government research grants from NIH, DOE, and AEC. He has never received research funds from industry and is presently supported by his own institution, the Nemours Foundation. He has been a consultant to Congress, AAP, NIH, FDA, CDC, and industry in his area of expertise, environmental causes of reproductive pathology and oncogenesis. He is a consultant to the Health Physics Society's Web site, "Ask the Expert," and counsels, at no fee, ~600 consultations each year. He has been an expert witness to the courts in the Bendectin and progestational drug lawsuits as a defense expert, the former resulting in the important Daubert decision, as well as other nonmeritorious litigation involving allegations of teratogenicity. He was one of the experts who volunteered to provide expert testimony in litigation against the alcoholic beverage industry to have all alcoholic beverages provide a warning for pregnant women. All of the fees for consulting were deposited in medical school departmental accounts and more recently in a philanthropic fund. He did not accept any fees from EPA for editing this supplement.

Reprint requests to (R.L.B.) Rm 308, R/A, Alfred I. duPont Hospital for Children, Box 269, Wilmington, DE 19899. E-mail: rbrent@nemours.org

TABLE 1. Sensitivity of Infants, Children, Adolescents, and Adults to Environmental Chemicals and Physical Agents*

Environmental Chemicals and Physical Agents	Specific Effects by Age	Ages Most Affected	
Asbestos	Schoolroom exposure has not been shown to result in increased risk of mesothelioma. The risk is related to the magnitude of the exposure, the shape and size of the particles, and the association of smoking in the exposed adult population.	Child?	Adult
Chlordecone (Kepone)	Tremors and neurologic effects were reported in adults who were manufacturing this chlorinated hydrocarbon insecticide, but there are no reports on differences in susceptibility between adults and children.	?	
Curare	Respiratory arrest from exposure. Survival shorter in adult than newborn.†		Adult
Cyanide	Respiratory arrest from injection. Survival shorter in adult than newborn.†		Adult
Dibromochloropropane	Exposure occurred in adults who were manufacturing this soil fumigant to control nematodes. Infertility and sterility as a result of a decrease or absence of sperm in adult male employees. There are no data on the susceptibility of children.		Adult
Endocrine disrupters	This is an issue that has multiple viewpoints that range from minimal concern to serious increased risks for environmental chemicals that have some affinity for sex steroid receptors.	?	
Lead	High exposure can result in convulsions, increased intracranial pressure, hypertension, and anemia for low exposures and decreased intellectual functioning and learning disabilities. The younger the child, the greater the susceptibility to these effects as a result of increased vulnerability from increased exposure, increased absorption, and the sensitivity of the developing brain. Intellectual decrements in children with blood levels above 10 μg/dL have been documented. In recent studies intellectual decrements with blood lead levels below 10 μg/dL have been suggested. Threshold or no-effect level has not been determined, neither has the mechanism of action at low levels.	Infant/child	
Mercury (inorganic)	Acrodynia (irritability, hypertension, flushing, erythema of palms) from hypersensitivity as a result of Hg-containing teething powders. This idiosyncratic reaction occurs most frequently in infants and children.	Infant	
Methyl mercury exposure resulting in central nervous system damage	High exposure of severe effects in the developing embryo and fetus. Threshold and NOAEL in children and adults under investigation.	?	
Mercury (Ethyl)	Low-level exposures in vaccines are unlikely to represent a risk.	?	
Organophosphate insecticide exposures	Data on effects in humans at levels characteristic of environmental exposures are uncertain in contrast to toxic exposures from ingestion or employment. Neurologic symptoms and death if the dose is high enough. High exposures are more toxic in young animal when compared with adults (cholinesterase inhibitors). Neurologic symptoms and death if the dose is high enough.	Infant/child (toxic doses)	
PCBs	Toxic effects of high-level exposure in fetus well demonstrated. Low-level exposure effects in infant and child uncertain. Because of their fat solubility, they are present in breast milk.	Infant/child?	
Radiation (ionizing) induced breast cancer	Adolescents exposed during puberty have the greatest risk from radiation exposure. Infants and children exposed during the preadolescent period are less susceptible to breast cancer induction.		Adolescent
Radiation, ionizing: leukemia risk from high-dose whole-body exposure	Children have a higher risk per unit of exposure for leukemia.	Infant/child	
Radioactive iodine (I) 131 released from Chernobyl resulting in thyroid cancer	Children were the most susceptible to the induction of cancer of the thyroid, although the data are still being analyzed and debated.	Infant/child	
Sarin and other potential terrorism chemical agents	Sarin, chlorine gas, nitrogen mustard. A higher density of gas places a higher concentration of the gas closer to the ground in the breathing zone of children.	Infant/child	
Second-hand tobacco smoke's (ETS) effects on multiple systems	Infants and children are at increased risk for lower pulmonary infections, asthma, otitis media, SIDS, behavior problems, and neurocognitive decrements. Increased risks for lung cancer in adults.	Infant/child	
Strychnine	Respiratory arrest from exposure. Survival shorter in adult than newborn.†		Adult

SIDS indicates sudden infant death syndrome; ETS, environmental tobacco smoke.
* Refer to Tables 6 and 7 on pp 962–964 dealing with the effects of intrauterine (gestational) exposure to environmental toxicants and teratogens.
† Based on animal model data.

discoveries of environmental toxicants by pediatricians and other alert physicians and scientists. It is a thrilling article that honors practicing pediatricians for their accomplishments in discovering environmental toxicants. Dr Miller would like all pediatricians to think of themselves as environmental detectives, and the article is really a charge to every practitioner to become interested in discovering new and unique environmental toxicants. Discoveries of environmental toxicants have been made by alert practitioners who identified a cluster of patients with illnesses associated with an environmental exposure. Such discoveries are a low-probability event in any practitioner's lifetime, given that most clusters of illnesses or diseases that are identified are not found to be causally associated with an environmental toxicant. However, "thinking environmentally" while practicing medicine will make every physician a better practitioner, even if not necessarily a famous one.[18] Please read Dr Miller's article.

2. To provide information about children's environmental health from a clinician's viewpoint rather than that of a toxicologist. Although most previous publications have focused on the effects of particular toxic agents, this supplement presents both the clinical and the toxicologic perspective. Because it is clinicians who evaluate clinical symptoms and clinical disease, we have asked a number of clinicians to discuss the maturation of organ systems during prenatal development, infancy, childhood, and adolescence and their sensitivity to toxicants at different stages of childhood development. There are articles on the heart, lungs, liver, gastrointestinal tract, skin, kidney, central nervous system, hematopoietic system, teeth, and endocrine systems as well as discussions of the present state of our knowledge of the more prominent environmental toxicants. We have asked the authors to present the data and information so that clinicians can use this information when confronted with a clinical problem that may be attributable to an environmental toxicant or drug.[19] In addition, there are articles that describe the role of federal agencies, recent changes in drug monitoring for children, and risk assessment. It is our hope that this supplement will provide pediatricians with a current overview of what is and is not known about the effect of the environment on children's health.

CONTROVERSIES AND CONCLUSIONS

Any discussion of the importance and magnitude of the contribution of environmental agents to human morbidity and mortality tends to provoke spokesmen on both sides of the issue. Segments of the scientific and lay community believe that environmental agents are major contributors to disease and death, whereas other scientists and lay individuals believe that environmental risks have been grossly exaggerated. When it comes to the issue of the vulnerability of children to environmental toxicants, a similar polarization of views exist. Only the facts, impeccable science, and more research will place the field of environmental toxicants and their effects on children into proper perspective. The facts clearly indicate that children are different from adults, which is amply documented in Tables 1 to 5. This necessitates obtaining data on each individual toxicant or potential toxicant to determine children's vulnerability to a particular agent and to determine the magnitude of their increased or decreased sensitivity and vulnerability. Unfortunately, few generalizations about children's vulnerability to environmental exposures apply, given that vulnerability and sensitivity are specific to a child's age and developmental stage and also to the agent.

We have accomplished a great deal in the past 40 years with regard to children's vulnerability to environmental toxicants, and some of the accomplishments have had a very positive effect. The most dramatic example is the reduction in blood lead levels in children in the United States. The topic of lead toxicity is discussed eloquently by David Bellinger in one of the articles in this supplement, but even in the area of lead toxicity, we still have many unanswered questions and much to do to protect children from being exposed. We do not know the no observable adverse effect level (NOAEL) for most environmental toxicants, and, of course, those agents with genotoxic potential are considered to have no threshold.

Some scientists have suggested that because we do not have valid information on most environmental toxicants in adults and children that we should use a factor of 10 in establishing MPEs for children. There is little scientific evidence to validate this suggestion, however. For example, drugs such as morphine and chloramphenicol would still be hazardous even with a 10-fold reduction in the medication dosage. Other drugs and chemicals may be more hazardous to the child than the infant, and in some instances, adults are the most vulnerable. Although as a generalization infants and children are the most sensitive and vulnerable to the effects of environmental toxicants, we should not regulate or practice medicine on the basis of generalizations.

Tables 1 to 5 list numerous differences between developing humans and adults. Most pediatricians and obstetricians are aware of many of these vulnerabilities. For example, we know that the infant's gastrointestinal tract will permit *Clostridium botulinum* to inhabit it and may result in infant botulism.[20] Conversely, we know that the developing embryo, infant, child, or adolescent has better recuperative powers from some insults. The child who has sustained brain damage from an infection, a stroke, or other types of brain injury may regain more function than an adult who sustains the same damage.

It is also important for the clinician to be aware that most environmental toxicants have a toxicologic dose-response curve after various exposures. As the exposure increases into the toxic range, the incidence and the magnitude of the deleterious effects increase. Below certain exposures, the NOAEL, there are no known deleterious effects.[21–24] (Fig 1) The problem for the clinician is that the NOAEL has not been determined or is controversial for many environmental toxicants and may differ by age as a result of

TABLE 2. Sensitivity of Infants, Children, Adolescents, and Adults to Drug Effects

Pharmacologic Drug	Specific Effects by Age	Ages Most Affected	
Acetaminophen overdose	Death from liver toxicity occurs in adults and more rarely in children.		Adult
Alcohol depression	Adults are more readily depressed than newborn; however, children are much more likely to develop profound hypoglycemia and seizures.	Child	Adult
Adrenocorticosteroids	Prolonged administration can reduce stature and skeletal maturation, which can occur only during childhood and adolescence. The younger the child, the greater the impact on growth and maturation	Child/ adolescent	
Alpha interferon	Spastic diplegia in infancy.	Infant	
Aminoglycosides	Infants who are treated with aminoglycosides and have *Clostridium botulinum* in their gastrointestinal tracts may have an increased neuromuscular blockade and prolonged severity of the paralytic phase.	Infant	
Aminoglycosides	Vestibular balance and hearing deficiencies as well as renal disease can occur after use. Rare in children, risk greatest in adults.		Adult
Androgens	May cause masculinization of girls, precocious puberty, exaggeration of masculine features in boys, and growth promotion in infants and children with the potential to reduce the child's mature stature. Exaggerated masculinization can also occur in adults or cause tumors of the liver.		
Aspirin or methyl salicylate overdose	Can lead to alkalosis, acidosis, respiratory distress, and death, occurring more frequently in children.	Child	
Bacitracin, neomycin, and polymyxin B	Nephrotoxicity more readily produced in adults.		Adult
Beta blockers	May cause hypoglycemia in infants and children.	Infant/child	
Chloramphenicol	When administered in the newborn, may cause "gray baby syndrome" with resulting vascular collapse and death. Most severe in the sick newborn. Blood levels may reach levels that are 10 to 20 times the expected therapeutic levels using mg/kg dosage schedule.	Infant	
Diethylene glycol	Was the diluent in an elixir containing sulfanilamide for use in children (1938); 107 children died from this medication, which was never tested for its toxicity.	Child	
Estrogens	Feminization of boys, precocious puberty, exaggeration of feminine features in girls, and growth promotion in infants and children, with the potential to reduce the child's mature stature. Exaggerated feminization can occur in adults.	?	
Fluorine ingestion	Causes tooth mottling and cosmetic damage. Children exposed during enamel formation most susceptible.	Infant/child	
Hexachlorophene	Applied to the skin as an antibacterial agent, there is greater risk of toxicity in premature and newborn infants with extensive skin exposure.	Infant	
Influenza vaccine	Less effective in infants <6 months.	Infant	
Isoniazid (INH)	Therapy with INH complicated by liver disease (ie, hepatitis) more common in adults.		Adult
Menadione (water-soluble vitamin K analogues)	Resulted in hyperbilirubinemia and kernicterus, with greatest sensitivity to effects in premature infants and neonates as a result of increased hemolysis.	Infant	
Meningococcal vaccine	Less effective in infants.	Infant	
Methemoglobinemia	From the administration of bismuth subnitrate, benzocaine and related topical anesthetics, sulfonamide rectal suppositories, phenacitin and long-acting sulfonamides and skin application of bitter almond oil, high levels of nitrates in the water supply or medications, aniline dyes, pesticides, and improperly canned foods. The infant is inordinately susceptible to the induction of methemoglobinemia. Nitrate conversion to nitrites can occur more readily in the neonate and infant's gastrointestinal tract because of bacterial flora.	Infant	
Methotrexate	May cause cirrhosis of the liver; primarily occurs in adults.		Adult
Methylphenidate therapy	May uncover a tic disorder. The majority of ADHD treatment occurs in children, and there are few data on this phenomenon in adults.	Child	
Morphine	A much lower dose of morphine must be administered to newborns because of the sensitivity of the newborn to morphine.	Infant	
Naloxone and other opioid antagonists	Infants who are exposed to morphine and whose respirations are markedly suppressed are treated with 0.01 mg/kg. Adults are treated with 40 times the infant dose for opiate overdose: 0.4 mg/kg	Infant	
Nitrobenzol	Respiratory arrest from injection. Survival shorter in adult than newborn.		Adult
Phenobarbital and diphenhydramine	May result in paradoxic irritability and agitation, which is seen more commonly in children or in the elderly.	Infant/child	
Phthalates	Most of the toxicologic data have been obtained in animal studies at high doses. The human has much lower exposures, and the theoretical risks depend on the phthalate and its source and use.	?	
Progestational drugs	When administered in large doses to pregnant women or children some progestational drugs can result in masculinizing effects to fetus or child. These are rare occurrences because the present-day dosages of progestational drugs are very low. The fetus and children are more susceptible to manifestations, such as clitoral hypertrophy from large exposures.	Infant/child	

TABLE 2. Continued

Pharmacologic Drug	Specific Effects by Age	Ages Most Affected	
Quinolone group of antibiotics	Results in cartilage damage in developing cartilage at very high doses in animal models and some tendon damage. Neither effect has yet been seen in children to any extent, but adults have been reported to have tendon pathology as a complication of therapy.		Adult
Rotavirus vaccine–induced intussusceptions	Occurred in infants and children.	Infant/child	
Seizure activity from strychnine, salicylate, and electroshock	Adult more sensitive to convulsions than newborn.		Adult
Sulfasoxazole	Administration in premature infants and newborns may result in an increase in kernicterus from the redistribution of bilirubin and transport across the blood-brain barrier, as a result of the uncoupling of bilirubin from serum proteins. Other drugs that have this potential are oxytetracycline, sodium salicylate, and sulfadimethoxine, possibly by a different mechanism.	Infant	
Tetracycline	Tooth and bone staining. At low exposures, the teeth and bone staining may have no deleterious effects, but if the exposure is very high, then there may be an effect on growth and tooth structure. The intensity of staining is greatest at the time of greatest enamel production, but children are susceptible as long as bone growth is still taking place. Premature infants treated with very high exposures to tetracycline have had reversible growth retardation.	Infant/child	
Tetracycline	May cause bulging fontanel and increased intracranial pressure in infants.	Infant	
Thiourea toxicity	Adult more sensitive to toxicity than newborn.		Adult
Thyroxine overdosage	More toxic in adults; may lead to atrial fibrillation.		Adult
Trimethoprim	Neurologic idiosyncratic reactions, possibly as a result of lowering of folic acid serum blood level after treatment, has been reported in adults.		Adult
Valproic acid	Therapy for epilepsy and psychiatric illnesses is complicated by hepatic injury (hepatitis) more commonly in adults.		Adult
Varicella vaccine	Less immunogenic in adults.		Adult
Verapamil	Occurrence of asystole in infants and children <2 years when Verapamil is used to treat surpaventricular tachycardia.	Infant/child	
Versed and other bezodiazepines	Adults seem to be more sensitive to these drugs, as in many instances the same total dose is used in children and adults (0.1 mg/kg; total dose in a 20-kg infant: 2 mg). An adult also might be treated with 20 mg.		Adult
Vitamin A /retinoids overdose	In children, can cause increased intracranial pressure, fever, retardation of bone growth, and periosteal bone hypertrophy. Adults can manifest increased intracranial pressure, headache, and bone pain.	Infant/child	Adult
Vitamin D deficiency	Rickets in children, osteomalacia in adults.	Infant	Adult
Vitamin E, alpha-tocopherol, high doses	Increased risk of necrotizing enterocolitis, hepatotoxicity, and thrombocytopenia in premature infants; may be lethal.	Infant	
Vitamin K3 and sulfasoxazole administration	Greatest risk in premature and newborn infants with a risk of clinically significant kernicterus from administration. Sulfadiazine and salicylates could lower the bilirubin serum level and increase the risk of kernicterus by uncoupling the bilirubin and permitting it to cross the blood-brain barrier.	Infant	

INH indicates Isoniazid; ADHD, attention-deficit/hyperactivity disorder

variations in absorption, metabolism, and excretion that themselves change over the course of the child's development. Similarly, when the clinician is confronted with a patient who has been "exposed," he or she may not be able to determine the amount or the length of exposure or even when it occurred. The clinician needs to know which environmental agents can have a greater impact on the developing child and at what exposure.

Animal studies can provide information on the variability of chemical sensitivity.[19] For example, some anesthetics are unable to anesthetize newborn animals at exposures that anesthetize adults, whereas ether alters reflexes at lower concentrations in newborn animals than in adults.[25] Newborn mice and other animal species have demonstrated a tolerance to hypoxic conditions that is not present in adult animals,[26–30] and newborn mice continue to breathe for a longer period when exposed to ether than adult mice.[31] Newborn mice also have a prolonged survival when compared with adults when asphyxiated as a result of exposure to CO, HCN, CO_2, H_2, and CH_3. Longer exposures to strychnine, curare, cyanide injection, strangulation, hypoxia, or nitrobenzol are necessary to produce respiratory arrest in newborn mice as compared with adult mice.[29]

In a summary of much of this animal information, Done[32] was cautious, pointing out the multiplicity and variability of experimental details in these studies. He concluded, "Some tentative generalizations and observations may be worth making.... It is apparent that immaturity does not necessarily entail greater sensitivity."

Another example in which infant animals are pro-

TABLE 3. Sensitivity of Infants, Children, Adolescents, and Adults to Infections

Infections	Specific Effects by Age	Ages Most Affected	
Acute hematogenous osteomyelitis	A greater risk in infancy and childhood.	Infant/child	
Chlamydia trachomatis	Pneumonia in young infants only.	Infant	
Clostridium difficile	More severe in adults.		Adult
Coxsackie A-16	Hand, foot, and mouth disease occurs almost always in young children.	Infant/child	
E coli O157:H7	Hemolytic uremic syndrome almost always occurs in young children.	Child	
Group B streptococcalepticemia and meningitis	Highest risk in the neonate.	Infant	
Hepatitis A infection	Clinically more severe in adults.		Adult
Hepatitis B infection	Can cause cirrhosis and hepatic cancer long term.		Adult
Hepatitis C infection			Adult
Herpes zoster	Usually mild in children outside the newborn period but can be devastating in newborns. Disease is more clinically severe and long lasting in older individuals. Post herpetic neuralgia primarily occurs in adults.	Infant	
Human herpes virus-6	Roseola in infants, fever of unknown origin in adults.	Infant	
Human herpes virus-8	No disease in children, Kaposi sarcoma in adults with HIV infection.		Adult
Infantile botulism	Paralysis from *Botulinum* toxin, as a result of ingestion of *Clostridium botulinum* spores, which are not destroyed in the stomach of infants because of the reduced acid secretion in their stomachs. Susceptible during the first several months of life because C *botulinum* spores are able to survive in the infant's gastrointestinal tract but not in a child's, adolescent's, or adult's gastrointestinal tract. Ingestion of toxin by adults results in food-bornebotulism.	Infant	
H influenza type B	Epiglottitis and meningitis in infants and children.	Infant/child	
Meningococcus	More susceptibility in the child and adolescent.	Child/ adolescent	
Influenza virus infection	Clinically more severe in adults with most of the mortality occurring in the aged.		Adult
Legionella pneumophila	Rare in children (a cold), life-threatening pneumonia in adults.		Adult
Listeria	Early/late-onset sepsis in the neonate. Occurs as meningitis in adults who are immunocompromised with AIDS.	Infant	
Mumps	Orchitis seen more often after puberty.		Adolescent/ adult
Parainfluenza virus	Croup in childhood but not in adults.	Infant/child	
Parvovirus B-19	Arthritis rare in childhood. More common in adults, especially women.		Adult
Pneumococcal lobar pneumonia	More severe in adults.		Adult
Poliomyelitis infection	Paralysis and bulbar symptoms are more frequent and severe in adults.		Adult
RSV virus infection	The younger the child, the greater the risk of bronchiolitis, which is especially dangerous in ex-premature infants with bronchopulmonary dysplasia.	Infant	
SARS	Mild disease if contracted in childhood, but nearly 10% mortality rate among adults.		Adult
Staphylococcal septicemia resulting in osteomyelitis	Occurs more commonly in children.	Infant/child	
Toxic epidermal necrolysis	More severe in adults.		Adult
Toxic shock syndrome	More severe in adults.		Adult
Varicella infection	Clinically more severe in a neonate whose mother was not immune, and in adults. Varicella pneumonia occurs primarily in adults and can be fatal. Varicella can be a very serious illness in adults, especially during pregnancy	Infant	Adult

HIV indicates human immunodeficiency virus; AIDS, acquired immune deficiency syndrome; RSV, respiratory syncytial virus; SARS, severe acute respiratory syndrome.

tected relative to adults is thiourea, which is 50 to 400 times as toxic in the adult as in infant rats.[33,34] Conversely, animal experiments with chloramphenicol clearly demonstrate that this drug is more toxic in the infant rat than in the adult, providing animal toxicity studies that corroborate the toxicity reported in human infants.[35–37] In Done's review of developmental toxicology,[32] he indicated that the newborn or infant animal was more sensitive to many drugs (chloramphenicol, morphine, some other opiates, picrotoxin, tetracycline, novobiocin, some organophosphate anticholinesterases, atropine, histamine, and sodium salicylate) and less sensitive to others (ethanol, strychnine, Metrazol, codeine, acet-cyclohexi-

TABLE 4. Sensitivity of Infants, Children, Adolescents, and Adults to Other Diseases and Physical Injury

	Specific Effects by Age	Ages Most Affected	
Addiction to alcohol and tobacco	Adolescents who start smoking and drinking in the preteenage and teenage years have a greater risk of permanent or life-long addiction.		Adolescent
Air bag activation injury	Greater risk for children, including death.	Infant/child	
Amblyopia	Blindness from eye disuse as a result of strabismus or discrepancy in visual acuity between the 2 eyes. Restricted to the first few years of life.	Infant	
Apnea of prematurity	Problems primarily related to premature infants and infants.	Infant	
Aseptic necrosis of femoral head	Greater risk in children	Child/ adolescent	
Brain damage from hypoxia	The severity of decrease in brain function is directly related to the length and severity of the hypoxia. Adult has less resistance to permanent brain damage and greater risk for permanent decrease in intellectual level.		Adult
Cardiac arrest	Uncommon in infants and children unless secondary to respiratory failure, or underlying congenital heart defect, but common in adults.		Adult
Colles' fracture	Greater risk for occurrence in adults with a fall.		Adult
Congenital heart block	Caused by maternal passage of anticardiolipin antibody among infants whose mothers have systemic lupus erythematosus. Heart block from localization of this antibody occurs only in newborns as a result of transplacental transfer of antibody. Adults with the antibody rarely have heart block.	Infant	
Convulsions from pyridoxine deficiency	Greater susceptibility in a group of infants who are more likely to convulse because of a need for higher amounts of pyridoxine administration.	Infant	
Epiphyseal disruption	Risk is present only in children.	Child	
Epiphyseal injury	Risk is present only in children with open growth plates.	Child	
Febrile seizures	Greatest risk in children 6 months to 5 years of life.	Infant/child	
Head injuries	Children are at greater risk for severe CNS injury but may have better recoverability if they survive.	Infant/child	
Hypoglycemia resulting in CNS damage	Greatest risk during brain development in neonates, infants, and children.	Infant	
Hypothyroidism resulting in mental retardation	The younger the child at onset, the greater the risk of mental retardation, with the greatest risk occurring in neonates with athyroidic cretinism.	Infant	
Intracranial hemorrhage	From hypoxia and electrolyte imbalance resulting in permanent CNS damage. Susceptibility in the neonate, with the greatest risk in the premature infant <34 wk gestational age.	Infant	
Intussusception	Most common in children <10 years of age; most are idiopathic. Intussusception rare, may be a complication of underlying GI anatomic pathology (eg, tumor).	Infant/child	
Iodine deficiency	Greater risk of decreased CNS functioning as a result of acquired hypothyroidism in infancy and childhood. Goiter in adults.	Infant	
Kernicterus	Resulting in deafness and neurologic problems from elevated bilirubin levels and increased blood-brain barrier permeability in the newborn period. Neonate most susceptible, although kernicterus has been rarely reported in older individuals. Very rare in adults as a result of well-developed blood-brain barrier.	Infant	
Osgood-Schlatter's disease	Occurs more commonly in childhood.	Child	
Osteoporosis	Primarily an adult disease.		Adult
Respiratory distress syndrome or hyaline membrane syndrome	Susceptibility greatest in premature infant.	Infant	
Respiratory failure	Susceptibility to pulmonary function decompensation because of the low ratio of vital capacity to tidal volume in infants. Pulmonary reserve lowest in the premature and newborn.	Infant	
Retinopathy of prematurity	Vascular injury secondary to use of oxygen therapy in the neonatal period, reducing visual acuity or blindness. Most severe in the premature infant.	Infant	
Reye's syndrome	Aspirin (ASA) and some infections (Varicella) are associated with the risk of Reye's syndrome, resulting in liver failure and death. Risk is greatest in children.	Infant/child	
Salter-Harris fracture	Limited to children and adolescents with open epiphyses.	Child/ adolescent	
Scalding from hot water and other heated agents	For each elevation of temperature and time of exposure, the child will sustain more severe damage and possible scarring because of the decrease in the thickness of the epidermis and dermis with decreasing age.	Infant/child	

TABLE 4. Continued

	Specific Effects by Age	Ages Most Affected
Steven Johnson syndrome	Secondary to drug therapy or some infections (diphenylhydantoin, sulfa drugs, varicella). Children and adolescents seem to have the greatest risk for being affected by this autoimmune reaction.	
Sudden infant death syndrome	Exclusively occurs in first year of life.	Infant
Sunburn	Identical physical exposures to the sun can result in more severe effects in the infant and child, which includes, first-, second-, and third-degree burns; hyperthermia, and heatstroke.	Infant/child
Temperature instability, including hypothermia	Greatest in premature infants and sick newborns, but more severe and greater risks in infants because of their decreased ability to maintain body temperature.	Infant
Transient tachypnea of the newborn	Early neonatal period: after cesarean section or birth to a mother with diabetes.	Infant
Volvulus	Susceptibility greatest in infancy and preschool years.	Infant/child

CNS indicates central nervous system; GI, gastrointestinal.

TABLE 5. Examples of Diseases That Primarily Occur in Infancy, Childhood, and/or Adolescence

Adenocarcinoma of the vagina from prenatal diethylstilbestrol exposure primarily in adolescence
Bronchiolitis
Caloric insufficiency as a result of failure to thrive resulting in neurocognitive impairment
Colic
Cow's milk allergy
Craniosynostosis
Croup
Disuse amblyopia
Ewing's sarcoma
Febrile seizures
Group B strep sepsis, pneumonia, and osteomyelitis
Henoch Schönlein purpura
Idiopathic intussusception
Impaired language development as a result of deafness
Increased susceptibility to caries as a result of environmental tobacco smoke
Infant botulism
Kernicterus
Medulloblastoma
Mental retardation as a result of hypothyroidism
Necrotizing enterocolitis
Neuroblastoma
Osteogenic sarcoma
Pyloric stenosis
Respiratory distress syndrome
Retinopathy of prematurity
Salter Harris fracture
Sudden infant death syndrome
Transient tachypnea of the newborn
Wilms' tumor

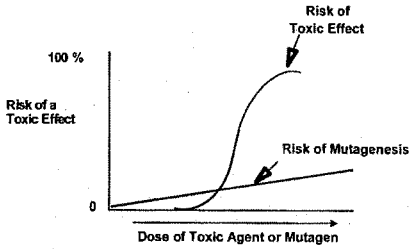


Fig 1. The dose-response curve of environmental toxicants (drugs, chemicals, and physical agents) can have deterministic (threshold) and/or stochastic effects. Mutagenic and carcinogenic events are stochastic phenomena and theoretically do not have a threshold exposure below which no risk exists. At low exposures, the risk still exists but is usually below the spontaneous risk of cancer and mutations. Whether the curve is linear or curvilinear for stochastic phenomena can be debated, but from a theoretical point, it traverses 0. Toxicologic phenomena, such as teratogenesis, that do not involve mutagenic and carcinogenic effects usually follow an S-shaped curve, with a threshold below which no increased risks are expected.

mide, thiourea, and thyroid hormone). Many other drugs have sensitivities that were similar in the neonate and the adult animal.

Tables 1 to 5 list a number of agents that are more toxic in the adult than in the infant and the child. There are many infections that produce more morbidity in adults than in children (eg, hepatitis, varicella, poliomyelitis). Drugs also may be more toxic or result in idiosyncratic effects in adults that occur rarely in children. For example, isoniazid produces hepatitis and methotrexate produces cirrhosis more frequently in adults.

Not only are adults sometimes more vulnerable than children, but also adolescents can be more vulnerable than infants and children. For example, a number of publications have indicated that exposure of adolescents to extensive and repeated radiology examinations increases their risk of developing breast cancer later in life.[38] One might expect that infants would be more susceptible to radiation-induced breast cancer than adolescents; however, the developing and proliferating adolescent breast seems to be more sensitive to radiation-induced oncogenesis than the infant breast.

In the following presentations, you will read about the vulnerability and sensitivity of the infant, child, and adolescent. In many instances, environmental agents will exploit these vulnerabilities and sensitivities. In other instances, there will be no difference between the developing organism and the adult when exposed to toxicants, and in some instances, the developing organism may even withstand the exposures with less insult. The difficulty that we have at this time is that we do not have enough data to arrive at conclusions about the relative sensitivity of the developing organism to many environmental agents. Rather than hypothesize about environmen-

tal agents or exposures for which there are insufficient data, we need to initiate investigative approaches to obtain the necessary data concerning agents and exposures that have not been clarified. It is important that there be an increase in quality research in environmental toxicology.

In human epidemiologic studies, we need to know the exposure sustained by infants, children, adolescents, and adults to environmental agents. In some instances, an apparent increase in sensitivity may actually be because certain child behaviors result in higher exposures. After the intense efforts of individual scientists and regulatory agencies in the United States, the exposures to lead and PCBs are dropping,[39] but that is not so with many other toxicants. The situation in the rest of the world varies considerably. Although some parts of Western Europe also have decreased their population's exposure to lead and PCBs, exposures have not been reduced in many third-world countries. Improving our epidemiologic surveillance is important to quantify more accurately the risks of environmental toxicants and any change in risks after interventional programs. With limited resources, we must invest in research and interventional programs that will have the greatest likelihood of success and the potential for affecting the most individuals.

What can we do to improve our knowledge of the risk of environmental toxicants for children? What information would be helpful to clinicians to assist them in understanding the complexity of the situation? Why are there scientists and clinicians who denigrate and others who exaggerate the impact of environmental toxicants on children as well as all humans?

We propose the following:

1. Rigorous methods must be used to evaluate environmental risks.[40–43] Diverse opinions occur because some scientists reach conclusions without adequate data. Single epidemiologic studies do not refute or demonstrate causality. The most important criteria to permit conclusions from epidemiologic studies are consistent, biologically plausible findings across a number of studies. Causality must be determined by a) epidemiologic studies; b) secular trends or ecological trends; c) mammalian animal toxicologic studies; d) pharmacokinetic and toxicokinetic studies; e) method-of-action studies; and f) biological plausibility: specificity, nature of the effect, receptor affinity, organ selectivity, stage of development, multiple causality, in vitro studies, etc.
2. Information on children's exposure to a wide range of environmental agents and how these exposures are changing over time must be improved.
3. Epidemiologic research dealing with environmental agents and using modern techniques of pharmacokinetics and toxicokinetics must be expanded. It is very difficult to determine toxic exposure levels, NOAEL, or therapeutic levels either in humans or from animal studies without the use of pharmacokinetics and toxicokinetics.
4. A national surveillance system, monitoring changes over time, must be created to determine the prevalence of a wide range of diseases and rapidly identify unusual clusters of conditions in children and in adults.
5. Whenever possible, animal studies at different stages of development should be included in the body of research on which we base public health and clinical policy and practices. It also is essential that we acknowledge the danger of generalizing findings across species.
6. Competent environmental epidemiologists should focus on the special vulnerabilities of developing children.
7. Physicians should be educated about the safe and toxic levels of chemicals and drugs to evaluate individual patients or perform epidemiologic studies.
8. We must counter the individuals who zealously exaggerate or denigrate the risks of environmental toxicants and drugs with data from rigorous scientific studies that treat each environmental agent as a separate entity with regard to its risks and benefits.

It is our hope that this volume will assist pediatricians, other health care workers, toxicologists, epidemiologists, and environmental health experts to understand our current state of knowledge about children's unique vulnerabilities and resistance to environmental agents. We also hope to encourage the investigations and activities of our many colleagues to determine the variable risks of these agents for the purpose of preventing or reducing environmentally produced diseases.

REFERENCES

1. Miller RW. How environmental efforts on child health are recognized. *Pediatrics*. 1974;53(suppl):792–796
2. Johnson TR, Moore WM, Jeffries JE. *Children are Different: Developmental Physiology*. 2nd ed. Columbus, Ohio: Ross Laboratories; 1978
3. Upton AC, Goldstein BD, eds. *Human Health and the Environment: Some Research Needs*. Washington, DC: US Department of Health and Human Services; 1984
4. Gazelian P, Henry C, Olin S, eds. *Similarities and Differences Between Children and Adults: Implications for risk assessment*. Washington, DC: ILSI Press; 1992
5. Etzel R, ed. *Handbook of Pediatric Environmental Health*. Elk Grove, IL: American Academy of Pediatrics; 1999
6. Goldman LR, Koduru S. Chemicals in the environment and developmental toxicity to children: a public health and policy perspective. *Environ Health Perspect*. 2000;108(suppl 3):443–448
7. Hoet JJ, Ozanne S, Reusens B. Influences of pre- and postnatal nutritional exposures on vascular/endocrine systems in animals. *Environ Health Perspect*. 2000;108(suppl 3):563–568
8. Holladay S, Smialowicz RJ. Development of the murine and human immune system: differential effects of immunotoxicants depend on time of exposure. *Environ Health Perspect*. 2000;108(suppl 3):463–473
9. Lemasters GK, Perreault SD, Hales BF, et al. Workshop to identify critical windows of exposure for children's health: reproductive health in children and adolescents work group summary. *Environ Health Perspect*. 2000;108(suppl 3):505–509
10. London E, Etzel RA. The environment as an etiologic factor in autism: a new direction for research. *Environ Health Perspect*. 2000;108(suppl 3):401–404
11. Porterfield SP. Thyroidal dysfunction and environmental chemicals—potential impact on brain development. *Environ Health Perspect*. 2000; 108(suppl 3):1–17
12. Pryor JL, Hughes C, Foster W, Hales BF, Robaire B. Critical windows of

exposure for children's health: the reproductive system in animals and humans. *Environ Health Perspect.* 2000;108(suppl 3):433–438
13. Rice D, Barone S Jr. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. *Environ Health Perspect.* 2000;108(suppl 3):511–533
14. Sadler TW. Susceptible periods during embryogenesis of the heart and endocrine glands. *Environ Health Perspect.* 2000;108(suppl 3):555–561
15. Sampson PD, Streissguth AP, Bookstein FL, Barr HM. On categorizations in analyses of alcohol teratogenesis. *Environ Health Perspect.* 2000; 108(suppl 3):421–428
16. Selevan S, Kimmel CA, Mendola P. Identifying critical windows of exposure for children's health. *Environ Health Perspect.* 2000;108(suppl 3):451–455
17. Weiss B, Landrigan PJ. The developing brain and the environment: an introduction. *Environ Health Perspect.* 2000;108(suppl 3):373–374
18. Graham JM Jr, Jones KL, Brent RL. Contribution of clinical teratologists and geneticists to the evaluation of the etiology of congenital malformations alleged to be used by environmental agents: ionizing radiation, electromagnetic fields, microwaves, radionuclides, and ultrasound. *Teratology.* 1999;59:307–313
19. Brent RL. Teratogen update: reproductive risks of leflunomide (Avara®); a pyrimidine synthesis inhibitor: counseling women taking leflunomide before or during pregnancy and men taking leflunomide who are contemplating fathering a child. *Teratology.* 2001;63:106–112
20. Spika JS, Shaffer N, Hargrett-Bean N. Risk factors for infant botulism in the United States. *Am J Dis Child.* 1989;143:828
21. Brent RL. The application of the principles of toxicology and teratology in evaluating the risks of new drugs for the treatment of drug addiction in women of reproductive age. In: Chiang CN, Finnegan LP, eds. *Research Monograph Series 149: Medications Development for the Treatment of Pregnant Addicts and Their Infants.* Rockville, MD: National Institute on Drug Abuse; 1995:130–184
22. Brent RL. Utilization of developmental basic science principles in the evaluation of reproductive risks from pre- and postconception environmental radiation exposures. *Teratology.* 1999;59:182–204
23. Brent RL, Beckman DA. Prescribed drugs, therapeutic agents, and fetal teratogenesis. In: Reece EA, Hobbins JC, eds. *Medicine of the Fetus and Mother.* 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers; 1999: 289–313
24. Beckman DA, Brent RL. Basic principles of teratology. In: Reece EA, Hobbins JC, eds. *Medicine of the Fetus and Mother.* 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers; 1999:281–288
25. Weatherall JAC. Anesthesia in newborn animals. *Br J Pharmacol.* 1960; 15:454–457
26. Cameron JA. Age and species differences among rodents in resistance to CO asphyxia. *J Cell Comp Physiol.* 1941;18:379–383
27. Cassin S, Herron CS Jr. Cerebral enzyme changes and tolerance to anoxia during maturation in the rabbit. *Am J Physiol.* 1961;201:440–442
28. Fazekas JF, Alexander FAD, Himwich HE. Tolerance of the newborn to anoxia. *Am J Physiol.* 1941;134:281–287
29. Reiss M, Haurowitz F. Uber das verhalten junger und alter tiere bei enstickung, klin. *Klinische Wochenshrift.* 1929;1:743–744
30. Stafford A, Weatherall JA. The survival of young rats in nitrogen. *J Physiol.* 1962;153:457–472
31. Barrow EF. Age and resistance to ether in mice. *Proc Soc Exp Biol Med.* 1933;30:1290–1292
32. Done AK. Developmental pharmacology. *Clin Pharmacol Ther.* 1964;5: 432–479
33. Mackenzie JB, Mackenzie CG. Production of pulmonary edema by thiourea in the rat and its relation to age. *Proc Soc Exp Biol Med.* 1943;54:34–37
34. Dieke SH, Richter CP. Acute toxicity of thiourea to rats in relation to age, diet, strain and species variation. *J Pharmacol Exp Ther.* 1945;83: 195–202
35. Kent SP, Tucker ES III, Taranenko A. The toxicity of chloramphenicol in newborn versus adult mice. *Am J Dis Child.* 1960;100:400–401
36. Michael AF, Giesel RG, Sutherland JM. Chloramphenicol toxicity in newborn rats. *Antibiotics Chemother.* 1960;10:368–370
37. Raynsford G. Technique of comparing acute toxicity in infants vs. adult rats. A comparative study of three antibiotics. *Am J Dis Child.* 1963;105: 323–328
38. Miller RW. Special susceptibility of the child to certain radiation-induced cancers. *Environ Health Perspect.* 1995;103(suppl 6):41–44
39. Needleman HL, Schell A, Bellingler D, Leviton A, Allred EN. The long-term effects of exposure to low doses of lead in childhood. An 11-year follow-up report. *N Engl J Med.* 1990;322:83–88
40. Brent RL. Methods of evaluating the alleged teratogenicity of environmental agents. In: Sever JL, Brent RL, eds. *Teratogen Update: Environmentally Induced Birth Defect Risks.* New York, NY: Alan R. Liss; 1986: 199–201
41. Brent RL. Bendectin: review of the medical literature of a comprehensively studied human non-teratogen and the most prevalent tortogenlitigen. *Reprod Toxicol.* 1995;9:337–349
42. Evaluating Chemical and Other Agent Exposures for Reproductive and Developmental Toxicity. Washington, DC: National Academy of Sciences; 2001:235
43. Brent RL. Critique: scientific frontiers in developmental toxicology and risk assessment by the National Research Council, National Academy of Sciences, National Academy Press, Washington, DC. *Teratology.* 2002; 65:88–96

A Pediatric Perspective on the Unique Vulnerability and Resilience of the Embryo and the Child to Environmental Toxicants: The Importance of Rigorous Research Concerning Age and Agent

Robert L. Brent, Susanne Tanski and Michael Weitzman

Pediatrics 2004;113;935-944
DOI: 10.1542/peds.113.4.S1.935

PEDIATRICS

Environmental Causes of Human Congenital Malformations: The Pediatrician's Role in Dealing With These Complex Clinical Problems Caused by a Multiplicity of Environmental and Genetic Factors

Robert L. Brent

Pediatrics 2004;113;957-968
DOI: 10.1542/peds.113.4.S1.957

Environmental Causes of Human Congenital Malformations: The Pediatrician's Role in Dealing With These Complex Clinical Problems Caused by a Multiplicity of Environmental and Genetic Factors

Robert L. Brent, MD, PhD

ABSTRACT. There have been amazing advances in embryology, teratology, reproductive biology, genetics, and epidemiology in the past 50 years that have provided scientists and clinicians with a better perspective on the causes of congenital malformations. We still cannot provide the families of children with malformations a definitive diagnosis and cause in every instance. The purpose of this article is to inform pediatricians about environmental drugs, chemicals, and physical agents that have been documented to produce congenital malformations and reproductive effects and to indicate that the multitude of teratogenic agents account for only a small proportion of malformations. The most common known cause is genetic, but the largest group, unfortunately, is unknown. There are a number of important clinical rules that are important for clinicians to use when determining the cause of their patient's congenital malformations:

1. No teratogenic agent should be described qualitatively as a teratogen, because a teratogenic exposure includes not only the agent but also the dose and the time in pregnancy when the exposure has to occur.
2. Even agents that have been demonstrated to result in malformations cannot produce every type of malformation. Known teratogens may be presumptively implicated by the spectrum of malformations that they produce. It is easier to exclude an agent as a cause of birth defects than to conclude definitively that it was responsible for birth defects, because of the existence of genocopies of some teratogenic syndromes.
3. When evaluating the risk of exposures, the dose is a crucial component in determining the risk. Teratogenic agents follow a toxicologic dose–response curve. This means that each teratogen has a threshold dose below which there is no risk of teratogenesis, no matter when in pregnancy the exposure occurred.
4. The evaluation of a child with congenital malformations cannot be performed adequately unless it is approached with the same scholarship and intensity as the evaluation of any other complicated medical problem.
5. Each physician must recognize the consequences of providing erroneous reproductive risks to pregnant women who are exposed to drugs and chemicals during pregnancy or alleging that a child's malformations are attributable to an environmental agent without performing a complete and scholarly evaluation.
6. Unfortunately, clinical teratology and clinical genetics is not emphasized in medical school and residency education programs, but pediatricians have a multitude of educational aids to assist them in their evaluations, which includes consultations with clinical teratologists and geneticists, the medical literature, and the OMIM web site. *Pediatrics* 2004;113:957–968; *etiology of congenital malformations, birth defects, threshold exposure, teratogenic syndrome, method of evaluation of etiology, stochastic and deterministic effects.*

From the Thomas Jefferson University, Alfred I. duPont Hospital for Children, Laboratory of Clinical and Environmental Teratology, Wilmington, Delaware.

Received for publication Oct 7, 2003; accepted Oct 20, 2003.

Reprint requests to (R.L.B.) Rm 308, R/A, Alfred I. duPont Hospital for Children, Box 269, Wilmington, DE 19899. E-mail rbrent@nemours.org

When I was a medical student at the University of Rochester, I was fortunate to have James G. Wilson, an embryologist, as one of my teachers in the anatomy course. He was working on the effects of radiation on the embryo, and that is how I became interested in congenital malformations. Many of the faculty members discouraged me from pursuing the study of the causes of birth defects as an academic goal, "Because we are never going to solve that problem." In 1955, when I had completed medical school and graduate school, the scientific world did not even have the correct figure for the number of human chromosomes. Gregg[1] had recently described the teratogenicity of rubella virus infection during pregnancy. The teratogenic risk of the folic acid antagonists was established,[2,3] and there were experimental studies indicating that nutritional deficiencies could produce birth defects in animals.[4]

What have we learned and accomplished in the past 50 years? Thousands of previously unknown genetic diseases have been described and many of their genes have been identified since the 1950s.[5,6] The fields of prenatal intrauterine diagnoses, intervention, and treatment have been created. Metabolic and biochemical screening have become standard care for pregnant women and newborns. More than 50 teratogenic environmental drugs, chemicals, and physical agents have been described[7–10] using modern epidemiologic tools and the talents of clinical dysmorphologists.[11–17] The basic science and clinical rules for evaluating teratogenic risks have been established[18] (Table 1). The development of the rubella vaccine and the recognition of the importance of adequate folic acid intake in women of reproductive age are forerunners for the prevention of birth defects from teratogenic infectious agents and nutritional components that are important for normal development. The completion of the first stage of the

TABLE 1. Evaluation of the Allegation That a Particular Environmental Agent Causes Congenital Malformations or Is Responsible for Malformations in an Individual Patient

Epidemiologic studies. Controlled epidemiologic studies consistently demonstrate an increased incidence of a particular spectrum of embryonic and/or fetal effects in exposed human populations.
Secular trend data. Secular trends demonstrate a positive relationship between the changing exposures to a common environmental agent in human populations and the incidence of a particular embryonic and/or fetal effect.
Animal developmental toxicity studies. An animal model that mimics the human developmental effect at clinically comparable exposures can be developed. Because mimicry may not occur in all animal species, animal models are more likely to be developed once there is good evidence for the embryotoxic effects reported in the human. Developmental toxicity studies in animals are indicative of a potential hazard in general rather than the potential for a specific adverse effect on the fetus when there are no human data on which to base the animal experiments.
Dose–response relationship (pharmacokinetics and toxicokinetics). Developmental toxicity in the human increases with dose (exposure) and the developmental toxicity in animal occurs at a dose that is pharmacokinetically (quantitatively) equivalent to the human exposure.
Biological plausibility. The mechanisms of developmental toxicity are understood, and the effects are biologically plausible. 1. MOA 2. Receptor studies 3. Nature of the malformations 4. Teratology principles

Modified from Brent. 1976, 1986, 1991, 1995.[7,8,18,36,37,39–41,53]

Human Genome Project in 2000 offers the geneticist and the teratologist immense opportunities to evaluate the concepts of polygenic and multifactorial causes[19,20] of congenital malformations.

EMOTIONAL IMPACT OF CONGENITAL MALFORMATIONS

Reproductive problems encompass a multiplicity of diseases, including sterility, infertility, abortion (miscarriage), stillbirth, congenital malformations (as a result of environmental or hereditary causes), fetal growth retardation, and prematurity. These clinical problems occur commonly in the general population, and therefore environmental causes are not always easy to corroborate (Table 2). Severe congenital malformations occur in 3% of births. According to the Centers for Disease Control and Prevention, severe congenital malformations include birth defects that cause death, hospitalization, mental retardation; necessitate significant or repeated surgical procedures; are disfiguring; or interfere with physical performance. That means that each year in the United States, 120 000 newborns are born with severe birth defects. Genetic diseases occur in approximately 11% of births. Spontaneous mutations account for <2% to 3% of genetic disease. Therefore, mutations induced from preconception exposures of environmental mutagens are difficult endpoints to document (Table 3).

Along with cancer, psychiatric illness, and hereditary diseases, reproductive problems have been viewed throughout history as diseases of affliction (Fig 1). Inherent in the reactions of most cultures is that these diseases have been viewed as punishments for misdeeds[21–24] (Fig 1). Regardless of the irrationality of this viewpoint, these feelings do exist. Ancient Babylonian writings recount tales of mothers being put to death because they delivered malformed infants. George Spencer was slain by the Puritans in New Haven in the 17th century, having been convicted of fathering a cyclopean pig, because the Puritans were unable to differentiate between George Spencer's cataract and the malformed pigs cloudy cornea.[21] In modern times, some individuals with reproductive problems reverse the historical perspective and blame others for the occurrence of their congenital malformations, infertility, abortions, and hereditary diseases. They place the responsibility of their illness on environmental agents dispensed by their health care provider or used by their employer.[21,22]

Reproductive problems alarm the public, the press, and some scientists to a greater degree than most other diseases. In fact, severely malformed children are disquieting to health care providers, espe-

TABLE 2. Background Reproductive Risks Per Million Pregnancies

Reproductive Risk	Frequency
Immunologically and clinically diagnosed spontaneous abortions per million conceptions	350 000
Clinically recognized spontaneous abortions per million clinically recognized pregnancies	150 000
Genetic diseases per million births	110 000
Multifactorial or polygenic genetic environmental interactions) (eg, neural tube defects, cleft lip, hypospadius, hyperlipidemia, diabetes)	90 000
Dominantly inherited disease (eg, achondroplasia, Huntingtons chorea, neurofibromatosis)	10 000
Autosomal and sex-linked genetic disease (eg, cystic fibrosis, hemophilia, sickle-cell disease, thalassemia)	1200
Cytogenetic (chromosomal abnormalities) (eg, Down syndrome [Trisomy 21]; Trisomy 13, 18; Turner syndrome; 22q deletion)	5000
New mutations*	3000
Severe congenital malformations† (as a result of all causes of birth defects: genetic, unknown, environmental per million births)	30 000
Prematurity/million births	40 000
Fetal growth retardation/million births	30 000
Stillbirths (>20 wk)/million births	2000–20 900
Infertility	7% of couples

* The mutation rate for many genetic diseases can be calculated. This can be readily performed with dominantly inherited diseases when offspring are born with a dominant genetic disease and neither parent has the disease (reference).
† Congenital malformations have multiple causes, including a significant proportion that are genetic.

TABLE 3. Cause of Human Congenital Malformations Observed During the First Year of Life

Suspected Cause	% of Total
Unknown	65–75
Polygenic	
Multifactorial (gene–environment interactions)	
Spontaneous errors of development	
Synergistic interactions of teratogens	
Genetic	15–25
Autosomal and sex-linked inherited genetic disease	
Cytogenetic (chromosomal abnormalities)	
New mutations	
Environmental	10
Maternal conditions: alcoholism, diabetes, endocrinopathies, phenylketonuria, smoking and nicotine, starvation, nutritional deficits	4
Infectious agents: rubella, toxoplasmosis, syphilis, herpes simplex, cytomegalovirus, varicella zoster, Venezuelan equine encephalitis, parvovirus B19	3
Mechanical problems (deformations): amniotic band contrictions, umbilical cord constraint, disparity in uterine size and uterine contents	1–2
Chemicals, prescription drugs, high-dose ionizing radiation, hyperthermia	<1

Modified from Brent.[7–9,14,23,26,36,37,39,40]

cially when they are not experienced in dealing with these problems. No physician will be comfortable informing a family that their child was born without arms and legs. The objective evaluation of environmental causes of reproductive diseases is clouded by the emotional climate that surrounds these diseases, resulting in the expression of partisan positions that either diminish or magnify the environmental risks. These nonobjective opinions can be expressed by scientists, the laity, or the press.[25,26] It is the responsibility of every physician to be aware of the emotionally charged situation when a family has a child with a birth defect. The inadvertent comment by the physician, nurse, resident, or student in attendance at the time of the child's delivery can have grave consequences for the physician and the family. Comments such as, "Oh, you had a radiograph during your pregnancy," or, "You did not tell me that you were prescribed tetracycline while you were pregnant," can direct the patient's family to an attorney rather than a teratology or genetic counselor.

BASIC PRINCIPLES OF TERATOLOGY

Labeling an environmental exposure as teratogenic is inappropriate unless one characterizes the exposure with regard to the dose, route of exposure, and the stage of pregnancy when the exposure occurred. Labeling an agent as teratogenic only indicates that it may have the potential for producing congenital malformations. A 50-mg dose of thalidomide administered on the 26th day postconception has a significant risk of malforming the embryo. That same dose taken during the 10th week of gestation will not result in congenital malformations. One milligram of thalidomide taken at any time during pregnancy will have no effect on the developing embryo. We know that X-irradiation can be teratogenic,[27–29] but if the dose is too low or the radiograph does not directly expose the embryo, then there is no risk of congenital malformations.[23] So a list of teratogens only indicates teratogenic potential. Evaluation of the dose and the time of exposure could indicate that there is no teratogenic risk or that the risk is significant.

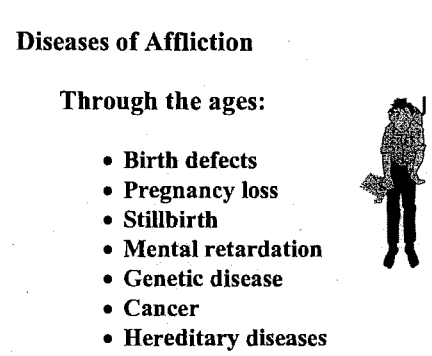


Fig 1. Through the ages these diseases have been interpreted or considered by multiple cultures to be stigmatizing; punishments for misdeeds or sins. In modern times, these are the diseases whose causation is thought to be due to environmental factors—thus converting the guilt of the past into anger that is projected onto others in our society and sometimes leads to litigation.

When evaluating studies that deal with the reproductive effects of any environmental agent, important principles should guide the analysis of human and animal reproductive studies. Paramount to this evaluation is the application of the basic science principles of teratology and developmental biology.[23] These principles are as follows:

1. Exposure to teratogens follows a toxicologic dose–response curve. There is a threshold below which no teratogenic effect will be observed, and as the dose of the teratogen is increased, both the severity and the frequency of reproductive effects will increase (Fig 2).
2. The embryonic stage of exposure is critical in determining which deleterious effects will be produced and whether any of these effects can be produced by a known teratogen. Some teratogenic effects have a broad and others a very narrow period of sensitivity. The most sensitive stage for

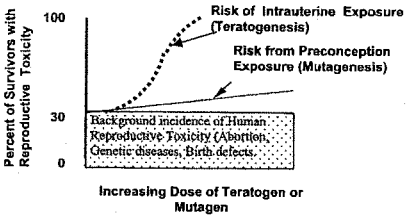


Fig 2. The dose response curve of environmental toxicants (drugs, chemicals, and physical agents) can have deterministic (threshold) and/or stochastic effects. Mutagenic and carcinogenic events are stochastic phenomena and theoretically do not have a threshold exposure below which no risk exists. At low exposures the risk still exists, but it is usually below the spontaneous risk of cancer and mutations. Whether the curve is linear or curvilinear for stochastic phenomena can be debated, but from a theoretical point, it traverses zero. Toxicological phenomena, such as teratogenesis, that do not involve mutagenic and carcinogenic effects usually follow an S-shaped curve, with a threshold below which no effects are expected.

the induction of mental retardation from ionizing radiation is from the 8th to the 15th week of pregnancy, a lengthy period. Thalidomide's period of sensitivity is approximately 2 weeks[24] (Table 4).

3. Even the most potent teratogenic agent cannot produce every malformation.
4. Most teratogens have a confined group of congenital malformations that result after exposure during a critical period of embryonic development. This confined group of malformations is referred to as the syndrome that describes the agent's teratogenic effects.
5. Although a group of malformations may suggest the possibility of certain teratogens, they cannot definitively confirm the causal agent because some teratogenic syndromes mimic genetic syndromes. However, the presence of certain malformations can eliminate the possibility that a particular teratogenic agent was responsible because those malformations have not been demonstrated to be part of the syndrome or because the production of that malformation is not biologically plausible for that particular alleged teratogen.[30]

TABLE 4. Developmental Stage Sensitivity to Thalidomide-Induced Limb Reduction Defects in the Human

Days From Conception for Induction of Defects	Limb Reduction Defects
21–26	Thumb aplasia
22–23	Microtia, deafness
23–34	Hip dislocation
24–29	Amelia, upper limbs
24–33	Phocomelia, upper limbs
25–31	Preaxial aplasia, upper limbs
27–31	Amelia, lower limbs
28–33	Preaxial aplasia, lower limbs; phocomelia, lower limbs; femoral hypoplasia; girdle hypoplasia
33–36	Triphalangeal thymb

Modified from Brent and Holmes.[24]

CAUSE OF CONGENITAL MALFORMATIONS

The cause of congenital malformations can be divided into 3 categories: unknown, genetic, and environmental (Table 3). The cause of a majority of human malformations is unknown. A significant proportion of congenital malformations of unknown cause is likely to have an important genetic component. Malformations with an increased recurrent risk, such as cleft lip and palate, anencephaly, spina bifida, certain congenital heart diseases, pyloric stenosis, hypospadias, inguinal hernia, talipes equinovarus, and congenital dislocation of the hip, fit in the category of multifactorial disease as well as in the category of polygenic inherited disease.[19,20] The multifactorial/threshold hypothesis postulates the modulation of a continuum of genetic characteristics by intrinsic and extrinsic (environmental) factors.

Spontaneous errors of development may account for some of the malformations that occur without apparent abnormalities of the genome or environmental influence. Spontaneous errors of development may indicate that we never achieve our goal of eliminating birth defects because a significant percentage of birth defects are attributable to the statistical probability of errors in the developmental process, similar to the concept of spontaneous mutation. It is estimated that the majority of all conceptions are lost before term, many within the first 3 weeks of development. The World Health Organization estimated that 15% of all clinically recognizable pregnancies end in a spontaneous abortion, 50% to 60% of which are attributable to chromosomal abnormalities.[31–34] Finally, 3T to 6% of offspring are malformed, which represents the background risk for human maldevelopment (Table 2).

FACTORS THAT AFFECT THE SUSCEPTIBILITY TO DEVELOPMENTAL TOXICANTS

A basic tenet of environmentally produced malformations is that teratogens or a teratogenic milieu have certain characteristics in common and follow certain basic principles. These principles determine the quantitative and qualitative aspects of environmentally produced malformations.

Embryonic Stage

The types and risk of malformations caused by teratogenic agents usually result in a spectrum of malformations that vary depending on the stage of exposure and the dose. The developmental period at which an exposure occurs will determine which structures are most susceptible to the deleterious effects of the drug or the chemical and to what extent the embryo can repair the damage. This period of sensitivity may be narrow or broad, depending on the environmental agent and the malformation in question. The period of susceptibility to thalidomide-induced limb defects is very narrow[24] (Table 4), whereas the susceptibility period for radiation-induced microcephaly is very broad.[23]

TABLE 5. Stochastic and Threshold Dose–Response Relationships of Diseases Produced by Environmental Agents

Relationship	Pathology	Site	Diseases	Risk	Definition
Stochastic phenomena	Damage to a single cell may result in disease	DNA	Cancer, mutation	Some risk exists at all dosages; at low exposures, the risk is below the spontaneous risk	The incidence of the disease increases with the dose, but the severity and nature of the disease remain the same
Threshold phenomena	Multicellular injury	High variation in cause, affecting many cell and organ processes	Malformation, growth retardation, death, chemical toxicity, etc	No increased risk below the threshold dose	Both the severity and incidence of the disease increase with dose

Modified from Brent.[23]

Dose or Magnitude of the Exposure

The quantitative correlation of the magnitude of the embryopathic effects to the dose of a drug, chemical, or other agent is referred to as the dose–response relationship. This is extremely important when comparing effects among different species because the use of mg/kg doses are, at most, rough approximations. Dose equivalence among species for drugs and chemicals can be accomplished only by performing pharmacokinetic studies, metabolic studies, and dose–response investigations in the human and the species being studied, whereas ionizing radiation exposures in rads or Sieverts (Sv) are comparable in most mammalian species.[23]

Threshold Dose

The threshold dose is the dosage below which the incidence of death, malformation, growth retardation, or functional deficit is not statistically greater than that of controls (Fig 2). The threshold level of exposure is usually from <1 to 2 orders of magnitude below the teratogenic or embryopathic dose for drugs and chemicals that kill or malform half of the embryos. An exogenous teratogenic agent, therefore, has a no-effect dose as compared with mutagens or carcinogens, which have a stochastic dose–response curve (Table 5, Fig 2). The severity and the incidence of malformations produced by every exogenous teratogenic agent that has been studied appropriately have exhibited threshold phenomena during organogenesis.

Pharmacokinetics and Metabolism of the Drug or the Chemical

The physiologic alterations in pregnancy and the bioconversion of compounds can significantly influence the teratogenic effects of drugs and chemicals by affecting absorption, body distribution, active form(s), and excretion of the compound. Physiologic alterations in the mother during pregnancy affect the pharmacokinetics of drugs:

1. Decreased gastrointestinal motility and increased intestinal transit time resulting in delayed absorption of drugs absorbed in the small intestine as a result of increased stomach retention and enhanced absorption of slowly absorbed drugs
2. Decreased plasma albumin concentration, which alters the kinetics of compound normally bound to albumin
3. Increased plasma and extracellular fluid volumes that affect concentration-dependent transfer of compounds
4. Renal elimination, which is generally increased but is influenced by body position during late pregnancy
5. Inhibition of metabolic inactivation in the maternal liver
6. Variation in uterine blood flow, although little is known about how this affects transfer across the placenta

The fetus also undergoes physiologic alterations that affect the pharmacokinetics of drugs:

1. The amount and distribution of fat varies with development and affects the distribution of lipid-soluble drugs and chemicals
2. The fetal circulation contains a higher concentration of unbound drug largely because the plasma fetal protein concentrations are lower than in the adult
3. The functional development of pharmacologic receptors is likely to proceed at different rates in the various tissues
4. Drugs that are excreted by the fetal kidneys may be recycled via amniotic fluid swallowing by the fetus

The role that the placenta plays in drug pharmacokinetics has been reviewed by Juchau and Rettie[35] and involves 1) transport, 2) the presence of receptor sites for a number of endogenous and xenobiotic compounds (β-adrenergic, glucocorticoid, epidermal growth factor, immunoglobulin G Fc, insulin, low-density lipoproteins, opiates, somatomedin, testosterone, transcobalamin II, transferrin, folate, and retinoid), and 3) the bioconversion of xenobiotics. Bioconversion of xenobiotics has been shown to be important in the teratogenic activity of several xenobiotics. There is strong evidence that reactive metabolites of cyclophosphamide, 2-acetylaminofluorene, and nitroheterocycles (niridazole) are the proximal teratogens. There is also experimental evidence that suggests that other chemicals undergo conversion to intermediates that have deleterious effects on embryonic development, including phenytoin, procarbazine, rifampicin, diethylstilbestrol, some benzhydrylpiperazine antihistamines, adriamycin, testosterone, benzo(a)pyrene, methoxyethanol, caffeine, and paraquat.

TABLE 6. Proven Human Teratogens or Embryotoxins—Drugs, Chemicals, Milieu and Physical Agents That Have Resulted in Human Congenital Malformations

Reproductive Toxin and Alleged Effects
Aminopterin, Methotrexate: Growth retardation, microcephaly, meningomyelocele mental retardation, hydrocephalus, and cleft palate.
Androgens: Masculinization of the developing fetus can occur from androgens and high doses of some male derived progestins.
Angiotensin Converting Enzyme (ACE) Inhibitors: Fetal hypotension syndrome in 2nd and 3rd trimester resulting in fetal kidney hypoperfusion, and anuria, oligohydramnios, pulmonary hypoplasia and cranial bone hypoplasia. No effect in the first trimester.
Antituberculous Therapy: INH, PAS has an increased risk for some CNS abnormalities.
Caffeine: Moderate caffeine exposure is not associated with birth defects; high exposures are associated with an increased risk of abortion but the data is inconsistent.
Chorionic Villous Sampling (CVS): Vascular disruption malformations, i.e., limb reduction defects.
Cobalt in hematemic multivitamins: Fetal goiter
Cocaine: Vascular disruptive type malformations in very low incidence, pregnancy loss.
Corticosteroids: High exposures administered systemically have a low risk for cleft palate in some studies, but the epidemiological studies are not consistent.
Coumarin Derivatives: Early exposure during pregnancy can result in nasal hypoplasia, stippling of secondary epiphysis, intrauterine growth retardation. CNS malformations can occur in late pregnancy exposure due to bleeding.
Cyclophosphamide and other chemotherapeutic agents and immunosuppressive agents like cyclosporine or leflunomide: Many chemotherapeutic agents used to treat cancer have a theoretical risk for producing malformations in the fetus when administered to pregnant women, especially since most of these drugs are teratogenic in animals, but the clinical data are not consistent. Many of these drugs have not been shown to be teratogenic, but the numbers of cases in the studies are small. Caution is the byword.
Diethylstilbestrol: Administration during pregnancy produces genital abnormalities, adenosis, clear cell adenocarcinoma of vagina in adolescents. The latter has a risk of 1:1000 to 1:10 000, but the other effects, such as adenosis can be quire high.
Ethyl Alcohol: Fetal Alcohol Syndrome consists of microcephaly, mental retardation, growth retardation, typical facial dysmorphogenesis, abnormal ears, small palpebral fissures.
Ionizing Radiation: The threshold is greater than 20 rad (0.2 Gy) can increased the risk for some fetal effects such as micocephaly or growth retardation, but the threshold for mental retardation is higher.
Insulin Shock Therapy: This therapeutic modality when administered to pregnant women resulted in microcephaly, mental retardation.
Lithium Therapy: Chronic sage for the treatment of manic depressive illness has an increased risk for Ebstein's Anomaly and other malformations, but the risk appears to be very low.
Minoxidil: The discovery of the growth promotion of hair was discovered for this drug because administration during pregnancy resulted in hirsutism in newborns.
Methimazole: Aplasia cutis has been reported to be increased in mothers administered this drug during pregnancy*.
Methylene blue intramniotic instillation: Fetal intestinal atresia, hemolytic anemia and jaundice in neonatal period. This procedure is no longer utilized to identify one twin.
Misoprostol: A low incidence of vascular disruptive phenomenon, such as limb reduction defects and Mobius syndrome have been reported in pregnancies in which this drug was used to induce an abortion.
Penicillamine (D-penicillamine): This drug results in the physical effects referred to as lathyrism, the results of poisoning by the seeds of the genus Lathyrus. It causes collagen disruption, cutis laxa, and hyperflexibility of joints. The condition appears to be reversible and the risk is low.
Progestin Therapy: Very high doses of androgen hormone derived progestins can produce masculinization. Many drugs with progestational activity do not have masculinizing potential. None of these drugs have the potential for producing non-genital malformations.
Propylthiouracil: This drug and other antithyroid medications administered during pregnancy can result in an infant born with a goiter.
Radioactive Isotopes: Tissue- and organ-specific damage is dependent on the radioisotope element and distribution, i.e. high doses of ^{131}I administered to a pregnant woman can cause fetal thyroid hypoplasia after the 8th week of development.
Retinoids (Acutane): Systemic retinoic acid, isotretinoin, Etretinate can cause increased risk of central nervous system, cardio-aortic, ear and clefting defects. Microtia, anotia, thymic aplasia and other branchial arch, aortic arch abnormalities and certain congenital heart malformations.
Retinoids, topical: Topical administration is very unlikely to have teratogenic potential because one cannot attain a teratogenic serum level from topical exposure to retinoids.
Streptomycin: Streptomycin and a group of ototoxic drugs can affect the eighth nerve and interfere with hearing; it is a relatively low risk phenomenon. Even children are less sensitive to the ototoxic effects of these drugs when compared to adults.
Sulfa drug and Vitamin K: These drugs can produce hemolysis in some subpopulations of fetuses.
Tetracycline: This drug produces bone and teeth staining, No other malformations are at increased risk.
Thalidomide: This drug results in an increased incidence of deafness, anotia, preaxial limb reduction defects, phocomelia, ventricular septal defects and GI atresias. The susceptible period is from the 22nd to the 36th day postconception.
Trimethorpin: This drug was frequently used to treat urinary tract infections and has been linked to an increased incidence of neural tube defects. The risk is not high, but it is biologically plausible because of the drug's effect on lowering folic acid levels. This has resulted in neurological symptoms in adults taking this drug.
Vitamin A: The same malformations that have been reported with the retinoids have been reported with very high doses of vitamin A (retinol). Dosages to produce birth defects would have to be in excess of 25 000 to 50 000 units per day.
Vitamin D*: Large doses given in vitamin D prophylaxis are possibly involved in the etiology of supravalvular aortic stenosis, elfin faces, and mental retardation.
Warfarin (Coumarin): Early exposure during pregnancy can result in nasal hypoplasia, stippling of secondary epiphysis, intrauterine growth retardation. CNS malfonnations can occur in late pregnancy exposure due to bleeding.

The major site of bioconversion of chemicals in vivo is likely to be the maternal liver. Placental P450-dependent mono-oxygenation of xenobiotics will occur at low rates unless induced by such compounds as those found in tobacco smoke. However, the rodent embryo and yolk sac have been shown to possess functional P450 oxidative isozymes capable of converting pro-teratogens to active metabolites dur-

TABLE 6. Continued

Anticonvulsants
Diphenylhydantoin: Treatment of convulsive disorders increases the risk of the Fetal Hydantoin Syndrome, consisting of facial dysmorphology, cleft palate, VSD, growth and mental retardation
Trimethadione and Paramethadione: Treatment of convulsive disorders increases the risk of characteristic facial dysmorphology, mental retardation, V-shaped eye brows, low-set ears with anteriorly folded helix, high-arched palate, irregular teeth, CNS anomalies, severe developmental delay.
Valproic Acid: Treatment of convulsive disorders increases the risk of spina bifida, facial dysmorphology and autism.
Carbamazepine: Treatment of convulsive disorders increases the risk facial dysmorphology.
Chemicals
Carbon Monoxide Poisoning: CNS Damage has been reported with very high exposures, but the risk appears to be low*.
Lead: Very high exposures can cause pregnancy loss; intrauterine teratogenesis is not established at very low exposures below 20 ugm% in the serum of pregnant mothers.
Gasoline Addiction Embryopathy: Facial dysmorphology, mental retardation.
Methyl Mercury: Minamata disease consists of cerebral palsy, microcephaly, mental retardation, blindness, cerebellum hypoplasia. Other endemics have occurred from adulteration of wheat with mercury containing chemicals that are used to prevent grain spoilage. Present environmental levels of mercury are unlikely to represent a teratogenic risk, but reducing or limiting the consumption of carnivorous fish has been suggested in order not to exceed the EPA's MPE (maximum permissible exposure), which is far below the toxic effects of mercury.
Polychlorinated Biphenyls: Poisoning has occurred from adulteration of food products (Cola-colored babies, CNS effects, pigmentation of gums, nails, teeth and groin; hypoplastic deformed nails; intrauterine growth retardation; abnormal skull calcification). The threshold exposure has not been determined, but it is unlikely to be teratogenic at the present environmental exposures.
Toluene Addiction Embryopathy: Facial dysmorphology, mental retardation.
Embryonic and Fetal Infections
Cytomegalovirus Infection: Retinopathy, CNS calcification, microcephaly, mental retardation.
Rubella: Deafness, congenital heart disease, microcephaly, cataracts, mental retardation).
Herpes Simplex: Fetal infection, liver disease, death.
Human Immunodeficiency Virus: Perinatal HIV infection.
Parvovirus Infection, B 19: Stillbirth, hydrops.
Syphilis: Maculopapular rash, hepatosplenomegaly, deformed nails, osteochondritis at joints of extremities, congenital neurosyphilis, abnormal epiphyses, chorioretinitis.
Toxoplasmosis: Hydrocephaly, microphthalmia, chorioretinitis, mental retardation.
Varicella – Zoster: Skin and muscle defects; intrauterine growth retardation; limb reduction defects, CNS damage (very low increase risk).
Venezuelan Equine Encephalitis: Hydranencephaly; microphthalmia; central nervous system destructive lesions; luxation of hip.
Maternal Disease States
Corticosteroid Secreting Endocrinopathy: Mothers with Cushings Disease can have infants with hyperadrenocortism, but anatomical malfromations do not appear to be increased.
Iodine Deficiency: Can result in embryonic goiter and mental retardation.
Intrauterine Problems of Constraint and Vascular disruption: These types of defects are more common in multiple-birth pregnancies, pregnancies with anatomical defects of the uterus, placental emboli, amniotic bands; birth defects such as club feet, limb reduction defects, aplasia cutis, cranial asymmetry, external ear malformations, midline closure defects, cleft palate and muscle aplasia, limb reduction defects, cleft lip, omphalocele, encephalocele).
Maternal Androgen Endocrinopathy (Adrenal tumors): Masculinization.
Maternal Diabetes: Caudal and femoral hypoplasia, transposition of great vessels.
Maternal Folic Acid in reduced amounts: An increased incidence of neural tube defects (NTDs).
Maternal Phenylketonuria: Abortion, microcephaly, and mental retardation. Very high risk in untreated patients.
Maternal Starvation: IUGR, abortion, NTDs.
Tobacco Smoking: Abortion, IUGR, and stillbirth.
Zinc Deficiency*: Neural Tube Defects*

* Controversial

ing early organogenesis. In addition, P450-independent bioactivation has been suggested: for example, there is strong evidence that the rat embryo can reductively convert niridazole to an embryotoxic metabolite.

As defined by Juchau and Rettie,[35] there are several experimental criteria that would suggest that a suspected metabolite is responsible for the in vivo teratogenic effects of a chemical or drug: 1) the chemical must be convertible to the intermediate, 2) the intermediate must be found in or have access to the tissue(s) affected, 3) the embryotoxic effect should increase with the concentration of the metabolite, 4) inhibiting the conversion should reduce the embryotoxic effect of the agent, 5) promoting the conversion should increase the embryotoxicity of the agent, 6) inhibiting or promoting the conversion should not alter the target tissues, and 7) inhibition of biochemical inactivation should increase the embryotoxicity of the agent. It is readily apparent why there may exist marked qualitative and quantitative differences in the species response to a teratogenic agent.

Placental Transport

The exchange between the embryo and the maternal organism is controlled by the placenta. The placenta varies in structure and function among species and for each stage of gestation. Thus, differences in placental function and structure may affect our ability to apply teratogenic data developed in one spe-

cies directly to other species, including the human, yet as pharmacokinetic techniques and the actual measurement of metabolic products in the embryo become more sophisticated, the appropriateness of using animal data to project human effects may improve.

Although it has been alleged that the placental barrier was protective and therefore harmful substances did not reach the embryo, it is now clear that there is no "placental barrier" per se, yet the package inserts on many drugs state that "this drug crosses the placental barrier."[26] The uninitiated may infer from this statement that this characteristic of a drug is both unusual and hazardous. The fact is that most drugs and chemicals cross the placenta. It will be a rare chemical that will cross the placental barrier in one species and be unable to reach the fetus in another. No such chemical exists except for selected proteins whose actions are species specific.

Genetic Differences

The genetic constitution of an organism is an important factor in the susceptibility of a species to a drug or a chemical. More than 30 disorders of increased sensitivity to drug toxicity or effects in the human are attributable to an inherited trait.

ENVIRONMENTAL AGENTS WHOSE EXPOSURE DURING PREGNANCY HAS BEEN DEMONSTRATED TO RESULT IN REPRODUCTIVE TOXICITY

Table 6 lists environmental agents that have resulted in reproductive toxicity and or congenital malformations in human populations. The list cannot be used in isolation because so many other parameters must be used in any analysis of the risks in individual patients. Many of these agents represent a very small risk, whereas others may represent substantial risks. The risks will vary with the magnitude, timing, and length of exposure. More information can be obtained from more extensive reviews or summary articles. You will also note that Table 7 includes agents that have had concerns raised about their reproductive risks, but after careful and complete evaluation, the agents were found not to represent an increased reproductive risk.[36–41]

References for the environmental agents can be found in review articles and texts that deal with teratogenesis.[5,6,11,16,34,42–47]

TABLE 7. Agents Erroneously Alleged to Have Caused Human Malformations

Bendectin: Alleged to cause numerous types of birth defects including limb reduction defects, heart malformations and many other malformations.
Diagnostic Ultrasonography: No significant hyperthermia, therefore no reproductive effects.
Electromagnetic Fields (EMF): Alleged to cause abortion, cancer, and birth defects.
Progestational drugs: Alleged to cause numerous types of nongenital birth defects, including limb reduction defects, heart malformations and many other malformations).

ROLE OF THE PEDIATRICIAN IN COUNSELING FAMILIES CONCERNING THE CAUSE OF THEIR CHILD'S CONGENITAL MALFORMATIONS

The clinician must be cognizant that many patients believe that most congenital malformations are caused by a drug or medication taken during pregnancy. Counseling patients about reproductive risks requires a significant degree of both knowledge and skill. Physicians must also realize that erroneous counseling by inexperienced health professionals may be a stimulus to nonmeritorious litigation.[22]

Unfortunately, some individuals have assumed that if a drug or chemical causes birth defects in an animal model or in vitro system at a high dose, then it has the potential for producing birth defects at any dose.[48,49] This may be reinforced by the fact that many teratology studies reported in the literature using several doses do not determine the no-effect dose.

Ignoring the basic tenets of teratology seems to occur most commonly in the evaluation of environmental toxic exposures in which the exposure was very low or unknown and the agent has been reported to be teratogenic at a very high dose or a maternally toxic dose. In most instances—but of course not all instances—the actual population exposure is revealed to be orders of magnitude below the threshold dose and the doses that were used in animal studies or toxic exposures in the population. This has occurred with 2,4,5-trichlorophenoxyacetic acid, polychlorinated biphenyls, lead, cadmium, arsenic, pesticides, herbicides, veterinary hormones, and industrial exposures.

Unfortunately, we do have examples in which environmental disasters have been responsible for birth defects or pregnancy loss in exposed populations (methyl mercury in Japan, polychlorinated biphenyls in Asia, organic mercury in the Middle East, lead poisoning in the 19th and early 20th centuries), and we do have many examples of the introduction of teratogenic drugs (Table 6). Therefore, we can never generalize as to whether a chemical or a drug is safe or hazardous unless we know the magnitude of the exposure.

Before their infant is born, parents may be concerned about the risks of various environmental exposures. If the child is born with congenital malformations, then they may question whether there was a causal relationship with an environmental exposure.

1. Has the environmental agent been proved to increase the risk of congenital malformations in exposed human populations? In other words, is the agent a proven human teratogen?
2. Should a woman of reproductive age or who is pregnant be concerned about increased risks of reproductive effects from exposure to a particular environmental agent?
3. If a child is born with congenital malformations and the mother was exposed during her pregnancy to a particular environmental agent, then was the agent responsible for the child's birth defects?

4. Should a physician report or publish a case of a patient or cluster of patients who were born with congenital malformations and whose mother was exposed to an environmental agent?[50]

Scholarly Evaluation

When a pediatrician responds to a parent's inquiry, "What caused my child's birth defect?" the pediatrician should respond in the same scholarly manner that would be used in performing a differential diagnosis for any clinical problem. Pediatricians have a protocol for evaluating complex clinical problems (eg, "fever of unknown origin," "failure to thrive," "congestive heart failure," "respiratory distress"). If a mother of a malformed infant had some type of exposure during pregnancy, such as a diagnostic radiologic examination or medication, then the consulting physician should not support or suggest the possibility of a causal relationship before performing a complete evaluation. Likewise, if a pregnant woman who had not yet delivered had some type of exposure during pregnancy, then the consulting physician should not support or suggest the possibility that the fetus is at increased risk before performing a complete evaluation. As mentioned previously, only a small percentage of birth defects are attributable to prescribed drugs, chemicals, and physical agents[9,36,51] (Table 3). Even when the drug is listed as a teratogen, it has to have been administered during the sensitive period of development for that drug and above the threshold dose for producing teratogenesis. Furthermore, the malformations in the child should be the malformations that are included in the teratogenic syndrome produced by that drug. It should be emphasized that in a recent analysis, it was pointed out that there are no drugs with measurable teratogenic potential in the list of the 200 most prescribed drugs in the United States.[51]

After a complete examination of the child and a review of the genetic and teratology medical literature, the clinician must decide whether the child's malformations are attributable to a genetic cause or an environmental toxin or agent. He may not be able to conclude definitively or presumptively the cause of the child's birth defects. This information must then be conveyed to the patient in an objective and compassionate manner. A similar situation exists if a pregnant woman has been exposed to a drug, chemical, or physical agent, because the mother will want to know the risk of that exposure to her unborn child. If one wishes to answer the generic question, "Is a particular environmental drug, chemical, or physical agent a reproductive toxicant?" then a formal approach that includes a 5-part evaluation is recommended as described in Table 1[18] and is summarized as follows:

1. Consistency of epidemiologic studies
2. Secular trend analysis
3. Animal reproductive studies
4. Dose–response relationships and pharmacokinetic studies comparing human and animal metabolism
5. Biological plausibility

Some typical analyses of the risks of reproductive effects for Bendectin, sex steroids, diagnostic ultrasound, and electromagnetic fields demonstrate the usefulness of an organized approach to determine whether an environmental agent has been demonstrated to be a reproductive toxin.[36–41] There are resources that can assist the physician with the medical literature evaluation and the clinical evaluation of the patient.[5,6,11,16,34,42–47]

Clinical Evaluation

There are many articles and books that can assist the physician with the clinical evaluation, although general pediatric training programs do not usually prepare generalists to perform sophisticated genetic counseling or teratology counseling.[11,16] Besides the usual history and physical evaluation, the physician has to obtain information about the nature, magnitude, and timing of the exposure. The physical examination should include descriptive and quantitative information about the physical characteristics of the child. Although some growth measurements are routine, many measurements used by these specialized counselors are not part of the usual physical examination (eg, palpebral fissure size, ear length, intercanthal distances, total height-to-trunk ratio). Important physical variations in facial, hand, and foot structure as well as other anatomic structures may be suggestive of known syndromes, either teratologic or genetic.

Evaluation of the Reproductive Risk of an Environmental Exposure That Occurred During Pregnancy or the Cause of a Child's Malformation in Which an Exposure Occurred During the Pregnancy

The vast majority of consultations involving pregnancy exposures conclude that the exposure does not change the reproductive risks in that pregnancy. In many instances, the information that is available is so vague that the counselor cannot reach a definitive conclusion about the magnitude of the risk. Information that is necessary for this evaluation is as follows:

1. What was the nature of the exposure?
2. Is the exposure agent identifiable? If the agent is identifiable, then has it been identified definitively as a reproductive toxin with a recognized constellation of malformations or other reproductive effects?
3. When did the exposure occur during embryonic and fetal development?
4. If the agent is known to produce reproductive toxic effects, then was the exposure above or below the threshold for these effects?
5. Were there other significant environmental exposures or medical problems during the pregnancy?
6. Is this is a wanted pregnancy, or is the family ambivalent about carrying this infant to term?
7. What is the medical and reproductive history of this mother with regard to previous pregnancies and the reproductive history of the family lineage?

Evaluation of the Reproductive Risk of an Environmental Exposure That Occurred During Pregnancy

After obtaining all of this information, the counselor is in a position to provide the family with an estimate of the reproductive risks of the exposure. Here are some examples of consultations that have been referred to our clinical teratology service.

Patient 1

A 34-year-old pregnant laboratory worker dropped and broke a reaction vessel that contained a mixture of chemical reagents. She proceeded to clean the floor with paper towels. Later she became concerned about the potential harmful effects of the exposure. She was in the sixth week of her pregnancy, which means that the embryo was in the period of early organogenesis. The chemicals in the spill were tetrahydrofuran (70%), pyridine (20%), and iodine (1%). It was not possible to estimate quantitatively the exposure to these agents, but the laboratory worker experienced no symptoms from the exposure. This was a planned, wanted pregnancy. Although iodine can interfere with thyroid development, the exposure in this situation would be inconsequential, because the thyroid is not yet present. The other 2 compounds have not been studied in epidemiologic studies of pregnant women. No other exposure to reproductive toxins occurred in this pregnancy, and the family history for congenital malformations was negative. The woman was advised that it would be very unlikely that this exposure would increase her teratogenic risk because the exposures to the embryo would be extremely low. She was also told that she still was faced with the background risks for birth defects and miscarriage. Therefore, her reproductive risks should be the same as the risks for the general population (Table 2).

Patient 2

A 26-year-old pregnant woman was in an automobile accident in her 10th week of pregnancy and sustained a severe concussion. Although she did not convulse postinjury, the treating neurosurgeon prescribed 300 mg of diphenylhydantoin during her first 24 hours in the hospital. Fortunately, she recovered from the injury without any sequelae, but her primary physician was concerned that she had received an anticonvulsant associated with a teratogenic syndrome. No other exposure to reproductive toxins occurred in this pregnancy, and the family history for congenital malformations was negative, except for an uncle with neurofibromatosis. The primary physician requested a consultation with regard to the teratogenic risk. Although diphenylhydantoin administered chronically throughout pregnancy has been associated with a low incidence of characteristic facial dysmorphogenesis, reduced mentation, cleft palate, and digital hypoplasia, there are no data to indicate that 1 day of therapy would cause any of the features of this syndrome. Furthermore, the lip and palate have completed their development by the 10th week. This was a wanted pregnancy, and the mother chose to continue her pregnancy. She delivered a normal 3370-g boy at term.

Patient 3

A 25-year-old woman was seen in the emergency service of her local hospital with nausea, vomiting, and diarrhea. She had just returned from a cruise on which a number of the passengers became ill on the last day of the trip with similar symptoms. The emergency department physician ordered a pregnancy test followed by a flat plate of the abdomen because there was evidence of peritoneal irritation. Both of these studies were negative, but 1 week later she missed her menstrual period and a week later her pregnancy test was positive. Her obstetrician was concerned because she had been exposed to a radiologic procedure at a time when she was pregnant. The obstetrician referred the patient for counseling after obtaining an ultrasound that indicated that the embryo was approximately 7 days postconception at the time of the radiologic examination. The patient advised the counselor that she was ambivalent about the pregnancy because of the "dangers" of the radiographs to her embryo. The estimated exposure to the embryo was <500 mrad (0.005 Sv). This exposure is far below the exposure that is known to affect the developing embryo. Just as important is that the embryo was exposed during the first 2 weeks postconception, a time that is less likely to increase the risk of teratogenesis, even if the exposure was much higher.[23,52] After evaluation of the family history and after she received counseling about the risks of the radiograph, the prospective mother decided to continue the pregnancy. She delivered a 3150-g normal infant.

Evaluation of Whether the Cause of Congenital Malformations Was an Environmental Exposure During Pregnancy, Is Genetic, or Cannot Be Determined

Patient 4

The mother of a 30-year-old man who was born in the Azores in 1960 with congenital absence of the right leg below the knee had pursued compensation for her son because she was certain that she must have received thalidomide during her pregnancy.[24] The German manufacturer of thalidomide refused compensation claiming that thalidomide had never been distributed in the Azores. The mother fervently believed that thalidomide was responsible for her son's malformations, and I received a letter from her asking for my opinion. I requested her son's medical records, radiographs, and photographs of the malformations. She sent me the radiograph studies of his hips and legs and his complete evaluation performed at the local hospital in the Azores. He had none of the other stigmata of thalidomide embryopathy (preaxial limb defects, phocomelia, facial hemangioma, ear malformations, deafness, crocodile tears, ventricular septal defect, intestinal or gall bladder atresia, kidney malformations). Most important, his limb malformations were not of the thalidomide type. He had a unilateral congenital amputation, with no digital remnants at the end of the limb. His pelvic girdle was

completely normal, which would be unusual in a thalidomide-malformed limb. Finally, his limb defect involved only 1 leg; the other leg was completely normal. This would be very unusual in a true thalidomide embryopathy. In this particular case, the young man had a congenital amputation, probably as a result of vascular disruption, cause unknown. Known causes of vascular disruptive malformations are cocaine, misoprostol, and chorionic villous sampling. It is difficult to determine whether any amount of appropriate counseling will put closure on this problem for this mother.

Patient 5

A family claimed that the antinausea medication Bendectin,[36,37,53] taken by the mother of a malformed boy, was responsible for her son's congenital limb reduction defects. Bendectin was taken during the mother's pregnancy after the period of limb organogenesis, but some limb malformations can be produced by teratogens later in pregnancy. The malformation was unaccompanied by any other dysmorphogenetic effects. The boys malformations were the classical split-hand, split-foot syndrome, which is dominantly inherited. This malformation has a significant portion of cases that are attributable to a new mutation. Because neither parent manifested the malformation, the conclusion had to be that a new mutation had occurred in the sex cells of 1 of the parents. Therefore, the risk of this malformation's occurring in the offspring of this boy would be 50%. Obviously, Bendectin was not responsible for this child's malformations. Despite the obvious genetic cause of the malformed child's birth defects, a legal suit was filed. A jury decided for the defendant; namely, that Bendectin was not responsible for the child's birth defects.

Patient 6

A woman visited the emergency department of an excellent university hospital complaining of severe lower abdominal pain. An obstetric resident saw her because she informed the staff that she had a previous ectopic pregnancy that necessitated the removal of her ovary and tube. A pregnancy test was positive, and she was scheduled to return to the obstetric clinic in 1 week. At that time, her chorionic gonadotropin level was repeated and had not changed from its previous level. Without performing an ultrasound, a diagnosis of ectopic pregnancy was made. To preserve the patient's reproductive potential, it was decided to treat the ectopic pregnancy with methotrexate rather than remove the remaining tube and ovary. After the administration of methotrexate, the patient was sent home, but a laboratory report indicated that the gonadotropin level had increased 5-fold. The laboratory report received earlier in the day was a copy of the original report performed a week earlier. The patient was called back to the hospital, and an ultrasound revealed a normally implanted embryo. The senior obstetric staff counseled the mother that the infant was at increased risk for having congenital malformations because of the exposure. The patient refused to abort the pregnancy. The obstetric department offered to provide care for the pregnancy and delivery that included a number of ultrasound examinations. At 28 weeks, the patient went into labor and delivered a live-born premature infant. During infancy, a diagnosis of hydrocephalus, developmental delay, and spastic cerebral symptoms was made. A lawsuit was filed by the family against the doctors and the university hospital. The attorney representing the child called me and asked me to evaluate the allegation that the abnormalities in the child were attributable to the administration of the methotrexate. Methotrexate has been reported to cause growth retardation, microcephaly, developmental delay, and hydrocephalus, but not prematurity. The clinical care provided by the resident doctor was unfortunate, but the offer of providing care by the senior obstetricians turned out to be fortunate for the defendants in this case. Review of the records revealed 2 important findings. First, an ultrasound examination taken 1 week before the premature delivery revealed that there was no evidence of hydrocephalus. Second, the birth weight was appropriate for the gestational stage. The exposure to methotrexate was not responsible for the serious problems in this infant, because the hydrocephalus and neurologic symptoms were attributable to a central nervous system bleed in the postnatal period as a complication of the prematurity.

It should be apparent that determining the reproductive risks of an exposure during pregnancy or the cause of a child's congenital malformations is not a simple process. It involves a careful analyses of the medical and scientific literature pertaining to the reproductive toxic effects of exogenous agents in humans and animals, as well as an evaluation of the exposure and biological plausibility of an increased risk or a causal connection between the exposure and a child's congenital malformation. It also involves a careful physical examination and a review of the scientific literature pertaining to genetic and environmental causes of the malformations in question. Abridged counseling on the basis of superficial and incomplete analyses is a disservice to the family.

REFERENCES

1. Gregg NM. Congenital cataract following German measles in the mother. *Trans Ophthalmol Soc Aust*. 1941;3:35–46
2. Thiersch JB. Therapeutic abortions with a folic acid antagonist, 4-aminopteroylglutamic acid (4-amino P. G. A.) administered by the oral route. *Am J Obstet Gynecol*. 1952;63:1298–1304
3. Warkany J, Beautry PH, Horstein S. Attempted abortion with aminopterin (4-aminopteroylglutamic acid). *Am J Dis Child*. 1959;97:274–281
4. Warkany J, Schraffenberger E. Congenital malformations of the eyes induced in rats by maternal vitamin A deficiency. *Proc Soc Exp Biol Med*. 1944;57:49–52
5. McKusick VA. *Mendelian Inheritance in Man: Catalogs of Autosomal Dominant, Autosomal Recessive, and X-linked Phenotypes*. 8th ed. Baltimore, MD: Johns Hopkins University Press; 1998
6. OMIM, Online Mendelian Inheritance of Man. Available at: www3./ncbi.nlm.nih.gov/omim
7. Brent RL, Beckman DA. Environmental teratogens. *Bull N Y Acad Med*. 1990;66:123–163
8. Beckman DA, Fawcett LB, Brent RL. Developmental toxicity. In: Massaro, EJ, ed. *Handbook of Human Toxicology*. New York, NY: CRC Press; 1997:1007–1084
9. Brent RL, Beckman DA. Prescribed drugs, therapeutic agents, and fetal teratogenesis. In: Reece EA, Hobbins JC, eds. *Medicine of the Fetus and*

Mother. 2nd ed. Philadelphia, PA: Lippincott-Raven Publishers; 1999: 289–313
10. Heinonen OP, Slone D, Shapiro S. *Birth Defects and Drugs in Pregnancy*, Littleton, MA: Publishing Sciences Group; 1977
11. Aase JM. *Diagnostic Dysmorphology*. New York, NY: Plenum Medical Book Co; 1990
12. Beckman DA, Brent RL. Fetal effects of prescribed and self-administered drugs during the second and third trimester. In: Avery GB, Fletcher MA, MacDonald MG, eds. *Neonatology: Pathophysiology and Treatment*. 4th ed. Philadelphia, PA: JB Lippincott Company; 1994:197–206
13. Brent RL. What is the relationship between birth defects and pregnancy bleeding? New perspectives provided by the NICHD workshop dealing with the association of chorionic villous sampling and the occurrence of limb reduction defects. *Teratology*. 1993;48:93–95
14. Brent RL, Beckman DA. Teratogens: an overview. In: Knobil E, Neill JD, eds. *Encyclopedia of Reproduction*. Vol 4. San Diego, CA: Academic Press; 1999:735–750
15. Graham JM Jr, Jones KL, Brent RL. Contribution of clinical teratologist and geneticists to the evaluation of the etiology of congenital malformations alleged to be caused by environmental agents, ionizing radiation, electromagnetic fields, microwaves, radionuclides, and ultrasound. *Teratology*. 1999;59:307–313
16. Jones KL. *Smith's Recognizable Patterns of Human Malformations*. 5th ed. Philadelphia, PA: WB Saunders Co; 1994
17. Brent RL, Beckman DA. Angiotensin-converting enzyme inhibitors, an embryopathic class of drugs with unique properties: information for clinical teratology counselors. *Teratology*. 1991;43:543
18. Brent RL. Methods of evaluating the alleged teratogenicity of environmental agents. In: Sever JL, Brent RL, eds. *Teratogen Update: Environmentally Induced Birth Defect Risks*. New York, NY: Alan R. Liss; 1986: 199–201
19. Carter CO. Genetics of common single malformations. *Br Med Bull*. 1976;32:21–26
20. Fraser FC. The multifactorial/threshold concept—uses and misuses. *Teratology*. 1976;14:267–280
21. Brent RL. Medicolegal aspects of teratology. *J Pediatr*. 1967;71:288–298
22. Brent RL. Litigation-produced pain, disease and suffering: an experience with congenital malformation lawsuits. *Teratology*. 1977;16:1–14
23. Brent RL. Utilization of developmental basic science principles in the evaluation of reproductive risks from pre- and postconception environmental radiation exposures. *Teratology*. 1999;59:182–204
24. Brent RL, Holmes LB. Clinical and basic science lessons from the thalidomide tragedy: what have we learned about the causes of limb defects? *Teratology*. 1988;38:241–251
25. Brent RL. The irresponsible expert witness: a failure of biomedical graduate education and professional accountability. *Pediatrics*. 1982;70: 754–762
26. Brent RL. Drugs and pregnancy: are the insert warnings too dire? *Contemp Obstet Gynecol*. 1982;20:42–49
27. Brent RL. Effects and risks of medically administered isotopes to the developing embryo. In: Fabro S, Scialli AR, eds. *Drug and Chemical Action in Pregnancy*. New York, NY: Marcel Dekker; 1986:427–439
28. Brent RL. Radiation teratogenesis. *Teratology*. 1980;21:281–298
29. Brent RL, Beckman DA. Developmental effects following radiation of embryonic and fetal exposure to x-ray and isotopes: counseling the pregnant and nonpregnant patient about these risks. In: Hendee WK, Edwards FM, eds. *Health Effects of Low Level Exposure to Ionizing Radiation*. Bristol, UK: Institute of Physics Publishing; 1996:169–213
30. Brent RL. Ionizing radiation. In: Queenan JT, ed. *Protocols High-Risk Pregnancy*, Contemporary Ob/Gyn. 1999;44(1):13–14,16,21,25–26
31. Boue J, Boue A, Lazar P. Retrospective and prospective epidemiological studies of 1,500 karyotyped spontaneous abortions. *Teratology*. 1975;12: 11–26
32. Hertig AT. The overall problem in man. In: Benirschke K, ed. *Comparative Aspects of Reproductive Failure*. Berlin, Germany: Springer-Verlag; 1967:11–41
33. Simpson JL. Genes, chromosomes and reproductive failure. *Fertil Steril*. 1980;33:107–116
34. Sever JL. Infections in pregnancy: highlights from the collaborative perinatal project. *Teratology*. 1982;25:227–237
35. Juchau MR, Rettie AE. The metabolic role of the placenta. In: Fabro S, Scialli AR, eds. *Drug and Chemical Action in Pregnancy: Pharmacologic and Toxicologic Principles*. New York, NY: Marcel Dekker, 1986;153–169
36. Brent RL. Bendectin: review of the medical literature of a comprehensively studied human non-teratogen and the most prevalent tortogenlitigen. *Reprod Toxicol*. 1995;9:337–349
37. Brent RL. Review of the scientific literature pertaining to the reproductive toxicity of Bendectin. In: Faigman DL, Kaye DH, Saks MJ, Sanders J eds. *Modern Scientific Evidence: The Law and Science of Expert Testimony*. Vol 2. St. Paul, MN: West Publishing Group; 1997:373–393
38. Brent RL. Microwaves and ultrasound. In: Queenan JT, Hobbins JC, eds. *Protocols for High-Risk Pregnancies*. 3rd ed. Cambridge, MA: Blackwell Scientific; 1995:37–43
39. Brent RL, Gordon WE, Bennett WR, Beckman DA. Reproductive and teratologic effects of electromagnetic fields. *Reprod Toxicol*. 1993;7: 535–580
40. Brent RL, Jensh RP, Beckman DA. Medical sonography: reproductive effects and risks. *Teratology*. 1991;44:123–146
41. Wilson JG, Brent RL. Are female sex hormones teratogenic? *Am J Obstet Gynecol*. 1981;141:567–580
42. Friedman JM, Polifka JE. *TERIS. The Teratogen Information System*. Seattle, WA: University of Washington; 1999
43. Scialli AR, Lione A, Padget GKB, eds. *Reproductive Effects of Chemical, Physical and Biologic Agents; Reprotox*. Baltimore, MD: The Johns Hopkins University Press; 1995
44. Sever JL, Brent RL, eds. *Teratogen Update: Environmentally Induced Birth Defect Risks*. New York, NY: Alan R. Liss; 1986
45. Shepard TH. *Catalogue of Teratogenic Agents*. 8th ed. Baltimore, MD: The Johns Hopkins University Press; 1995
46. Schardein JL. *Chemically Induced Birth Defects*. 3rd ed. New York, NY: Marcel Dekker; 2000
47. Briggs GG, Freeman RK, Yaffe SJ. *Drugs in Pregnancy and Lactation*. 3rd ed. Baltimore, MD: Williams and Wilkins; 1990:502–508
48. Brent RL. Drug testing in animals for teratogenic effects: thalidomide in the pregnant rat. *J Pediatr*. 1964;64:762–770
49. Brent RL. Predicting teratogenic and reproductive risks in humans from exposure to various environmental agents using in vitro techniques and in vivo animal studies. *Cong Anom*. 1988;28(suppl):S41–S55
50. Brent RL. Congenital malformation case reports: the editor's and reviewer's dilemma. *Am J Med Genet*. 1993;47:872–874
51. Friedman JM, Little BB, Brent RL, Cordero JF, Hanson JW, Shepard TH. Potential human teratogenicity of frequently prescribed drugs. *Obstet Gynecol*. 1990;75:594–599
52. Wilson JG, Brent RL, Jordan HC. Differentiation as a determinant of the reaction of rat embryos to x-irradiation. *Proc Soc Exp Biol Med*. 1953;82: 67–70
53. Brent RL. Commentary on Bendectin and birth defects: hopefully, the final chapter. *Birth Defects Res*. 2003;67:79–87

Environmental Causes of Human Congenital Malformations: The Pediatrician's Role in Dealing With These Complex Clinical Problems Caused by a Multiplicity of Environmental and Genetic Factors

Robert L. Brent

Pediatrics 2004;113;957-968
DOI: 10.1542/peds.113.4.S1.957

PEDIATRICS

Utilization of Animal Studies to Determine the Effects and Human Risks of Environmental Toxicants (Drugs, Chemicals, and Physical Agents)

Robert L. Brent

Pediatrics 2004;113;984-995
DOI: 10.1542/peds.113.4.S1.984

Utilization of Animal Studies to Determine the Effects and Human Risks of Environmental Toxicants (Drugs, Chemicals, and Physical Agents)

Robert L. Brent, MD, PhD

ABSTRACT. Toxicology studies using animals and in vitro cellular or tissue preparations have been used to study the toxic effects and mechanism of action of drugs and chemicals and to determine the effective and safe dose of drugs in humans and the risk of toxicity from chemical exposures. Studies in pregnant animals are used to determine the risk of birth defects and other reproductive effects. There is no question that whole animal teratology studies are helpful in raising concerns about the reproductive effects of drugs and chemicals, but negative animal studies do not guarantee that these agents are free from reproductive effects. There are examples in which drug testing was negative in animals (rat and mouse) but was teratogenic in the human (thalidomide), and there are examples in which a drug was teratogenic in an animal model but not in the human (diflunisal). Testing in animals could be improved if animal dosing using the mg/kg basis were abandoned and drugs and chemicals were administered to achieve pharmacokinetically equivalent serum levels in the animal and the human. Because most human teratogens have been discovered by alert physicians or epidemiology studies, not animal studies, animal studies play a minor role in discovering teratogens. In vitro studies play an even less important role, although they are helpful in describing the cellular or tissue effects of the drugs or chemicals. One cannot determine the magnitude of human risks from these in vitro studies. Performing toxicology studies on adult animals is performed by pharmaceutical companies, chemical companies, the Food and Drug Administration, many laboratories at the National Institutes of Health, and scientific investigators in laboratories throughout the world. Although a vast amount of animal toxicology studies are performed on pregnant animals and numerous toxicology studies are performed on adult animals, there is a paucity of animal studies using newborn, infant, and juvenile animals. This deficiency is compounded by the fact that there are very few toxicology studies performed in children. That is why pregnant women and children are referred to as "therapeutic orphans." When animal studies are performed with newborn and developing animals, the results demonstrate that generalizations are less applicable and less predictable than the toxicology studies in pregnant animals. Although many studies reveal that the infant and the developing animal have difficulty in metabolizing drugs and are more vulnerable to the toxic effects of environmental chemicals, there are exceptions that indicate that infant and developing animals may be less vulnerable and more resilient to some drugs and chemicals. In other words, the generalization indicating that developing animals are always more sensitive to environmental toxicants is not valid. For animal toxicology studies to be useful, animal studies have to use modern concepts of pharmacokinetics and toxicokinetics, as well as method-of-action studies to determine whether animal data can be used for determining human risk. One example is the inability to determine carcinogenic risks in humans for some drugs and chemicals that produce tumors in rodents, because the oncogenesis is the result of peroxisome proliferation, a reaction that is of diminished importance in humans. Scientists can use animal studies to study the toxicokinetic and toxicodynamic aspects of environmental toxicants, but they have to be performed with the most modern techniques and interpreted with the highest level of scholarship and objectivity. Threshold exposures, maximum permissible exposures, and toxic effects can be estimated but have to be interpreted with caution when applying them to the human. Well-performed epidemiology studies are still the best method for determining the human risk and the effects of environmental toxicants. *Pediatrics* 2004;113:984–995; *methods of evaluation, environmental toxicology, pharmacokinetics, pharmacodynamics, toxicokinetics, toxicodynamics, MOA (method of action), deterministic, threshold phenomenon, stochastic, biologic plausibility, in vitro systems, in vivo animal studies.*

ABBREVIATIONS. MOA, method of action; FDA, Food and Drug Administration; CNS, central nervous system.

This article deals with a complicated and important issue. Can the magnitude and type of environmental risks to the embryo, child, and adolescent be determined from animal studies, and how different are these risks when compared with adults? In many instances, environmental agents will exploit the vulnerabilities and sensitivities of developing organisms. In other instances, there will be no difference between the developing organism and the adult when exposed to toxicants, and in some instances, children and adolescents may even withstand the exposures with less insult. The difficulty that we have at this time is that in many situations, we do not have enough data and/or scholarly techniques to arrive at a conclusion about the relative sensitivity of the developing organism to some environmental agents. Rather than arrive at conclusions

From the Thomas Jefferson University, Alfred I. duPont Hospital for Children, Laboratory of Clinical and Environmental Teratology, Wilmington, Delaware.

Received for publication Oct 7, 2003; accepted Oct 20, 2003.

Reprint requests to (R.L.B.) Rm 308, R/A, Alfred I. duPont Hospital for Children, Box 269, Wilmington, DE 19899. E-mail: rbrent@nemours.org

about environmental agents or exposures for which there are insufficient data, we need to initiate investigative approaches to obtain the necessary data concerning agents and exposures that have not been clarified, so it is important that we initiate and expand quality research in environmental toxicology.

Although chemicals and drugs can be evaluated for their toxic potential by using in vivo animal studies and in vitro systems, it should be recognized that these testing procedures are only 1 component in the process of evaluating the potential toxic risk of drugs and chemicals. The evaluation of the toxicity of drugs and chemicals should include, when possible, data obtained from a number of investigative approaches[1]: 1) epidemiologic studies[1,2]; 2) secular trend or ecological trend analysis; 3) animal studies[3–7]; 4) pharmacokinetic, toxicokinetic, pharmacodynamic, and toxicodynamic studies; 5) mechanism of action (MOA) studies; and 6) basic science studies that pertain specifically to the agent, such as MOA studies, which include receptor affinity, cytotoxicity, genotoxicity, organ toxicity, neurotoxicity, etc.[1,4,6,8] Human studies are expensive and take years to complete. Therefore, scientists have asked whether appropriate animal models are available to evaluate the risks of environmental toxicants to the embryo, infant, child, and adolescent. This is not an easy task.

There are a few toxicologic principles that should precede the specific discussion. Frequently, drugs or chemicals are grouped into categories (pesticides, trihalomethanes, organochlorines, solvents, progestins, heavy metals, chemotherapeutic agents). It is important to note that this type of classification may be useful for some purposes but not for concluding generalizations about the toxic effects of all of the agents in the group. As an example, the Food and Drug Administration (FDA)[9] published a report in the *Federal Register* disclaiming the term "progestins" to describe a group of drugs with identical effects and toxicity. Second, chemicals may be referred to as "poisons." This is not a useful label because every known chemical or drug has an exposure that is toxic. Paracelsus stated in the 16th century, "What is there that is not poison? All things are poison and nothing is without poison. Solely, the dose determines that a thing is without poison."

Three areas of animal testing are discussed: 1) reproductive effects from exposures during embryonic and fetal development; 2) toxic effects of drugs and chemicals administered to animals after birth as newborns, infants, juvenile animals, and adults; and 3) oncogenic effects of environmental toxicants.

USE OF ANIMAL STUDIES TO DETERMINE REPRODUCTIVE RISKS IN HUMANS (TERATOGENESIS, GROWTH RETARDATION, PREGNANCY LOSS, STILLBIRTH, AND INFERTILITY)

Pediatricians and other clinicians have little training on how to interpret animal toxicology studies during medical school and residency training. This is probably more true of reproductive toxicology studies than in any other area of animal testing. Unfortunately, for physicians, the most frequent source and contact with animal testing information is in the package insert or the Physician's Desk Reference.[10] The Physician's Desk Reference uses the FDA's classification of reproductive risks, partly based on animal testing. The categories are A, B, C, D, and X. The A category includes drugs that have no risk for reproductive effects. The B, C, and D categories have increasing risks, and the X category includes drugs such as methotrexate, Accutane, and thalidomide that should not be used in pregnant women or women of reproductive age who are not on contraceptives. These categories are misleading more than they are helpful. Teratologists, obstetricians, and other clinicians who counsel pregnant women have been very critical of the FDA classification[11] because the classification ignores the basic principles of teratology[12] and the importance of modern pharmacokinetics when evaluating animal studies.[5] In 1990, a published article indicated that of the 200 most frequently prescribed drugs, none of them represented a significant teratogenic risk,[13] yet only a small proportion of these drugs were placed in category A by the FDA. There are many reasons for these misclassifications, but the most important reason is the misapplication of animal testing results. Let me give you some examples.

When a new drug is marketed or a new environmental toxicant is discovered, frequently the only information that is available is the animal data. Three examples are used to emphasize the difficulties that occur: 1) meclizine produces cleft palate at very high exposures in the rat; 2) leflunomide and its MOA; and 3) radiation produced mental retardation; a deterministic or stochastic effect (Table 1)?

TABLE 1. Stochastic and Threshold (Deterministic) Dose–Response Relationships of Diseases Produced by Environmental Agents

Phenomenon	Pathology	Site	Diseases	Risk	Definition
Stochastic	Damage to a single cell may result in disease	DNA	Cancer, germ cell mutation	Some risk exists at all dosages; at low doses, risk is less than spontaneous risk	The incidence of the disease increases, but the severity and nature of the disease remain the same
Threshold Deterministic	Multicellular injury	Multiple, variable cause, affecting many cell and organ processes	Malformation, growth retardation, death, toxicity, etc	No increased risk below the threshold dose	Both the severity and incidence of the disease increase with dose

Modified from Brent.[12]

Meclizine Produces Cleft Palate at Very High Exposures in the Rat

Meclizine is an antihistamine with a lengthy history and like most antihistamines has not been demonstrated to have reproductive toxicity in multiple epidemiologic studies, yet its pregnancy category classification is B, primarily because "reproductive studies in rats have shown cleft palates at 25 to 50 times the human dose." Actually, what the clinician needs to know is what the blood level is in the rat and mouse when teratogenesis is produced and how that blood level compares with the level in patients who receive therapeutic doses of the medication. Without this information, the animal experiments are meaningless. There are hundreds of drugs in categories B and C with animal studies using the archaic mg/kg dose. This same failing has occurred in toxicologic studies with environmental toxicants (lead, mercury, polychlorinated biphenyls, pesticides, fungicides), namely, using mg/kg exposures in rodents or other animals rather than determining serum levels in the animal and the human population for which there was concern. Fortunately, more recent environmental toxicology studies have been using modern toxicokinetic techniques, but serum levels of these toxicants are not always available in humans.

Leflunomide and Its MOA

Leflunomide[8] is a relatively new drug (1998) that is used to treat rheumatoid arthritis. It has a box warning for reproductive effects (teratogenesis) and has been placed in category X. Because there were no human data available at the time of marketing, the label was based on the animal studies: "There are no adequate and well-controlled studies evaluating Arava (leflunomide) in pregnant women. However, based on animal studies, leflunomide may cause fetal death or teratogenic effects when administered to a pregnant woman."

Leflunomide is a novel isoxazole immunomodulatory agent that inhibits de novo pyrimidine synthesis and has antiproliferative activity. In vitro, after mitogen stimulation, the active metabolite of leflunomide inhibits T-cell proliferation, DNA synthesis, and the expression of certain cell surface and nuclear antigens directly involved in T-cell activation and proliferation. It inhibits mitogen-stimulated proliferation of human peripheral blood mononuclear cells and proliferation in transformed murine and human cell lines in a dose-dependent manner. It has been demonstrated that the active metabolite binds to and is a potent inhibitor of dihydroorotate dehydrogenase, an enzyme in the de novo pyrimidine synthesis pathway important for DNA synthesis. Together, these data suggest that at serum concentrations achievable in patients, leflunomide inhibits de novo pyrimidine synthesis in activated lymphocytes and other rapidly dividing cell populations, resulting in reversible cell cycle arrest.

In oral embryotoxicity and teratogenicity studies in rats and in rabbits, leflunomide was embryotoxic (growth retardation, embryolethality, and teratogenicity) in rats, consisting of malformations of the head, rump, vertebral column, ribs, and limbs; and in rabbits, malformation of the head and bilateral dysplasia of the spine of the scapula. The no-effect level for embryotoxicity and teratogenicity in rats and rabbits was 1 mg/kg body weight, which resulted in serum levels of 3.7 and 4.1 μg/mL, respectively.

The active metabolite of leflunomide, which is the pyrimidine antagonist, is maintained at a blood level of 40 μg/mL in patients being treated. The decision to label leflunomide as having a teratogenic risk was based on the fact that the human serum level was in the range of the teratogenic blood level in the animal models, so the initial labeling was an appropriate precaution to prevent birth defects.

After 4 years of treatment of patients with rheumatoid arthritis and no indication of an increase in teratogenesis in a very small group of pregnant patients who were treated and continued their pregnancy to term, we can reanalyze the animal data as follows. This is referred to as the MOA approach. The potential mechanisms of teratogenicity for leflunomide are as follows:

1. Suppression of DNA synthesis by interfering with pyrimidine synthesis based on the presumption that suppression is equal in the rat, rabbit, and human at the same serum levels of the active metabolite of leflunomide. This was the basis of the X category labeling.
2. The susceptibility of the enzyme to the active leflunomide metabolite that is involved in pyrimidine incorporation into DNA in the human and animal models.
3. The ability of the active metabolite of leflunomide to interfere with cell proliferation in the human and animal models.

If all 3 mechanisms of action were operative to the same degree at the same serum level in the animals and the patients, then there would be concurrence and the human risks would be determined to be identical from studying all 3 mechanisms. In vitro studies of the active metabolite of leflunomide revealed that the rat was 40 times more sensitive to the suppression of dihydroorotate dehydrogenase than the human and that the rat was 328 times more sensitive to the active metabolite of leflunomide than was the human in suppressing cell proliferation.

What this means is that if enzyme suppression or antiproliferative activity is the MOA of teratogenicity in the rat, then the clinical use of leflunomide in pregnant women would probably not be teratogenic, but no one would act on these findings without confirmation from the ongoing epidemiologic surveillance of this drug. This is an example of modern pharmacokinetic studies having improved risk assessment and made epidemiologic studies understandable.

In Utero Effects of Ionizing Radiation on the Risk of Mental Retardation

Here is an example in which animal behavioral studies and concomitant pathology were helpful in resolving an important issue with regard to in utero radiation–induced mental retardation. The main is-

TABLE 2. Effect of In Utero Ionizing Radiation on Developmental and Neurologic Parameters in the Rat

Dose of X-ray (Gy)	Embryonic or Fetal Age							
	9th Day				16th Day			
	0.1	0.2	0.4	0.6	0.1	0.2	0.4	0.6
Effect								
Growth retardation at term	–	–	–	–	–	–	–	–
Growth retardation postpartum	–	–	–	–	–	+	+	+
Developmental parameters (4)	–	–	–	–	–	–	+(2)	+(2)
Reflexes (5)	–	–	–	–	–	+(1)*	+(1)	+(1)

sue with regard to the risk of mental retardation after an in utero exposure to ionizing radiation pertains to whether the risk from exposure is stochastic (no threshold) or deterministic (threshold effect; Table 1). The possibility that 0.01 Sv (1 rad) might double the risk of mental retardation was suggested in 1984.[14]

From the perspective of biological plausibility and the results of animal studies, it seems that the data favor the viewpoint that mental retardation is a deterministic effect with a threshold above 0.2 Sv.[12,15–22] Histologic examination of the irradiated brain exposed to 0.01 Sv reveals no pathologic consequences that could account for severe mental retardation.[23] That would mean that the pattern of effects produced by ionizing radiation that accounts for mental retardation when the fetus is exposed to 0.5 to 2 Sv does not occur at very low exposures. Furthermore, additional studies by Schull and Otake[24] revealed that these authors were able to quantify the risk of reduced intellect after in utero ionizing radiation exposures. They estimated that there was a reduction in intellect of approximately 30 IQ points per Sv in their studies. Even if there were a linear relationship between the dose and IQ reduction, one could predict that 0.01 Sv could not account for a doubling of the incidence of mental retardation, because a linear extrapolation of Otake and Schull's data would represent only a maximum reduction of 0.3 of an IQ point at 0.01 Gy. Behavioral studies in animals were unable to demonstrate neurobehavioral effects below 0.02 Gy[15–17] (Table 2). Although one has to be careful in extrapolating animal data to humans, the lack of neurobehavioral effects from in utero irradiation supports the other findings that indicate that mental retardation is a threshold (deterministic) effect (Tables 1 and 2).

Once a drug, chemical, or other agent is suspected of producing congenital malformations or other reproductive effects, appropriate use of in vitro and in vivo testing can be helpful in evaluating the specific allegation and in determining the mechanism of action of the agent. Whole animal testing, although serving important and useful purposes, can still be improved so that they can be better used to estimate human reproductive risks. These improvements are listed in Table 3.

In vitro tests can be used to study the mechanisms of teratogenesis and embryogenesis and for preliminary screening procedures, but in vitro studies will never be able to be predictive of human teratogenic risks at particular exposures without the benefit of data obtained from whole animal studies (Table 3) and epidemiologic studies.[5,7,25–27] Despite the advances in in vitro and in vivo testing for teratogenicity, human epidemiologic surveillance by various methods is and will be our most powerful tool for discovering human reproductive toxins and teratogens. It may be difficult for experimental teratologists to accept that alert physicians and scientists have been the most prominent contributors to the discovery of the environmental causes of birth defects[2] (Table 4).

TABLE 3. A Whole-Animal Teratology-Reproductive Toxicity Protocol Should Include the Following Parameters and Goals

1. Determine the reproductive effects at stages of gestation that may have markedly different endpoints, namely, preimplantation, organogenesis, and early fetal and late fetal stages.
2. The importance of various reproductive endpoints may vary considerably by the gestational stages being evaluated, and exposures at one stage may exaggerate, modify, or eliminate effects that occur at another stage
   1. Teratogenesis
   2. Embryolethality
   3. Growth retardation
   4. Postnatal physiologic, biochemical, developmental, and behavioral effects
3. Determine the no-effect dose for the parameters mentioned in item 2 at various stages of gestation.
4. Determine the ratio of the no-effect dose to the human therapeutic dose, usual exposure dose, or maximal permissible exposure for the parameters mentioned in item 2.
5. Determine the quantitative relationship between the human and animal model pharmacokinetics and toxicokinetics concerning the dose and the blood levels and the metabolism in the animal model and human.
6. Determine the MOA of the environmental toxicant.
7. Determine the ratio of the LD/50 for the mother and the embryo.

TABLE 4. How Some Human Teratogens Have Been Discovered

Agent or Drug	Major Means of Discovery			
	Human Epidemiology Studies	Alert Physician or Scientist; Cluster	Animal Studies	In Vitro Studies
Rubella		+++		
Aminopterin		++		
Anticonvulsants		+++		
Hydantoins 1963				
Trimethadione 1970		++		
Valproic acid 1982	+++			
Vitamin A, 1953			+++	
Isotretinoin 1983		++		
Etretinate 1984		++		
PCBs 1968		++		
Coumarin 1968		++		
Alcohol 1967		++		
Lithium 1970		++		
Diethylstillbesterol 1971		++		
Penicillamine 1971		++		
Misoprostol		++		
Trimethorpin	+			
Chorionic villous sampling		++		

PCB indicates polychlorinated biphenyl.

EFFECTS OF ENVIRONMENTAL TOXICANTS THAT ARE ADMINISTERED TO ANIMALS AFTER BIRTH AS NEWBORNS, INFANTS, JUVENILE ANIMALS, AND ADULTS FOR DETERMINING HUMAN RISKS

It is obvious that animal experiments cannot be planned to consider all of the variables that occur in the human. In fact, there are situations in animal studies that differentiate the animal species from the human. For example, coprophagy and other behaviors in rodents and other species can markedly alter the dynamics of toxicity studies. Differences in absorption, metabolism, and excretion of drugs and chemicals represent the greatest barrier to applying risks obtained from animal studies directly to the human.

It is hoped that regulatory agencies and toxicologists who deal with issues of developmental toxicity will develop animal models that will predict toxicologic effects in children and adolescents from exposure to drugs and chemicals. Although this is an optimistic view, Done[28] pointed out that although the number of drug hazards that have proved to be unique in the infant have proved to be small: "Without exception, recognition of the proved hazard has come about only after widespread use, and then usually when tragic consequences focused attention on the drug."[28]

Animal Toxicology Studies

Historically, the administration of drugs and chemicals to humans and animals in experimental studies has used the mg/kg exposure method. Even in the 1800s, there was recognition that there was not a proportional relationship between body weight and dose between the infant and the adult human.[29] It was apparent that appropriate infant doses would in some cases be toxic in the adult and appropriate adult doses would be inadequate for the infant if the mg/kg approach were used. Animal investigators have long been aware of this dilemma. It became apparent that comparisons of toxicity or therapeutic effects bore a closer relationship to the 0.7 power of body weight, and this figure was closely related to surface area.[30,31] Many physiologic functions are proportional to surface area because the extracellular volume in humans is constant on a surface area basis. Therefore, the serum concentrations obtained from administration or exposure to drugs and chemicals on a surface area basis would result in serum concentrations that would be similar. This is more closely related to the 0.73 power of the weight at all ages in humans.[32,33] If, however, drugs or chemicals are also distributed in the total body water, then neither the mg/kg nor the surface area model will be accurate, because total body water is not a constant using the surface area constant or the mg/kg relationship. It is obvious that no one method of dose calculation for the young will be satisfactory for evaluating appropriate therapeutic doses or for determining toxic risks. If that is the case for human exposures, then animal toxicology studies that are based on the mg/kg or surface area will not be universally appropriate for determining human risks or proper doses. In fact, the fields of pharmacokinetics and toxicokinetics have demonstrated that animal toxicology experiments have to be performed knowing the serum level of the drug or chemical in the human and using those levels in animal toxicology studies.

We are interested in the usefulness of information obtained from animal toxicology studies, using drugs and chemicals for determining the risks to children and adolescents from these exposures. The largest literature in this field pertains to animal toxicology studies using newborn and infant animal models. Most of these studies are acute toxicology studies and use the mg/kg method of dosing the adult and infant animals. Much of the information is simply the determination of the lethal exposure or the effect on growth. The most important finding in

these studies is that newborn and infant animals are not always more sensitive or more deleteriously affected by drugs and chemicals when compared with adults.

Urethane, an anesthetic that is no longer used for that purpose, was unable to anesthetize newborn animals at exposures that anesthetized adults, whereas ether altered reflexes at lower concentration in newborn animals than in adults.[34] Newborn mice and other animal species have demonstrated a tolerance to hypoxic conditions that is not present in adult animals.[35–39] Newborn mice continued to breathe for a longer period when exposed to ether than adult mice.[40] Newborn mice had a prolonged survival when compared with adults that were exposed to asphyxia as a result of exposure to CO, HCN, CO_2, H_2, and CH_3. Longer exposures to strychnine, curare, cyanide injection, strangulation, hypoxia, or nitrobenzol were necessary to produce respiratory arrest in newborn mice as compared with adult mice.[38]

In summarizing this information, Done[28] was cautious, pointing out the multiplicity and variability of experimental details in these studies. He concluded, "Some tentative generalizations and observations may be worth making. First, it is apparent that immaturity does not necessarily entail greater sensitivity. A notable example is thiourea, which is 50 to 400 times as toxic in the adult as in infant rats."[41,42] Conversely, the animal experiments with chloramphenicol clearly demonstrated that this drug was more toxic in the infant rat than in the adult. Animal toxicity studies corroborated the toxicity reported in infants.[43–45]

In Done's[28] review of developmental toxicology, he indicated that the newborn or infant animal was more sensitive to many drugs (eg, chloramphenicol, morphine, some other opiates, picrotoxin, tetracycline, novobiocin, some organophosphate anticholinesterases, atropine, histamine, sodium salicylate) and less sensitive to others (eg, ethanol, strychnine, metrazol, codeine, acetocycloheximide, thiourea, thyroid hormone). Many other drugs had sensitivities that were similar in the neonate and adult animal, but, of course, most of these data were based on the mg/kg dosage and the endpoints were simplistic, ie, death or cessation of respiration.

Development Toxicity Studies in Juvenile Animal Models: Relevance for Estimating Developmental Risks in Humans

Can concerns about developmental problems from exposure to developmental toxicants in children and adolescent be evaluated with appropriately designed animal studies? Selevan et al[46] indicated "that little concrete information exists on critical windows for exposure during the postnatal period."[47,48] However, a systematic examination has not been done of available data on critical windows of vulnerability during postnatal development. Most available data are focused on prenatal exposures. Postnatal exposures have been examined for only a few agents (eg, lead, pesticides, radiation),[49–52] and it can be stated that the pesticide analysis is far from definitive. The most important aspects in designing these animal studies are the application of modern toxicokinetics and pharmacokinetics. Exposure levels should include exposures that occur in the environment, and a major effort should be made to determine the no-effect level.

The developmental events that can be affected by environmental exposures to drugs, chemicals, and physical agents include the following developmental events that occur during childhood and adolescent development.

Interference With Growth, Epiphyseal Development, and Epiphyseal Closure

Alterations in growth from exposure to environmental toxicants can result in accelerated growth or growth retardation. Accelerated growth and maturation can result in larger stature or smaller stature. Smaller stature can result from the combination of growth acceleration and earlier epiphyseal closure. Drugs and chemicals that are cytotoxic or interfere with normal hormonal and endocrine relationships have the potential for altering growth and development, but the exposure has to be above the threshold for producing results. Useful information about the effect of environmental toxicants can be obtained by exposing animals during various developmental stages before puberty.

Reproductive and Hormonal Effects

Do exposures during childhood and adolescence from environmental agents having hormonal activity, cytotoxicity, or other effects alter the timing of puberty, alter the maturation of sexual organs including breast development, or affect fertility or the normalcy of spermatogenesis and oogenesis?[53] Gamete production in both the male and female begins at puberty: spermatogenesis in the male and ovulation in the female. Immature and pubertal rats seem to be more sensitive than adults to testicular toxicity induced by phthalate esters,[54–56] but the primate does not have the same susceptibility as the rat. The pesticide 1,2-dibromo-3chloropropane affects the immature rat testes more severely than the adult, although the testes of the adult are also affected, as 1,2-dibromo-3chloropropane was banned because occupational exposure in adult males resulted in infertility.[57,58] Lemasters et al[59] pointed out that immature animals are not always more sensitive than adults. Fetal Leydig cells are less sensitive than adult Leydig cells to ethane dimethane sulfonate, a known Leydig cell toxicant.[60] Before the onset of puberty, rats are insensitive to testicular toxicity after exposure to 1,3-dinitrobenzene, a Sertoli cell toxicant, and young adults are less sensitive than mature male adults.[61] Although spermatogenesis has many similarities among mammalian species, oogenesis varies considerably. Even the number of primordial ova varies in different mammalian species.[53] Exposure of female rats to 4-vinylcyclohexene diepoxide results in destruction of oocytes in small follicles, and adult rats are less sensitive to the ovatoxicity of this compound.[62] Would the onset of menopause be affected

by certain chemical and drug exposures during childhood and adolescence?

Environmental toxicants can affect thyroid development and therefore have a direct impact on neurologic normalcy, because normal thyroid function is crucial for normal central nervous system (CNS) development.[63] The most common environmental cause of mental retardation in the world is endemic cretinism as a result of iodine deficiency and is not an environmental toxicity in the usual sense.[64,65] Conversely, children's thyroids have been demonstrated to be more sensitive to the oncogenic effect of external ionizing radiation exposure as well as radioactive iodine localization in the thyroid.[66–69]

With regard to environmental toxicity, questions have been raised about the effect of organochlorine compounds (polychlorinated biphenyls, dioxins) on thyroid function.[70–75] It is difficult to determine the magnitude of the risk of these compounds on thyroid function with the data that are available. The worldwide problem of endemic cretinism from iodine deficiency is without question a real problem. Few studies have evaluated the risk of environmental toxicants on thyroid function and other endocrine organs when exposed during childhood and adolescence.

In the article by Pryor et al[53] dealing with reproductive effects, the authors stated, "Although it is the dose that makes the poison, there is no doubt that timing of the exposure may be as important as dose in determining the potential toxicity of a compound to the reproductive system." This is not a rare statement in the "environmental literature," but it is not correct. Timing of exposure is important, but it is not important if the actual exposure is below the threshold. If the threshold dose for an effect at any stage of development is not exceeded, then timing is irrelevant.

Do Exposures to Environmental Agents During Childhood and Adolescence Affect the Normalcy of the Adult Immune System?

Although it is true that many chemicals can affect the immune system at high exposures, the question of whether environmental exposures play any role in altering the immune system has not been answered. It has not even been determined whether this is a high priority area to be studied using appropriate animal models. In the review on this subject by Holladay and Smialowicz,[76] the authors stated, "The possibility that developmental exposure to immunotoxicants may play a role in inducing or exacerbating hypersensitivity or autoimmune responses needs to be investigated in laboratory animals."

Vulnerability of the Nervous System to Environmental Agents During Childhood and Adolescence

Critical developmental processes during the development of the CNS include 1) the development of the germ layers, 2) neurulation, 3) the closure of the neural tube, 4) neuronal proliferation, 5) neuronal migration, 6) differentiation, 7) synaptogenesis, 8) myelination, and 9) apoptosis. These processes can be studied in animal models.[77,78] The first 5 or 6 developmental events have occurred before the period of CNS development during childhood and adolescence. Rice and Barone[79] raised the question as to whether schizophrenia, dyslexia, epilepsy, and autism may be caused by environmental influences. Weiss and Landrigan[80] speculated that attention-deficit/hyperactivity disorder and Parkinson's disease may be attributable to exposures that occurred during development. We know that epilepsy can be caused by trauma, infection, and genetic abnormalities and that autism can be produced by an insult to the nervous system very early in embryonic development.[81,82] Rice and Barone[79] also raise the question as to whether early exposures to toxicants can cause acceleration of age-related decline in CNS function. Some of these questions are amenable to animal studies in both rodents and primates, but these studies are neither easy to perform nor inexpensive, especially in the primate. Two important problems exist with regard to evaluating the risk of neurotoxicity of environmental toxicants at various stages of development using animal models: 1) we do not have precise information that equates various stages of prepartum and postpartum brain development in the human and animal models,[83] and 2) we cannot be certain of our ability to identify and recognize the most important neurologic diseases in animal models (eg, attention-deficit/hyperactivity disorder, dyslexia, autism, schizophrenia, Parkinson's disease).

In the publication by Adams et al,[84] a number of important concepts are discussed. The authors indicated, "Inherent in the brain's protracted period of development is also the phenomenon of neuroplasticity, and the nervous system's consequent potential for compensation after insult." This is probably the most difficult area to investigate in both human and animal models. In fact, it is such a difficult area that the authors indicated that it was beyond the scope of their review, but it is an area that could be investigated using animal models. Adams et al[84] specifically discussed the topic of the "vulnerability during the adolescent period of development." They indicated that the brain of the adolescent undergoes "striking" transformations, which is observed in many mammalian species. These regions include areas of remodeling of the prefrontal cortex and other forebrain regions that receive projections of the mesolimbic dopaminergic terminal projections. In addition, there is a decline in the volume of the prefrontal cortex in humans[85] and the rat.[86] According to Adams et al,[84] there is also substantial synapse elimination of presumed glutaminergic excitatory input to the motor cortex,[87] whereas dopaminergic input to the prefrontal cortex increases during adolescence to reach levels higher than that seen earlier or later in life.[88] Estimates of basal synthesis and turnover of dopamine decline in prefrontal cortex during adolescence in rats, which contrasts with the increase in these measures reported in the nucleus accumbens and striatal dopamine terminal region of adolescent rats.[89,90] Maturational events have also been reported in a variety of other areas, including the hippocampus in humans[91] and rodents[92] and in the hypothalamus.[93] Adams et al[84] suggested that the adolescent

brain may be especially vulnerable during this period of remodeling and referred to the publications of Salimov et al,[94] who reported the toxic influence of alcohol exposure during this stage of development in the rat. All of these studies are of interest and inform the reader about the developmental processes that may be occurring in the brain of adolescents, but few of these studies reveal whether environmental toxicants have any effects on these developmental processes.

USE OF ANIMAL STUDIES TO DETERMINE THE ONCOGENIC RISKS OF ENVIRONMENTAL TOXICANTS

There is a truism in medicine that indicates that children are at greater risk for the induction of cancer than adults from exposure to agents that are mutagenic or have demonstrated oncogenic potential.[67–69,95] That is certainly proved for high doses of ionizing radiation and for exposures to radioactive ^{131}I.[51,66–69] Studies of the oncogenic effects of radiation in Hiroshima and Nagasaki demonstrated that children have a higher risk of cancer after whole-body irradiation. However, this increased risk is magnified by the higher proportion of acute lymphocytic leukemia in children and the increased risk of this disease in radiated children. The calculated overall risk of cancer in irradiated children has 95% confidence limits of 1.0 to 1.8.[68,69]

There are very few cancer studies in animals that expose the animals during a narrow window of time that would be equivalent to childhood or adolescence. Most animal cancer studies using environmental chemicals and drugs involve life-long exposures. The children who were exposed to high doses of ionizing radiation in Hiroshima and Nagasaki did have an increased incidence of leukemia to a greater extent than did the exposed adults.[67–69] There are studies involving children and adolescents who have been treated for cancer with chemotherapeutic drugs and radiation, and these survivors are at an increased risk of second cancers. However, when they become parents, they do not have offspring with an increased incidence of cancer.[96] Animal studies that would involve only short exposures to proven human carcinogens during the equivalent of childhood or adolescence could be performed. The most appropriate first approach would be to select agents that have been demonstrated to be positive in a life-long animal study or agents that are definitely mutagenic as a first approach to determine the oncogenic sensitivity to environmental toxicants during various developmental stages.

There are extensive reports concerning the oncogenic effect of drugs and chemicals in life-long animal studies. Many of these cancer studies have evaluated environmental chemicals (eg, organochlorine chemicals, ethylene oxide, pesticides, organic solvents, phthalates, acrylonitriles, trihalomethanes). Most of these cancer studies have used rodents and have also exposed the animals at relatively high exposures.

Most agents that have been demonstrated to be carcinogenic in humans will produce cancer in some laboratory animals but not all laboratory animals, but the converse is not true, namely, that all agents that have been demonstrated to be carcinogenic in animals are carcinogenic in humans.[97–99] When the MOA of a carcinogenic agent is understood, the relevance of the animal studies can be placed into proper perspective. The following 2 examples are animal studies that indicated a carcinogenic potential, but when the MOA was understood, these agents were determined not to have human carcinogenic potential.

Animal studies have revealed marked differences among species with regard to the oncogenic susceptibility to environmental chemicals and drugs as exemplified by the phthalates.[100–108] For example, chemicals such as the phthalates induce peroxisome proliferation in the rodent resulting in hepatocarcinogenicity, but there is less responsiveness in primates or human liver cells.[109–119] There is much discussion and controversy in the literature regarding the mechanism of this carcinogenic effect, namely, the role of increased cell division as the cause of mutation and eventual carcinogenicity.[120–125] Whether the carcinogenicity is the result of mutation or some other mechanism related to peroxisome proliferation is of interest, but the important aspect of this topic is the marked difference in oncogenic susceptibility in various species.[101,107,114,126] Animal carcinogenicity studies using the phthalates and other chemicals that stimulate the peroxisome proliferation response may not be appropriate models to determine human cancer risks.

The second agent that received much attention is saccharin, which produced bladder cancer when high doses of saccharin were administered to rodents. At high doses, precipitates of saccharin develop in the rodent bladder, producing inflammation and proliferation that ultimately result in bladder tumors.[127,128] Other experiments indicated that human exposures of saccharin would never result in the situation that occurred in the rodent.

The phthalate and saccharin experiences indicate that when the MOA for carcinogenesis is deterministic (a threshold effect), the risk may not be present at lower exposures and that species differences in metabolism and response may make it difficult to apply animal risks to human risks. Conversely, when the oncogenic effect is related to a mutagenic agent, the theoretical risk for a no-threshold or stochastic effect exists (Table 1).

For determining whether the oncogenic risk for drugs and chemicals is greater during postpartum animal development, protocols would have to be developed during these stages of animal development. Before embarking on the initiation of such testing, it would be important to determine whether these studies would be of benefit for human assessment of oncogenic risks. Pilot studies could be performed using known mutagenic or carcinogenic agents. The increased costs and possible benefits of the new information would have to be evaluated to determine whether we should initiate these developmental oncogenic studies. This is a difficult issue to settle. It might be better to perform research on MOA

TABLE 5. Protocol for Environmental Toxicant Studies Using Animals During Developmental Stages (Neonatal, Infant, and Juvenile Animals)

1. The toxicant exposure should occur by the same route in the animal as it occurs in the human.
2. Exposure should include a wide range and include the level to which humans are exposed.
3. Serum or tissue concentrations of the toxicant or its active metabolite should be determined, whichever is more appropriate.
4. Metabolism, half-life, turnover, mechanism of detoxification, and excretion should be determined.
5. Biomarkers for evaluating the effects of toxicants in developing organisms should include growth, maturation, time of puberty, neurobehavioral effects, fertility, specific organ and tissue toxicity, and pathology at windows during various stages of development.
6. The no-effect or threshold exposure should be determined for all toxic or detrimental findings.
7. The concentration of the toxicant should be determined in the sera or tissues of humans to determine whether the human is being exposed to concentrations that deleteriously affect the animal model.
8. Mechanism of action studies should be initiated to determine the active metabolites that result in deleterious effects and determine whether the animal and human respond similarly or much differently to the toxicant and its metabolites.

of carcinogenic agents and use that information in combination with the usual animal carcinogenicity studies.

CONCLUSION

There are a number of important observations that one could derive from reviewing the literature on using in vivo animal studies for studying the effects of environmental toxicants in developing fetuses and postpartum developing animals. A few federal agencies are requesting protocols to improve animal testing to study the sensitivity of neonatal, infant, and juvenile animals to determine the effects of environmental toxicants. Attempting to expose animals during narrow windows of development is more difficult and more expensive, but because of the differences in animals and humans, infant and juvenile studies have to be designed to correct for these differences. It is true that the multigenerational studies performed in animals are expensive, but they provide information on growth, reproductive capacity, cancer, and lethality, and these studies would have to be performed before embarking on selected targeted studies at various stages of development. There is no question that animal studies can provide valuable information pertaining to human and animal vulnerability to environmental toxicants at different stages of development. If risk estimates and maximum permissible exposures are to be determined, then they have to be based on quality studies in animals and humans using modern pharmacokinetics and toxicokinetic methods, as well as MOA studies. Protocols for such studies are contained in Tables 3 and 5. One useful aspect of animal studies is for corroborating findings reported in epidemiologic studies. Attempts at risk assessment can be made using toxicokinetic data that have been obtained in an animal model and exposure levels of the alleged toxicant and its metabolites that have been determined in the human. Studies determining the mechanism of action in the animal model and whether the same mechanism is functioning in the human would further add to the toxicologist's ability to estimate human risks. This is not a simple process, and that is why quality epidemiologic studies are so valuable in evaluating human risks and toxicity.

REFERENCES

1. Brent RL. Evaluating the alleged teratogenicity of environmental agents. In: Brent RL, Beckman DA, eds. *Clinics in Perinatology*. Vol 13. Philadelphia, PA: WB Saunders; 1986: 609–613
2. Brent RL. Protecting the public from teratogenic and mutagenic hazards. *J Clin Pharmacol*. 1972;12:61–70
3. Brent RL. Drug testing in animals for teratogenic effects: thalidomide in the pregnant rat. *J Pediatr*. 1964;64:762–770
4. Brent RL. The prediction of human diseases from laboratory and animal tests for teratogenicity, carcinogenicity and mutagenicity. In: Lasagna L ed. *Controversies in Therapeutics*. Philadelphia, PA: WB Saunders; 1980:134–150
5. Brent RL. Predicting teratogenic and reproductive risks in humans from exposure to various environmental agents using in vitro techniques and in vivo animal studies. *Congenit Anom Kyoto*. 1988; 28(suppl):S41–S55
6. Christian MS, Brent RL. Teratogen update: evaluation of the reproductive and developmental risks of caffeine. *Teratology*. 2001;64:51–78
7. Brent RL. Book review: Scientific Frontiers in Developmental Toxicology and Risk Assessment by the National Research Council, National Academy of Sciences, National Academy Press, Washington, DC, 327 pp., 2000. *Teratology*. 2002;65:88–96
8. Brent RL. Teratogen update: reproductive risks of leflunomide (Avara); a pyrimidine synthesis inhibitor: counseling women taking leflunomide before or during pregnancy and men taking leflunomide who are contemplating fathering a child. *Teratology*. 2001;63:106–112
9. FDA, Progestational Drug Products for Human Use; Requirements for Labeling Directed to the Patient. Proposed Rules, Department of Health and Human Services, Public Health Service, Food and Drug Administration, 21 CFR Part 310 [Docket No. 99N-0188], 64 FR 17985, Tuesday, April 13, 1999; Federal Register, Vol. 64, No. 70
10. *Physicians Desk Reference*. 57th ed. Montvale, NJ: Medical Economics Co; 2003
11. Brent RL. Drugs and pregnancy: are the insert warnings too dire? *Contemp OB-GYN*. 1982;20:42–49
12. Brent RL. Utilization of developmental basic science principles in the evaluation of reproductive risks from pre- and post-conception environmental radiation exposures. *Teratology*. 1999;59:182–204
13. Friedman JM, Little BB, Brent RL, Cordero JF, Hanson JW, Shepard TH. Potential human teratogenicity of frequently prescribed drugs. *Obstet Gynecol*. 1990;75:594–599
14. Otake M, Schull WJ. In utero exposure to A-bomb radiation and mental retardation. A reassessment. *Br J Radiol*. 1984;57:409–414
15. Jensh RP, Brent RL, Vogel WH. Studies concerning the effects of low level prenatal x-irradiation on postnatal growth and adult behavior in the Wistar rat. *Int J Radiat Biol*. 1986;50:1069–1081
16. Jensh RP, Brent RL, Vogel WH. Studies of the effect of 0.4 Gy and 0.6-Gy prenatal x-irradiation on postnatal adult behavior in the Wistar rat. *Teratology*. 1987;35:53–61
17. Jensh RP, Brent RL. Effects of 0.6-Gy postnatal neurophysiologic development in the Wistar rat. *Proc Soc Exp Biol Med*. 1986;181:611–619
18. Jensh RP, Brent RL. The effect of low-level prenatal x-irradiation on postnatal development in the Wistar rat. *Proc Soc Exp Med*. 1987;184: 256–263

19. Brent RL, Beckman DA, Jensh RP. Relative radiosensitivity of fetal tissues. In: Lett JT, Altman KI, eds. *Relative Radiation Sensitivities of Human Organ Systems.* Vol 12. Orlando, FL: Academic Press; 1987: 239–256
20. Jensh RP, Brent RL. The effects of prenatal x-irradiation in the 14th-18th days of gestation on postnatal growth and development in the rat. *Teratology.* 1988;38:431–441
21. Brent RL, Beckman DA, Jensh RP. The relationship of animal experiments in predicting the effects of intrauterine effects in the human. In: Kriegel H, Schmahl W, Gerber GB, Stieve FE, eds. *Radiation Risks to the Developing Nervous System.* New York, NY: Gustav Fisher; 1986: 367–397
22. Miller RW. Discussion: severe mental retardation and cancer among atomic bomb survivors exposed in utero. *Teratology.* 1999;59:234–235
23. Jensh RP, Eisenman LM, Brent RL. Postnatal neurophysiologic effects of prenatal x-irradiation. *Int J Radiat Biol.* 1995;67:217–227
24. Schull WJ, Otake M. Cognitive function and prenatal exposure to ionizing radiation. *Teratology.* 1999;59:222–226
25. Brent RL. Evaluating the alleged teratogenicity of environmental agents. In: Brent RL, Beckman DA, eds. *Clinics in Perinatology.* Vol 13. Philadelphia, PA: WB Saunders; 1986:609–613
26. Schardein JL. *Chemically Induced Birth Defects.* New York, NY: Marcel Dekker; 2000:272–278
27. Bremer S, Pellizzer C, Adler S, Paparella M, de Lange J. Development of testing strategy for detecting embryotoxic hazards of chemicals in vitro by using embryonic stem cells. *Altern Lab Anim.* 2002;30(suppl 2):107–109
28. Done AK. Developmental pharmacology. *Clin Pharmacol Ther.* 1964;5: 432–479
29. Hufeland CW. Lehrbuch der allgemeinen Heilkunde: Zwetze Auflage, aus dem System der praktischen Heilkunde besonders abgedruckt zum Gebrauch bei Vorlesungen, ed 2, Jena1830, F. Frommann
30. Dreyer B, Walker EWA. Therapeutical and pharmacological section: dosage of drugs, toxins and antitoxins. *Proc R Soc Med.* 1914;7:51–70
31. Behnke AR. The relation of lean body weight to metabolism and some consequent systematizations. *Ann N Y Acad Sci.* 1956;56:1095-1142
32. Friis-Hansen B. Changes in body water compartments during growth. *Acta Paediatr.* 1957;43:1–68
33. Friis-Hansen B. Body water compartments in children: changes during growth and related changes in body composition. *Pediatrics.* 1961;28: 169–181
34. Weatherall JAC. Anesthesia in newborn animals. *Br J Pharmacol.* 1960; 15:454–457
35. Cameron JA. Age and species differences among rodents in resistance to CO asphyxia. *J Cell Comp Physiol.* 1941;18:379–383
36. Cassin S, Herron CS Jr. Cerebral enzyme changes and tolerance to anoxia during maturation in the rabbit. *Am J Physiol.* 1961;201:440–442
37. Fazekas JF, Alexander FAD, Himwich HE. Tolerance of the newborn to anoxia. *Am J Physiol.* 1941;134:281–287
38. Reiss M, Haurowitz F. Uber das Verhalten Junger und Alter Tiere bei Enstickung, Klin. *Klinische Wochenshrift.* 1929;1:743–744
39. Stafford A, Weatherall JA. The survival of young rats in nitrogen. *J Physiol.* 1962;153:457–472
40. Barrow EF. Age and resistance to ether in mice. *Proc Soc Exp Biol Med.* 1933;30:1290–1292
41. Mackenzie JB, Mackenzie CG. Production of pulmonary edema by thiourea in the rat and its relation to age. *Proc Soc Exp Biol Med.* 1943;54:34–37
42. Dieke SH, Richter CP. Acute toxicity of thiourea to rats in relation to age, diet, strain and species variation. *J Pharmacol Exp Ther.* 1945;83: 195–202
43. Kent SP, Tucker ES III, Taranenko A. The toxicity of chloramphenicol in newborn versus adult mice. *Am J Dis Child.* 1960;100:400–401
44. Michael AF, Giesel RG, Sutherland JM. Chloramphenicol toxicity in newborn rats. *Antibiotics Chemother.* 1960;10:368–370
45. Raynsford G. Technique of comparing acute toxicity in infants vs. adult rats. A comparative study of three antibiotics. *Am J Dis Child.* 1963;105:323–328
46. Selevan S, Kimmel CA, Mendola P. Identifying critical windows of exposure for children's health. *Environ Health Perspect.* 2000;108(suppl 3):451–455
47. Hunt VR, Smith MK, Worth D, eds. *Environmental Factors in Human Growth and Development. Banbury Report.* Cold Spring Harbor, NY: Cold Spring Harbor Laboratory; 1982
48. Kimmel CA, Kavlock RJ, Francis EZ. Animal models for assessing developmental toxicity. In: Guzelian PS, Henry CJ, Olin SS, eds. *Similarities and Differences Between Children and Adults: Implications for Risk Assessment.* Washington, DC: ILSI Press; 1992:43
49. Daniels JL, Olshan AF, Savitz DA. Pesticides and childhood cancers. *Environ Health Perspect.* 1997;105:1068–1077
50. Needleman HL, Schell A, Bellingler D, Leviton A, Allred EN. The long-term effects of exposure to low doses of lead in childhood. An 11-year follow-up report. *N Engl J Med.* 1990;322:83–88
51. Miller RW. Special susceptibility of the child to certain radiation-induced cancers. *Environ Health Perspect.* 1995;103(suppl 6):41–44
52. Wadsworth ME, Kuh DJ. Childhood influences on adult health: a review of recent work from the British 1946 national birth cohort study, the MRC National Survey of Health and Development. *Paediatr Perinat Epidemiol.* 1997;11:2–20
53. Pryor JL, Hughes C, Foster W, Hales BF, Robaire B. Critical windows of exposure for children's health: the reproductive system in animals and humans. *Environ Health Perspect.* 2000;108(suppl 3):433–438
54. Gray JB, Gangolli SD. Aspects of the testicular toxicity of phthalate esters. *Environ Health Perspect.* 1986;65:229–235
55. Sjorberg P, Lindqvist NG, Ploen L. Age-dependent response of the rat testes to di(2-ethylhexyl)phthalate. *Environ Health Perspect.* 1986;65: 237–242
56. Dostal LA, Chapin RE, Stefanski SA, Harris MW, Schwetz BA. Testicular toxicity and reduced Sertoli cell numbers in neonatal rats by di(2-ethylhexyl) phthalate and recovery of fertility as adults. *Toxicol Appl Pharmacol.* 1988;95:104–121
57. Lui EM, Wysocki GP. Reproductive tract defects induced in adult male rats by postnatal 1,2-dibromo-3-chlorpropane exposure. *Toxicol Appl Pharmacol.* 1987;15:299–314
58. Warren DW, Ahmad N, Rudeen PK. The effects of fetal exposure to 1,2-dibromo-3-chloropropane on adult reproductive function. *Biol Reprod.* 1988;39:707–716
59. Lemasters GK, Perreault SD, Hales BF, et al. Workshop to identify critical windows of exposure for children's health: reproductive health in children and adolescents work group summary. *Environ Health Perspect.* 2000;108(suppl 3):505–509
60. Kelce WR, Zirkin BR, Ewing LL. Immature rat Leydig cells are intrinsically less sensitive than adult Leydig cells to ethane dimethanesulfonate. *Toxicol Appl Pharmacol.* 1991;111:189–200
61. Brown CD, Forman CL, McEuen SF, Miller MG. Metabolism and testicular toxicity of 1,3-dinitrobenzene in rats of different ages. *Fundam Appl Toxicol.* 1994;23:439–446
62. Flaws JA, Salyers KL, Sipes IG, Hoyer PB. Reduced ability of rat preantral ovarian follicles to metabolize 4-vinyl-1-cyclohexene diepoxide in vitro. *Toxicol Appl Pharmacol.* 1994;126:286–294
63. Brouwer A, Ahlborg UG, Van Den Berg M, et al. Functional aspects of developmental toxicity of polyhalogenated aromatic hydrocarbons in experimental animals and human infants. *Eur J Pharmacol.* 1995;293: 1–40
64. Morreale de Escobar G, Obregon MJ, Calvo R, Pedraza P, Escobar del Rey F. Iodine deficiency, the hidden scourge: the rat model of human neurological cretinism. In: Hendrich CE, ed. *Recent Research Development in Neuroendocrinology—Thyroid Hormone and Brain Maturation.* Kerala State, IN: Research Signpost; 1997:66–70
65. Donati L, Antonelli A, Bertoni F, et al. Clinical picture of endemic cretinism in central Apennines (Montefeltro). *Thyroid.* 1992;2:283–290
66. Miller RW. How environmental efforts on child health are recognized. *Pediatrics.* 1974;53(suppl):792–796
67. Miller RW. Radiation injury. In: Behrman R, ed. *Nelson's Textbook of Pediatrics.* 14th ed. Philadelphia, PA: WB Saunders; 1996:769–770
68. Preston DL, Mattsson A, Homberg E, Shore R, Hildreth NG, Boice JD Jr. Radiation effects of breast cancer risk: a pooled analysis of eight cohorts. *Radiat Res.* 2002;158:220–235
69. Pierce DA, Shimizu Y, Preston D, Vaeth M, Mabuchi K. Studies of the mortality of atomic bomb survivors. Report 12, Part 1. Cancer: 1950–1990. Radiat Res. 1996;146:1–27
70. McKinney JD, Waller CL. Polychlorinated biphenyls as hormonally active structural analogues. *Environ Health Perspect.* 1994;102:290–297
71. Maier WE, Kodavanti PR, Harry GJ, Tilson HA. Sensitivity of adenosine triphosphatases in different brain regions to polychlorinated biphenyl congeners. *J Appl Toxicol.* 1994;14:225–229
72. McKinney JD, Chae K, Oatley SJ, Blake CCF. Molecular interactions of toxic chlorinated dibeno-p-dioxins and dibenzofurans with thyroxine binding prealbumin. *J Med Chem.* 1985;28:375–381
73. Ness DK, Schantz SL, Moshtaghian J, Hansen LG. Effects of perinatal exposure to specific PCB congeners on thyroid hormone concentrations and thyroid histology in the rat. *Toxicol Lett.* 1993;68:311–323
74. Koopman-Esseboom C, Morse DC, Weisglas-Kuperus N, et al. Effects of dioxins and polychlorinated biphenyls on thyroid hormone status of pregnant women and their infants. *Pediatr Res.* 1994;36:468–473

75. Morse DC, Wehler EK, Wesseling W, Koeman JH, Brouwer A. Alterations in rat brain thyroid hormone status following pre- and postnatal exposure to polychlorinated biphenyls (Aroclor 1254). *Toxicol Appl Pharmacol.* 1996;136:269–279
76. Holladay S, Smialowicz RJ Development of the murine and human immune system: differential effects of immunotoxicants depend on time of exposure. *Environ Health Perspect.* 2000;108(suppl 3):463–473
77. Rodier PM, Reynolds SS. Morphological correlates of behavioral abnormalities in experimental congenital brain damage. *Exp Neurol.* 1977; 57:81–93
78. Rodier PM. Chronology of neuron development. Animal studies and their clinical implications. *Dev Med Child Neurol.* 1980;22:525–545
79. Rice D, Barone S Jr. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. *Environ Health Perspect.* 2000;108(suppl 3):511–533
80. Weiss B, Landrigan PJ. The developing brain and the environment: an introduction. *Environ Health Perspect.* 2000;108(suppl 3):373–374
81. Stromland K, Nordin V, Miller M, Akerstrom B, Gilberg C. Autism in the thalidomide embryopathy: a population study. *Dev Med Child Neurol.* 1994;36:351–356
82. Rodier PM, Ingram JL. Tisdale B, Nelson S, Romano J. Embryological origin for autism: developmental anomalies of the cranial nerve motor nuclei. *J Comp Neurol.* 1996;370:247–261
83. Otis EM, Brent RL. Equivalent ages in mouse and human embryos. *Anat Rec.* 1954;12:33–65
84. Adams J, Barone S Jr, LaMantia A, et al. Workshop to identify critical windows of exposure for children's health: Neurobehavioral Work Group Study. *Environ Health Perspect.* 2000;108(suppl 3):535–544
85. Jernigan TL, Trauner DA, Hesselink JR, Tallal PA. Maturation of human cerebrum observed in vivo during adolescence. *Brain.* 1991;114: 2037–2049
86. Van Eden CG, Kros JM, Uylings HBM. The development of the rat prefrontal cortex: its size and development of connections with thalamus, spinal cord and other cortical areas. In: Uylings HBM, vanEden CG, DeBruin JPC, Corner MA, Feenstra MGP, eds. *The Prefrontal Cortex: Its Structure, Function, and Pathology.* Vol 85. Amsterdam, the Netherlands: Elsevier; 1999:169–183
87. Zecevic N, Rakic P. Synaptogenesis in monkey somatosensory cortex. *Cereb Cortex.* 1991;1:510–523
88. Lewis DA. Development of the prefrontal cortex during adolescence: insights into vulnerable neural circuits in schizophrenia. *Neuropsychopharmacology.* 1997;16:385–398
89. Anderson SL, Dumont NL, Teicher MH. Developmental differences in dopamine synthesis inhibition by (+)-7-OH-DPAT. *Naunyn Schmeidelbergs Arch Pharmacol.* 1997;356:173–181
90. Teicher MH, Barbara NI, Gelbard HA, et al. Developmental differences in acute nigrostriatal and mesocorticolimbic system response to haloperidol. *Neuropsychopharmacology.* 1993;9:147–156
91. Benes FM. Myelination of cortical-hippocampal relays during late adolescence. *Schizophr Bull.* 1989;15:585–593
92. Dumas TC, Foster TC. Late developmental changes in the ability of adenosine A1 receptors to regulate synaptic transmission in the hippocampus. *Dev Brain Res.* 1998;105:137–139
93. Choi S, Weisberg SN, Kellogg CK. Control of endogenous norepinephrine release in the hypothalamus of male rat changes over adolescent development. *Dev Brain Res.* 1997;98:134–141
94. Salimov RM, McBride WJ, McKinzie DL, Lumeng L, Li TK. Effects of ethanol consumption by adolescent alcohol-preferring P rats on subsequent behavioral performance in the cross-maze and slip funnel tests. *Alcohol.* 1996;13:297–300
95. Zahm SH, Devesa SS. Childhood cancer: overview of incidence trends and environmental carcinogens. *Environ Health Perspect.* 1995;103:177–184
96. Byrne J. Long-term genetic and reproductive effects of ionizing radiation and chemotherapeutic agents on cancer patients and their offspring. *Teratology.* 1999;59:210–215
97. Dybing E, Sanner T. Species differences in chemical carcinogenesis of the thyroid gland, kidney and urinary bladder. *IARC Sci Publ.* 1999; 147:15–32
98. Grisham JW. Interspecies comparisons of liver carcinogenesis: implications for cancer risk assessment. *Carcinogenesis.* 1997;19:59–81
99. Hengstler JG, Van der Burg B, Steinberg P, et al. Interspecies differences in cancer susceptibility and toxicity. *Drug Metab Rev.* 1999;31: 917–970
100. Astill BD. Metabolism of DEHP: effects of prefeeding and dose variation, and comparative studies in rodents and the cynomolgus monkey (CMA studies). *Drug Metab Rev.* 1989;21:35–53
101. Elcombe CR, Mitchell AM. Peroxisome proliferation due to di(2-ethylhexyl)phthalate (DEHP): species differences and possible mechanism. *Environ Health Perspect.* 1986;70:211–219
102. Goll V, Alexandre E, Viollon-Abadie C, Nicod L, Jaeck D, Richert L. Comparison of the effects of various peroxisome proliferators on peroxisomal enzyme activities, DNA synthesis, and apoptosis in rat and human hepatocyte cultures. *Toxicol Appl Pharmacol.* 1999;160:21–32
103. Hasmall SC, James NH, McDonald N, et al. Suppression of apoptosis and induction of DNA synthesis in vitro by the phthalate plasticizers monoethylhexylphthalate (MEHP) and diisononylphthalate (DINP): a comparison of rat and human hepatocytes in vitro. *Arch Toxicol.* 1999; 73:451–456
104. Hasmall SC, James NH, Macdonald N, Soames AR, Roberts RA. Species differences in response to diethylhexylphthalate (DEHP): suppression of apoptosis, induction of DNA synthesis and PPAR-mediated gene expression. *Arch Toxicol.* 2000;74:85–91
105. Huber WW, Kraupp-Grasl B, Schulte-Hermann R. Hepatocarcinogenic potential of DEHP in rodents and its implications on human risk. *Crit Rev Toxicol.* 1996;26:365–481
106. Kedderis GL, Batra R. Species differences in the hydrolysis of 2-cyanoethylene oxide, the epoxide metabolite of acrylonitrile. *Carcinogenesis.* 1993;14:685–689
107. Kurata Y, Kidachi F, Yokoyama M, Toyota N, Tsuchitani M, Katoh M. Subchronic toxicity of di(2-ethylthexyl)phthalate in common marmosets lack of hepatic peroxisome proliferation, testicular atrophy of pancreatic acinar cell hyperplasia. *Toxicol Sci.* 1998;42:49–56
108. Woodyatt NJ, Lambe KG, Myers KA, Tugwood JD, Roberts RA. The peroxisome proliferator (PP) response element upstream of the human acyl CoA oxidase gene is inactive among a sample human population: significance for species differences in response to PPs. *Carcinogenesis.* 1999;20:369–372
109. Ashby J, Brady A, Elcombe CR, et al. Mechanistically-based human hazard assessment of peroxisome proliferator induced hepatocarcinogenesis. *Hum Exp Toxicol.* 1994;13(suppl 2):S1–S117
110. Conway JG, Tomaszewski KE, Olson MJ, Cattley RC, Marsman DS, Popp JA. Relationship of oxidative damage to carcinogenicity with peroxisome proliferators di(2-eythlhexyl)phthalate (DEHP) and Wy-14643. *Carcinogenesis.* 1989;10:513–520
111. David RM, Moore MR, Cifone MA, Finney DC, Guest D. Chronic peroxisome proliferation and hepatomegaly associated with the hepatocellular tumorigenesis of di(2-ethylhexyl)phthalate and the effects of recovery. *Toxicol Sci.* 1999;50:195–205
112. Kluwe WM. The nephrotoxicity of low molecular weight halogenated alkane solvents, pesticides, and chemical intermediates. In: Hook JB, ed. *Toxicology of the Kidney.* New York, NY: Raven Press; 1981:179–226
113. Kluwe WM. The carcinogenicity of dietary di(2-ethylhexyl) phthalate (DEHP) in Fischer 344 rats and B6C3F1 mice. *J Toxicol Environ Health.* 1982;10:797–815
114. Lawrence JW, Li Y, Chen S, et al. Differential gene regulation in human versus rodent hepatocytes by peroxisome proliferator-activated receptor (PPAR) alpha. PPARalpha fails to induce peroxisome proliferation-associated genes in human cells independently of the level of receptor expression. *J Biol Chem.* 2001;276:31521–31527
115. Marsman DS, Cattley RC, Conway JG, Popp JA. Relationship of hepatic peroxisome proliferation and replicative DNA synthesis to the hepatocarcinogenicity of the peroxisome proliferators di(2ethylhexyl)phthalate and [4-chloro-6-(2,3-xylidino)-2-pryimidinylthio] acetic acid (Wy-14, 643) in rats. *Cancer Res.* 1988;48:6739–6744
116. Mukherjee R, Jow L, Noonan D, McDonnell DP. Human and rat peroxisome proliferator activated receptors (PPARs) demonstrate similar tissue distribution but different responsiveness to PPAR activators. *J Steroid Biochem Mol Biol.* 1994;51:157–166
117. Palmer CN, Hsu MH, Griffin KJ, Raucy JL, Johnson EF. Peroxisome proliferator activated receptor-alpha expression in human liver. *Mol Pharmacol.* 1998;53:14–22
118. Schmid P, Schlatte C. Excretion and metabolism of di(2-ethylhexy)-phthalate in man. *Xenobiotica.* 1985;15:251–256
119. Short RD, Robinson EC, Lington AW, Chin AE. Metabolis and peroxisome proliferation studies with di(2-ethylhexy)phthalate in rats and monkeys. *Toxicol Ind Health.* 1987;3:185–194
120. Ames BN, Gold LS. Chemical carcinogenesis: too many rodent carcinogens. *Proc Natl Acad Sci U S A.* 1990;87:7772–7776
121. Cohen SM. Role of cell proliferation in regenerative and neoplastic disease. *Toxicol Lett.* 1995;82–83:15–21
122. Farber E. Cell proliferation as a major risk factor for cancer: a concept of doubtful validity. *Cancer Res.* 1995;55:3759–3762
123. Melnick RL, Kohn MC, Anderson D, Herbst A. Regenerative hyperplasia is not required for liver tumor induction in female B6C3F1 mice exposed to trihalomethanes. *Toxicol Appl Pharmacol.* 1998;148:137–147

124. Preston-Martin S, Pike MC, Ross RK, Jones PA, Henderson BE. Increased cell division as a cause of human cancer. *Cancer Res.* 1990;50:7415–7421
125. Smith-Oliver T, Butterworth BE. Correlation of the carcinogenic potential of di(2-ethylhexy)-phthalate (DEHP) with induced hyperplasia rather than with genotoxic activity. *Mutat Res.* 1987;188:21–28
126. Lambe KG, Woodyatt NJ, Macdonald N, Chevalier S, Roberts RA. Species differences in sequence and activity of the peroxisome proliferator response element (PPRE) within the acyl CoA oxidase gene promoter. *Toxicol Lett.* 1999;110:119–127
127. Cohen SM. Cell proliferation and carcinogenesis. *Drug Metab Rev.* 1998;30:339–357
128. Cohen SM. Calcium phosphate-containing urinary precipitate in rat urinary carcinogenesis. *IARC Sci Publ.* 1999;147:175–189

Utilization of Animal Studies to Determine the Effects and Human Risks of Environmental Toxicants (Drugs, Chemicals, and Physical Agents)

Robert L. Brent

Pediatrics 2004;113;984-995
DOI: 10.1542/peds.113.4.S1.984

Environment and Public Works Committee Hearing

September 16,2008

Follow-Up Questions for Written Submission

Questions for Brent

Questions from:

Senator James M. Inhofe

1) Can you elaborate on your point made to the Committee suggesting that the word "safe" is an unscientific term; that you "can not simply label a chemical as safe or not safe;" and that you "must understand exposure?"

The term safe is a lay term and should not be used by scientists and physicians who are concerned about any risk, especially the risk of environmental drugs and chemicals. What is safe is primarily the perception of the individual, news reporter and even some scientists. For some individuals flying an airplane or driving a car may appear to be unsafe.To an experienced policeman handling a gun may be safe but for a five year old child the public would consider it to be unsafe. So safety is a perception.

With regard to chemicals the term "safe" is inappropriate for the following reasons. Toxicological substances, like environmental chemical have what is know as a NOAEL (No adverse effective exposure). That means that every chemical has an exposure below which there is no effect. So a chemical may have no effect even when it is present in your body at 5 ppb (five parts per billion). If the exposure increased and the level exceeds the no effect level then the exposure represents an increased risk. AS the exposure rises above the NOAEL the risk increases. So what I was saying is that you cannot label all the chemicals in the environment and within living organisms unless you know three pieces of information.

1. The NOAEL

2. The concentrations in the environment, the water supply, the food supply etc

3. The concentration in the serum and tissues of living organisms

Dr. Trasande's testimony refers to chemicals as being unsafe without providing any data on exposures or NOAELs

As a citizen, I wish there were not any chemicals in the environment. But many chemicals like mercury, radon, uranium, natural chemicals in foods, have been there for thousand of years. In addition industry has added to the chemical environment for a hundred years and we are now beginning to realize that we have to care for the environment. Dr.Bruce Ames, a member of the National Academy of Sciences and the discover of the Ames Test is well know for indicating that the natural "chemicals" in our food supply can cause problems if their NOAEL are exceeded.

2) Can you elaborate on your point about the sensitivity of children to chemicals - i.e. during your testimony at the hearing you suggested that sensitivity is chemical specific determination rather than an "across the board" assumption that children are always more sensitive to chemicals and other environmental factors?

There has been conclusions without the facts to support the dogma that children are much more sensitive to environmental toxicants than adults. In fact, some individuals have inferred that children are 10 to 15 times more sensitive than adults. The problem is that we do not have any data on the NOAEL for all for almost all chemicals for children and adults. It is true that if a child and an adult is exposed to a very high dose of some pesticides the child may die and the adult may survive. That is anecdotal information that provides little information on sensitivity, As I pointed our in my presentation, that is why "The National Children's Study " is so important because it provide actual exposures to human beings. In 2004 we Robert Brent and Michael Weizman published a supplement to "Pediatrics the journal of the America Academy of Pediatrics. The first chapter listed all the known drug and chemical exposures and indicated that about in 20% of cases the infant and developing child was less sensitive than adults due to the child's resiliency. So you cannot say that the child is always more sensitive. That is why we need to support environmental toxicology research in the laboratory and assessment of exposures in living organisms.

3) Can you elaborate on your point about the need to be careful in interpreting information about the incidences of diseases going up, such as birth defects (i.e., Dr. Trasande's testimony regarding the "epidemic of birth defects") and other childhood diseases, as well as assertions that exposures to environmentally relevant levels of chemicals are known to be causal factors for these conditions?

Dr. Trasande's testimony is the testimony of a dedicated Pediatrician who believes that environmental chemicals are a major health problem in this country. Fortunately, the country has reduced exposures to many chemicals. The serum level of lead is at its lowest level. PCB's and dioxin levels have decreased and efforts are being made to decrease

exposures to other chemicals. Chemical landfills are economic disasters, however, that does not means that they contribute to human exposure. The disaster of the Love Canal was an economic and social disaster but all the epidemiological studies did not indicate that there were biological effects. Of course that does not mean that careless disposal of chemicals is acceptable.

Dr. Trasande said that birth defects and cancer are increasing and that pesticides cause cancer. Most pesticides do not have mutagenic potential and the epidemiological studies are ecological studies (no exposure measurements) that are not consistent. If you examine the Center for Disease Control (CDC) reports and the SEER reports of the National Cancer Institute on the occurrence of Cancer, there has been no increase in leukemia, brain tumors and other childhood cancers. While Dr. Trasande is concerned about children's health, which is admirable, the public is frightened when on infers that so many diseases are due to environmental toxicants. The cause of death in children during the first year of life are prematurity, congenital malformations, infections and sudden infant death syndrome. From age one to four, accident (auto, bike,guns), falls, burns, drowning, chocking. These causes of death are all preventable

Robert Brent MD, Ph.D.
Distinguished Professor of Pediatrics, Radiology and Pathology
Thomas Jefferson University
A.I. duPont Hospital for Children
Box 269, Wilmington, DE 19899

Reference: The vulnerability, Sensitivity and Resiliency of the Developing Embry, Infant, Child and Adolescent to the Effects of Environmental Chemicals, Drugs and Physical Agents as Compared to the Adult. Pediatrics (supplement) Volume 113, number 4, part 2 of 2; p 933-1172, 2004.

Senator BOXER. Thank you, Doctor.

I want to correct the record. I never said there was an epidemic of birth defects. You must have misheard it. I was quoting from Dr. Trasande's work in which he says over the past 30 years chronic diseases of environmental origin have become epidemic in American children and are the diseases of greatest current concern. So that is a fellow doctor who didn't say birth defects, he said diseases of environmental origin, so let's set the record straight.

Speaking of that, I notice in 2004 in a New York Times interview, Dr. Brent, you said Love Canal was an example of a terrible environmental problem that should be cleaned up but there is no evidence of risk to the people who live there. Many fears are irrational. EPA scientists concluded that, taken together, the studies suggest significant health risk. Do you still stand by what you said in 2004.

Dr. BRENT. What I said was that you have got to determine the exposure. If people live around a contaminated area, you can't make an assumption that they have a risk because they live there.

Senator BOXER. OK. I am just asking you if you stand by the statement, since you said that many fears are irrational and the EPA said that the scientific studies suggest significant health risks. Do you still stand by what you said in 2004 is my question.

Dr. BRENT. I think that many, many fears are irrational.

Senator BOXER. OK. Very good. OK. Trying to get at that.

First of all, this was a terrific panel. I wanted to underscore and make sure, Dr. Trasande, that I heard you right. You said that lead, asthma, developmental disabilities, and you added childhood cancer, and I am not sure I left anything out of that, adds up to $59 billion per year cost.

Dr. TRASANDE. Just a minor correction to your statement, Senator.

Senator BOXER. Yes?

Dr. TRASANDE. It is $54.9 billion, and you did State them correctly.

Senator BOXER. That is 4.9 billion? I wrote down 59. I wanted to make sure. So 4.9 billion. And do you believe that that number is being incorporated into most of these risk benefit studies?

Dr. TRASANDE. I believe in general that they have not been fully incorporated. All too frequently, the costs of childhood disease are not being incorporated, and we have seen before efforts to discount children's health care costs and children's economic productivity at higher rates than most health economists would accept as thoughtful.

Senator BOXER. Well, we have seen this across the board where the EPA is devaluing our productivity, and we have a bill that we are readying now be dropped because we want to correct that. They have lowered the dollar value they put on a human life and the worth of it, which is unbelievable to me.

Dr. Trasande, GAO's report shows that EPA rejected the advice of its clean air science advisors, because we are talking about science advisors. And I agree with Dr. Brent. Scientists are terrific at the EPA and I support them. What I rail against is the politicians over there that just don't follow the scientists. Frankly, we are all elected officials and our job is to balance everything. The

scientists are supposed to tell the Administration what is the right thing to do, and from there he has got to stand by that. That is his mission.

So I am asking you, Dr. Trasande, GAO's report shows that EPA rejected the advice of its clean air scientific advisors and its children's health experts in setting clean air standards for dangerous soot called particulate matter. Could you use your doctor-to-parent way of explaining what are the impacts of particulate matter on children's health?

Dr. TRASANDE. Well, based on what we currently know, and based on what the scientific evidence would permit us to say, we know that children who are exposed to higher levels of particulate matter who are susceptible can develop more asthma exacerbations, which is an added economic consequence besides the health consequence and the consequence to families' lives. So by allowing and permitting higher levels of particulate matter in the air, levels at which health effects have been documented, you are permitting children to suffer the long-term consequences of more asthma hospitalizations, emergency room visits, and other medically preventable events.

Senator BOXER. OK. I want to ask you about another time that EPA went against its scientific advisors, which is Dr. Brent's point. He said they are terrific, and they are, those scientific advisors.

GAO's report shows that EPA's proposal on a new Clean Air Act lead standard goes against the advice of its clean air science advisors and its children's health experts. Could you describe the impacts of lead on children's health, including recent studies on the health impacts of low-dose exposures to lead?

Dr. TRASANDE. Well, what we know now is that, especially with lead, is that the dose doesn't necessarily make the poison. I think there are a number of studies that have documented that even the lowest level of lead exposure in a child's blood stream can have significant consequences. We used to think that it was the levels of 25 and 40 micrograms per density level—that is the terminology that pediatricians use to measure the levels—were the ones that were unsafe. We now know that levels at one and two, three, four, five—levels that you really can't do anything about in a clinical practice setting, we simply can advise parents to do their best to prevent it. Those are levels that are associated with impacts on learning and cognition. Those are impacts that not only have consequences for children's learning and long-term capacity; it has to do with their long-term economic productivity. A large amount of that economic cost that I quoted you is lost lifetime economic productivity from low-level lead exposure.

Senator BOXER. OK. My time is gone, so I am just going to put in the record—and I hope all of you could take a look at this—testimony on behalf of the American Academy of Pediatrics. This is a whole different subject which we will get into next year as we write our global warming bill. This is stunning. We are told here that as the climate changes, environmental hazards will change and often increase, and children are likely to suffer disproportionately from these changes. So once again the red flag is up here. Anticipated health threats from climate change include extreme weather,

weather disasters, increases to certain infectious diseases, air pollution, and thermal stress.

Within all of these categories, children have increased vulnerability compared to other groups. This is something we haven't looked at, colleagues in the Committee, but we are going to take this up very soon after we either have a lame duck, which is possible. We may take it up in the lame duck, or we may take it up next year. So I will place that in the record and call on Senator Barrasso, to be followed by Senator Lautenberg, Senator Clinton, and then we will be done.

Senator BARRASSO. Thank you, Madam Chairman.

Dr. Trasande, thank you. Looking through your testimony, there are a couple of areas that I took some exception with. You said children are uniquely vulnerable to many of the 90,000 chemicals that are released into the environment every day. By our numbers, there are actually only 82,000 chemicals on inventory. An estimated no more than 12,000 are currently in commerce. I think you may want to re-check your numbers on that.

Dr. TRASANDE. If I may respectfully respond, the estimate of 82,000 is a very old number. There are 1,000 to 3,000 new chemicals introduced into commerce each year. I think it is fair to say that that number has increased to 90,000 at the present time.

Senator BARRASSO. You go on to say of the 3,000 most highly used chemicals, fewer than half have any toxicity testing, but you take a look at what has been submitted to the EPA and now publicly available on the EPA website, 97 percent of the chemicals on that high-production volume chemical challenge program are already out there.

I know you are very bright, Harvard undergraduate, Harvard Medical School, Harvard master's program. You worked for Senator Clinton's staff. I understand. I imagine you are going to continue to testify over the years. Just, if we could, make sure we have all that accurate.

Dr. Brent, it is a privilege to have you here. The incredible background. I have known of your name and admire all that you have done in your incredible career.

I have three-and-a-half minutes left. You had a lot more to say when you were talking. I would be happy to just give you the three-and-a-half minutes to say continue talking about what you wanted to talk about in terms of what you really see as important for children's health and what we need to do in terms of safety factors for protecting our children.

Dr. BRENT. First of all, it is a privilege to be here.

I want to say that we find out that some of our beliefs with science turn out to be wrong. For instance, in 1956 Alice Stewart in England wrote a paper about the fact that a fetus was very sensitive to the leukemogenic effect of x-rays. She said the fetus was 100 times more sensitive than the child or the adult to the leukemia effects of x-rays. Well, we got a contract from the Atomic Energy Commission and Robert Drew at Columbia got a contract from the Atomic Energy Commission and we did animal studies and we didn't get one or two rads, which she had from pelvimetry, very low doses she claimed that cause leukemia. We get 30, 60, and 90 rads. We couldn't produce tumors in an animal model.

Well, I am schooled in the fact that you don't refute human epidemiology studies with animal studies. You just don't.

Well, in March of this year Dr. Preston from the Atomic Energy Commission in Japan just did the 60-year followup study on the fetuses, and they found that the fetus was much less sensitive to the leukemogenic effects than the children. In fact, there was a threshold. You have to get way above the diagnostic level before we even begin to see any tumor induction.

So we learn with research, you know. Unfortunately for the Japanese they have learned a lot about radiation, but that is exactly what the animal studies told us. Alice Stewart was wrong in her study, a case control study. So we are learning all the time, and that is why I am so warm on the fact that we have got to continue investigations at the animal level, the in vitro studies, and human epidemiology, and that the child study is so crucial for our future to get information and find out how important environmental toxicants are, because there are big question marks about so many of them.

Senator BARRASSO. Anything else in terms of how we are doing? I mean, you were a graduate of medical school when I was 1 year old, and I was probably graduating when Dr. Trasande was 1 year old, so you look at this. How are we doing?

Dr. BRENT. How do you know I didn't start when I was seven? Actually, I started college when I was 15, so I got a head start.

Well, I just think, you know, as a scientist I just believe in the importance of science. There is no other. I mean, I happen not to agree with my colleague over there. I think he exaggerates a great deal, I mean really exaggerates a great deal. Those numbers that he pulls out of his hat, I don't know where he gets them from with regard to—certainly, there is no question there is an asthma epidemic, and I wish I knew the etiology. I can tell you this about asthma, though: when I became chairman of the Department of Pediatrics, the allergists in our department requested a four-bed intensive care unit for status asthmatic. That is when children would come in with intractable asthma. We don't need it any more because we can manage asthma now.

Now, the fact that the disease is there is terrible, but we don't have children dying from asthma like we did 30 or 40 years ago, so our treatment has gotten better. Now if we could only find out what the etiology is, because I can tell you for some people tobacco smoke does it, perfume does it, air pollution does it. I mean, it is a trigger there. We just don't know the answer.

Senator BARRASSO. And Teddy Roosevelt's dad believed that cigar smoke was actually a good treatment, so he would have Teddy Roosevelt at the age of eight, when he was having asthma problems, be treated with cigar smoke.

Dr. BRENT. Cigars are all right if you don't light them up.

Senator BARRASSO. Thank you very much, Dr. Brent.

Thank you, Madam Chairman.

Senator BOXER. Thank you.

Chairman's prerogative here. First of all, asthma is controllable. We know diseases are controllable. We all know that. But you should have been here when Jonah Ramirez testified, 11 years old, what his life is like. Frankly, Doctor, you have it all over me on

degrees in medicine. I am just a Jewish mother and grandmother. I know about chicken soup and other things.

Dr. BRENT. Well, that works.

Senator BOXER. But this is the first time I ever heard we don't know the cause of asthma, but maybe I have missed the boat and not done enough reading. But let me just say you and Senator Barrasso have attacked Dr. Trasande. You said what he said was wrong, and I think we are going to give him 2 minutes to respond at that point.

I just need to reiterate this. I don't know who Alice Stewart is and I never mentioned her name. I do know that the scientists at the EPA have given advice to the EPA Administrator and he has ignored it, so you keep raising the need for science, and so does Senator Barrasso, without making the necessary next step, which is that is all we are fighting for on our side here is that the science that is being given to Mr. Johnson has been ignored.

I am going to let Dr. Trasande have 2 minutes.

Dr. TRASANDE. I thank the Chair. I don't think I will take the whole 2 minutes, but I will flesh out some points in response.

I know Senator Barrasso commented about some of the data that have been preliminarily put up about the voluntary children's chemical evaluation program. The EPA has essentially produced data on essentially a total of six chemicals at this current juncture, and are well behind any goal that would have been realistic to expect of the EPA to achieve. I think we all had hoped that the VCEP would be a tremendous opportunity to identify chemical safety thresholds in a way that was driven by the science. I would fully respect that, and I supported it when I saw the idea. It just has not delivered and we still have major gaps.

I do stand by my estimates. They are the most recently publicly available EPA estimates about the percentage of chemicals for which there are data regarding their safety.

With regard to a number of the comments that perhaps some of the data I presented might be exaggerated, I would be happy to show Dr. Brent and Senator Barrasso, I would be happy to introduce for the record a manuscript published in pediatrics about a year after Dr. Brent's package of manuscripts was published in which we document the case for the National Children's Study, and every one of the points that I have made and documented in this testimony is supported in reference and quote and chapter and verse in that manuscript, so I would be happy to submit that for the record.

I am not a fearmonger. I simply State the science. I stick to it. I State what we can make in terms of logical consequences of that. I think we can agree to disagree about policy implications of that science, but I think we can agree about the science.

I appreciate the thoughts. We will always have a vigorous debate about them.

I thank the Senator, and I have great respect for Dr. Brent, as well. Thank you.

Dr. BRENT. Can I say one word?

Senator CLINTON. [Presiding] Yes, you can say one word.

Dr. BRENT. When you use the word safe, that a compound is safe, that is an unscientific term because a compound is safe or not safe

depending on its exposure, and so you have to know the exposure. If the compound is going to be in parts per trillion, any compound will be safe. If it is going to be in milligrams per kilogram, most compounds are going to be unsafe. So you can't label a compound as safe or unsafe; you have to know what the population is going to be exposed to.

Senator CLINTON. You know, Dr. Brent, I think we are having a vigorous agreement here. I believe that your emphasis on science and doing the best science is exactly in line with Dr. Trasande's similar commitment. Sometimes when you put into lay language what it is you are talking about you might use terms that are not scientific but which are understandable. But I think it is important that each of our witnesses has underscored the significance of the National Children's Study, something that we must proceed on. I am hoping that we will get a lot of support to do that from both sides of the aisle, because that is the best way for us to proceed—to have the rigorous scientific inquiry that we know will lead to answers.

Senator Lautenberg?

Senator LAUTENBERG. Thank you very much, Senator Clinton.

A couple things here strike me immediately, and I thank you, Dr. Brent, for the advice that I will send up to my daughter right away. I think we have probably tried everything.

Dr. BRENT. Children are uncompliant. It is one thing to get an adult to inhale a steroid every day; the next thing is to get a child to do it every day. That is the problem.

Senator LAUTENBERG. Well, I thank you. And I assume this comes without charge.

Dr. BRENT. I don't charge anybody.

Senator LAUTENBERG. In any event, it has been very interesting, and you have a role as a grandfather. You said you have 11.

Dr. BRENT. Great.

Senator LAUTENBERG. A great-grandfather?

Dr. BRENT. Both.

Senator LAUTENBERG. Both. I don't have any great-grandchildren, but I have 11 grandchildren, composed of my wife's family and mine. So we thank you for your contribution, all of you.

Dr. Trasande, with that youthful appearance, how did you get so much knowledge in this period of time? Do you know Dr. Holland? Do you know who he is?

Dr. TRASANDE. I can't say I know him.

Senator LAUTENBERG. He is at Mount Sinai as well.

Dr. TRASANDE. Oh, Dr. Eric Hollander? Yes, I mis-heard you. I apologize.

Senator LAUTENBERG. Holland. Jim Holland?

Dr. TRASANDE. Jim Holland? I am sorry. I can't say I do.

Senator LAUTENBERG. In any event, as the use of chemicals in everyday products has increased, so have the rates of autism. Autism has grown nationally over the last 10 to 17 percent annually. In my State of New Jersey it has been an annual growth rate over a period of some years of 22 percent.

Now, as the use of chemicals in everyday products, so have rates of autism, birth defects, and other health problems. Now, are these

coincidental relationships? Are they real? I kind of held off by Dr. Brent's view on things, and respectfully so.

Dr. TRASANDE. Well, respectfully, I would agree that the evidence is not Mount Kilamanjaro in size, but it is increasing in consistency and reproducibility. Those are the criterion by which, in our field, we make decisions about what consequences to communicate to families for prevention and for management of conditions. I think, based upon what we know, there is very strong and compelling evidence to support that air pollutants contribute to asthma, and potentially even to the causation of asthma. I would say the evidence is much stronger with regard to the exacerbation of asthma.

With regard to the origin of developmental disabilities, there is a National Academy of Sciences report that documented that 28 percent of developmental disabilities can be attributed at least in part due to environmental factors. The majority of that is probably a complex mix of genetics and environment, the gene being the gun and the environment being the trigger, to borrow a poor analogy. But, based on that evidence, at least just for those two examples, there is enough to drive what I think you are in a position to do, to make decisions about what policy actions need to be taken proactively to prevent disease and to prevent costly diseases.

These diseases are clearly extremely complex. The National Children's Study, because of its sample size of 100,000, will be able to get at all of the potential interacting factors and really tease them out. That is really what has made determining the role of chemicals in human disease after the fact so difficult. Ideally we would have the chemical data for toxicity before they would go on the market, but we are now back-peddling constantly as scientists and clinicians, and that is really why I see a two-pronged approach, an approach through toxic chemical reform simultaneously with moving proactively with the National Children's Study so that we can work at it from both ends and really prevent childhood morbidity.

Senator LAUTENBERG. We are kind of running out of time. I want to say thank you for your comments about my bill, Kid-Safe Chemical Act, because I believe I have used the term right to know for several things that I have done, chemical hazards in areas, bottled water most recently. I wanted to know more about what is in those bottles. And kid-safe chemicals is that type of thing where the information is given in advance so it can be examined.

We thank you for your testimony, Ms. Marmagas and Dr. Trasande and Dr. Brent, of course. We respect what you had to say.

With that, Madam Chairman, I assume that we will keep this record open so that we can submit questions to the witnesses in writing?

Senator CLINTON. Without objection, we will.

I want to thank all of our witnesses. I want to take a moment to tout the work of New York's Mount Sinai Medical Center. I am very proud to represent it as part of my constituency. It is a leader in children's environmental health research and home to one of the EPA-funded pediatric environmental health specialty units. It is also a vanguard site for the National Children's Study. I am very proud of Dr. Trasande, who is a pediatrician and assistant professor of community and preventive medicine in pediatrics at

Mount Sinai and co-directs the Children's Environmental Health Center, the first academic policy center devoted to learning more about the environmental threats to the health of children.

As I said earlier, I think we are in vigorous agreement. There is a lot of work to be done. None of us has the answers. The purpose of this hearing was to point out that in many ways the current Administration and certainly the leaders of the EPA have been disregarding science. We saw the big chart from the GAO where several scientific advisory groups made a certain recommendation with respect to particulate matter in the quality of our air, both of which were disregarded.

I have a personal experience going back to 9/11 where the scientists at EPA wanted to issue warnings for vulnerable populations with respect to the air quality following the collapse of the World Trade Center and the enormous number of chemicals that were unfortunately heated and brought together in those terrible events. The scientists were very clear that warnings should go out—people subject to asthma, people whose immune systems were vulnerable, et cetera. Changed in the White House for political reasons.

So our goal in this Committee is not to have a Republican or a Democratic view of science; it is to respect the work of science and to try to provide a pathway for scientific research to inform and guide our decisionmaking.

There will be differences on policy, but I think we are united in our efforts to try to support scientific research in appropriate ways and to fund it adequately. That is why I am so committed to the support of the National Children's Study. It is going to be essential if we are going to find answers to a lot of these questions.

I agree with Dr. Brent. There are so many complex factors at work—the level of toxicity, the vulnerability of the person who is exposed. There is all of that. But we are at a point now where we have got to begin to understand the variations and to be able to provide adequate information to people to protect themselves. I appreciate the testimony from Ms. Marmagas about her service on the Children's Health Protection Advisory Committee. That was an effort to try to bring together somewhere in our Government, appropriately at EPA, the expertise and the resources to help us further our understanding as to what we need to do to better protect our children, as well as adults.

So I am looking forward to continuing the work on this Committee, and particularly summoning up support for the National Children's Study and getting it funded so that we can have these benchmarks that we need to educate the public and to inform our policymaking.

With that, Senator, unless you have any further questions I want to thank the witnesses very much. We will keep the record open so that additional questions and information can be submitted.

[Whereupon, at 12:12 p.m., the committee was adjourned.]

[Additional material submitted for the record follows.]

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

Today we will again examine the adequacy of EPA's regulatory process by hearing testimony regarding whether the Agency appropriately considers children's health

concerns. As a father and grandfather, protecting the health and well-being of children is of great personal importance to me. That is precisely why I believe that EPA's risk based regulatory process and science based review is the best way to ensure that human health—particularly the health of children—is protected in a way that also protects the way of life enjoyed by the American family.

This morning, we will hear from the official who directs the science of EPA's regulatory process, as well as from a representative of the agency tasked with critiquing EPA's success. We will also hear from stakeholders with their own views about how best to protect the health of our nation's children. I believe in the integrity of EPA's scientific process, and particularly in the Agency's ability to evaluate risk and formulate regulations that properly mitigate those risks.

Whether the concern is air, water, chemicals or other environmental factors, assessment of risk based on validated science must rule the day. Uncertainty, fear and precaution are not based in science, and actually prevent us from enjoying the benefits of technology and innovation.

I do believe that it is important for EPA to seek out and consider the advice of non-governmental experts and public opinion. However, the ultimate responsibility to the implement the law falls squarely on the Agency's doorstep. EPA is barraged with formal and informal advice from a variety of sources—it is their duty to sort through that information and seek balance among the many competing perspectives. It is no secret that I have certainly disagreed with some of the Agency's actions and decisions. However, at the end of the day, I firmly believe that EPA holds the preeminent expertise in evaluating the risks posed to human health from environmental exposures. That expertise makes EPA most qualified to establish how best to protect the health of every man, women and child.

I look forward to hearing from each of the witnesses, and I thank you for taking the time to be here and share your perspectives on protecting children—born and unborn—from environmental risks.

TESTIMONY OF DANA BEST, MD, MPH, FAAP ON BEHALF OF THE AMERICAN ACADEMY OF PEDIATRICS

SELECT COMMITTEE ON ENERGY INDEPENDENCE AND GLOBAL WARMING

"Healthy Planet, Healthy People: Global Warming and Public Health"

April 9, 2008

Department of Federal Affairs
The Homer Building
601 Thirteenth Street, N.W.
Suite 400 North
Washington, D.C. 20005
202-347-8600 / 800-336-5475 / Fax 202-393-6137

Good morning. I appreciate this opportunity to testify today before the Select Committee on Energy Independence and Global Warming on the impact of climate change on child health. My name is Dana Best, MD, MPH, FAAP, and I am proud to represent the American Academy of Pediatrics (AAP), a non-profit professional organization of 60,000 primary care pediatricians, pediatric medical sub-specialists, and pediatric surgical specialists dedicated to the health, safety, and well-being of infants, children, adolescents, and young adults. I am an Assistant Professor of Pediatrics at the George Washington University School of Medicine and an attending physician at Children's National Medical Center in Washington, D.C. I also serve on the AAP's Committee on Environmental Health.

There is strong consensus among expert scientists that Earth is undergoing rapid, global climate change.[1,2] Human activities, primarily the burning of fossil fuels, are very likely (>90% probability) the main cause of this warming. In October 2007, the American Academy of Pediatrics issued a new policy statement and technical report, entitled, "Global Climate Change and Children's Health."[3,4] This statement sounded a warning to pediatricians and policymakers alike that we should expect global climate change to have a disproportionately severe impact on the health of children everywhere.

Impact of Global Climate Change on Child Health

Human health is affected by the condition of the physical environment.[5] Because of their physical, physiologic, and cognitive immaturity, children are often most vulnerable to

adverse health effects from environmental hazards.[6] As the climate changes, environmental hazards will change and often increase, and children are likely to suffer disproportionately from these changes.[7] Anticipated health threats from climate change include extreme weather events and weather disasters, increases in certain infectious diseases, air pollution, and thermal stress. Within all of these categories, children have increased vulnerability compared with other groups.

Extreme Weather Events and Weather Disasters: The health consequences associated with extreme weather events include death, injury, increases in infectious diseases, and posttraumatic mental health and behavior problems.[8] Unfortunately, few studies have specifically examined such consequences in children.

Children everywhere are at risk of injury and death from storms and floods.[9] In the developed world, infectious disease outbreaks follow natural disasters when sanitation, sewage treatment, and water-purification plants become damaged or overwhelmed, refrigeration and cooking facilities are disrupted, and people are unusually crowded in temporary shelter. These outbreaks are usually mild and well controlled, which is in contrast to the aftermath of similar catastrophes in developing nations, where disease outbreaks can be deadly.[10] Mosquito-borne and other vector-borne illnesses may also be increased when storms or floods create large amounts of standing water suitable for breeding.

Mental and emotional distress documented for children and adolescents after weather disasters include posttraumatic stress disorder and high rates of sleep disturbance, aggressive behavior, sadness, and substance use and/or abuse.[11] Some studies have suggested that children have more persistent symptoms than adults who experience the same disaster,[12] but more studies specific to children's experience are required.[13] Community support services[14] and early therapeutic intervention and postdisaster counseling[15,16] can significantly reduce the medium- and long-term mental health burden on children. Experiences with Hurricanes Katrina and Rita demonstrated the difficulties with tracking children's whereabouts, keeping children and caregivers together, and special needs of hospitalized infants and children during and after major natural disasters.

Infectious Diseases: Vector-borne infections are affected by climate change.[17] Both the hosts (eg, rodents, insects, snails) and the pathogens (eg, bacteria, viruses, parasites) can be sensitive to climatic variables such as temperature, humidity, and rainfall. The ability to predict disease rates related to climate change is complicated by a large number of additional variables such as topography, land use, urbanization, human population distribution, level of economic development, and public health infrastructure.[18] There is no easy formula that predicts climate change–related infection risk with confidence.

For example, malaria is a climate-sensitive vector-borne illness to which children are particularly vulnerable. Because they lack specific immunity, children experience disproportionately high levels of both sickness and death from malaria; 75% of malaria deaths occur in children younger than 5 years. The young are also more susceptible to

cerebral malaria, which can lead to lifelong brain damage in those who survive. Climate change is expanding the range of host mosquitoes to higher altitudes and higher latitudes, and warmer temperatures speed the development of the parasite within the host vector.[19] Small children will be most affected by the expansion of malaria zones and the success or failure of societal response to this change.

Ambient Air Pollution: Children are especially vulnerable to both short-term illness and long-term damage from ambient air pollution, because their lungs are developing and growing, they breathe at a higher rate than adults, and they spend more time outdoors engaging in vigorous physical activity.[20] Air pollution (such as ozone and particulate matter) causes respiratory and asthma hospitalizations, school absences, increased respiratory symptoms, and decrements in lung function.[17] Formation of ozone, in particular, is known to increase with increasing temperature, even without increases in the precursor primary pollutants (volatile organic hydrocarbons and oxides of nitrogen).[21] Children who are active in outdoor sports in communities with high ozone are at increased risk of developing asthma.[22] In addition, high levels of particulate matter and other pollutants affect the ability of children's lungs to grow regardless of history of asthma.[23] Rates of preterm births, low birth weight, and infant mortality are increased in communities with high levels of particulate air pollution.[24]

A second change that is being observed is the temperature-related increases in pollen production and other allergens in some regions and some cities. Increased temperature causes increases in amounts of pollens produced by some plants[25] and can also affect

spatial distribution and density of plants, fungi, and molds that produce allergens.[26] To the extent that exposure to allergens contributes to the incidence, prevalence, and severity of asthma, allergic reactions, and other respiratory disease, climate change will affect the pattern of disease in children. Some investigators have argued that part of the current global increase in childhood asthma can be explained by increased exposure to aeroallergens driven by climate change.[27]

Thermal Stress: For all organisms, there exists a range of ideal temperature above and below which mortality increases. Humans are no exception, although temperature-mortality relationships vary significantly by latitude, climatic zone, and level of socioeconomic development.[28] As ambient temperatures increase, the frequency of heat waves will increase. Populations that live in temperate climates, such as in the United States and Europe, are likely to be hard hit initially, because global warming is most dramatic in these latitudes and there has been little time for populations to acclimatize to changes in temperature.

Heat-related deaths and hospitalizations are most common in the elderly, especially if they are ill.[29,30] One study has found that infants and young children may represent a second, albeit smaller, higher-risk group,[31] but effects on children have not been studied adequately. In addition, children spend more time outside, especially playing sports in the heat of the afternoon, which puts them at increased risk of heat stroke and heat exhaustion.[32] Increased outdoor time during hot weather may also put children at increased risk of UV radiation–related skin damage, including skin cancer.[33]

Additional Long-Term and Indirect Impacts: Food availability may be affected as land and ocean food-productivity patterns shift.[34] Water availability may change and become much reduced in some regions, including during summer in the snow run-off–dependent American west coast.[35] Coastal populations could be forced to move because of rises in sea level, and massive forced migrations, driven by abrupt climate change, natural disaster, or political instability over resource availability, are conceivable.[36] In addition, world population is expected to grow by 50% to 9 billion by 2050, which would place additional stress on ecosystem services and increase the demand for energy, fresh water, and food.[37] As these changes evolve, social and political institutions will need to respond with aggressive mitigation strategies and flexible adaptation strategies to preserve and protect public health, particularly for children.

Recommendations

In addition to its recommendations to pediatricians for reducing their energy demands and incorporating sustainable practices into their personal and professional lives, the American Academy of Pediatrics calls upon government at all levels, from the smallest municipalities to the national and international levels, to implement aggressive policies to halt man-made contributions to climate change and to mitigate its impact on children's health. Policymakers should:

- Develop aggressive, long-term policies to reduce the major contributing factors to global climate change. For example, the Environmental Protection Agency

should set the National Ambient Air Quality Standard for ozone at 0.060 parts per million.[38]

- Invest in prudent and vital preparations for our public health care systems, including immunization programs and disease surveillance, reporting, and tracking.
- Give specific attention to the needs of children in emergency management and disaster response.[39,40]
- Support education and public awareness of the threats from climate change and their implications for public and children's health now and in the future.
- Fund interdisciplinary research to develop, implement, and measure outcomes of innovative strategies to both mitigate and adapt to climate change, particularly in areas with direct implications for children's health.

In conclusion, the American Academy of Pediatrics commends you, Mr. Chairman, for holding this hearing today to call attention to the potential impacts of global climate change on children's health. We look forward to working with Congress to prevent the adverse impacts on child health caused by global climate change and to plan for those that may be unavoidable. I appreciate this opportunity to testify, and I will be pleased to answer any questions you may have.

---

[1] Intergovernmental Panel on Climate Change. Climate change 2007: the physical science basis—summary for policy makers. Available at: www.ipcc.ch/SPM2feb07.pdf.
[2] US Environmental Protection Agency. Climate change-science: state of knowledge. Available at: www.epa.gov/climatechange/science/stateofknowledge.html.
[3] Shea K and Committee on Environmental Health. Global Climate Change and Children's Health. *Pediatrics.* 2007:120:1149-1152.

[4] Shea K and Committee on Environmental Health. Global Climate Change and Children's Health. *Pediatrics.* 2007:120:e1359-e1367.
[5] World Health Organization. Ecosystems and human wellbeing: health synthesis. Available at: www.who.int/globalchange/ecosystems/ecosystems05/en/index.html.
[6] Etzel RA, Balk SJ, eds. *Pediatric Environmental Health.* 2nd ed., Elk Grove Village, IL: American Academy of Pediatrics; 2003.
[7] Shea K. Global environmental change and children's health: understanding the challenges and finding solutions. *J Pediatr.* 2003;143:149–154.
[8] Greenough G, McGeehin M, Bernard SM, Trtanj J, Riad J, Engelberg D. The potential impacts of climate variability and change on health impacts of extreme weather events in the United States. *Environ Health Perspect.* 2001;109(suppl 2): 191–198.
[9] Ahern M, Kovats RS, Wilkinson P, Few R, Matthies F. Global health impacts of floods: epidemiologic evidence. *Epidemiol Rev.* 2005;27:36–46.
[10] McMichael A, Githeko A. Human health. In: McCarthy JT, Canziani OF, Leary NA, Dokken DJ, White KS, eds. *Climate Change 2001: Impacts, Adaptations, and Vulnerability.* Geneva, Switzerland: Intergovernmental Panel on Climate Change; 2001:453–485. Available at: www.grida.no/climate/ipcc_tar/wg2/pdf/wg2TARchap9.pdf.
[11] Ahern M, Kovats RS, Wilkinson P, Few R, Matthies F. Global health impacts of floods: epidemiologic evidence. *Epidemiol Rev.* 2005;27:36–46.
[12] Shaw JA, Applegate B, Schorr C. Twenty-one-month follow- up of school-age children exposed to Hurricane Andrew. *J Am Acad Child Adolesc Psychiatry.* 1996;35:359–364.
[13] Hoven CW, Duarte CS, Mandell DJ. Mental health after disasters: the impact of the World Trade Center attack. *Curr Psychiatry Rep.* 2003;5:101–107.
[14] Kostelny K, Wessells M. Psychological aid to children after the 26 Dec tsunami. *Lancet.* 2005;366:2066–2067.
[15] Wolmer L, Laor N, Dedeoglu S, Siev J, Yazgan Y. Teachermediated intervention after disaster: a controlled three-year follow-up of children's functioning. *J Child Psychol Psychiatry.* 2005;46:1161–1168.
[16] Goenjian AK, Walling D, Steinberg AM, Karayan I, Najarian LM, Pynoose R. A prospective study of posttraumatic stress and depressive reactions among treated and untreated adolescents 5 years after a catastrophic disaster. *Am J Psychiatry.* 2005;162: 2302–2308.
[17] Epstein PR. Is global warming harmful to health? *Sci Am.* 2000;283(2):50–57.
[18] Sutherst RW. Global change and human vulnerability to vector-borne diseases. *Clin Microbiol Rev.* 2004;17:136–173.
[19] Epstein RP, Mills E, eds. *Climate Change Futures: Health, Ecological and Economic Dimensions.* Boston, MA: Center of Health and the Global Environment, Harvard Medical School; 2005. Available at: www.climatechangefutures.org/pdf/CCF_Report_Final_10.27.pdf.
[20] Kim JJ. American Academy of Pediatrics, Committee on Environmental Health. Ambient air pollution: health hazards to children. *Pediatrics.* 2004;114:1699–1707.

[21] Knowlton K, Rosenthal JE, Hogrefe C, et al. Assessing ozonerelated health impacts under a climate change. *Environ Health Perspect.* 2004;112:1557–1563.
[22] McConnell R, Berhane K, Gilliland F, et al. Asthma in exercising children exposed to ozone: a cohort study [published correction appears in *Lancet.* 2002;359:896]. *Lancet.* 2002;359: 386–391.
[23] Gauderman WJ, Gilliland GF, Vora H, et al. Association between air pollution and lung function growth in southern California children: results from a second cohort. *Am J Respir Crit Care Med.* 2002;166:76–84.
24 Epstein RP, Mills E, eds. *Climate Change Futures: Health, Ecological and Economic Dimensions.* Boston, MA: Center of Health and the Global Environment, Harvard Medical School; 2005. Available at: www.climatechangefutures.org/pdf/CCF_Report_Final_10.27.pdf.
[25] Beggs PJ. Impacts of climate change on aeroallergens: past and future. *Clin Exp Allergy.* 2004;34:1507–1513.
[26] Ziska LH, Gebhard DE, Frenz DA, Faulkner S, Singer BD, Straka JG. Cities as harbingers of climate change: common ragweed, urbanization, and public health. *J Allergy Clin Immunol.* 2003;111:290–295.
[27] Beggs PJ, Bambrick HJ. Is the global rise of asthma an early impact of anthropogenic climate change? *Environ Health Perspect.* 2005;113:915–919.

[28] McMichael AJ, Woodruff RE, Hales S. Climate change and human health: present and future risks. *Lancet.* 2006;367: 859–869.
[29] Kovats RS, Hajat S, Wilkinson P. Contrasting patterns of mortality and hospital admissions during hot weather and heat waves in Greater London, UK. *Occup Environ Med.* 2004;61: 893–898.
[30] Wyndham CH, Fellingham SA. Climate and disease. *S Afr Med J.* 1978;53:1051–1061.
[31] Anonymous. Heat-related deaths: four states, July–August 2001, and United States, 1979–1999. *MMWR Morb Mortal Wkly Rep.* 2002;51:567–570. Available at: www.cdc.gov/mmwr/preview/mmwrhtml/mm5126a2.htm.
[32] American Academy of Pediatrics, Committee on Sports Medicine and Fitness. Climatic heat stress and the exercising child and adolescent. *Pediatrics.* 2000;106:158–159.
[33] American Academy of Pediatrics, Committee on Environmental Health. Ultraviolet light: a hazard to children. *Pediatrics.* 1999;104:328–333.
[34] Slingo JM, Challinor AJ, Hoskins BJ, Wheeler TR. Introduction: food crops in a changing climate. *Philos Trans R Soc Lond B Biol Sci.* 2005;360:1983–1989.
[35] Barnett TP, Adam JC, Lettenmaier DP. Potential impacts of a warmer climate on water availability in snow-dominated regions. *Nature.* 2005;438:303–309.
[36] McMichael A, Githeko A. Human health. In: McCarthy JT, Canziani OF, Leary NA, Dokken DJ, White KS, eds. *Climate Change 2001: Impacts, Adaptations, and Vulnerability.* Geneva, Switzerland: Intergovernmental Panel on Climate Change; 2001:453–485. Available at: www.grida.no/climate/ipcc_tar/wg2/pdf/wg2TARchap9.pdf.
[37] United Nations Population Division. World population prospects: the 2006 Revision Population Database. Available at: http://esa.un.org/unpp.
[38] Comment letter submitted by Jay Berkelhamer, MD FAAP, President, American Academy of Pediatrics to EPA Administrator Steven Johnson on ozone NAAQS, Docket ID: EPA-HQ-OAR-2005-0172, October 10, 2007.
[39] McMichael A, Githek OA. Human health. In: McCarthy JT, Canziani OF, Leary NA, Dokken DJ, White KS, eds. Climate Change 2001: Impacts, Adaptations, and Vulnerability. Geneva, Switzerland: Intergovernmental Panel on Climate Change; 2001:453–485. Available at: www.grida.no/climate/ipcc_tar/wg2/pdf/wg2TARchap9.pdf.
[40] US Department of Health and Human Services, Agency for Healthcare Research and Quality. Pediatric terrorism and disaster preparedness: a resource guide for pediatricians. Available at: www.ahrq.gov/research/pedprep/resource.htm.