ENDOCRINE-DISRUPTING CHEMICALS IN DRINKING WATER: RISKS TO HUMAN HEALTH AND THE ENVIRONMENT

HEARING

BEFORE THE

SUBCOMMITTEE ON ENERGY AND ENVIRONMENT

OF THE

COMMITTEE ON ENERGY AND COMMERCE

HOUSE OF REPRESENTATIVES

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CONTENTS

ENDOCRINE-DISRUPTING CHEMICALS IN DRINKING WATER: RISKS TO HUMAN HEALTH AND THE ENVIRONMENT

THURSDAY, FEBRUARY 25, 2010

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON ENERGY AND ENVIRONMENT,
COMMITTEE ON ENERGY AND COMMERCE,
Washington, DC.

The Subcommittee met, pursuant to call, at 9:34 a.m., in Room 2123 of the Rayburn House Office Building, Hon. Edward J. Markey [Chairman of the Subcommittee] presiding.

Members present: Representatives Markey, Inslee, McNerney, Green, Capps, Matheson, Barrow, Moran, Stearns, Shimkus, Burgess, and Scalise.

Staff present: Jackie Cohen, Counsel; Tracy Sheppard, Counsel; Melissa Cheatham, Professional staff; Michael Freedhoff, Professional staff; Peter Ketcham-Colwill, Special Assistant; Caitlin Haberman, Special Assistant; Earley Green, Chief Clerk; Jerry Couri, Minority Professional Staff; and Garrett Golding, Minority Legislation Analyst.

OPENING STATEMENT OF HON. EDWARD J. MARKEY, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF MASSACHUSETTS

Mr. MARKEY. Welcome, ladies and gentlemen. Lately not a day goes by where the public is not reminded of the presence of toxic chemicals in the air we breathe and in the water we drink, and the potential harmful effect that these chemicals can have on public health and the environment. Just last week, a local newspaper warned that the Potomac River and other Mid-Atlantic rivers are awaste with toxins that may be responsible for bizarre deformities in fish, frogs, and other wildlife that come in contact with the contaminated water. This includes male fish that have begun growing female sexual organs and female fish that can no longer reproduce.

W.C. Fields once said I never drink water because of the disgusting things that fish do in it. Well, today people wonder whether they should be drinking the water that comes out of their taps because of the disgusting things it is doing to the fish and possibly to them. There are serious concerns that the same chemicals that are responsible for these deformities in wildlife may also have similar effects in humans. They may be the culprit for the widespread increase in human disorders such as infertility, obesity, diabetes, and cardiovascular disease. These contaminants which fall under a

class of chemicals called endocrine disruptors are pervasively showing up in our Nation's waterways including in water that millions of people rely on for drinking.

For example, bisphenol-A BPA, which is used in many plastic containers and as a lining in canned food is associated with developmental and reproductive disorders in humans. To this end, the FDA recently announced that it is concerned about these health effects and I have got a bill to ban its use in food and beverage containers in hope that we can finally stop limiting our exposure.

Tyclasin is another example of an endocrine disruptor which is used as an anti-microbial in hand soaps. Tyclasin has been shown to interfere with the development of the brain and nervous systems of laboratory animals, and I am concerned about the consequences on human health. I have asked both FDA and EPA what they plan on doing about evaluating and regulating Tyclasin's widespread use.

Perchlorate used as an ingredient in rocket fuel is pervasively showing up in drinking water all across the Nation. We are looking for that extra boost in the morning, but I would personally rather stick to a large cup of coffee.

Massachusetts is one of the few states that regularly monitors perchlorate and has also set a statewide water standard for the contaminant. Exposure to this chemical during pregnancy can cause serious neurological deficits and could be one of the contributing causes of increased attention deficit disorders and other cognitive problems in our Nation's children.

All of these dangerous chemicals along with others whose health effects are less well known have been found by government scientists to be contained in our Nation's surface water, ground water, and drinking water. In 1996, The Food Quality Protection Act and Safe Drinking Water Act amendments authorized EPA to screen for endocrine disruptors in sources of drinking water.

In response to that statute, the EPA established the endocrine disruptor screening program designed to evaluate the safety of chemicals that might cause adverse health effects to the body's endocrine system. EPA's progress with this screening program has been slow, but late last year the first 67 chemicals designated for screening were announced, and the process of collecting information has finally begun. Given the advancements in science and technology that have occurred over the last decade, it is appropriate to reevaluate what we know about endocrine disruptors and assess the effectiveness of EPA screening program in identifying and evaluating the safety of endocrine disruptors found in sources of drinking water.

I thank you for coming here today to the witnesses, and let me turn now to recognize the gentleman from Florida, Mr. Stearns, for an opening statement.

Mr. STEARNS. Thank you, Mr. Chairman, and I ask unanimous consent that all members have 5 days for submission of their opening statements.

Mr. MARKEY. Without objection.

OPENING STATEMENT OF HON. CLIFF STEARNS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF FLORIDA

Mr. STEARNS. And thank you for having this important hearing. Examining the science and the regulation of endocrine disrupting chemicals that I think all of us are concerned about. We all take this subject very seriously. There are some substances in the water that can pose real problems, and I want to know more about it. I think most members do. I would particularly like to welcome a constituent. Not oftentimes you have someone from your congressional district here. Dr. Christopher Borgert, the president and principal scientist at Applied Pharmacology and Toxicology Incorporated, which is located in my congressional district at the home of the University of Florida in Gainesville. Applied Pharmacology and Toxicology is one of the leading consulting firms that specializes in the pharmacological and toxicological effects of chemicals on living systems. And so I am honored to have a constituent with that kind of broad-based experience with us this morning.

As the chairman mentioned, endocrine disrupting chemicals are natural chemicals that interfere with or mimic the hormones responsible for growth and development of an organism. Endocrine disrupting chemicals can be found in commonly used products such as personal care products, obviously soaps and cosmetics, industrial by-products, plastic, pesticides, and pharmaceuticals. As testing has become more sophisticated, minute traces of certain chemical substances suspected to be endocrine disruptors have been detected in surface water and drinking water supplies. These chemicals enter into our environment from various sources, obviously including industrial and municipal discharges, agricultural runoffs, and hospital residues.

And while many researchers agree that field and laboratory studies of animals providing compelling evidence of the effect of these chemicals, the scientific community remains sharply divided of whether organic chemicals are responsible for increases of certain human cancers, diseases of the human reproductive system, the immune system, and the thyroid glands. Nevertheless, environmental advocates have increasingly pushed for the aggressive federal regulation of the substances.

In 1996, Congress recognized that arbitrary, legislatively mandated regulation can bog EPA down and delay urgent public health needs. So to address this, the Safe Drinking Water Act amendments of 1996 replaced mandatory drinking water regulations with directions to EPA that it use simply deliberative rigorous and objective science in making any further rules on drinking water contaminant levels. EPA and the scientific community need to continue to study the occurrence and movement of endocrine-disrupting chemicals in our environment, and then EPA, not Congress, should set a standard that best protects the public health.

So, Mr. Chairman, I thank you for this hearing, and we look forward to the witnesses this morning.

Mr. MARKEY. We thank you. We thank the gentleman, and we have with us the gentlemen from Virginia—I am sorry. Chair recognizes the gentleman from Illinois, Mr. Shimkus, for an opening statement.

OPENING STATEMENT OF HON. JOHN SHIMKUS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF ILLINOIS

Mr. SHIMKUS. Thank you, Mr. Chairman. We need to just make sure that when we go down a route that that is—we are using high quality science whose results are repeatable, whose objective is not to answer questions for which we already have decided the answer. We have a tendency of doing that.

We made some precautionary decisions in the toy bill, and that has just been one disaster after another. The whole debate on climate has just been a great exercise in how this climate-gate thing all unfolded. Science wanted the data to see if the projections by scientists were relevant and true. These scientists withheld data. They would not provide those. Under the Freedom of Information Act, we finally started getting the data. And guess what.

Are the Himalayan glaciers melting in 35 years? We made a mistake. What about sea levels? That was a miscalculation. We have people walking away from or leaving the IPCC. We have the U.N. guy now stepping down. And why? Because we didn't use science. We didn't use the scientific method to put the bats on the table, put data on the table, and do the research to replicate these assumptions. So we have to be very, very careful that we don't go down a route.

This is the "Washington Post" Tuesday, February 23, "Replacing BPA cans gives foodmaker fits." At the end of this, it says—they are talking about tuna. They spent thousands of dollars. Is it in the cutting board? Is it in the fish? Is it in the tuna itself? We don't know. We are trying to figure it out. Let us use real science. Let us be able to replicate the data. Let us just don't go on an emotional rollercoaster to impinge on our ability to create jobs in this America which increased regulations always does, and I yield back my time.

Mr. MARKEY. The gentleman's time has expired. The chair recognizes the gentlelady from California, Mrs. Capps, for an opening statement.

OPENING STATEMENT OF HON. LOIS CAPPS, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF CALIFORNIA

Mrs. CAPPS. Thank you, Mr. Chairman, and thank you for holding this hearing on the growing pandemics of endocrine related health disorders. Like you, I am very concerned about exposure that may be occurring through drinking water supplies. I am particularly concerned given the very pervasive nature of endocrine-disrupting chemicals, which are everywhere in our environment.

Many of these chemicals are either unregulated or underregulated and include toxics, pesticides, even pharmaceuticals. As many of you, I spent my early professional years as a public health nurse. It is from this experience that I have been very mindful of threats to human health. While the Safe Drinking Water Act was successful at controlling some substances, it is clear that today's contaminants of concern are not the pollutants of yesteryear.

For example, there are currently 80,000 chemicals in use. This is a threefold increase from 1941 to 1995. 8,000 of these are known to be carcinogens. One would hope that all of these 8,000 cancer-causing chemicals are somehow addressed under federal and state

laws, including the Safe Drinking Water Act. Shockingly, this is not the case. It seems that less than 300 chemicals have permitted limits.

Today's hearing provides us with an opportunity to ask why this is the case. It is not as if endocrine-disrupting chemicals are new issues of concern for either Congress or EPA. Through the Safe Drinking Water Act, Congress instructed EPA to develop a screening program to determine if certain chemicals disrupt hormones in humans. In the 14 years since this mandate was put in place, EPA has begun to test few chemicals under the program, despite the potential for these chemicals to cause great harm to individuals, especially to children and pregnant women.

Today, I hope to hear about where these chemicals are coming from, what the impact to human and ecological health is, and what should and can be done to protect us from harm. So I do look forward to the testimony from our witnesses today on this very important hearing. And again I thank you for calling it to order, and I yield back.

Mr. MARKEY. Thank you. Thank the gentlelady. We see no other members of the subcommittee seeking recognition for the purpose of making an opening statement. So we will turn to our witnesses, but we will begin first with our friend Congressman Jim Moran who has worked for many years on this issue and who has joined us here this morning. We welcome you to the committee, and we look forward to your testimony.

STATEMENT OF HON. JAMES P. MORAN, A REPRESENTATIVE IN CONGRESS FROM THE COMMONWEALTH OF VIRGINIA

Mr. MORAN. Mr. Chairman, thank you very, very much, and thank you for your leadership on this issue. And it is good to see my colleagues and friends Ms. Capps and Mr. Stearns. I first came to be concerned about this when we looked at the fish in the Potomac River. Now, this is just between northern Virginia and Washington, D.C., and almost 100 percent of the fish—they are smallmouth basses—are intersex. They are both male and female sexual organs. There is something wrong with that, and so we looked into what might be the cause. And invariably, we came back to endocrine disruptors.

The problem is that the scientific research is inadequate to give us the kind of determination that we need to get, but we have the authority. Back in 1996, the amendments to the Safe Drinking Water Act call for EPA to ensure testing of chemicals with endocrine-disrupting effects. Congress directed the EPA to develop an endocrine-disruption screening program as part of the Food Quality Protection Act, as Ms. Capps suggested. Unfortunately, for a number of reasons—I will mention some of them—this program has not been effective. It has been deliberately delayed. Here we are 14 years later, and over $100 million has been put into this program. And it wasn't until October of this past year, just a few months ago, that EPA announced the availability of the national SAs and its testing guidelines for a limited number of chemicals.

Chairman Markey, you have been monitoring the progress of the EPA and performing these studies, and you have been expressing your concern about the public's exposure to these chemicals while

the issue continues to be studied. We can't study it forever if we know that people are really suffering because we haven't been able to come up with determinations on what is causing it. What is especially frustrating that, despite slow progress by the EPA, the science has continued to evolve through robust research by the scientific and academic communities through basically no help from the EPA who is charged with this work.

And the work that the scientific community has done convincingly demonstrates a link between synthetic endocrine-disrupting chemicals and a number of disorders of the human endocrine system. It has seriously undermined the health of our Nation. It is costing hundreds of billions of dollars. Now, it is autism, hyperactivity disorder, asthma, juvenile and adult diabetes, juvenile cancer, osteoporosis, Parkinson's, Alzheimer's. What we know is that these disorders began to increase noticeably in the early 1970s when the first generation was exposed in the womb to post World War II synthetic chemicals. And they reach maturity, and that is when we see this phenomenal increase in these kinds of disorders.

The endocrine disruptors were a fringe concept a decade ago. Now, they are accepted by the scientific community. But think of this, asthma rates have tripled in the past three decades. One in six American children has a developmental disorder. One in 59 boys has autism. Cancer is the leading cause of death among children now. Primary brain cancer has increased by nearly 40 percent. We know about childhood obesity. One in two minority children develop diabetes. Testosterone levels have declined dramatically over the last 20 years.

We have to be concerned about this. Something is happening, and it is happening on an accelerating pace. The scientific community is telling us that there is very likely a link to these dramatic increases in diseases in EDCs. What is happening, according to an environmental working group, that analyzed the umbilical cord blood that was collected from minority infants, they identified industrial compounds and pollutants that there were complex mixtures of compounds in each infant. And it shows that industrial chemicals cross the placenta in large numbers and contaminate babies in the womb. And it is that synergistic effect of these chemicals that is likely causing the problem.

In November of this past year, the AMA said that the federal government needs to minimize the public's exposure to endocrine-disrupting chemicals. So this is no longer a fringe issue. This is a very important issue for the entire Nation. But despite the profound improvements in scientists' knowledge, the chemical industry, because of legislation that said that basically all the stakeholders have a veto if they choose to use it.

The chemical industry, being one of those stakeholders, has been able to manipulate the process that has been undertaken by the Environmental Protection Agency so that they could produce results that were contrary to all of the research conducted by qualified endocrinologists that have found health consequences from EDCs.

And through the process of buying up the stakeholders, EPA has been prevented from using the most appropriate modern protocols. That is the problem. EPA has not been able to conduct these ex-

periments in the way that they know they need to. They have been conducting them in an outdated way. I won't go into all the details because I suspect your speakers will describe it. But basically they use this dose response method. The dose establishes the poison. At higher doses, the effects are often nullified causing organs to stop producing more hormones and receptors.

It is in low doses where the damage oftentimes occurs, but I will let the experts explain that. We have to be using modern, 21st century testing paradigms that recognize the unique subtle and complex properties that affects EDCs. I know that is what you want to be doing, Mr. Chairman.

We need to be guided by the scientific community instead of stakeholders who we know have a major financial interest in not allowing EPA to be able to pursue the authority and charge that the Congress gave it. I don't think I am going to get into the fact that EPA hasn't done these studies properly, but the National Institutes of Environmental Health Sciences has the expertise and the objectivity. And you are going to hear from them. We strongly support them.

For what it is worth, we have some role in the Environmental Appropriations Subcommittee. We want to do everything we can to support your efforts, Chairman Markey. This is a very important issue. It is affecting tens of millions of children across the country, and it is more than past time that we started doing the right thing in finding out the real impact of these EDCs and how we can get them out of the bloodstream of American society.

So, Mr. Chairman, thank you very, very much for your leadership. I really do appreciate it. I appreciate the opportunity to add my two cents this morning.

[The prepared statement of Mr. Moran follows:]

Statement of Rep. James P. Moran
House Energy and Commerce Subcommittee on Energy and the Environment
Hearing on Chemicals in Drinking Water

Thursday, February 25, 2010

Chairman Markey, Ranking Member Upton, thank you for scheduling a hearing on an issue that is very important to me, the need to study and regulate endocrine-disrupting chemicals (EDCs). Extensive studies to date have shown a correlation between exposure to EDCs and all manner of adverse health effects.

As you know, the 1996 amendments to the Safe Drinking Water Act called for the U.S. Environmental Protection Agency (EPA) to ensure testing of chemicals for endocrine disrupting effects. In 1996, Congress also directed the EPA to develop an endocrine disruption screening program as part of the Food Quality Protection Act. Unfortunately, for various reasons, EPA's EDC program has been plagued by delays. Here we are, fourteen years and over $100 million later, and it wasn't until October of 2009 that EPA announced the availability of initial assays and testing guidelines for a limited number of chemicals. Chairman Markey, you have been monitoring the progress of the EPA in performing these studies, and have expressed concern about the public's exposure to these chemicals while the issue continues to be studied. It is especially frustrating that, despite slow progress by the EPA, the science has continued to evolve through robust research by the scientific and academic communities.

This work convincingly demonstrates a disturbing link between synthetic EDCs and a number of disorders of the human endocrine system that is seriously undermining the health of our Nation. These disorders include autism, attention deficit hyperactivity disorder, asthma, juvenile and adult diabetes, juvenile cancer, autoimmune diseases, obesity, osteoporosis, Parkinson's disease, and Alzheimer's dementia. These disorders began to increase noticeably in the early 1970s when the first generation exposed in the womb to post-World War II synthetic chemicals reached maturity. According to the Director of Mount Sinai's Children's Environmental Health Center (CEHC), endocrine disruptors were a fringe concept ten years ago, but now their significance is accepted by the scientific community. CEHC reports that:

- Asthma rates have nearly tripled in the past three decades.

- One of every six American children has a development disorder (ADHD, dyslexia, mental retardation).
- One in every 150 American children is now diagnosed with autism (the Centers for Disease Control have updated this to 1 in 101 children, and 1 in 59 for boys).
- Cancer, after accidents, is the leading cause of death among children in the United States.
- Primary brain cancer increased by nearly 40% and leukemia increased by over 60% among children 14 years and younger from 1975 to 2004.
- Childhood obesity has quadrupled in the past 10 years.

Other studies indicate:

- 1 in 3 children and 1 in 2 minority children will develop diabetes; and
- Age-independent decline in testosterone levels has occurred over the past 20 years in American men.

Something in the environment is making Americans sick in epidemic proportions, and studies indicate a link to EDCs. Exposure to EDCs begins in the womb. A study commissioned by The Environmental Working Group analyzed umbilical cord blood collected from ten minority infants born in 2007 and 2008. The laboratories identified up to 232 industrial compounds and pollutants, finding complex mixtures of compounds in each infant. This research shows industrial chemicals cross the placenta in large numbers to contaminate babies in the womb. No one can predict the synergistic effects of these chemicals, or the impacts with repeated exposure over a lifetime.

The Endocrine Society, comprising 14,000 hormone researchers and medical specialists in more than 100 countries, warned that "even infinitesimally low levels of exposure" to endocrine-disrupting chemicals may cause endocrine or reproductive abnormalities, particularly if exposure occurs during a critical developmental window. At its annual meeting in June 2009 the Society released a statement identifying exposure to endocrine disrupting chemicals as the issue of greatest public health concern to the Society.

In November 2009, the American Medical Association Board of Delegates approved a resolution that called on the federal government to minimize the public's exposure to endocrine-disrupting chemicals. The measure was advanced by the Endocrine Society, the American Society for Reproductive Medicine and the American College of Obstetricians and Gynecologists. This is not just a national problem – the UN has also called upon members to undertake the study of endocrine disrupting chemicals.

The cost of failure to act is enormous. The American Diabetes Association reports that the occurrence of diabetes is reaching epidemic proportions. The cost in the U.S. for

treating diabetes in 2007 was estimated at $116 billion. About one in every ten dollars spent on health care was related to diabetes. This is just one disease of the many believed to be attributable in part to endocrine disruptors.

EPA's work has been at a glacial pace. Moreover, many question whether testing conducted under EPA's program will be as relevant or effective as it should be. Despite profound improvements in scientists' knowledge and understanding of endocrine disrupting chemicals, the chemical industry has been able to manipulate the process undertaken by EPA in order to produce results contrary to all of the research conducted by qualified endocrinologists that have found health consequences from EDCs. Through a process that requires the buy-in of stakeholders, including the chemical industry, EPA has been prevented from utilizing the most appropriate, modern protocols.

Stakeholders, most notably the chemical industry, have vetoed all but outmoded study concepts, in effect using the fourteen years EPA has had to study EDCs to take a giant step backwards. For example, all endocrinologists would use a positive control to establish a baseline to compare to the effects of the studied chemical. The tests industry sponsor do not follow this protocol. More egregious, industry-sponsored studies use the dose-response method, known as "the dose establishes the poison." This means that the testing assumes the higher the dose, the greater the response. In fact, in the case of EDCs, it is the small doses, such as the levels that occur in drinking water, that cause the effect. At higher doses the effects are often nullified causing organs to stop producing more hormones and receptors in target tissues to shut down. The dose/response is not a slope, but an inverted horseshoe curve. Nonetheless, industry studies have taken the results of high doses and concluded that with no response, the chemical poses no risk.

We need to use a modern, 21st century testing paradigm that recognizes the known unique, subtle, and complex properties and effects of EDCs. Only then will we have accurate, practical data to inform appropriate and expeditious regulation of these chemicals. The experience of the last fourteen years has shown us that the regulatory agencies lack the ability or the integrity to conduct scientific investigations without interference by the industries they regulate. The scientific inquiry should be driven by scientists, not advisory panels stacked with industry experts who have an inherent conflict of interest. Once the scientific investigation is complete, and a clear link has been established between a chemical and its impact on human health, once science has spoken, I have no problem with the responsible regulatory agencies evaluating the risk and at that point working with the affected stakeholders to develop appropriate risk management strategies.

Congress now has an opportunity to assess what has gone wrong in the past as far as developing an effective testing and screening program, and to ensure that steps are taken to move forward. Last year I, and several of our colleagues, introduced the "Endocrine Disruption Prevention Act of 2009," legislation that will establish a much-needed comprehensive research program and process to identify chemicals that interfere with human reproduction and development. More important, it will require regulatory agencies to come together and provide an appropriate public response to the scientific

findings, including identifying what actions they will take to protect humans from exposure to such chemicals.

In this legislation science, not politics, will set the stage for determining the impact on these chemicals on human health. I propose that we authorize and fund additional efforts to study EDCs by an organization dedicated to research. Such studies should not be conducted by the regulatory component of EPA. Risk management considerations should only be made after risks have been identified through competent research. I believe that the National Institutes of Environmental Health Sciences (NIEHS) could provide the expertise and objectivity needed. NIEHS (or possibly EPA's Office of Research and Development) needs to undertake a comprehensive research and testing program, using the best available science, to identify chemicals with endocrine disruption potential. In addition, the process would include an independent expert panel, guided by the scientific research, to develop a list of the chemicals and evaluate the potential threat they pose. When the science has been developed, regulatory agencies like EPA, the Consumer Product Safety Commission (CPSC), and the Food and Drug Administration (FDA), need to coordinate a timely response to those scientific findings. Regulating such chemicals to reduce exposure would be ideal; public outreach, so that the public can avoid exposure to such chemicals absent regulation, would also be beneficial. In any event, action will be based on sound, unbiased science.

In 2009 we saw much debate on the issue of health care costs in America. Every coverage option developed carries with it enormous costs. One rarely-discussed approach to bringing down health care costs is increased attention to improving the health of Americans, particularly the most vulnerable, those that require extensive health care support, even from infancy.

Let us not, ten years from now, be sorry that we did not take action sooner to prevent this health crisis. I urge my colleagues to support this important work.

Thank you.

Mr. MARKEY. Well, it is more than two cents, and since you are on the Appropriations Committee, you have a chance to put in a few more than that too. We thank you so much for your leadership on this issue over the years, and we thank you for coming here today. And I would like to partner with you as we go forward between our two committees to try to find a way that we can properly fund and properly regulate this incredible lies in disease that we know is related to something that we are doing to ourselves would cure most of the diseases that over the years have afflicted people.

Now we have to deal with issues that we do it to ourselves, you know, that we just make decisions with regard to chemicals, with drugs, with alcohol, with overeating. These are things that here we have a chance, you know, just with preventative measures to protect against the diseases, and your leadership has been fantastic.

The gentleman from Florida.

Mr. STEARNS. You know I would ask the staff about your opening statement, and my good friend has been on this issue for some time. And I have heard you before, and I think many of us have gone down to the Chesapeake, and so we are a little bit aware of what happened. And then, of course, we look at the Potomac occasionally and see what happened there. Many of us sometimes go fishing on the Potomac, either part of fundraising events or just social events. And so it is disturbing. I live in Old Town. I go down to King Street where you were mayor of Alexandria, and sometimes you get alarmed.

So I think it is an important issue. For all of us, I think the idea is there hard, repeatable science that can show this? Because we are asking the federal government to step in. So I think, Mr. Chairman, that is probably the crucial aspect to see that there is hard, repeatable science. Thank you.

Mr. MARKEY. And we thank you again. We very much appreciate your work and your staff's work on this issue. Now let us turn to our witness panel, and first of all, the subcommittee has received several letters and documents related to the subject matter. And I ask unanimous consent that the materials be included in the record without objection.

[The information appears at the conclusion of the hearing.]

Mr. MARKEY. We will turn to our first witness, Dr. Linda Birnbaum. She serves as the director of the National Institute of Environmental Health Sciences and the National Toxicology Program. She is a board-certified toxicologist and has served as a federal scientist for nearly 30 years. Dr. Birnbaum previously served for 16 years as director of the experimental toxicology division of the Environmental Protection Agency. We welcome you, Doctor. Whenever you feel comfortable, please begin.

STATEMENTS OF LINDA BIRNBAUM, DIRECTOR, NATIONAL INSTITUTE FOR ENVIRONMENTAL HEALTH SCIENCES; JAMES JONES, DEPUTY ASSISTANT ADMINISTRATOR, OFFICE OF PREVENTION, PESTICIDES AND TOXIC SUBSTANCES, ENVIRONMENTAL PROTECTION AGENCY; GINA SOLOMON, SENIOR SCIENTIST, NATIONAL RESOURCES DEFENSE COUNCIL; AND CHRISTOPHER J. BORGERT, PRESIDENT AND PRINCIPAL SCIENTIST, APPLIED PHARMACOLOGY AND TOXICOLOGY, INC.

STATEMENT OF LINDA BIRNBAUM

Ms. BIRNBAUM. Thank you. Mr. Chairman and distinguished members, I am pleased to present testimony on our current understanding and ongoing research on endocrine-disrupting chemicals or EDCs. My name is Linda Birnbaum. I am director of the NIEHS and the National Toxicology Program.

Some endocrine disruptors are naturally occurring, but many are manmade substances that mimic or interfere with hormonal signals in the body and therefore alter the normal functions of tissues and organs. NIEHS has had a long-standing interest in these chemicals with its support for research dating back to the beginning of the institute in the 1960s. Over the past 50 years, we have seen increases in health problems such as breast and prostate cancer, ectopic pregnancies, undescended testicles, and a 42 percent decrease in sperm count.

These findings along with observations of abnormal sexual development in frogs and fish and the widespread detection of endocrine-disrupting chemicals in our bodies lead NIEHS to increase its research on the effects of these chemicals on human health.

The detection of numerous pharmaceutical agents and chemicals with endocrine-disrupting potential in surface waters around the country has raised concern about drinking water as a significant route of human exposure.

I would like to emphasize four things about endocrine disruption. First, low dose. Our endocrine system works on tiny amounts of hormones that have significant biological effects. As a result, some chemical exposures, even at low doses, may disrupt the body's delicate endocrine system and lead to disease.

Second, wide range of health effects. Endocrine signals govern every organ and process in the body. That means when chemicals interfere with endocrine signaling, effects can be seen in many different conditions and diseases.

Third, persistence of biological effects. We are finding that the health effects of exposure to endocrine disruptors can be observed long after the actual exposure has ceased. This is especially true when exposures occur during growth and development, processes that are very sensitive to endocrine regulation.

Fourth, ubiquitous exposure. Because of widespread use as drugs and components of consumer products, chemicals with endocrine-disrupting activity are widely dispersed in our environment often at biologically effective levels, and exposure to humans is common. This is well-documented by the CDC National Exposure Report. I will give you a few examples regarding low dose. For some endocrine disruptors, biological changes can be seen at low but not at

high doses. This is different from the usual dose response curve which shows continually increasing responses with increases in dose.

Low doses of BPA and EDC change brain structure, function and behavior in rats and mice exposed during critical periods of development. Regarding the broad range of health effects, early work on endocrine disruption focused on health problems such as reproductive cancers that were known to be hormonally sensitive. More recently, the universe of potential health effects has grown to include immune function, metabolism, brain development, and behavior.

Animal studies have identified how exposure to environmental endocrine disruptors such as tributyltin, genistein and diethylstilbestrol can cause weight gain later in life. EDCs have also been linked to cancers, altered behavior, diabetes, immune dysfunction, reproductive dysfunction, and cardiovascular disease.

Regarding the persistence of biological effects. Exposure to endocrine disruptors during development can result in profound changes in later life. Animal researchers recently discovered that EDCs can produce these latent effects by subtly altering the structure of the DNA molecules and chromosomes. These changes may affect gene expression for several generations.

NIEHS is also conducting human studies on the latent effect of EDC exposure including studies of children showing behavioral, mental, and physical abnormalities who were exposed to phthalates or flame retardants before birth.

Regarding ubiquitous exposure. The NTP is conducting a study of triclosan, an antimicrobial that is one of the most frequently detected water contaminants. Our understanding of the endocrine-disrupting chemicals has lead to new approaches for studying EDCs including research on whether mixtures of chemicals known to occur in drinking water impact development.

Other novel approaches are being developed to characterize the potential for environment agents to perturb endocrine function. NTP's high throughput screening initiative and Tox 21 partnership with EPA includes assays designed to assess activity of chemicals as hormonal targets. Initial results have shown that EPA and triclosan are among the most active of hundreds of chemicals tested so far. Such novel screening tests can be used for a basis for deciding whether to conduct more intensive animal studies.

To ensure that our science is shared with those who need it, we are partnering with the agencies that use our research, and we are sponsoring scientific forums for sharing this information with affected communities and stakeholders. For example, our breast cancer and environmental research program distributes fact sheets for clinicians and the public on likely sources of EDC exposures.

In conclusion, I believe this area of environmental health sciences to be of utmost importance. Our endocrine systems keep our bodies in balance, maintaining homeostasis and guiding proper growth and development. With NIEHS's leadership, we are all learning more about how these finely-tuned systems are sensitive to unanticipated effects from chemical exposure.

This information is critically important for creating effective strategies to ensure safe drinking water and the health of the American public. I welcome your questions.

[The prepared statement of Dr. Birnbaum follows:]

Testimony
Before the Subcommittee on
Energy and Environment
Committee on Energy and Commerce
United States House of Representatives

Statement for hearing entitled, "Endocrine Disrupting Chemicals in Drinking Water: Risks to Human Health and the Environment"

Statement of
Linda Birnbaum, Ph.D., D.A.B.T., A.T.S.
Director, National Institute of Environmental Health Sciences, National Institutes of Health, and Director, National Toxicology Program
U.S. Department of Health and Human Services

For Release on Delivery
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Mr. Chairman and distinguished members of the Subcommittee—I am pleased to appear before you today to present testimony on current understanding and ongoing research on endocrine disrupting chemicals (EDCs). I am Linda Birnbaum, the Director of the National Institute of Environmental Health Sciences (NIEHS), part of the National Institutes of Health (NIH), as well as of the National Toxicology Program (NTP). NIH and NTP are entities of the U.S. Department of Health and Human Services.

Endocrine disruptors are naturally occurring or man-made substances that may mimic or interfere with the function of hormones in the body. Endocrine disruptors may turn on, shut off, or modify signals that hormones carry and thus affect the normal functions of tissues and organs. NIEHS has had a longstanding interest in these chemicals with its support for research dating back to the beginning of the Institute in the 1960s.

Over the past fifty years, researchers observed increases in endocrine-sensitive health outcomes. Breast and prostatic cancer incidence increased between 1969 and 1986[1]; there was a four-fold increase in ectopic pregnancies (development of the fertilized egg outside of the uterus) in the U.S. between 1970 and 1987[2]; the incidence of cryptorchidism (undescended testicles) doubled in the U.K. between 1960 and the mid 1980s[3]; and there was an approximately 42% decrease in sperm count worldwide between 1940 and 1990[4].

These observations, set against the numerous observations of abnormalities of sexual development in amphibians and fish[5] and the widespread detection of chemicals with endocrine disrupting properties in our bodies[6], have led NIEHS to increase its support for research on the effects of chemical exposures on the various endocrine systems. The detection of numerous pharmaceutical agents and chemicals with endocrine disrupting potential in surface waters around the country[7] has raised concern about drinking water as a significant route of exposure.

There are four aspects of exposure to endocrine disruption which I want to emphasize:

- First, the effect of low doses. Normal endocrine signaling involves very small changes in hormone levels, yet these changes can have significant biological effects. That means subtle disruptions of endocrine signaling is a plausible mechanism by which chemical exposures at low doses can have effects on the body.

- Second, the wide range of effects. Endocrine signals govern virtually every organ and process in the body. That means that when outside chemicals interfere with those systems,

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[1] Hoel DG et al. J Natl Cancer Inst 84:313-320(1992)
[2] Nederlof KP et al. MMWR 39:9-17 (1990)
[3] Group JRHCS. Br Med J 293:1401-1404(1986)
[4] Carlsen E et al. Br Med J 305:609-613(1992)
[5] e.g., Reeder et al., Environ Health Perspect 113(3) 261-265 (2005); Gross-Sorokin et al., Environ Health Perspect 114 (S-1):147-151 (2006)
[6] CDC, Fourth National Report on Human Exposure to Environmental Chemicals (2009), http://www.cdc.gov/exposurereport/
[7] USGS, Pharmaceuticals, Hormones, and Other Organic Wastewater Contaminants in U.S. Streams (2002); http://toxics.usgs.gov/pubs/FS-027-02/

the effects can be seen in many different diseases and conditions – some of which we are just learning to recognize as the result of endocrine disruption.

- Third, the persistence of effects. We are finding that the effects of exposure to endocrine disruptors can be observed long after the actual exposure has ceased. This is especially true for growth and development, processes that are very sensitive to endocrine regulation. The question of how these kinds of latent effects occur is an active area of investigation.

- Fourth, the ubiquity of exposure. Both naturally occurring and manmade substances can be endocrine disruptors. Some, e.g., arsenic and agricultural chemicals, are ubiquitous in the environment. In addition to the growing use of hormonally-active pharmaceuticals that pass through the bodies of those taking them and end up in water treatment systems and surface waters, many of the chemicals that are being found to have endocrine effects are components of a wide range of consumer products, including some water bottles, cosmetics, sunscreens, and other personal care products. Substances applied to the skin can be directly absorbed but also end up getting washed off our bodies and into our water systems. As a result, chemicals with endocrine disrupting activity are widely dispersed in our environment, often at levels plausibly associated with biological effects; exposure to humans is widespread.

Looking at these four points together, it is apparent that endocrine disruption is an important emerging public health concern. NIEHS is responding to the importance of this concern through our research investments, and we are starting to understand these health risks better, but there are still many gaps in our understanding. We are therefore gathering more information to help assess and manage EDCs appropriately.
Here are some examples to illustrate the first three of the take-home messages about endocrine disruption that I listed above. As for the fourth, I would point you to the Centers for Disease Control and Prevention's National Exposure Report[8] for evidence of the widespread exposure to these chemicals.

Regarding low dose: Early studies of EDCs in sensitive animal models established examples in which no threshold dose could be detected; that is, effects were already apparent at the lowest doses tested.[9] Moreover, there are some endocrine disrupting chemicals whose effects can be seen at low doses but not at high doses, in opposition to the usual dose-response curve familiar to toxicologists, which shows continually increasing responses with increases in dose. A 2007 NIEHS-sponsored review of studies of *in vivo* effects of Bisphenol A (BPA), for example, identified evidence for effects of low dose exposure during development on subsequent brain structure, function and behavior in rats and mice.[10]

An NIEHS-funded group at the Dartmouth College Superfund Research Program discovered that arsenic can act as a potent endocrine disruptor. They have shown that arsenic profoundly affects the function of five steroid hormone receptors (the receptors for glucocorticoid, androgen, progesterone, mineralocorticoid, and estrogen hormones) as well as the function of related

[8] See http://www.cdc.gov/exposurereport/pdf/FourthReport.pdf for most recent version of the report.
[9] Sheehan DM et al., Environ Health Perspect 1999 Feb;107(2):155-9
[10] Richter CA et al., Reprod Toxicol 24 (2007) pp. 199-224

nuclear receptors for thyroid hormone and retinoic acid.[11] These effects were observed at levels of 0.01 to 2.0 micromolars in cell culture and at or below 10 ppb in several animal models. They have also shown that arsenic has a significant effect on the ability of an activated hormone receptor to regulate gene expression, and that low level drinking water arsenic has strong, tissue-specific effects on expression of genes and proteins involved in the innate immune response in mouse lung.[12] They found that mice that were exposed to 100 ppb arsenic in drinking water had a significantly compromised response to H1N1 influenza infection.[13]

Regarding the broad range of effects: As our understanding of mechanisms has grown, so has our recognition of the many ways these compounds interact with the body and the many health outcomes that are influenced. The early work on endocrine disruption started out focusing mostly on outcomes that were known to be sensitive to the effects of steroid hormones, such as cancers of the reproductive system, and on mechanisms that involved hormonal receptors located in the cells' nuclei. However, in addition to working through normal nuclear hormone receptors such as estrogen, androgen, thyroid, and retinoid receptors, we find that these molecules interact with many other kinds of receptors, such as membrane (non-nuclear) receptors, neurotransmitter receptors, enzymatic pathways involved in steroid biosynthesis and metabolism, and all the other mechanisms that enable hormone systems to do the work they need to do, which in turn enables the organism to function normally and react to changes. So the universe of potential health effects has grown commensurately to include non-reproductive cancers, immune effects, metabolic effects, and brain development and behavior, in addition to non-cancer abnormalities of the reproductive system, such as reproductive tract abnormalities, precocious puberty, disorders of fertility and fecundity, and endometriosis.[14] For example, endocrine control of glucose homeostasis can impact development of diabetes, obesity, and cardiovascular disease. Researchers have now identified model systems and mechanisms by which developmental exposure to EDCs such as tributyltin [15], genistein and diethylstilbestrol[16] may potentially cause weight gain in animals later in life. NIEHS-funded researchers are working on understanding biochemical and physiological aspects of environmental contributions to obesity, and we expect this work to have an impact on the development of interventions and preventive strategies to deal with this huge public health issue.

There are concerns about multiple possible health effects of BPA exposure. BPA is a selective endocrine modulator with widespread human exposure. The Department's Food and Drug Administration (FDA) recently announced that it has some concern about the potential effects of BPA, partly based on the conclusions of the NTP-CERHR Monograph on Potential Human Reproductive and Developmental Effects of Bisphenol A (see summary[17]), which in turn built on the earlier consensus statement report from the expert panel workshop convened by the NIEHS[18]. While much of the exposure to BPA in humans occurs through the diet, other sources of

[11] Davey JC et al. Environ Health Perspect (2008)116:165-172.
[12] Kozul CD et al. Environ Health Perspect (2009)117(7):1108-15.
[13] Kozul CD et al. Environ Health Perspect (2009)117:1441-1447.
[14] Diamanti-Kandarakis et al., Endocrine Reviews (2009) June;30(4):293-342
[15] Grun F, Blumberg B. Endocrinology (2006) 147:S50-S55
[16] Newbold RR et al. Mol Cell Endocrinol (2009) May 25;304(1-2):84-89
[17] http://www.niehs.nih.gov/news/media/questions/sya-bpa.cfm
[18] vom Saal et al. Reprod Toxicol (2007)24:131-138

exposure include air, dust, and water. NIEHS invested approximately $20M in FY2009 to study health effects of BPA exposure, including $10.7M from ARRA funding. We have developed a program to assess differences in routes of exposure and metabolism across species, as well as the replication and expansion of experiments that linked BPA exposure to disease endpoints such as cancers, ADHD, obesity/diabetes/metabolic syndrome, immune dysfunction, reproductive diseases and dyfunctions, and cardiovascular disease. In addition, an NTP study is being conducted with FDA measuring the effects of long term exposures to a wide dose range of BPA in rats.

Regarding persistence of biological effects: Because of the existence of special windows of susceptibility in developmental processes, we know that exposure to EDCs at very sensitive stages of development can result in profound changes in physiology and function that may not emerge clinically until much later in life.[19] The exposure itself may cease, but the developmental impact and the subsequent adverse effect have already been set in motion. NIEHS leads the cross-NIH effort to understand how exposure-related changes in an individual's epigenetic status in one stage of their life can affect the health of the individual in later stages of their lifespan. Epigenetics is one recently discovered mechanism by which EDCs can produce these latent effects by altering the three dimensional structure of the chromosomes. The addition of methyl groups to DNA and changes to the histone proteins in chromosomes alter gene expression, leading to effects that can persist not just through one lifetime, but potentially for generations.

These delayed effects are the subject of a number of human studies funded by NIEHS. A group of researchers at Mt. Sinai School of Medicine recently reported that adverse behaviors of children aged 4-9 years (conduct or ADHD disorders) were associated with prenatal exposure to low molecular weight phthalates.[20] Other scientists at Columbia University's Center for Children's Environmental Health (co-funded by NIEHS and the Environmental Protection Agency (EPA)) examined cord blood exposure to polybrominated diphenyl ethers (PBDEs), which are ubiquitous flame retardants, and associations with neurodevelopment at ages 1-4 and 6 years. Children with higher concentrations of specific PBDEs while *in utero* scored lower on tests of mental and physical development.[21] Previous data linking these compounds to altered thyroid hormones and thyroid function might provide a plausible mechanism for these effects.

The NIEHS Breast Cancer and Environment Research Program (co-funded with the NIH's National Cancer Institute) is investigating whether periods of susceptibility exist in the development of the mammary gland, when exposures to environmental agents may impact the breast and endocrine systems that can influence breast cancer risk in adulthood. It is examining the determinants of puberty in girls, integrating environmental, genetic, biologic, lifestyle, and socioeconomic factors, in recognition of the epidemiology linking breast cancer risk to pubertal maturation. A major area of study is the role of exposures to EDCs. Center scientists have measured 51 environmental agents and their metabolites in biospecimens from approximately

[19] Diamanti-Kandarakis et alia, Endocrine Reviews (2009) June;30(4):293-342
[20] Engel SM et al. Environ Health Perspect 2010 Jan 8 [Epub ahead of print]
[21] Herbstman JB et al. Environ Health Perspect 2010 Jan 4 [Epub ahead of print]

1,190 girls. The data include the first report in children of high levels of a number of hormonally active chemicals such as enterolactone, benzophenone-3, and monoethyl-phthalate.[22]

A separate follow-up study is now in progress in response to observations of high perfluoroalkyl compound (PFC) levels measured in a geographically distinct subset of the Breast Cancer and the Environment Research Center cohort.[23] PFCs such as perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) are of concern because of their presence in air, food, drinking water and human tissues, their persistence and long half-life, and their adverse effects on development in animal models. NIEHS is supporting numerous studies on these compounds. One of our intramural investigators is following up previous observations of an association between PFOS and PFOA and increased time-to-pregnancy (a measure of decreased fecundability).[24] At the request of the EPA, the NTP initiated a large research program on this class of compounds that includes PFOS, PFOA and shorter and longer chain perfluoroalkyl compounds.[25] These studies include an evaluation of multiple aspects of post-natal development following exposure *in utero* and will provide a sound basis for assessing cumulative human health risks for these ubiquitous contaminants.

New science to promote new understanding: Given our growing understanding of the myriad of cellular hormonal targets of EDCs, new approaches have to be developed in order to characterize the potential for environmental agents to perturb endocrine function. NTP's high throughput screening initiative (HTS) and Tox21 partnership, in collaboration with EPA and the NIH Chemical Genomics Center,[26] include multiple assays designed to assess activity of chemicals at hormonal targets. Initial results have shown that among the most active of hundreds of chemicals tested so far in these assay systems is BPA. Triclosan, an antimicrobial in hand soaps, toothpaste, cosmetics, and many other products, and one of the most frequently detected water contaminants, also exhibits endocrine activity in these tests and is one of the most active compounds across multiple assays.[27]

By linking pre-existing and newly developed information on toxicological activity in whole animal studies of compounds registering as positive in these endocrine-relevant assays, we are able to explore the *in vivo* significance of signals picked up in HTS. As we move forward and develop and include additional assays for endocrine activity, HTS will help us decide which chemicals need further investigation.

The NTP is employing *in vitro* and short term animal models to detect perturbations in endocrine function that can be used as a basis for deciding whether to conduct more rigorous long-term studies. Short term models are also being used to address questions of cumulative risk, that is, whether exposure to mixtures of similar compounds causes additive or synergistic (whole greater than the sum of the parts) effects. For example, through a collaborative arrangement with EPA's

[22] Wolff MS et al. Environ Health Perspect 2007, 115(1):116-121
[23] R21ES017176 PI: Susan Pinney, Univ of Cincinnati. Exposure biomarkers of polyfluoroalkyl compounds in persons living in the Ohio River valley.
[24] PI: Matthew Longnecker, NIEHS. Perfluorinated alkyls and fecundability.
[25] http://ntp.niehs.nih.gov/files/PFOAConcept.pdf
[26] http://ntp.niehs.nih.gov/go/28213
[27] http://www.epa.gov/ncct/practice_community/category_priority.html

Office of Research and Development, the NTP is conducting studies to evaluate effects on male reproductive endpoints for many combinations of phthalates to allow more precise comparisons of potency and a better understanding of cumulative risk for this class of compounds found in many plastics.

The NTP is also planning new research relevant specifically to EDCs in drinking water. One set of studies will investigate the potential for mixtures of chemicals known to occur in drinking water to impact pre- and early post-natal development. These studies will focus on structurally dissimilar drugs and other industrial chemicals that perturb a common biological pathway, e.g. cholesterol and lipid metabolism.

New information on endocrine activity has led the NTP to develop toxicological research programs on additional compounds such as bisphenol AF,[28] used to make certain industrial polymers; butylparaben,[29] a preservative used in cosmetics; oxybenzone,[30] a sunscreen ingredient; and triclosan.[31] The relevance of cosmetics, sunscreens and other personal care products to drinking water exposures has previously been highlighted. Endocrine activity is also of potential concern for herbal products taken as dietary supplements. NTP research programs on several of these, such as gum guggul, Dong quai, and valerian, includes evaluations of hormonal activity.

In addition to generating new knowledge, we also need to make sure our science is shared with those who need to use it. This includes other Federal, state and local agencies as well as communities and individuals. Many of our research efforts are done in partnership with the agencies who will be the consumers of the research. We have also supported some excellent scientific forums for sharing this information with government and non-government scientists. For example, the NIEHS/NTP, along with other NIH components, FDA, CDC, the Agency for Toxic Substances and Disease Registry, EPA, the Society of Toxicology, the World Health Organization, and the European Environment Agency, recently sponsored a workshop on prenatal programming and toxicology entitled, "PPTOXII: Role of environmental stressors in the developmental origins of disease." The meeting, attended by 280 scientists, focused on the developmental origins of disease with the goal of stimulating collaborations in the area of effects of endocrine disrupting chemicals on developmental toxicity. We are also mindful of the need to keep dialog open with affected communities. In our Breast Cancer and Environmental Research Program, researchers have created public messages to convey information about endocrine disrupting chemicals and their potential role in the prevention and understanding of breast cancer, including fact sheets for clinicians and the public on likely sources of exposures.

In conclusion, let me stress that I believe this area of environmental health sciences to be of the utmost importance. Our endocrine systems keep our bodies in balance, maintaining homeostasis and guiding proper growth and development. With NIEHS's leadership, we are learning more and more about how these finely tuned systems are sensitive to unanticipated effects from

[28] http://ntp.niehs.nih.gov/index.cfm?objectid=F609B028-F1F6-975E-715EE7E97E4CCB16
[29] http://ntp.niehs.nih.gov/files/ButylparabenConcept.pdf
[30] http://ntp.niehs.nih.gov/index.cfm?objectid=072CEB9A-A49B-F6AA-91E25964528B914A
[31] http://ntp.niehs.nih.gov/index.cfm?objectid=F610E7F7-F1F6-975E-76E92BC0B5CC47B3

chemical exposures. This information is critically important for creating effective strategies to prevent disease and promote better health, as well as to ensure safe drinking water.

Thank you for the opportunity to present information on this important topic. I would be happy to answer your questions.

Mr. MARKEY. Thank you, Dr. Birnbaum, very much. Our next witness, James Jones, who is Deputy Assistant Administrator of the Office of Prevention, Pesticides and Toxic Substances at the Environmental Protection Agency. He is responsible for managing the daily operation of the office which oversees the Nation's pesticide, toxic chemical, and pollution prevention laws. He previously served as the director of the agency's office of pesticide programs. We welcome you, sir.

STATEMENT OF JAMES JONES

Mr. JONES. Good morning, Mr. Chairman.

Mr. MARKEY. Move that microphone in a little bit closer please.

Mr. JONES. Good morning, Mr. Chairman and members of the subcommittee. I am Jim Jones, the deputy assistant administrator of EPA's Office of Prevention of Pesticides and Toxic Substances. I appreciate the opportunity to appear before the subcommittee to provide an update on EPA's endocrine-disruptor screening program and plans for its future implementation.

The implementation of the EDSP is part of one of Administrator Jackson's top priorities. To make significant and long-overdue progress in assuring the safety of chemicals. Issuing test orders for the generation of data to better understand potential endocrine effects is an important step in improving our ability to protect the public health and the environment from chemicals.

The Food Quality Protection Act of 1996 required EPA to develop and implement a program to screen all pesticides for any effect in human that is similar to effects produced by naturally-occurring estrogen and such other endocrine effects as EPA may designate.

Upon the recommendations of our advisory committee, the EDSP was expanded to include the assessment of androgen and thyroid hormone systems and effects on wildlife. The EDSP is a two-tiered screening program. Tier one is composed of a battery of 11 invitro and short-term invivo assays to identify chemicals that have the potential to interact with estrogen, androgen and thyroid systems. Chemicals that are positive in tier one would be subject to the tier two testing requirements.

The purpose of the tier two test is to provide information that can be used as a risk assessment such as identification and characterization of adverse effects resulting from the interaction of the chemicals with the hormone system and exposure levels required to produce them in assays involving developmental life stages in whole animals.

The validation of the tier one assays took far longer than anyone in EPA anticipated. Because of the many complexities of methods developed in the validation for such a large number of assays, validation of tier one assays took 10 years and is still ongoing for tier two assays. Validation of the tier two assays will be complete in 2012.

The good news is that the EPA has begun to issue test orders. The first list of chemicals for testing consists of 67 chemicals, 58 pesticide active ingredient and 9 inert ingredients that are also high-production volume chemicals.

EPA began issuing its first EDSP test orders in October of 2009, and it will issue the last test orders for list one chemicals this

week. A total of 750 plus test orders will have been sent to manufacturers of these 67 chemicals. EPA has created a database of the initial pesticides chemicals to be screened in the EDSP and has made this information available on EPA's Web site.

In addition to the EPA provisions that require the screening of all pesticide chemicals, the Safe Drinking Water Act amendments of 1996 provide EPA with the authority to test substances that may be found in sources of drinking water, to which a substantial population may be exposed. Right now, EPA is preparing a second list of no less than 100 chemicals, a draft of which will be released in the near term.

The list two chemicals will be drawn from three sources: national primary drinking water regulations, the Contaminant Candidate List, CCL 3, and pesticides that are on the registration review schedule in the near term. The CCL 3 list is a list of contaminants that are currently not subject to any proposed or promulgated national primary drinking water regulations that are known or anticipated to occur in public water systems, and which may require regulation under the Safe Drinking Water Act. The CCL 3 list includes pesticides, other chemicals used in commerce, and disinfection byproducts and degredates.

In summary, EPA is on track to obtain tier one endocrine screening data on several hundred chemicals within the next several years. Although it has taken a long time to develop the tests necessary for this program, we have begun to meaningfully implement the EDSP and allow to expand the universe of chemicals for testing beyond pesticides to include drinking water contaminants.

Thank you for your continued interest in this program, and I would be happy to answer any questions.

[The prepared statement of Mr. Jones follows:]

TESTIMONY OF
JAMES J. JONES
Deputy Assistant Administrator
Office of Prevention, Pesticides and Toxic Substances
U.S. Environmental Protection Agency
Before the
Subcommittee on Energy and the Environment
Committee on Energy and Commerce
U.S. House of Representatives

February 25, 2010

Introduction

Good morning Mr. Chairman, Ranking Member Upton and members of the Subcommittee. I am Jim Jones, the Deputy Assistant Administrator of the Environmental Protection Agency's (EPA) Office of Prevention, Pesticides, and Toxic Substances. I appreciate the opportunity to appear before the Subcommittee to provide an update on EPA's Endocrine Disruptor Screening Program (EDSP) and plans for its future implementation.

Background

The implementation of the EDSP is part of one of Administrator Jackson's top priorities--to make significant and long overdue progress in assuring the safety of chemicals in our products, our environment and our bodies. Issuing test orders for the generation of data to better understand potential endocrine effects is an important step in improving our ability to protect the public health and the environment from chemicals.

The Food Quality Protection Act of 1996 (FQPA) required EPA to develop and implement a program to screen all pesticides for any "effect in humans that is similar to an effect produced by a naturally occurring estrogen and such other endocrine effect" as EPA may designate. Because endocrine disruption was on the cutting edge of science, shortly after the Act was passed, EPA formed the Endocrine Disruptor Screening and Testing Advisory Committee, composed of scientists from government, stakeholder organizations and academia, and charged it with providing advice on how to design a screening program for endocrine disrupting chemicals. Considering EDSTAC's diverse membership and expertise, EPA found its consensus compelling and scientifically rigorous. Therefore, EPA relied heavily on EDSTAC's advice and recommendations in developing the EDSP.

Developing the Program

Upon the recommendations from EDSTAC, the EDSP was expanded to include assessment of the androgen and thyroid hormone systems and effects on wildlife. EDSTAC also recommended a two tier screening program. Tier 1 is composed of a battery of *in vitro* and short-term *in vivo* assays to identify chemicals that have the potential to interact with the estrogen, androgen or thyroid systems. Although EPA is still refining the process for evaluating Tier 1 results, chemicals that are positive in Tier 1 for potential endocrine effects would be subject to the Tier 2 testing requirements. The purpose of the Tier 2 tests is to confirm chemical interactions observed in Tier 1 screens, and provide information that can be used in risk assessment such as identification and characterization of adverse effects resulting from the interaction of the chemicals with the hormone system and the exposure levels required to produce them in assays involving developmental life-stages in whole animals. EDSTAC recommended a number of assays for EPA's consideration as potential Tier 1 screens and Tier 2 tests for detecting and characterizing endocrine disrupting chemicals.

Validation of Tier 1 Protocols

The FQPA requires the use of validated tests. The purpose of validation is to ensure that the tests are based on solid science and requires that the relevance and reliability of the assay be demonstrated, that is, that it truly measures what it is supposed to measure and that it does so consistently within and across laboratories. Validation of the assays comprising Tiers 1 and 2 was by far the biggest challenge facing EPA. In fact, Tier 2 assay validation is still in progress. As recognized by EDSTAC, no assays were validated to detect or characterize endocrine disruptors when EPA began this task. From 2001 through 2006, EPA consulted with stakeholders and scientific experts through a series of advisory committees regarding the validation of Tier 1 assays. EPA is continuing to involve stakeholders by working through the Organization for Economic Cooperation Development (OECD) validation management workgroups.

The validation of the Tier 1 assays took far longer than anyone at EPA anticipated. The validation process commenced with test method development. Many of these methods were developed or refined within EPA's own laboratories. Once the test protocols were developed and optimized, their reliability and relevance had to be demonstrated in studies conducted in parallel in multiple laboratories outside of EPA. Through most of this process, EPA solicited stakeholders' and the public's views through the advisory committee process. This process has been used in the development and validation of 19 different Tier 1 and Tier 2 assays. Because of the many complexities of methods development and validation for such a large number of assays, validation of Tier 1 assays took 10 years and is still ongoing for Tier 2 assays. Most of the testing in outside laboratories was performed under EPA's contracts and many assays were validated in conjunction with the Organization for Economic Cooperation

and Development to produce internationally harmonized test guidelines. Working with OECD has saved the Agency resources as it leveraged the efforts of other countries, and it promises to reduce testing costs since the data generated under the OECD test guidelines will be accepted by all member countries, reducing the likelihood that tests will be repeated to meet the differing regulatory needs of each member country. After the laboratory work and analysis was completed and approved by EPA, the entire body of work supporting validation of each assay was summarized and submitted to a panel of independent scientific experts for peer review. EPA chose the eleven assays for the Tier 1 battery based upon their performance in validation and their ability to complement one another. EPA's recommendations for the Tier 1 battery were reviewed by the FIFRA Scientific Advisory Panel in March 2008. Validation of the Tier 2 tests, including peer review, should be completed in 2012.

Priority Setting and Development of Policies and Procedures

There were two other key activities needed for implementation of the EDSP: the development of a process for selecting chemicals followed by the actual selection of chemicals for the first list, and the development of policies and procedures for issuing test orders to pesticide registrants and chemical manufacturers. The first list of chemicals was selected solely on the basis of exposure because other methods for incorporating endocrine-relevant toxicity information were not yet ready for use. The first list consists of 67 chemicals—58 pesticide active ingredients and 9 inert ingredients that also are high production volume chemicals.

The Agency's policies and procedures instruct how the Agency will issue test orders and the obligations of test order recipients to respond. The Agency is allowing test order recipients 90 days (150 days if they group together to form a consortium) to cite or provide existing data or inform the Agency that they will conduct Tier 1 testing. Test order recipients have up to 24 months from the date of the orders to submit required Tier 1 test data.

Recent Accomplishments

EPA began issuing its first EDSP test orders in October 2009. It will issue the last test orders for List 1 chemicals this month. The test orders are not tailored for specific chemicals and will require the full battery of Tier 1 assays. However, test order recipients can either cite or provide existing data that they believe meet some or all of the requirements of the test order. The Agency is now receiving and evaluating the first of the responses to the test orders and will communicate its determination to recipients. Test orders, responses to test orders, and EPA's final determination of the required testing are being tracked on the EDSP website. Test order recipients have two years from the receipt of the test order to conduct required studies and submit the results to the EPA. The Agency will review the data on each chemical. When test data from all 67 chemicals have been

reviewed, EPA will conduct a scientific evaluation of the screening data and determine whether revisions to the battery should be made.

Creation of a Database

EPA has created a database of the initial pesticide chemicals to be screened in the EDSP and made this information available on EPA's website. The database includes the date a test order is issued and to whom; the due date for completing and submitting the data; the recipient's response to the order, including requests for extensions, if any; and a summary of the results of Tier 1 screening or Tier 2 testing for each chemical listed.

List 2 and Substances in Drinking Water

In addition to the FQPA provisions that require the screening of all pesticide chemicals, the Safe Drinking Water Act Amendments of 1996 (SDWA) provide EPA with the authority to test substances that may be found in sources of drinking water to which a substantial population may be exposed. As instructed by the House Appropriations Committee[1], EPA is preparing a second list of no less than 100 chemicals, a draft of which will be released shortly. The List 2 chemicals will be drawn from three sources: National Primary Drinking Water Regulations, the Contaminant Candidate List 3 (CCL 3), and pesticides that are on the reregistration schedule for 2007 through 2008. The CCL3 List is a list of contaminants that are currently not subject to any proposed or promulgated national primary drinking water regulations, that are known or anticipated to occur in public water systems, and which may require regulation under SDWA. The CCL3 list includes pesticides, other chemicals used in commerce, and disinfection byproducts and degredates.

ToxCast

Several years ago, EPA's Office of Research and Development began carrying out a large-scale experiment, called ToxCast™ , which is a part of the Tox 21 program, to test a high throughput screening *in vitro* approach to identify potential toxicity of chemicals. The aim of ToxCast is to more efficiently screen thousands of environmental contaminants using a battery of *in vitro* assays and to prioritize chemicals for further testing based on the biological activity associated with molecular pathways leading to toxicity. EPA is exploring the use of ToxCast, other computational tools, and other data to assist with choosing those chemicals for future lists that show potential to interact with the endocrine system. Fifty-seven of the chemicals on List 1 for EDSP screening have been put through the

[1] H. Rep. No. 180, 111th Cong., 1st Sess. 105 (2009), http://frwebgate.access.gpo.gov/cgi-bin/getdoc.cgi?dbname=111_cong_reports&docid=f:hr180.111.pdf#Page=105.

ToxCast battery of assays. Once those chemicals have been tested through the EDSP Tier 1 battery, results can be compared. So for now, while ToxCast, at its current state of development will initially be used to help select chemicals for future Tier 1 screening lists, it is envisioned that eventually it may be able to replace, at least, some Tier 1 assays. For the current set of test orders, EPA will review ToxCast data along with the claims the order recipients submit. Data generated from Tier 1 assays on the first and second lists of chemicals will play an important role in advancing our understanding of the endocrine disrupting potential of these chemicals, refining the predictions made by ToxCast, and moving us toward the point where some lower throughput assays that still rely on using laboratory animals and some whole animal assays may be replaced by higher throughput, shorter term laboratory results combined with predictive methods.

Closing

In summary, EPA is on track to obtain Tier 1 endocrine screening data on several hundred chemicals within the next several years. Although it has taken a long time to develop and implement the EDSP, we have developed and validated some useful tools and learned lessons that can be applied to other areas.

Thank you for your continued interest in the EDSP. I will be happy to answer any questions.

Mr. MARKEY. We thank you, Mr. Jones, very much. Our next witness is Dr. Gina Solomon, who is a senior scientist in the health and environmental program of the National Resources Defense Council, and is a specialist in adult internal medicine, preventative medicine, and occupational and environmental medicine. Dr. Solomon also serves as an associate clinical professor of medicine at the University of California at San Francisco where she is the director of the occupational and environmental medicine residency program and the associate director of the ECSF pediatric environmental health specialty unit. So we welcome you, Doctor. Whenever you are ready, please begin.

STATEMENT OF GINA SOLOMON

Dr. SOLOMON. Good morning, Mr. Chairman and members of the subcommittee. Thank you very much for the opportunity to testify today. You introduced me very well, but I also want to mention that I was on the EPA's endocrine disruptor screening and testing advisory committee from 1996 to 1998 and was therefore involved in the early stages of the EDSP program. I now serve on the EPA science advisory board drinking water committee, and as such, have been involved in reviewing EPA's efforts on drinking water contaminants.

Some years ago, I was invited to speak at the Riverside County Medical Association. It is in southern California in an area where a chemical called perchlorate had recently been detected in drinking water. The local physicians were concerned, and I went and gave them a talk about the health data at that time on perchlorate, including the fact that perchlorate was known to block uptake of iodine into the thyroid gland and thereby disrupt the thyroid's ability to create normal thyroid hormones.

And I also reviewed the science on how subtle disruption of thyroid function in fetal or early neonatal life can permanently alter normal brain development. Finally, I described the multiple sources of perchlorate pollution in clean water contamination from rocket fuel and fireworks manufacturing, and I closed by sharing some of the latest monitoring data, which showed that 402 public water systems serving 40.8 million people in 27 states, the District of Columbia, and two U.S. territories had perchlorate in their treated water or in their water sources, and California had the largest number of systems with perchlorate detections, over 180 at that time.

After my talk that day, an elderly physician in the audience stood up and explained that he had spent his entire career treating patients with thyroid disease in this community. And he said now we learn that something in the water supply may be contributing to this problem. What am I supposed to do about it? And more importantly, what am I supposed to tell my patients about it? He said should I tell them not to drink the water?

And he further went on to say that he wasn't a fan of big government, but in this case, he said, we need to get government involved to deal with this problem. And I agree with him because this is not something that health care providers and their patients can deal with alone. This is EPA's job.

Over 5 years have passed since the day when I spoke at that medical society, and although California and other states have taken some action on this known endocrine disruptor, EPA has still failed to act. Meanwhile, there are other chemicals that are known or suspected endocrine disruptors that have been turning up with increasing frequency in water. Studies by the U.S. geological surveys toxic substances hydrology program have revealed that an unsavory mixture of pharmaceuticals, steroid hormones, unregulated pesticides, flame retardants, rocket fuel chemicals, plasticizers, detergents, stain repellents in both surface water and ground water that we rely on for drinking.

For example, the USGS surface water study found a median of seven and as many as 38 chemical contaminants in any single water sample. And among the chemicals that were most commonly detected in this national survey were many known and suspected endocrine disruptors, some pesticides, triclosan, alkylphenols and alkylphenol polyethoxylates, bisphenol A, phthalates and steroid hormones. And unfortunately so far, the response to these water findings has tended a bit more toward killing the messenger rather than acting on the message. Over the most recent years, funding for the USGS water monitoring programs, already small, has been reduced, resulting in major cutbacks in water quality sampling and less data to inform science-based decisions.

Meanwhile, over a decade has passed since EPA has promulgated a single regulatory standard for a chemical contaminate in drinking water. Now there is a large and growing backlog of chemicals like perchlorate that still have no regulatory standard, and then there are others that were regulated over a decade ago whose standards are outdated and in need of revision. For example, one endocrine disruptor ethylate known as DEHP, which stands for dyethol hexophthalate, does have a maximal contaminate leveler in MCL in drinking water, but it is terribly outdated.

Now, these phthalates like DEHP are used in an enormous range of products such as cosmetics, personal care products, vinyl, medical devices, inks and adhesives, and they are also used as inert ingredients in pesticides and until last year, were in plastic toys.

National monitoring studies have reported phthalates in about 10 percent of surface water samples taken. And these chemicals cause lower testosterone levels, decreased sperm counts and lower sperm quality in animals, and exposure to phthalates during development can cause malformations of the male reproductive tract and testicular cancer. Preliminary studies in humans also show abnormalities in male reproductive development.

Mr. MARKEY. If you could sum up please.

Dr. SOLOMON. Sure. The MCL for DHP was set in July of 1992 and was based on gastrointestinal disturbances, nausea, and vertigo. It is not likely to protect against endocrine disrupting effects. Other chemicals like bisphenol A also have no MCLs at all.

So in summary, there are numerous steps that EPA should be taking to implement testing under the endocrine disruptor screening program for priority drinking water contaminants, implementing aspects of the endocrine disruptor screening and testing advisory committee report that have been ignored, and improving

wastewater and drinking water treatment. So thank you very much.

[The prepared statement of Dr. Solomon follows:]

TESTIMONY OF

GINA M. SOLOMON, M.D., M.P.H.
SENIOR SCIENTIST, NATURAL RESOURCES DEFENSE COUNCIL
ASSOCIATE CLINICAL PROFESSOR, U.C. SAN FRANCISCO
ASSOCIATE DIRECTOR, UCSF PEDIATRIC ENVIRONMENTAL
HEALTH SPECIALTY UNIT

ON BEHALF OF:
NATURAL RESOURCES DEFENSE COUNCIL

BEFORE THE U.S. CONGRESS
COMMITTEE ON ENERGY AND COMMERCE
SUBCOMMITTEE ON ENERGY AND THE ENVIRONMENT

AT HEARING ENTITLED:

ENDOCRINE DISRUPTING CHEMICALS IN DRINKING WATER: RISKS TO HUMAN HEALTH AND THE ENVIRONMENT

FEBRUARY 25, 2010

Thank you for the opportunity to submit testimony to this Committee. My name is Gina Solomon, and I am a Senior Scientist at the Natural Resources Defense Council (NRDC). NRDC is a not-for-profit environmental advocacy organization with over one million members and activists whose mission is to safeguard the Earth: its people, its plants and animals and the natural systems on which all life depends. In addition to my work at NRDC, I am an Associate Clinical Professor of Medicine at the University of California at San Francisco (UCSF) where I am the Director of the Occupational and Environmental Medicine Residency and Fellowship Program, and the Associate Director of the Pediatric Environmental Health Specialty Unit. I have subspecialty training and expertise in environmental medicine, and have done research, education, and advocacy for over 15 years to protect people from contaminants in their food, air and drinking water, and from hazardous pesticides.

I served on the U.S. Environmental Protection Agency (EPA) Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) from 1996-1998, the National Academy of Sciences Committee on Toxicity Testing and Assessment of Environmental Agents from 2004-2007, and the EPA Science Advisory Board Drinking Water Committee from 2004 through the present. My educational and professional credentials are supplied in the attached *Curriculum Vitae*.

Endocrine Disruptors in Water: A Widespread Problem

There are serious concerns about contaminants in our nation's drinking water and source waters. Fish have been found in numerous rivers, including the Potomac, with disrupted sexual development -- specifically feminized male fish. When this finding was first noted in England in the 1990's,[1] it was considered possibly a fluke. But what was once a localized, spotty observation is now being recognized as a widespread, pervasive phenomenon. Four months ago, scientists from the U.S. Geological Survey reported finding intersex fish in one third of sites surveyed in eight river basins (the Apalachicola, Colorado, Columbia, Mobile, Mississippi, Pee Dee, Rio Grande, and Savannah river basins).[2] The problems were most severe in the Southeastern United States (see Appendix 1 for a map of locations where intersex fish were found).

The same kind of thing happened with deformed frogs: local observations in the Midwest led to the eventual realization that these amphibian abnormalities are widespread. A recent review by researchers at Yale University concluded that the mystery of these deformities remains unsolved.[3] Even the alligators in Florida's Lake Apopka with the famously tiny penises are not alone: research in other Florida lakes has revealed that the male deformities just keep turning up.[4] Essentially, wherever researchers look, they are finding problems with sexual development in wildlife. Now the question is: what does this mean for humans? Some scientists are concerned that increased incidence of cancer of the testis, prostate, and breast, along with increases in birth defects of the penis, might mean that humans are not immune to the problems in our environment.

Scientists have come up with a term to describe this general phenomenon: endocrine disruption. An endocrine disruptor is defined as "an exogenous agent or mixture of agents

that interferes or alters the synthesis, secretion, transport, metabolism, binding action, or elimination of hormones that are present in the body and are responsible for homeostasis, growth, neurological signaling, reproduction and developmental processes."[5] In other words, endocrine disruptors are chemicals that interfere with the body's key signaling pathways, and they can cause harm, especially during fetal and early life development.

Multiple contaminants are turning up in our nation's waterways, including in water millions of people rely on for drinking. Studies by the U.S. Geological Survey (USGS) have revealed an unsavory mix of pharmaceuticals, steroid hormones, unregulated pesticides, flame retardants, rocket fuel chemicals, plasticizers, detergents, and stain repellants in both the surface water and the groundwater we rely on for drinking, and in our drinking water itself.[6] [7] [8] The USGS surface water study found a median of seven and as many as 38 chemical contaminants in any given water sample (see Appendix 2 for more details). Among the chemicals most commonly detected in this national survey are known and suspected endocrine disruptors, including triclosan, alkylphenols and alkylphenol polyethoxylates, bisphenol A, and estriol. As a scientist, I wish I could tell you these chemicals are unlikely to be a problem at the concentrations measured. Unfortunately I can't tell you that, because my assessment of the data suggests a problem.

Here's what I can tell you: wildlife populations are showing signs of harm, many of these chemicals are not eliminated by conventional drinking water treatment, and mixtures of these chemicals are present in our water supply. Although they are at low levels in water, hormones are known to have effects even in trace amounts. Furthermore, biomonitoring studies have detected these chemicals in our bodies.[9] Water is certainly not the only source of these chemicals, but trace amounts from one source add up with traces from other sources, and the sum total becomes a problem. The Endocrine Society evaluated the science on endocrine disruptors last year and concluded:

> *The evidence for adverse reproductive outcomes (infertility, cancers, malformations) from exposure to endocrine disrupting chemicals is strong, and there is mounting evidence for effects on other endocrine systems, including thyroid, neuroendocrine, obesity and metabolism, and insulin and glucose homeostasis.*[10]

The Endocrine Society is the premier professional organization devoted to research on hormones and the clinical practice of endocrinology, comprised of over 14,000 research scientists and physicians from over 100 countries. This statement has since been endorsed by the American Medical Association. The American Chemical Society just issued a similar statement with additional recommendations for: "More rapid advancement of the congressionally-mandated effort by the EPA, called the Endocrine Disruptor Screening Program (EDSP)."[11]

There are two opportunities for action on this issue: First, many chemicals have never been adequately tested for their toxicity, and especially not for their endocrine effects; EPA's Endocrine Disruptor Screening Program which was supposed to accomplish this goal has yet to live up to its promise; Second, some of the chemicals in our water supply

are known endocrine disruptors and can alter hormone function and disrupt development even when they are in very dilute concentrations, yet EPA has not yet taken action to appropriately regulate these hazards.

EPA's Endocrine Disruptor Screening Program (EDSP): A Missed Opportunity

In 1996, EPA created the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) in response to a Congressional mandate in the Food Quality Protection Act and authorization in the Safe Drinking Water Act Amendments of 1996. These laws specified that EPA:

> *develop a screening program, using appropriate validated test systems and other scientifically relevant information, to determine whether certain substances may have an effect in humans that is similar to an effect produced by a naturally occurring estrogen, or other such endocrine effect as the Administrator may designate.*

The laws required EPA to develop a screening program by August 1998, to implement the program by August 1999, and to report on the program's progress by August 2000. Unfortunately, EPA is now about a decade behind.

EDSTAC was composed of representatives from industry, government, environmental and public health groups, and academia. The committee members were charged with developing consensus-based recommendations for a screening program that would provide EPA the necessary information to make regulatory decisions about the endocrine effects of chemicals.

I served on the EDSTAC, and it was an intense experience. The Committee struggled under time pressure, and delivered a final report by the statutory deadline of August 1998.[12] Over a period of 20 months, the committee fashioned a groundbreaking priority setting, screening and testing approach that encompasses the universe of chemicals in use today, evaluates a range of human health and ecological effects, and recommends a feasible, health-protective, approach:

- The committee recognized that problems with endocrine disruption go beyond estrogen, and called for screening of chemicals for interference with male androgens, and with thyroid hormone.
- The EDSTAC recommended the use of new technology to rapidly pre-screen numerous chemicals to see if they interact with hormone receptors *in vitro* (in the "test-tube"). The committee recommended that this technology be used to rapidly evaluate the ten thousand most widely-used chemicals within one year.
- Another new approach was a computer-based tracking system allowing information about health effects and exposure to be collected in one place to facilitate prioritization. Some people would be stunned that such a database didn't exist then, and still doesn't exist to this day.

- Finally, the committee urged EPA to accept nominations from the public of chemicals or *chemical mixtures* for expedited testing. This would allow workers, or impacted communities to press for more information about chemicals to which they are exposed.

Unfortunately, the vision of the EDSTAC was never realized. EPA missed deadline after deadline and became bogged down in an endless "do loop" of validation. It is discouraging to report that EPA scrapped the rapid "high-throughput pre-screen", has still failed to validate the definitive "tier 2" tests, and has never created the Endocrine Disruptor Priority Setting Database. The nominations process was also discarded, as was the Committee's unanimous recommendation to test six priority chemical mixtures (Table 1). EPA finally implemented the program, over a decade late, when it issued the first test orders on October 29, 2009; only 67 chemicals are on the list for this first round of screening – mostly pesticides, including a number of chemicals that are already well-known endocrine disruptors.[13] What a wasted opportunity. Meanwhile tens of thousands of chemicals in daily use, in consumer products and even in foods, have not been tested, and contaminants continue to build up in our water supply.

Table 1: EDSTAC Priority Chemical Mixtures

a) Contaminants in human breast milk
b) Phytoestrogens in soy-based infant formulas
c) Mixtures of chemicals most commonly found at hazardous waste sites
d) Common pesticide/fertilizer mixtures found in surface water
e) Disinfection byproducts commonly found in drinking water
f) Gasoline

Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC) Final Report. pp. 4-49 – 4-51

Section 136 of the SDWA Amendments states that:

> *in addition to the substances referred to in (FQPA), the Administrator may provide for testing under the screening program authorized by (FQPA) for any other substance that may be found in sources of drinking water if the Administrator determines that a substantial population may be exposed to such substance.*

Unfortunately EPA has not yet used the authority granted by Congress under the SDWA, and has not prioritized drinking water contaminants for testing.

The result of the decade of foot-dragging on testing chemicals for hormonal activity means that the vast majority of chemicals in our water supply and environment are "unknowns" when it comes to their hormonal effects. Due to the well-known flaws in the Toxic Substances Control Act (TSCA), almost all chemicals come onto the market with no toxicity information, and older chemicals remain untested too. The EPA Office of the Inspector General's report, released just last week outlines these problems clearly.[14] As a scientist, this absence of data appalls me. As a physician, it puts me in a position where I cannot counsel many of my patients because I don't have the data I need.

Known Endocrine Disruptors in Drinking Water: Regulatory Action Needed Now

Not all chemicals are of unknown toxicity. Some chemicals have been tested and are already flagged as known endocrine disruptors. I'd like to highlight three examples of such chemicals that are crying out for EPA action: perchlorate, plastic chemicals (including bisphenol A and phthalates), and steroid hormones.

The SDWA requires EPA every five years to publish a list of currently unregulated contaminants that should be considered for potential regulation. EPA is then required to make a final determination about whether or not to regulate at least five of the contaminants identified on the Candidate Contaminant List (CCL). To date, the Candidate Contaminant List listing process has gone through 3 iterations, beginning in 1998 with the publication of CCL1 and then CCL2 in 2005. CCL1 contained 50 chemical contaminants, including industrial organic chemicals, pesticides, and inorganic chemicals; in July 2003, EPA decided not to regulate any of the nine chemicals it evaluated on the CCL1. CCL2 consisted of a subset of the chemical contaminants listed on CCL1; and in May 2007, EPA again decided not to regulate any of the 11 chemicals it considered from the CCL2.

The CCL3, finalized on October 8, 2009, contains 104 chemicals or chemical groups. Several important endocrine disrupting chemicals are on this list, including perchlorate and several steroid hormones. Other important endocrine disruptors that are known to be water contaminants, such as bisphenol A and other phthalates, are not on the CCL3. Only one of the chemicals I'm going to talk about today - bis(2-ethylhexyl) phthalate - has been regulated by EPA under the SDWA – and it wasn't even regulated on the basis of endocrine disruption.

Perchlorate

Perchlorate has emerged as an important threat to drinking water sources over vast areas of the United States, with over 400 public water systems, large and small, reporting perchlorate in their water. As a result, millions of people are being exposed to this chemical in their drinking water. Perchlorate is on the EPA's Candidate Contaminate List 3 (CCL3). It was also on the CCL2, and was the subject of an Unregulated Contaminant Monitoring Rule (UCMR). It has been a significant problem since the late-1990's, but unfortunately EPA has not even begun the process of setting a drinking water standard for this chemical. Individual states are left to do the best they can, and the result is a wide-ranging patchwork of standards around the country, and many states with no enforceable drinking water standard.

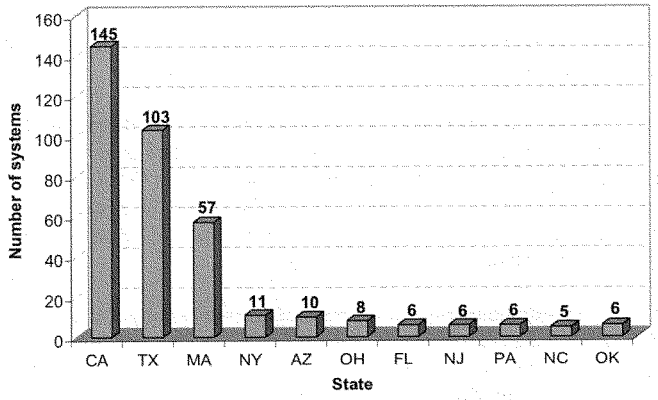
Perchlorate is a contaminant that comes from rocket fuel, fireworks, road flares, fertilizer, and other sources. It is known to interfere with the normal function of the thyroid gland.[15] Iodine is needed by the thyroid in order to create thyroid hormones. Normally, iodine is transported into the thyroid gland through an energy-requiring mechanism called the

sodium-iodide symporter. Perchlorate blocks this transport and prevents uptake of iodine into the gland, therefore interfering with the production of these vital hormones.

A decrease in circulating thyroid hormone during gestation or the first year of life can result in neurodevelopmental abnormalities leading to permanent brain dysfunction.[16] Many studies have shown subtle but lasting deficits in cognitive function, language, hearing, behavior, attention span, and vestibular function (balance) in those that had early-life or prenatal thyroid suppression.[17]

An NRDC analysis of available perchlorate data in 2005 showed that public water systems (PWS) in 27 states, the District of Columbia and two U.S. territories have reported detecting perchlorate in treated water or in their water sources, with concentrations ranging from 0.2 to 1,300 parts per billion (ppb).[18] Of 5,369 systems tested, 402 (7.5 percent) detected perchlorate in their water. California has the largest number of systems with perchlorate detections, followed by Texas and Massachusetts (see Figure 1). These are also the states with the most perchlorate monitoring conducted to date.

Figure 1: States with the largest number of water systems with perchlorate detections.



The 402 systems that have found perchlorate serve 40.8 million people.[19] There was no remarkable difference between the frequency of perchlorate contamination in PWS that had groundwater as their primary water source and those that relied on surface water. Groundwater systems accounted for 60.9 percent of all systems sampled, and for 63.7 percent of the systems with perchlorate.

U.S. EPA, the U.S. Department of Defense (DoD) and state environmental agencies have identified at least 143 sites in 31 states and the District of Columbia where perchlorate releases have occurred, as well as an additional 281 sites in 45 states, one commonwealth and the District of Columbia where perchlorate or perchlorate-containing materials have been used, manufactured, or disposed.[20] DoD facilities account for 77 of the 143 known

release sites. Perchlorate releases have also been confirmed in eight federal facilities of other types, most of which belong to the Department of Energy (DoE). The remaining 58 are currently non-federal or private sites. Most of these are owned by aerospace companies, defense contractors, and explosives or pyrotechnics manufacturers.

EPA must set an enforceable drinking water standard for perchlorate that will protect pregnant women, children, and people with underlying thyroid disease or iodine deficiency. It is unconscionable that millions of people are drinking water contaminated with this known endocrine disruptor and remain unprotected.

Plasticizers: Phthalates and Bisphenol A

Phthalates are hormone-disrupting chemicals used in an enormous range of products, including air fresheners, plastic toys, cosmetic and personal care products (including fragrances and nail polish), vinyl, medical devices, inks and adhesives. They are also used as food additives and as inert ingredients in pesticides.

Phthalates are known to interfere with the production of male reproductive hormones in animals and likely have similar effects in humans.[21] [22] [23] Their effects in animal studies are well recognized and include lower testosterone levels, decreased sperm counts and lower sperm quality. Exposure to phthalates during development can also cause malformations of the male reproductive tract and testicular cancer. Young children and the developing fetus are most at risk.[24] [25]

National monitoring studies have found one or more phthalates in over 10 percent of streams sampled.[6] The only phthalate that has a drinking water standard is bis 2-ethylhexyl phthalate (DEHP) which has a maximum contaminant level (MCL). Unfortunately the MCL was set in July 1992, and was based on potential to cause mild gastrointestinal disturbances, nausea, and vertigo, not on endocrine disrupting effects. The other phthalates have no drinking water standards at all.

BPA, or bisphenol A, is a hormone-disrupting chemical used in making plastics and epoxy resins. BPA is used in the resin lining of all food and beverage cans. It is the building block of polycarbonate plastic and is used in a wide range of products, including clear plastic baby bottles and sippy cups, clear plastic water bottles, and other kitchen plastics such as measuring cups, drinkware and storage containers. BPA is also found in some dental sealants and fillings, medical devices, paints, epoxy adhesives and cash register receipts.

In animal studies, BPA has been shown to mimic the female hormone estrogen. Exposure to this chemical early in life is associated with pre-cancerous changes in the mammary and prostate glands, as well as altered development of the brain, causing behavioral abnormalities and earlier onset of puberty.[26] Developmental exposure to BPA at low doses has also been associated with reproductive abnormalities such as lower sperm counts, hormonal changes, enlarged prostate glands, and abnormalities in the number of

chromosomes in eggs.[27] It also has been associated with obesity and insulin resistance—a condition that commonly precedes the development of diabetes.[28]

A study of Mississippi River water in Louisiana, which is used for drinking by the city of New Orleans, found numerous contaminants. Most relevant to our discussion today, monthly testing at the drinking water treatment plant in Jefferson Parish, Louisiana revealed detectable concentrations on bisphenol A in most of the samples. [29] The researchers in this study planned to determine if these widespread detections represented contamination from the laboratory, or contamination in the drinking water; no definitive results are available.[30] National groundwater sampling reported BPA in about 30 percent of groundwater samples.[7]

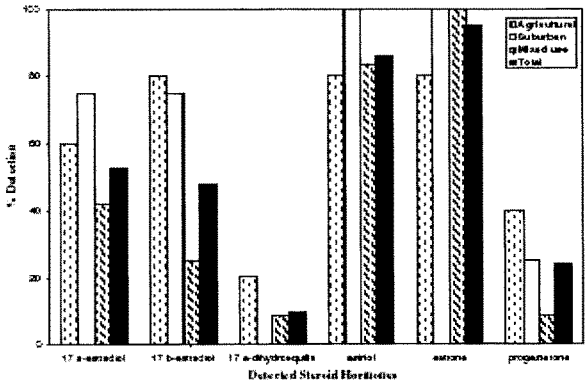
Both phthalates and bisphenol A are contaminants in wastewater. 18 of 19 wastewater samples tested in the San Francisco Bay Area contained at least one of three unregulated, widely-used endocrine disruptors – phthalates, bisphenol A, and triclosan. Two samples contained all three substances. [31] Despite sophisticated wastewater treatment, these chemicals were detected in treated waters discharged into the Bay and have also been detected in the Bay itself.[32] While wastewater treatment is extremely effective in removing biodegradable food and human waste, it was never designed to address this broad spectrum of unregulated chemical pollution.

There is no EPA drinking water standard for bisphenol A even though it is a known endocrine disruptor and a known water contaminant. Unfortunately this chemical is not even on the CCL3, so the likelihood of any appropriate EPA action to protect consumers from this chemical in drinking water appears small. Several states such as Minnesota, Washington and Connecticut, as well as major retailers such as Walmart and Target have taken action to eliminate phthalates and bisphenol A in children's products, and Congress banned phthalates in children's toys over a year ago.

Steroid Hormones

Studies of water sources around the U.S. have detected widespread contamination with steroid hormones. For example, a recent study in Pennsylvania collected data from 21 locations in suburban, agricultural, and mixed suburban/agricultural areas. At least one steroid hormone was detected in every stream; two hormones, estrone and estriol, were detected at more than 80 percent of the sampling sites (see Figure 2).[33] Potential sources of the hormones include municipal wastewater discharges, septic tanks, and animal manure.

Figure 2: Percent Detection of Steroid Hormones in Pennsylvania Surface Water Samples



An important source of hormonal contaminants in water is steroids used in livestock operations which contribute to widespread environmental contamination. Beef cattle raised in large feedlots are treated with anabolic steroids to promote the growth of muscle. One of the most common steroids used is a male sex hormone (androgen) mimic, trebolone acetate. Exposure to trebolone metabolites at concentrations as low as parts per trillion can cause masculinization of female fish and reduced fertility. [34] A recent study at an Ohio-based animal feeding operation with a capacity for 9,800 cattle found detectable concentrations of trebolone in the discharge from the facility at levels that were sufficient to induce gene expression associated with exposure to androgens.[34] Other research has found environmental androgens associated with masculinization in female fish living downstream of pulp and paper mills and concentrated animal feeding operations. These pharmaceuticals interfere not only with sex hormones but also with other hormonal systems including the thyroid gland, which is critical for proper growth and development of the brain during fetal growth, infancy, and childhood.

Confined animal feeding operations (CAFOs; also known as "factory farms") are large-scale producers of hogs, poultry, beef or dairy cows – typically housing from thousands to tens of thousands or even hundreds of thousands of animals. These facilities often treat the animals with hormones to promote growth, and they produce enormous amounts of waste, which pose significant challenges for storage and disposal. Hog waste, for example, is typically stored in open lagoons, roughly the size of football fields. Drier animal waste, such as "chicken litter," is stored in piles, often outside where rain can lead to runoff into nearby waters. After being stored, animal waste is typically spread on surrounding crop fields as fertilizer for crops. These "spray fields," as well as the lagoons and litter piles, are sources of pollution that can introduce hormones, and other contaminants into our waterways.

Several important veterinary steroids that have been detected in drinking water are on the CCL3, including estriol, estrone, ethinyl estradiol, and mestranol. Some of these are also breakdown products of human pharmaceuticals. These are reasonable priority chemicals that deserve scrutiny and action. Trebolone acetate and its metabolites, are unfortunately not on the CCL3, even though they have been detected downstream of many animal feeding operations.

Recommendations to Address the Problem of Endocrine Disruptors in Drinking Water

Under the Safe Drinking Water Act and the Food Quality Protection Act, EPA has the authority and obligation to ensure the safety of our drinking water. EPA should:

- Implement testing under the endocrine disruptor screening program for priority drinking water contaminants, including all chemicals on the CCL3, as well as other chemicals in pharmaceuticals and personal care products that have been detected by USGS in surface or groundwater.
- Implement aspects of the EDSTAC report that have been ignored, such as creating the Endocrine Disruptor Priority Setting Database, integrating the High-Throughput Pre-Screen (or ToxCast) into the program for priority-setting, screening common mixtures, and inviting public nominations for testing;
- Evaluate and identify wastewater and drinking water treatment practices for removing endocrine disrupting chemicals, including pharmaceuticals;
- Work with other federal agencies and states to prevent or limit the use of hormones in agriculture.

Congress needs to take additional steps to help address this issue, including:

- Require EPA to prioritize and screen chemicals in drinking water, including mixtures, for endocrine disrupting effects;
- Restore adequate funding for the USGS Toxic Substances Hydrology Program and the USGS National Water Quality Assessment Program (NAWQA), so more data are available on contaminants in source water and drinking water; NAWQA started with 500 sites in 1991, and has now been reduced to 113, of which only 12 are monitored annually. 86 sites are monitored only once every four years;
- Reform the Toxic Substances Control Act to require testing of chemicals for toxicity, and require EPA action to promptly regulate hazardous chemicals.

Appendix 1
Results of the USGS Survey of Intersex Fish in the United States, 1995-2004

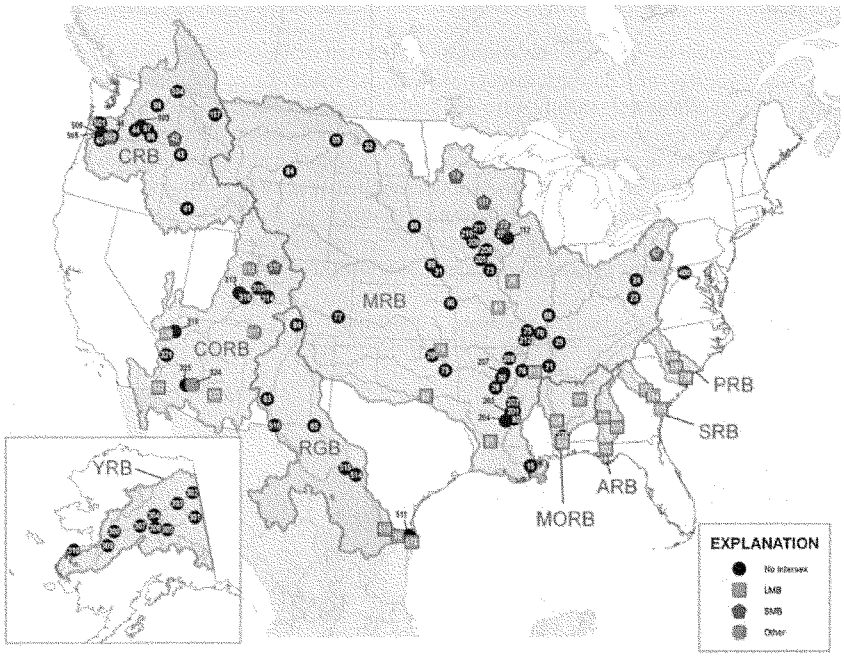
Of the 16 fish species researchers examined from 1995 to 2004, intersex was most common by far in smallmouth and largemouth bass: a third of all male smallmouth bass and a fifth of all male largemouth bass were intersex (Figure 3). This condition is primarily revealed in male fish that have immature female egg cells in their testes, but occasionally female fish will have male characteristics as well.

•Intersex smallmouth bass were found in a third of male bass at almost half of the sites examined in the Columbia, Colorado, and Mississippi River basins. The percentage of intersex smallmouth bass ranged from 14 to 73 percent at different sites. It was highest (73 percent) in the Mississippi River at Lake City, Minn., Yampa River at Lay, Colo. (70 percent), Salmon River at Riggins, Idaho (43 percent), and the Columbia River at Warrendale, Oreg. (67 percent).

•Intersex largemouth bass were found in nearly a fifth of the fish examined from the Colorado, Rio Grande, Mississippi, Mobile, Apalachicola, Savannah, and Pee Dee River basins; intersex was not observed in male largemouth bass from the Columbia River Basin. The percentage of intersex largemouth bass per site ranged from 8 to 91 percent and was most prevalent in the southeastern United States. The Pee Dee River at Bucksport, S.C., contained the highest percentage of intersex fish (91 percent), with high percentages occurring elsewhere on the Pee Dee too. Sixty percent of male bass examined at the Apalachicola River at Blountstown, Fla., were intersex, 50 percent in the Savannah River at Port Wentworth and Sylvania, Ga, 43 percent in the Savannah River at Augusta, Ga., and 30 percent in the Chattahoochee River at Omaha, Ga., and the Flint River at Albany, Ga. Lower percent intersex (10-25 percent) were found in bass from sites in the Mobile River in Alabama.

•In addition, relatively high proportions of intersex largemouth bass were observed at three sites in the lower Rio Grande Basin including Rio Grande at Brownsville, Texas (50 percent), Rio Grande at Falcon Dam, Texas (44 percent), and Rio Grande at Mission, Texas (20 percent). In addition, 40 percent of male largemouth bass from the Colorado River at Imperial Dam, Ariz. and at the Gila River at Hayden, Ariz., in the Colorado River Basin were intersex.

Figure 3: Locations where intersex smallmouth bass and largemouth bass were found in the United States

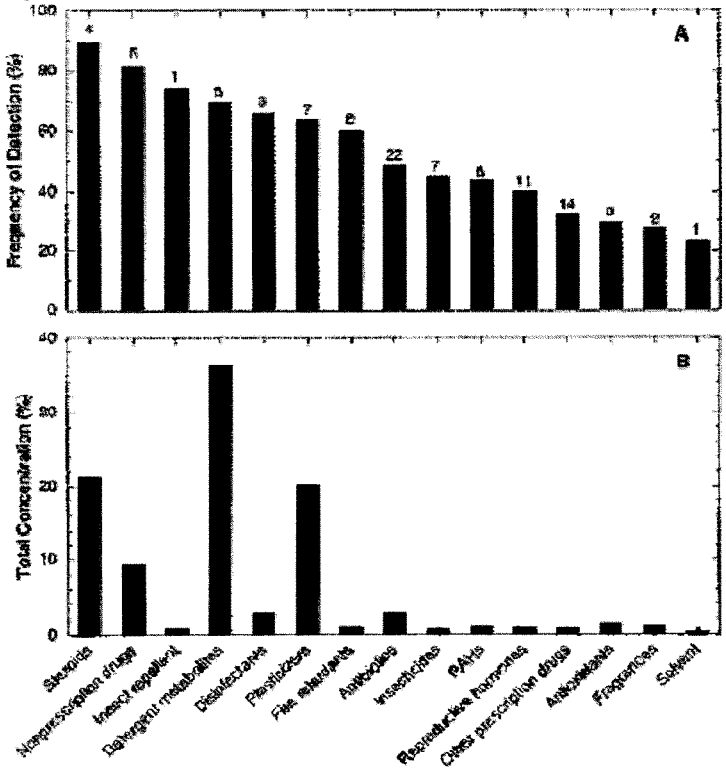


Source: Hinck JE, Blazer VS, Schmitt CJ, Papoulias DM, Tillitt DE. Widespread occurrence of intersex in black basses (Micropterus spp.) from U.S. rivers, 1995-2004. Aquat Toxicol. 2009 Oct 19;95(1):60-70.

Appendix 2
Contaminants in Source Water in the United States

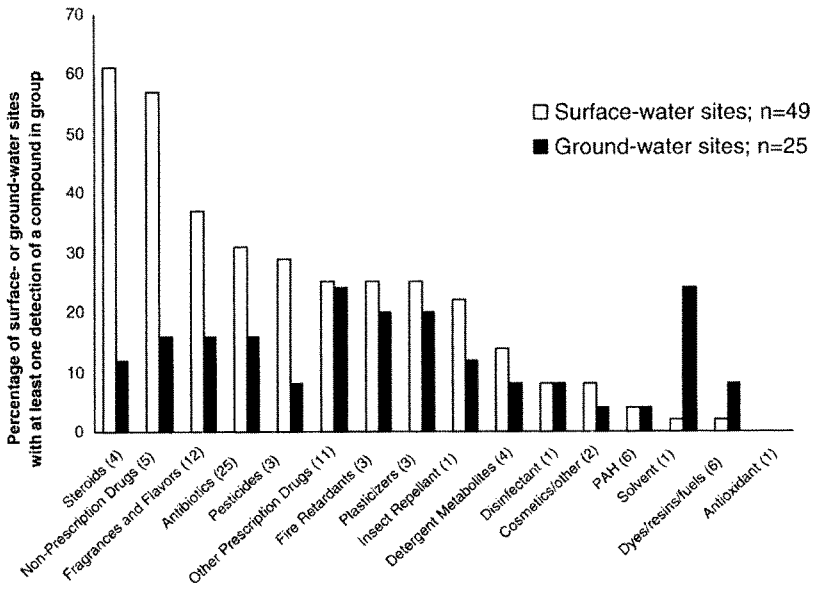
The most common unregulated contaminants detected in surface water include steroid hormones, nonprescription drugs, insect repellent, detergent chemicals, disinfectants, and plasticizers; all of these chemicals were detected at 70 percent or more of sites tested. The concentrations of the steroids, detergents, and plasticizers were among the highest of all the emerging contaminants (Figure 4). Water used as source water for drinking water systems has a lower detection frequency of unregulated compounds (Figure 5). However steroid hormones and prescription drugs were found in more than 50 percent of surface water sources of drinking water, and groundwater sources in more than 20 percent of cases contained solvents, prescription drugs, fire retardant chemicals and plasticizers.

Figure 4: Contaminants in U.S. Streams, 1999-2000



Source: Kolpin DW, Furlong ET, Meyer MT, Thurman EM, Zaugg SD, Barber LB, Buxton HT. Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999-2000: a national reconnaissance. Environ Sci Technol. 2002 Mar 15;36(6):1202-11.

Figure 5: Detections of organic wastewater compounds by general use category at surface- and ground-water sites.



Source: Focazio MJ, Kolpin DW, Barnes KK, Furlong ET, Meyer MT, Zaugg SD, Barber LB, Thurman ME. A national reconnaissance for pharmaceuticals and other organic wastewater contaminants in the United States--II) untreated drinking water sources. Sci Total Environ. 2008 Sep 1;402(2-3):201-16.

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Mr. MARKEY. Thank you, Dr. Solomon, very much. And our final witness, Dr. Christopher Borgert is the president and principal scientist of Applied Pharmacology and Toxicology Incorporated, a consulting firm that specializes in assessing the pharmacological and toxicological effects of chemicals on living systems. Dr. Borgert received his doctorates in medical science from the University of Florida College of Medicine. We welcome you, sir.

STATEMENT OF CHRISTOPHER J. BORGERT

Mr. BORGERT. Thank you, Mr. Chairman.

Mr. MARKEY. If you can turn on the microphone and move it in closer please. There we go. Thank you.

Mr. BORGERT. Thank you, Mr. Chairman. Thank you for giving me the opportunity to provide you my perspectives on this important issue. I come to you today speaking for myself. I don't represent any particular entity, but I do come to you as a father and as a consumer, as a taxpayer, as an operator of small business, and a scientist with considerable background on this issue.

And I too am very concerned about the chemicals that we use in commerce. I want to make sure that my family and my children and the people of Florida and all the people that come into contact with those chemicals are protected. That is a very big concern to me. That has been a large part of my work over the years. But I am most concerned that when we act, we do it based on solid science, science that is reliable and relevant for the purpose to which we put it. And what I would caution you about is that many of the decisions that are being urged to be made are being urged to be made on the basis of someone's latest pet theory on what is causing certain human diseases, rather on solid, repeatable data.

Let us remember that the diseases that were touted to be due to endocrine disruption a decade or so ago have shifted. So as some theories fall by the wayside, new theories replace them. These are theories. We don't know what the punitive results of endocrine disruptors will be in a few years, and so I think it is very important that we use solid science.

What do I mean by solid science? I mean science that comports with three very common sense tenets: that we know what we are measuring unequivocally and we know the precision of that measurement. These are very common sense rules. Number two, that we know our measurements are taken under controlled conditions that are relevant for the purpose we are putting them to. And third, that they are repeatable in independent hands.

Now, the endocrine screening program that is at issue here has been through such a validation exercise, but let us be clear. That validation really was able to address only the first of my three tenets. So we now have some confidence that those assays measure what we believe they are measuring and we know something about the precision. But for some of the assays, that isn't even entirely clear.

Two of the assays, for instance, failed to produce negative results in a wide array of chemicals that we might expect to be negative. So we are not really sure that the results are relevant to the use we are going to put them to. We don't know that they won't simply move everything forward with positive results and a screen that

doesn't differentiate between what should be moved forward to tier two testing and what is a very low priority for tier two testing is rather useless.

The EPA has issued test orders for 67 chemicals. Its science advisory panel back in 1999 advised that it do this, and we just heard that that will be complete in 2012. That will hopefully complete the validation exercise so that we will know the controlled conditions under which our measurements have to be made and whether they are relevant and useful for actually deciding which chemicals need to be tested and which are a lower priority.

So my recommendation is to allow that science to occur, allow EPA the time, to give them the resources they need to formulate the criteria for moving chemicals forward based on the data, not based on the level of emotion and the latest concern, but based on the data. We don't know what those data will be until they are collected. Allow that process to go forward, and I think that then we may emerge with science that we can rely on. And remember there are consequences to getting it wrong.

Decisions about which chemicals are in commerce, if they are made based on a false notion of what the risks, the real risks are, can be the wrong decisions and actually not be precautionary. Bad decisions can imperil the public health and the environment rather than protect it. So there are consequences to getting it wrong. I urge you to give EPA the time to get it right. And thank you for your attention. I very much appreciate being able to provide my perspectives.

[The prepared statement of Mr. Borgert follows:]

Testimony of
Christopher J. Borgert, Ph.D.

before the
House Subcommittee on Energy and Environment

"Endocrine Disrupting Chemicals in Drinking Water:
Risks to Human Health and the Environment"

February 25, 2010
Washington, D.C.

Background and Expertise

I sincerely thank the Subcommittee for inviting me to testify. I am pleased to be given the opportunity to address you regarding endocrine disrupting chemicals and their potential human and environmental health risks.

It has been almost 20 years since I first began tracking the scientific literature on the endocrine effects of environmental chemicals, and since then, I've devoted a significant portion of my professional career as a pharmacologist and toxicologist to this issue.

My work generally involves evaluating the relationship between basic research discoveries and their application to real world problems, especially health risks posed by chemical substances.

My expertise is typically sought by private individuals and firms who rely on an accurate understanding of the relationships between basic research and health risks to ensure the safety of products they bring to the marketplace. These are primarily manufacturers of industrial chemicals, pesticides, pharmaceuticals, cosmetics, dietary supplements, and other chemical substances, and their trade associations and legal counsel.

Today, I am here of my own volition and represent only myself. My testimony is based on my my scientific training and expertise and my own experience with the issues at hand.

I have given special attention to the subject of evaluating potential health risks posed by combined exposures to multiple chemicals, such as may occur from drinking water. As someone knowledgeable in these areas, I have been invited to advise governmental agencies and organizations on such issues.

In December of 2008, I addressed a workshop of the National Research Council investigating the issue of evaluating exposures and risks posed by mixtures of pharmaceuticals in the water supply.

I've been a part of several working groups convened by professional and scientific societies interested in endocrine issues. From 1996 - 1998, I served on the Endocrine Disruptor Screening and Testing Advisory Committee (EDSTAC), which was the Federal Advisory Committee to EPA that initially devised and recommended the two-tiered endocrine screening and testing program that it has now begun to implement.

I served on the EDSTAC as the representative for small business stakeholders, and I also served on the workgroup of that committee charged with evaluating and recommending the specific screening assays that comprise the Tier 1 Screening Battery.

In keeping with the Congressional mandate for EPA to use validated test systems in constructing its screening program for estrogen-like effects in humans, the EDSTAC recommended to EPA that it undertake a formal validation program for the proposed screening and testing batteries. EPA did so, using the EDSTAC final report as its template.

Since my EDSTAC experience, I have followed closely the EPA and OECD validation programs for the endocrine screening assays comprising the Tier 1 screening battery, now ordered to be conducted on an initial set of 67 chemicals.

I have assisted various industries in following this validation program, and I also served on an OECD peer-review panel that evaluated the validation program for the uterotrophic assay, one of the mainstays of the endocrine screening battery.

Just to make sure, you will remember that the Tier 1 battery of assays is intended to be a preliminary screen used to select items that could then be tested in the more specific Tier 2 battery of tests.

It is about this Tier 1 endocrine screening battery that I wish to focus my comments to this subcommittee, and my first objective is the most necessary clarification of some common misconceptions about the Tier 1 screening battery and the validation program conducted for the Tier 1 screening assays.

Basic Scientific Principles are Applicable to Endocrine Screening

Dispelling misconceptions is essential in order to see clearly what this endocrine screening program offers, and what it does not offer, and thus, to consider how the program might best be utilized.

In order to do that, I will review some of the most basic tenets that validate scientific information so that the existing knowledge base on the endocrine screening battery, and on endocrine disruption in general, can be understood in its proper context.

For data to be considered an established scientific observation, it must, at a minimum, conform to three fundamental tenets that have been well explained by Dr. Gio Gori, formerly Deputy Director of the Division of Cancer Cause and Prevention at the National Cancer Institute. These three tenets are simple, understandable, and undeniable, applying to the basic language of science that enables reliable measurement of the natural world.

First, the identity and authenticity of scientific measurements must be verifiable within a defined range of precision. In other words, we must be able to demonstrate unequivocally that we have measured what we claim to have measured and that we know the margin of error on our measurements.

Second, measurements and observations must not be confounded by extraneous factors and influences known to corrupt their accuracy and precision. In other words, we must be able to demonstrate that our measurements are taken under well-controlled conditions.

Third, the measurements and observations must be replicable in independent hands. In other words, other scientists using the same or similar methods must be able to repeat the results.

These three tenets are common sense, but often become confused amidst the technical complexity and nuanced jargon of modern science, even by scientists.

It is in the context of these simple, common-sense tenets that the opportunities and pitfalls of the endocrine screening program must be understood. This is also the context in which I explained to the National Research Council what valid methods exist for evaluating cumulative risks of pharmaceuticals in the water supply.

Correcting Misperceptions Concerning Validation and Implementation of the EDSP Assays and the Tier 1 Battery

First, regarding validation of the endocrine screening assays, validation and subsequent implementation of the EDSP has not been unreasonably delayed.

While there is no disputing that validation programs for these assays have been protracted and have required more in-depth experimentation than initially envisioned by some individuals who served on EDSTAC, this lengthy process was completely predictable given the complex biology of the systems these assays were intended to measure.

The Tier 1 endocrine screening battery includes 11 separate assays that range from single-day procedures conducted in the laboratory to multi-week assays requiring many experimental animals, large animal housing facilities, many personnel to care for and observe the animals, animal surgeons, and the evaluation of numerous tissues and organs by fastidious histopathological methods.

Scientists who understand the process of scientific validation - i.e., that the results of the assay conform to the three tenets described above and are relevant to their intended purpose - expected a much longer validation process due to the ambitious nature of the proposed endocrine screening program and the need to answer a number of important questions regarding the sensitivity and specificity of the individual assays and the battery as a whole, since the battery was intended to be interpreted as a unit.

Unfortunately, because of time-constraints imposed on EPA by Congress, the Agency conducted the minimum validation work that might satisfy the Congressional mandate to use validated test systems so that screening could begin.

The complexity of many of these assays and the novel uses to which they are being put in the Endocrine Screening Program - the detection of potentially weak hormonal activity for a broad array of diverse chemical types and molecular structures - fully accounts for the decade needed to complete even the abbreviated validation program that was conducted on these assays.

It must be appreciated that neither EPA nor any scientist or scientific body is able to dictate the results of scientific research and the timeframe on which it will yield useable results. To my knowledge and from my perspective, EPA worked as rapidly as it could, taking advantage of cooperative efforts by the OECD and other international organizations, to conduct validation experiments and to adjust the experimental plan as necessary based on results of the studies as they were obtained. Some results enabled rapid progress; other results dictated abandoning initial approaches and evaluating alternatives instead. Scientific results simply cannot be force-fit to meet a predetermined schedule.

Second, and perhaps more unfortunately, the endocrine screening battery, as a whole, has not yet been shown to be useful for its intended purpose. Because many of the assays are protracted and complex, the expedited validation programs were able to focus only on the ability of the individual assays to detect known positive and negative endocrine active compounds specific to each test. Only limited testing of unknowns was possible given the

intense pressure on the Agency to implement the screening program rapidly. Moreover, the performance of the battery as a whole has been left unaddressed.

Validation efforts for some of the assays, the pubertal male and female assays in particular, were unable to verify that the assays could yield negative results for a range of chemicals lacking endocrine activity. Indeed, the criteria for interpreting ambiguous results had to be modified in order to claim that these assays could yield a negative result for even one chemical.

The assay protocols left standing at the end of the validation exercises, which have now been formalized as EPA test guideline series 890, leave unaddressed a number of technical problems that will complicate and confound the development of interpretive criteria for the individual assays as well as for the battery as a whole.

In short, the validation process has provided increased confidence that we are measuring what we claim to measure with the endocrine screening assays, but the precision of some of those measurements is still uncertain, and the conditions under which extraneous factors might influence the measurements are not well controlled in all the assays. This makes tenuous the assumption that the screening battery will actually differentiate chemicals with the potential to interact with the endocrine system in definitive studies from those that do not.

Presently, no one knows how useful the endocrine screening battery will be, as a whole, for predicting which chemicals should undergo definitive testing and which should be considered a low priority for further analysis of endocrine effects. If the endocrine screening battery forwards everything to further testing, it has absolutely no utility whatsoever.

EPA, on the advice of its Scientific Advisory Panel, has attempted to address this problem by ordering an initial phase of EDSP screening on 67 pesticide chemicals. The purpose of this approach is to evaluate the Tier 1 assays and battery, as well as the Agency's policies and procedures, using a discrete set of chemicals. To be an effective approach, additional screening must await completion of the initial phase, at which time EPA would modify its assays, battery and procedures as necessary.

Make no mistake; the status of the endocrine screening battery is analogous to a new but unproven clinical screening procedure. Assuming that a precautionary approach is without harm and that all important decisions will await the definitive test ignores the very real fact that life altering decisions are made daily on the basis of clinical screens. There are consequences to getting it wrong, even if it is only a screen and not the definitive test.

In the same way, we might inadvertently presume great risk for relatively safe chemicals, and instead use riskier replacements, simply because some chemicals were assumed to be harmful based on highly publicized endocrine screening results. As a scientist who is also a father, a consumer and operator of a small business, I would like to know that products in commerce are evaluated on the basis of real risks, demonstrable by objective science, not upon hypothetical connections between screening results and serious diseases that are easily and conveniently sensationalized.

Third, endocrine screening will not identify "endocrine disruptors." This issue concerns the predictive value of the endocrine screening battery and whether so called environmental endocrine disruptors have been unequivocally identified. Highly publicized statements have been made repeatedly over the years declaring that serious human diseases are known consequences of exposure to environmental endocrine disrupting chemicals. These speculations have often been made on the basis of epidemiological studies that used methodologies appropriate for hypothesis generation but wholly incapable of confirming putative associations or demonstrating causes. Interestingly, the list of human disease associated with

endocrine disruption has shifted as initial speculations were debunked or severely tempered - breast cancer related to chlorinated organic chemicals; reduced sperm counts related to higher chemical exposures in industrialized nations; feminized male fish in UK rivers caused by exposure to soaps and detergents - only to be replaced by newer and relatively less scrutinized speculations. Rather than convincing us by the sheer number of speculations that are based on hypothetical studies, the failure to reproducibly demonstrate these associations and to support a true causal role for chemical exposures should lead us to suspect them.

There is a also a widely held misconception that the endocrine screening battery provides a sensitive means of identifying chemicals that may cause subtle health effects in the human population or in wildlife. Since those subtle effects have not been demonstrated, nothing could be more misrepresentative of what the screening battery can be expected to do. Indeed, the endocrine screening battery is intended to detect only chemicals that have the potential to interact with the endocrine system in live animals; it does not and cannot test for adverse health effects.

Interaction with the endocrine system *per se*, i.e., positive results in the endocrine screening battery, does not signify that adverse endocrine effects are likely. The endocrine system is a homeostatic system that functions to maintain relatively consistent internal body conditions. An endocrine response is merely an indication that the system is working. The endocrine screening battery utilizes this responsiveness to screen chemicals for potential interaction with the system, but it does not determine whether the endocrine system is merely responding or is irrevocably perturbed by the chemical. The endocrine system is like a thermostat on a heating and air conditioning system; the fact that it turns off and on many times during the day does not signify that it is damaged, but merely that it is responding to changes in room temperature. Without knowing whether room temperature was properly controlled, it is impossible to conclude that the thermostat or heating system malfunctioned.

In the same way, the endocrine screening battery cannot determine that a chemical poses a risk to human or environmental health, but merely indicates that some component of the endocrine system recognizes the presence of the chemical. A more thorough analysis - tier 2 tests - must be conducted to determine whether that potential interaction with the endocrine system leads to adverse effects. It may for some chemicals, but for many it might not, or if so, only at doses that far exceed doses that produce some other serious toxic health effect. In the latter case, adverse endocrine effects would never be observed.

This last case underscores another reason the endocrine screening battery cannot be interpreted as indicating adverse effects: the extraordinarily and unrealistically high doses of chemicals that will be used in screening may elicit responses that could never occur at lower levels typically encountered in the environment. A similar conclusion, and others, have been explained in a recent publication by Dr. Richard Sharpe of the UK, who was one of the original voices of concern for the possible effects of environmental endocrine disrupting chemicals.

These basic pharmacological and toxicological concepts of dose-response were at the core of my presentation to the National Research Council concerning risks posed by mixtures of pharmaceuticals in the water supply. These concepts have not been supplanted by hypothetical low-dose theories or by the speculation that mixture effects observable at high doses also operate and manifest adverse effects at low, environmentally relevant levels of exposure.

Although good health trumps money in my value system, it is nevertheless important to recognize that endocrine screening is very expensive and should not be required of more than the initial 67 chemicals until its utility has been demonstrated. The costs of screening alone are on the order of 1 to 1.5 million dollars per chemical, but this figure does not account for the full cost to consumers who ultimately must bear the burden of funding the activities of the EPA and

Congress on this issue, nor does it include the costs of conducting tier 2 testing on chemicals that are false positives in the screens. Finally, such monetary figures fail to give due consideration to the tens of thousands of laboratory animals that must be sacrificed to conduct this screening, and the tens of thousands more that will be sacrificed in tier 2 testing.

Four months ago, in October of 2009, EPA began issuing Tier 1 test orders for 67 chemicals comprising pesticide active ingredients and inert ingredients in pesticide products. Many of these chemicals have already undergone the more extensive, long-term animal tests typical of tier 2 that are capable of defining adverse effects on reproduction and development in rodent species. Thus, it can only be hoped that the initial round of test orders will yield data upon which the predictive utility of the endocrine screening battery for adverse effects in laboratory rodents may finally be evaluated.

Expanding the program within the first year of its implementation, as has been proposed, will not only be costly, but it will needlessly squander an opportunity to evaluate the data from the first 67 chemicals screened and to improve the screening battery based on those results. In short, premature expansion carries great risk of getting the science wrong, with the consequence of poor decision-making that imperils rather than protects public health and the environment.

From a scientific perspective, precious resources would be better directed toward evaluating the utility of the endocrine screening battery for identifying adverse endocrine effects in laboratory rodent tests, which are known to capture adverse effects on reproduction and development mediated by all physiologically relevant pathways, including endocrine disruption.

Rather than expanding the program prematurely, this path would allow EPA time to determine the best criteria for moving chemicals from tier 1 screening to tier 2 testing based on the data, and to determine whether enhancements, deletions, or replacements for the current assays are needed.

Without such a deliberate approach that relies on established scientific principles rather than on precautionary rhetoric and speculative hypotheses, the credibility of the endocrine screening program and the government agencies that drive it is likely to suffer.

Mr. MARKEY. Thank you, Dr. Borgert, and thank you for being here. That concludes testimony from our panel. Now we will turn to a question-and-answer period. The chair will recognize himself for a round of questions.

I have introduced a bill to ban BPA in food and beverage containers in the past two Congresses, and recently the FDA announced that it had concerns about its health effects. It has also been found in 30 percent of groundwater sites sampled nationally.

Dr. Birnbaum, the endocrine-disruptor screening program is intended to screen chemicals to see whether they are endocrine disruptors, but it seems to me that we already know that BPA qualifies. Do you agree with that?

Ms. BIRNBAUM. I certainly support the recent decision of the EPA to suggest that they have some concern about the effects of BPA, which are based in large part upon the plethora of information that is being produced demonstrating that BPA is an endocrine disruptor and is associated with, at least potentially associated with a wide range of health effects.

Mr. MARKEY. Dr. Jones—Mr. Jones, do you generally agree that if there is enough scientific data showing that a chemical is an endocrine disruptor that causes adverse health effects, that EPA shouldn't have to screen it again and could use its authority to move straight to regulation?

Mr. JONES. Well, I would generally agree that the agency would not need to do screening level assessments to determine whether it is an endocrine disruptor, BPA being a perfect example. We don't think that that requires screening to understand whether it is. I don't believe as a general matter we necessarily will therefore have enough information to go to regulation. I think that is the situation where we need to make sure we understand we can characterize the adverse outcomes of a compound before we can go to regulation.

Now, that may not be true in all cases, but I think it would be an overstatement for me to say I think that we can go from we know it is a disruptor to regulation as a general matter.

Mr. MARKEY. Dr. Solomon, since BPA is a known endocrine disruptor that is known to be in drinking water, do you think EPA should have included BPA on its list of chemicals to evaluate to consider whether a drinking water standard should be set for it?

Dr. SOLOMON. Yes, I do.

Mr. MARKEY. Could you expand on that briefly please?

Dr. SOLOMON. BPA fits the criteria—clearly fits the criteria for a priority substance for regulation in drinking water because it is, a, known to be present in drinking water source waters, and, b—and actually in some studies in drinking water at the treatment plant, and, b, is a chemical that has very strong data on health effects at levels that are actually not that far off from what people are being exposed to today. Drinking water is not the only source of exposure, but it is certainly something that EPA can and should be controlling.

Mr. MARKEY. OK, a recent press article, Dr. Solomon, suggested that EPA did consider including BPA on its list of chemicals of concern, which would put it into the regulatory process. But it was pulled off the list shortly after the chemical industry met with OMB. Do you think that EPA should decide which chemicals to

evaluate using a process that is more transparent and gives more opportunities for all stakeholders to participate?

Dr. SOLOMON. Yes, I believe it is extremely important for EPA to have more public involvement in the process, and the candidate contaminant list was not vetted until it was pretty much almost a done deal. And there were some significant concerns raised by members of the public and by the drinking water committee about the list itself and the chemicals that were not on and were on that list.

Mr. MARKEY. Mr. Jones, what can you tell us about why BPA was not included on EPA's list of chemicals of concern?

Mr. JONES. Well, first, Mr. Chairman, I do want to point out it is a public record because what we submit to OMB is made public, and what comes back out of that process is public as well. And BPA was not on the list when it went to OMB, so a characterization that it was removed through that process would just not be accurate.

My understanding is that BPA, when the agency did the CCL 3 list, did not meet the criteria we had in terms of our understanding related to the known health effects associated with it. It is found in drinking water, but that the knowledge we had related to known effects associated with the compound, it did not meet the criteria that we use for listing chemicals under CCL 3.

Mr. MARKEY. And back to you for a final question, Dr. Solomon. We often hear that the European Food Safety Authority thinks that BPA is safe and that we therefore don't need to worry about it in this country. However, just a few days ago, the Danish parliament voted to ban BPA in children's products, and a spokesperson for the European commission indicated it is looking at new scientific evidence.

Do you agree with the European Food Safety Authority's current policy on BPA? And if not, what did it get so wrong?

Dr. SOLOMON. The European Food Safety Authority's review of BPA was based on a fairly limited review of the data that focused on a number of the studies done by industry, and it unfortunately did not include many of the most important independent studies done by academics. And so, I am very pleased to see that the Danish authorities and that others, such as the Canadian government, have been reevaluating the science more fully, that the FDA is doing so as well because there is really a very extraordinary amount of science showing a serious concern related to health effects at low levels.

Mr. MARKEY. Thank you, Dr. Solomon. Chair recognizes the gentleman from Florida, Mr. Stearns.

Mr. STEARNS. Thank you, Mr. Chairman. Dr. Borgert, the chairman brought up this BPA, and he has made quite significant statements on it. In your opinion, should BPA be totally banned? I know it is omnipresent in very small quantities in everything from eyeglasses to liners in cans and everywhere. So I mean I will just give you a chance to respond since he has asked these three witnesses, what your opinion is.

Mr. BORGERT. Well, thank you, sir. I have not formally reviewed all of the data on bisphenol A, but I know that it is still controversial among some. But I know that a number of well-qualified groups that have determined that at the levels people are exposed

to and that are in the environment in the food supply, et cetera, are present at levels that are unlikely to pose any significant human risk. And they do that not based on limited studies. They do that based on studies on comport with generally those three tenets that I explained.

It is important not only that we look at the quality of the data, but we look at the quality of the methods we are using to select the relevant data. And so when you select the relevant data that are of high quality, you don't come out with an answer that BPA is a significant health concern. You come out with a different answer, and many well-qualified groups have done that.

So no, I think it would be a mistake to rush to regulation. I think we need to use the best science, and that science needs to be vetted not on the basis of stakeholder opinions but on good science.

Mr. STEARNS. So in your opinion right now there has not been the scientific study done to totally ban it? Is that——

Mr. BORGERT. I don't think the science would support that.

Mr. STEARNS. OK, so it is your opinion that science would not support the total banning of the BPA as the levels we are using it today in America?

Mr. BORGERT. Correct.

Mr. STEARNS. Is that your opinion? And has there been any demonstrable evidence that in the levels we are using it, any science to show that it is harmful in the levels we have? Where is the people that are saying for the ban? Where are they getting their evidence to say it needs to be banned? You have a Scandinavian country saying they are banning it. So there must be some scientific evidence somewhere to back it up?

Mr. BORGERT. Well, there are many, many studies conducted on BPA that can be used to raise concern.

Mr. STEARNS. As well as to raise not concern.

Mr. BORGERT. As well as to raise questions.

Mr. STEARNS. Yes, so there are all studies across the spectrum is what you are saying?

Mr. BORGERT. That is correct, but when we select the highest quality studies that are most relevant for the question, we don't come up with the answer that it poses a risk and that it should be banned.

Mr. STEARNS. Why do we use it so omnipresent everywhere? It is because it works in an efficacious way?

Mr. BORGERT. Well, it is a plasticizer that enhances physical properties of the plastics. I am not a chemist who could——

Mr. STEARNS. No, I understand.

Mr. BORGERT [continuing]. Explain that to you fully. But there are benefits to the products that are in the marketplace, and if we choose different alternatives, they may not confer the same benefits. We may actually incur real risks like bacterial infections, et cetera, if our products are less effective.

Mr. STEARNS. Let me go to the heart now, the hearing we have here. So far, what chemicals are classified as proven endocrine disruptors in human? I mean that have been scientifically proven to be disruptors in humans? Do you know?

Mr. BORGERT. Well, I haven't prepared a list, and so I would hesitate to go on the record and provide one, but——

Mr. STEARNS. Sixty-seven are being studied by the EPA. And then some of those have been pulled off. But I mean do you have a list in your own mind's eye of the number of disruptors that actually could be classified?

Mr. BORGERT. Well, no, and I think that is a large unknown at this point.

Mr. STEARNS. So it is still unknown. I mean regardless of what we hear, testimony and so forth, but there is nobody that scientifically has classified as proven endocrine disruptors in any studies that affect humans. Is that true?

Mr. BORGERT. Well, it is not that there are no chemicals that I think we could call endocrine disruptors. I think diethylstilbestrol is a classic example. I think that many of the drugs that we use today are used for their hormonal activity and that at that certain doses in certain people are certainly going to disrupt the endocrine system.

I think that other chemicals in very high doses may be able to do that, but we have to consider two things: the dose and the potency. In other words, how much of it there is and how strong it really is. So doing animal studies where we give doses that may not reflect the human situation or the human physiology are not able to tell us whether a compound is an endocrine disruptor in humans.

And I want to clarify that the endocrine disruptor screening program won't do that for us either. It is a screen. It simply tells us which chemicals really deserve a close full-fledged definitive test and which are of lower concern. We don't even know that the battery is going to be effective for that yet until the data from this first 67 comes in and we have time to digest it.

Mr. STEARNS. OK, my questions are over. Based on what you are saying, we don't—also the dosage at which they are damaging is very crucial is what you are saying. And that is part of this whole difficult challenge is to get a hold of, OK, this chemical is bad, but at what dosage is it bad? And that is probably what you are alluding to. Thank you, Mr. Chairman.

Mr. MARKEY. Thank the gentleman. The gentleman's time has expired. The chair recognizes the gentlelady from California, Ms. Capps.

Mrs. CAPPS. Thank you, Mr. Chairman. I mentioned in my opening statement my background as a public health nurse. And working so many years as I did with my local public health department—and I know this to be the case amongst many public health agencies throughout our local communities across the country—this is a very important topic to our local health directors and facilitators.

I want to ask several of you short questions, if I could, back and forth way. Mr. Jones, starting with you. I am concerned that the screens that EPA is using to test a very short list of possible endocrine disruptors will not even begin to capture the long list of chemicals being reported in drinking water supplies today. This is a bit of a repeat to what the chairman has already asked you, but I want to get it clearly on the record.

Once an endocrine disruptor is identified through your screening, will that be adequate to regulate it?

Mr. JONES. The first step in the process is to screen for potential interactions with the endocrine system. Chemicals that come out of that process as positive will then go into a more in-depth testing regime that it is that information, a tier two test, that will give us the information that is necessary for regulating.

Mrs. CAPPS. So after tier two, then you can regulate?

Mr. JONES. That is correct.

Mrs. CAPPS. How long does that process take usually?

Mr. JONES. Going from today the 67 chemicals that have been tested up through having the results of the tier two test is going to be about five plus years.

Mrs. CAPPS. Five years?

Mr. JONES. That is correct.

Mrs. CAPPS. That is remarkable. Dr. Solomon, what steps are necessary to determine if regulation is needed once an endocrine disruptor is identified through screening? You talked about this in your statement.

Dr. SOLOMON. When an endocrine disruptor is identified, you know, I think there is a public health imperative to take action.

Mrs. CAPPS. Immediately?

Dr. SOLOMON. And so, you know, the EPA moves at its own pace, but it really needs to move quickly on these chemicals. And the ones that are known endocrine disruptors, that have been sort of sitting in the queue——

Mrs. CAPPS. Yes.

Dr. SOLOMON [continuing]. Or even put back into the queue, for example, numerous phthalates that I would already classify as known endocrine disruptors are now going through the first tier of screening, entering 5 five-year process at a point when they actually should be gainfully heading toward regulation.

Mrs. CAPPS. Well, you know, and the interesting thing is when the public knows, when the parents of the school kids I used to work with understand that there is a problem, they don't want to wait 5 years. Their children will be adults by then, and the damage will have been done. So I hear your urgency.

Back to you, Mr. Jones. Does the Safe Drinking Water Act provide EPA with the necessary mechanisms to regulate the chemicals being identified as endocrine disruptors?

Mr. JONES. The Safe Drinking Water Act provides the necessary tools to do that. I will point out that the testing for endocrine disruption under the Safe Drinking Water Act was discretionary authority, which, I think, probably explains why it has not been——

Mrs. CAPPS. Do you believe it should be discretionary?

Mr. JONES. I will leave that up to——

Mrs. CAPPS. OK.

Mr. JONES [continuing]. Congress. We are now exercising our discretion, but it was discretionary in that we——

Mrs. CAPPS. I hear you. Back to you, Dr. Solomon. Do you think EPA has an effective mechanism to regulate the chemicals being identified as endocrine disruptors? And if you don't, what should that mechanism be?

Dr. SOLOMON. One of the problems with endocrine disruptors that came up was this issue of low doses, and EPA's regulatory mechanisms in general are not very good at dealing with the kind

of unusual data where a chemical may have one set of effects at a high dose and a different set or even more severe effects at low doses at key periods of infant development. And this is really where we, you know, where the regulatory system stumbles.

Mrs. CAPPS. And where groups like yours and Dr. Birnbaum's can be perhaps useful in updating some of the procedures? That was a question kind of.

Dr. SOLOMON. Yes, I certainly hope and believe that EPA is starting to look at these issues more seriously in all of the environmental media.

Mrs. CAPPS. Dr. Birnbaum, I want to make sure that—because you have been nodding as I have been asking other questions. Does NIEHS have the capacity to provide the science and the protocols needed to regulate the chemicals being identified as endocrine disruptors?

Ms. BIRNBAUM. NIEHS has a long-standing program in studying endocrine disruptors. In fact, in 2007, we convened a panel of over about 35 different experts from across the country and across the world looking, for example, at the issues of BPA. And the consensus of that panel was that BPA was an endocrine disruptor and was causing effects in multiple different animal species, not just rats and mice, and that there was evidence that there was at least the potential to cause those effects in humans.

Since that time, the NTP Seer Panel has issued the report which again was an extensively peer-reviewed report involving many experts, which concluded that there was some concern for a number of developmental and reproductive endpoints including development neurological effects following exposure to BPA.

At the same time, we have continued to fund additional work to look at the issues not only of BPA, but of many other endocrine-disrupting chemicals. So I would say that there are demonstrated endocrine-disrupting effects of a number of chemicals in humans. There are now several epidemiology studies that cannot prove causality but can demonstrate associations between, for example, BPA and developmental neurobehavioral changes in children between cardiovascular effects, between diabetes, for example. Again associations, but they are backed up by our animal studies.

I think one point I would like to make is that we need to be careful when we talk about low dose. What I think many of us should be meaning when we talk about low dose are what are the levels that are present in people. So the epidemiology studies I referred to BPA, for example, are being seen in the general population. These are not necessarily high levels of exposure.

And when you do animal studies, what you really need to understand is not how much you give the animal, not how much is in the drinking water, but how much is in the animal if you want to compare the effects in animals to the effects in people. And under those conditions, we often find that the puditive high-dose animal studies in fact are not high dose at all.

Mrs. CAPPS. Thank you, Mr. Chairman, for allowing this to go forward. It appears to me, if I could just put these comments that the three of you have made together, that the scientific community in many resources in many settings has done a lot of studies that could be very useful to the EPA in terms of perhaps updating or

looking in more depth at what the sciences has out there and that would be very valuable for the public to have the benefit of. Thank you very much.

Mr. MARKEY. The gentlelady's time has expired. The chair recognizes Dr. Burgess from Texas.

Dr. BURGESS. Thank you, Mr. Chairman. And, Mr. Chairman, just for a point of clarification, have you introduced a bill to ban the EPA or BPA? Because I was almost ready to sign on to your bill——

Mr. MARKEY. I know that the governor's race in Texas is turning on that question, OK. It is amazing watching it from afar.

Dr. BURGESS. Thank you for that clarification. Dr. Borgert and perhaps Dr. Solomon as well, Mr. Stearns was questioning you just a moment ago. We were kind of getting into the questions between dosage and potency, Dr. Borgert. Dr. Solomon, you were either nodding your head or shaking your head while that was going on. Did you have something you wanted to add to that discussion about the discussion of potency and dosage?

We all know anything in the wrong dosage, water intoxication can happen. Water is generally regarded as safe, but there are people who are injured, and in fact, there have even been deaths from overdoses of just simply water. So what about this issue of dosage and potency?

Dr. SOLOMON. Hormones are almost unique in the way that they act in our bodies because there are receptors on our cells that are basically sort of scanning our bloodstream for even minute traces of these hormones. And those receptors are primed basically hugely magnify the cellular and organ system response in our bodies to even slight hormonal fluctuations.

So actually it is almost like a megaphone into the cells in our bodies when even a trace amount of a hormone enters our bloodstream, and that is true of natural hormones. It also is true of many endocrine disruptors.

Dr. BURGESS. I don't mean to interrupt, but I have only a short period of time. And you know how testy the chairman is with the person who sits immediately to his left. There is also a question of how rapidly that compound is metabolized in the body. Some are metabolized rapidly. Some will tend to have a cumulative effect. That may have been what Dr. Birnbaum was just referring to, that there are some things that will just sequester in the body and leave only more slowly. And, in fact, there may be populations where this behaves differently as we learn more and more about medicine.

There may be people who are—I think this is some of the things we have learned about Gulf War syndrome and how quickly people are able to metabolize or not metabolize some of these organic phosphate compounds. So that is a lot of stuff to have to put into the equation. Dr. Borgert, did you want to say something about that?

Mr. BORGERT. I do. Thank you. Potency is important, but it is potency at the receptor. And the hormone system is not unique in utilizing receptors. The neurological system uses the same concept. So the receptor-based physiology, receptor-based pharmacology is actually, you know, a cornerstone of the way we understand many sys-

tems work. And it is the potency of the molecule of the drug or the chemical at that receptor that is important.

I want to put this into perspective for you. A very fine study by a scientist, the group Katsenel and Bogens Group, not working on endocrine disruptors per se, but looking at steroid hormone receptors showed that testosterone can activate the estrogen receptor. Now, testosterone is the basic male hormone. It is not an estrogen, but at its very low potency at the estrogen receptor, but it can activate it.

And so we need to consider these potency issues, and we need to remember that these low-dose theories are theories. In some instances, they may tell us that compounds are having adverse effects. In other instances, the import of those low-dose effects may be compensatory and adaptive and merely tell us that the system is working well to manage the tens of thousands of chemicals that we experience in our natural environment as well as the synthetic chemicals. Thank you.

Dr. BURGESS. It has been a while since I have dealt with the biochemical aspects of this, but there are also places in the body where, in an extraglandular way, hormones can be produced in fat cells, for example. Estrogen can be—under the right circumstances, fat cells, adipose cells can produce estrogen if they are given the right precursors in the right setting.

The reason I am bringing all this up is we passed a bill in the last Congress, H.R. 4040, the Consumer Products Safety Improvement Act, and the unintended consequences of that. The bill passed for the best of reasons. I voted for it. We passed that bill, and the unintended consequences have just been extremely disruptive for the American people that have to live under the legislation that we passed.

I have motorcycle dealers who sell motorcycles that are designed for young people, youth motorcycles, which they are now not sure that they can sell because of the battery is taken out of the motorcycle and ingested, the lead levels, of course, would be horrendously high. And under the language of the bill, the lack of flexibility that we built into the language of the bill, I have motorcycle dealers in my district that tell me they have vast quantities of inventory that they can do nothing with. They can't send it back. They can't sell it. They can't even sell parts to people who have previously purchased devices and come in for help.

So it gets to your point, Dr. Borgert, about being so careful about this not wasting resources on chasing things that may be of minimal to no impact. But also then the downstream consequences of legislation are significant. There are some crystals that might have lead in them only if you pulverize them to a fine powder and ingest them. And, of course, the molars of a very young child are not capable of that level of grinding even if they were to ingest the rhinestone. There are multiple examples, and I have people through my office all the time who come and tell me about the bad things I did while I was trying to be protective of the public good with the CPSIA through this committee. You like you wanted to say something to that.

Mr. BORGERT. Well, I just wanted to agree, and I wanted to summarize, I think, what you are saying is, you know, there is always

time after we realize we have made a mistake to go back and correct it. We have to do that. It is a shame there is often not enough time to be deliberative and get it right the first time. And I think we want to take that lesson here.

Dr. BURGESS. Well, the other part of the lesson is with the change of administrations and the change of people at the Consumer Product Safety Commission, we haven't made those changes. And we have left people hanging with either inventory that they cannot sell, resale shops that don't know because of the level of lead testing we have required is not even available in some areas. Can we resell these books or toys? Libraries that don't know if they can leave vinyl-covered books on their shelves.

It is a huge problem that we created in this committee, and 2 years later, we are not even talking about fixing any of those problems. And the agency now with a different head—and not that they are not good people—but the agency is focusing on new things and not looking at correcting the problems that we caused.

This is one problem the Bush Administration didn't cause. Yes, he signed the bill, but we caused the problem. And it has not been fixed.

Can I just ask one additional question? With all the stimulus money we spent on computer IT, and you referenced a lot of the data, Dr. Birnbaum, that you have. Are you getting that stuff electronically in a place where you can search it and where those databases are actually going to be useful to you? Because you have collected a lot of data. You are continuing to collect a lot of data. But is it in a format that will actually be useful to us?

Ms. BIRNBAUM. Thank you very much for the question. All the, for example, published studies are available electronically on the Web site. All the approximately $10 to $15 million that we are funding under the American Recovery and Reinvestment Act, all the information about what those studies are, who has conducted them, what these objectives are of those studies, are available on the usagovernment.recovery Web site as well as on our NIEHS Web site. And those results, as they come to fruition, will all be available for the general public.

Dr. BURGESS. What sort of backlog do you have with putting data in there?

Ms. BIRNBAUM. Excuse me?

Dr. BURGESS. What sort of backlog do you have with putting the data in there?

Ms. BIRNBAUM. It goes on almost as soon as it becomes available.

Dr. BURGESS. The historical that has been collected.

Ms. BIRNBAUM. All the historical data is currently available right now.

Mr. MARKEY. OK, the gentleman's time has expired. We thank the gentleman for identifying a problem that was not created during the Bush Administration. That is also very helpful, I think, historically. The chair recognizes the gentleman from California, Mr. McNerney.

Mr. MCNERNEY. Thank you, Mr. Chairman. I am recovering from laryngitis so I don't know if I have 8 minutes of voice or 9 minutes to compete with the gentleman from Texas, but I will give it a shot.

I am glad that he was as concerned about your testiness on this issue as he is.

Mr. Jones, we have a town in my district, Morgan Hill, that has a large perchlorate spill in the region. Now, California has set pretty good standards for perchlorate, but there is no national standards in place. Do you think that would be a good idea to move forward with a national standard for perchlorate and other endocrine disruptors?

Mr. JONES. Thank you, Mr. Congressman. The agency is going to make a determination this year as to whether or not we feel it is appropriate to establish an MCL, maximum contaminant level for perchlorate. That is referred to as a regulatory determination under the Safe Drinking Water Act, and in 2010, that decision will be made.

Mr. MCNERNEY. Then your opinion is not to be given this morning?

Mr. JONES. I am sorry. We are trying at EPA to coordinate better across our offices. I am actually not in the office that manages the Safe Drinking Water Act. I am in the office that manages the endocrine disruptor screening program, so although I am familiar with where the office of water is with respect to that determination. Because I am not intimately familiar with the facts around perchlorate, I think it would not be wise for me to offer an opinion on that.

Mr. MCNERNEY. OK, thank you. Dr. Solomon, do you think the Safe Drinking Water Act worked effectively in regulating hazardous chemicals in drinking water? And if not—and I suspect that you are going to say that you don't—do you have specific recommendations?

Dr. SOLOMON. The Safe Drinking Water Act as amended in 1996 required the creation of these various candidate contaminant lists. We are now on the third iteration, and in each case, EPA has gone through an extensive exercise to create the list and then has actually not taken any action to regulate any of the chemicals on these priority lists and has simply moved on to create another priority list.

And so I am very much hoping that, you know, EPA will take action and start setting some regulatory standards on these chemicals. There is now well over 100 chemicals that have been identified as priorities, and, you know, on the CCL 3 as potential priorities. And a number of those really do need to move forward.

Mr. MCNERNEY. So in other words, you don't think they have been that effective so far and could be more effective?

Dr. SOLOMON. Yes, EPA does have the authority to, you know, take the action that it needs to, but it is, you know, since it just needs to make a determination, it can, you know, on each of the previous CCL lists, the determination has just been that various chemicals did not need to be regulated.

So it is very easy for the agency to avoid taking any action if it doesn't want to take action.

Mr. MCNERNEY. Thank you. Dr. Borgert, good morning.

Mr. BORGERT. Good morning.

Mr. MCNERNEY. You know I was a scientist or a mathematician in a past life. So I appreciate your comments about having repeat-

able science; however, I think the people in Morgan Hill would say there should have been precautions taken before they put the perchlorate in the ground even though they didn't know it was an endocrine disruptor and a cancer-causing agent at that time.

So my point is that when human health is at risk, when human health is on the line, we shouldn't wait for permanent or absolute certainty. Absolute certainty in science is very, very hard to come by, and if we wait for absolute certainty, we are going to be dying from all kinds of problems.

So I think we need to put some sort of risk into the consideration in making these kinds of decisions even though absolute certainty has not been achieved. Do you have a comment?

Mr. BORGERT. Yes, I do. I couldn't agree with you more that we need to be precautionary when we actually know what the risks are. But let me give you an example of what can happen when you think you know what the risks are and, in fact, you don't fully appreciate them.

Now, I think you gave us an example with perchlorate in the drinking water. And certainly I am not an engineer, but if there were good and valid methods, engineering methods for protecting against that, maybe those precautions should have been taken.

But on the human health side, I want you to consider the example of dietary fat. There was a day when we thought fat was, you know, across the board a bad thing, and we tried to eliminate, many of us did, tried to eliminate fats from our diet.

Today many of us take fish oil, which is a fat. With a little more reliable research and a little more understanding, we recognize that what we thought was a precautionary approach may actually have been harmful. It is not good to remove all the fat from your diet. Some are very beneficial.

So sometimes you act with very good intentions to do what you believe is precautionary, and because you have rushed to judgment, you actually have done the opposite of what you intended.

Mr. MCNERNEY. Well, I don't know that we need to rush to judgment, Dr. Borgert, but I think we need to be precautionary when there is evidence, even association, that there is risk. I think we need to be precautionary and take steps ahead of time before the city of Morgan Hill has a $100 million cleanup on their hands and no company left again to do the cleanup.

And I think across the board when there is evidence and associations of risk, we need to act accordingly. Mr. Chairman, I don't have another 3 minutes of voice, so I am going to refer back to you.

Mr. MARKEY. Thank you. William Shakespeare said that brevity is the soul of wit, and I think you got right at the heart of the matter, and we thank you for that.

The gentleman from Texas, Mr. Green.

Mr. GREEN. Thank you, Mr. Chairman. I would like to ask unanimous consent to place a statement in the record.

Mr. MARKEY. Without objection, it will be so ordered.

[The prepared statement of Mr. Green follows:]

Congressman Gene Green
Subcommittee on Energy and Environment
"Endocrine Disrupting Chemicals in Drinking Water: Risks to the Human Health and the Environment"
February 25, 2010

Mr. Chairman, thank you for holding today's hearing on "Endocrine Disrupting Chemicals in Drinking Water: Risks to the Human Health and the Environment."

Protecting our nation's drinking water supply from contaminants and microbiological diseases is of utmost importance to communities across the nation.

Of particular growing concern is the presence of endocrine disrupting chemicals, or EDC's, and their potential health impacts on humans and wildlife.

The prevalence of EDC's in consumer products, food, pharmaceuticals, and the environment have led scientists and the federal government to evaluate the impact of EDC's on endocrine systems.

Several studies have linked EDC's to increased birth defects, premature births, infertility, or even cancers.

Increased levels of certain chemicals in the ambient environment have also led scientists to find abnormal impacts on insects and aquatic life, including the discovery of intersex fish species in the Potomac River.

As a result of these concerns, Congress directed the Environmental Protection Agency (EPA) in 1996 to create an endocrine-disruptor screening program for drinking water and pesticide contaminants.

Surprisingly, it was not until October 2009 that the EPA issued the first test orders for the program, identifying 67 chemicals to undergo Tier 1 testing.

That same month, the EPA also published a list of unregulated drinking water contaminants that may require regulation under the Safe Drinking Water Act.

I look forward to learning more from the EPA today about the status of these regulations and research on these chemicals.

I also look forward to continue working through Congress to address the health and safety of our water supplies.

That is why I am an original cosponsor of the Safe Drug Disposal Act of 2009, introduced by my good friend and colleague Rep. Jay Inslee, which seeks to keep chemicals from prescription drugs – including EDC's -- out of our drinking water supply.

I also supported the Safe Drinking Water for Healthy Communities Act last Congress to set a time line for the EPA to set a national drinking water standard for perchlorate, a known EDC.

Thank you Mr. Chairman. I look forward to the testimony this morning of our distinguished witnesses.

I yield back the balance of my time.

Mr. GREEN. Dr. Solomon, this is for you and I would enjoy hearing other on the panel that has an opinion. Some have suggested that the present endocrine disruptors in drinking water isn't really that alarming because the levels at which they are detected are so low.

First, are there adverse health effects associated with low-dose exposure to these chemicals?

Dr. SOLOMON. There are a few reasons why I am concerned about these chemicals in drinking water. One was actually raised by the chairman and other members of the committee, which is the fact that wildlife populations exposed to some of these source waters in which various low doses of endocrine disruptors are present are showing abnormalities such as the intersex fish seen in the Potomac River and in many other rivers and streams across the United States.

I am also concerned because there are quite persuasive data showing that multiple chemicals can actually act together to create greater effects as mixtures or at least additive effects. And there are complex mixtures of various endocrine disruptors. As I mentioned in my testimony, up to more than 30 chemicals in a single water sample have been reported by the USGS.

And in addition, I am concerned because of the remarkable sensitivity of hormone systems, not so much in the adult, where, as Dr. Borgert mentioned, there are some ability to sort of almost, you know, respond or buffer some alterations in hormones that occur, you know, transiently or even longer term, but in fetuses and infants where short-term alterations in hormones can actually have long-term effects on normal development. And so it is really those populations that I am most concerned about.

Mr. GREEN. My second question, and again open it to the panel. What you are saying then is when someone is exposed to low doses from several different potential endocrine disruptors has a problem, so you answered the second question. Dr. Borgert or anyone else have a response to that question?

Mr. BORGERT. Yes, I do. I think it is on point and raises an issue of one of the things that Dr. Solomon said. Mixtures are definitely an important area of research. I have devoted a large portion of my career to that, have several publications on it. About a year ago in December, I addressed the National Research Council on the issue of mixtures of pharmaceuticals in the water supply.

And here again my message was similar. We need to rely on demonstrated scientific methods, and it hasn't been demonstrated by any stretch of the imagination that these very low levels of chemicals with low potency actually have synergistic effects or even additive effects at the levels in the environment at which we encounter them.

At higher levels, perhaps, but one of the rules of mixtures is what happens at one level and one ratio of components is not predictive of what happens at other levels and other ratios of those components. So we can't make those extrapolations. And one of the things we know is it is incorrect to do that, so it is best not to do that.

Mr. GREEN. Obviously we have a difference here from both our doctors.

Ms. BIRNBAUM. I would like to comment on that, if possible.

Mr. GREEN. In fact, let me actually get you a question though. Obviously it has been suggested that although endocrine-disrupting affects animals, it has been demonstrated humans are better able to deal with low doses of chemicals without suffering adverse effects. Can you talk about the low dose issue earlier? And along with that, are humans any different from other animals that may consume drinking water?

Ms. BIRNBAUM. Nature is inherently conservative, and the endocrine system is well conserved across from fish to amphibians to all the way up to mammals, and that includes us. There are numerous effects of endocrine effects in wildlife, not only fish, but for example amphibians, bird, and mammalian wildlife as well as beginning, we are seeing effects in people.

I have to say that there is a great deal of data on mixtures at low environmentally-relevant concentrations for a number of different endocrine kinds of effects, effects on estrogens, effects on the androgen system, effects on the thyroid system, which demonstrate in animal models that additivity—at low concentrations again I am talking about. I am not talking about high levels. I am talking about low levels—appear to act in an additive fashion. So I think we have a real issue when we look at one chemical at a time instead of looking at multiple chemicals at low levels in the body at a time.

Mr. GREEN. And again is there research being done now on the low level for multiple exposure?

Ms. BIRNBAUM. Yes, there is. We are funding a great deal of research in that area, and I should mention that I have published extensively myself in this area of mixtures, and it is very important that you work at low levels because if you go to very high levels, I agree with Dr. Borgert that different things can happen. But you need to work at low levels.

And we are funding work. For example, we are actually funding some studies right now at the Environmental Protection Agency's Office of Research and Development to look at the interaction of multiple phthalates which have been shown to interact additively in blocking androgen action.

Mr. GREEN. Thank you, Mr. Chairman. Any other response from anyone on the panel?

Mr. BORGERT. Just one. I think we are using qualitative terms like low doses, and I think we have probably a difference of viewpoint on what is low. And I don't think that it has been demonstrated that the levels of these chemicals to which humans are exposed are acting in an additive fashion. That is an unresolved question, and again my caution I think have stated.

Mr. GREEN. Well, and again no matter what level we make the low dosage, the concern and the question was low dosage of a multiple number of endocrine disruptors in low dosage because we may not have a high dosage. But because of our lifestyle, we have multiple opportunities to have that.

So thank you, Mr. Chairman. I know I have run out of time.

Mr. MARKEY. Gentleman's time has expired. Chair recognizes the gentleman from Louisiana, Mr. Scalise.

Mr. SCALISE. Thank you, Mr. Chairman. A couple of questions. First for Dr. Birnbaum. I think you had spoken or there was something written about your agency a few months ago that there were a number of research grants to university professors and others as part of the stimulus bill that, I think, totaled somewhere around $30 million. Primarily they were supposed to be used to conduct additional research on BPA. Can you tell me what processing criteria you used through the agency for the awarding of the grants and then also if you can give us an idea of how many new jobs were created by that stimulus money?

Ms. BIRNBAUM. The stimulus money, we funded somewhere in the neighborhood of $10 to $15 million worth of research on BPA. The process that was used by NIH to give the stimulus money as part of our usual very, very extensive extramural peer review process. So some of the BPA work was funded under a special program coming from funding partly directly from our agency and partly from the office of the director, which is called the Challenge Program and the GO Program. And these were for high-priority needs to address health effects in the Nation.

So that there was a request made for innovative research to address projects. The GO projects, known as the Grand Opportunity, were for projects. And in our agency, one of the topics that we put out was for understanding and expanding our knowledge base on BPA.

We have funded 11 specific grants that are looking at the effects of BPA. These are effects looking at cancer, both prostate and mammary, but looking at the immune system, looking at developmental neurological effects, looking at cardiovascular effects and a variety of animal models.

In addition, BPA has been in our sites for a number of years and in our regular extramurally-funded and peer-reviewed grants programs. We are looking at effects of BPA in human populations as well, and as I mentioned, one of the first results from that was recently published in the peer review literature, clearly needs to be repeated, but demonstrates an association between the mother's exposure of BPA during her first trimester and neural behavioral effects in her children of 2 years of age.

We are also funding ongoing studies with FDA to look at long-term effects in both rats and mice to BPA. We are also funding some studies in our intramural program in collaboration with outside investigators.

Mr. SCALISE. I apologize for pulling back because I am limited on my time.

Ms. BIRNBAUM. I was going to mention the——

Mr. SCALISE. But I did want to ask—and I don't know if all those grants you were talking about, how much was stimulus money versus just regular department money.

Ms. BIRNBAUM. About $10 to $15 million.

Mr. SCALISE. So all that $10 to $15 million of stimulus money which was supposedly brought forward to create jobs, how many jobs were created with the $10 to $15 million of stimulus money?

Ms. BIRNBAUM. Specifically with the BPA, I can tell you with the approximately $168 million of funding that NIEHS was allotted to send to the extramural community with the stimulus money, that

that has funded about 300 different grants. And we know that new jobs—I am not talking about continuation of jobs—but new jobs was about 436 new jobs.

Mr. SCALISE. OK, and if you can get us the information on those new jobs.

Ms. BIRNBAUM. We can get you more specifics.

Mr. SCALISE. And specifically with the stimulus money portion, not your regular department.

Ms. BIRNBAUM. I am just talking about—the 430 plus jobs——

Mr. SCALISE. Right, but we were told during the passage of the stimulus bill that there would be transparency in actually tracking the jobs created with that money, not with other money, with the stimulus money. I am just asking you for that transparency if you could get that to me.

Ms. BIRNBAUM. I would be happy to provide it.

Mr. SCALISE. Thanks.

Ms. BIRNBAUM. I believe that is available——

Mr. SCALISE. Next question because I only have a minute left. During your written statement, you had mentioned that you try to ensure that focus on doing high-quality science or ensuring that its work adheres to the basic tenets of good objective science. Your statement didn't mention that. What I am asking you is would you give us a pledge that when you are doing this work that you would only adhere to the basic tenets of good objective science since that wasn't in your testimony?

Ms. BIRNBAUM. Peer-reviewed science stands the nature of time, and our studies are undergoing extensive peer review both in the funding of studies, in the conduct of studies, and in the actual publication of studies. The NTP studies, which are funded are considered the gold standard for traditional toxicity kinds of testing. I think it is very important to understand that science is moving on, and the best studies of 20 and 30 years ago may not be the best studies.

Mr. SCALISE. But would you base the decisions on the best science?

Ms. BIRNBAUM. My studies are always based on the best study of all the peer-reviewed science.

Mr. SCALISE. Thank you, and I yield back.

Mr. MARKEY. Gentleman's time has expired. The chair recognizes the gentleman from Washington State, Mr. Inslee.

Mr. INSLEE. Thank you. I am just looking at an article from the Seattle Times. I am from Seattle. In 2007, it talked about fish, English sole, carrying something in their bodies not supposed to be there, a protein usually found only in female fish with developed eggs. And we found these chemicals, and the article quotes sources of suggestion that birth control pills, plastic bottles, detergent, makeup, and more chemicals from various sources may be associated with that protein.

Dr. Birnbaum, first of all, I don't understand this biology as well as I should. Is that protein that this article is referencing the chemical itself, or it is an expression or result of the presence of a chemical that causes that protein to be there where it shouldn't be?

Ms. BIRNBAUM. You are talking about fatelegenin, which is a protein that is normally only present in female fish, and if the females are exposed to endocrine-disrupting chemicals, then in fact the males begin to produce fatelegenin. So just like in the Potomac River and parts of Puget Sound and many other waterways in our Nation, we are finding male fish that have eggs in their testes, and they are producing fatelegenin.

Mr. INSLEE. And what is that mechanism? I don't understand. You said if the female is—you mean the mother of the male?

Ms. BIRNBAUM. No, these are the fish, female fish produce fatelegenin, which is a protein that actually goes into making the egg. It goes into the egg and provides nutrition for the baby, you know, the developing embryonic fish. Males, when exposed to environmental endocrine disruption, they begin producing fatelegenin, and they also begin making eggs.

Mr. INSLEE. They pick it up from the water?

Ms. BIRNBAUM. No, they get the endocrine-disrupting chemicals from the water or food particles in the water. But then they make—that is their response to the disruption.

Mr. INSLEE. So is there a question about whether that is in fact occurring in our waters or not? Is that subtle science?

Ms. BIRNBAUM. I think there is extensive evidence for the presence of male fish producing female responses.

Mr. INSLEE. And is there any other hypothesis been suggested that it is other than endocrine disruptors that are causing this?

Ms. BIRNBAUM. I don't know of any.

Mr. INSLEE. Does anybody in the panel have any other hypothesis as to what is causing this other than endocrine disruptors?

Mr. BORGERT. I think it is important to understand what we mean when we say endocrine disruptors, and Dr. Birnbaum mentioned this, I believe, in her answer. But we don't know exactly which chemicals might be doing that, for instance, and there have been instances where we again rush to judgment on similar findings of fatelegenin in male fish in the U.K. And based on those preliminary suspicions, a number of products were taken off the market because they were suspected endocrine disruptors.

Turns out the most likely culprit was simply female hormones from human beings, and the water treatment plants were not up to snuff. They were not state-of-the-art, and they were not properly breaking down those compounds. Some of the compounds also may have been birth control pills.

So it is important to recognize that when you see an effect, that doesn't automatically tell you which chemicals might be involved. And so I think that is one of the critical questions.

Mr. INSLEE. So is it——

Mr. BORGERT. Brings up another—well, I just wanted to make a quick point is that our analytical techniques are now thousands if not ten thousand-fold better than they were a decade or so ago. So what would appear to have been a perfectly clean water sample a decade ago now looks very contaminated, and that is simply because our analytical techniques are so much better.

Mr. INSLEE. Well, I guess——

Mr. BORGERT. Finding what the cause is is not always easy.

Mr. INSLEE. What I am trying to get at is it relatively clear that the presence of maybe not specifically identified but generally defined as endocrine disruptors in our waterways are causing the presence of proteins in male fish that are not normally there. When I say normally meaning absent an industrial base that pollutes our water. Is that fairly well established, Dr. Birnbaum? I will just ask your opinion about that.

Ms. BIRNBAUM. Absolutely.

Mr. INSLEE. OK, Mr. Jones?

Mr. JONES. Yes, I would agree with that.

Mr. INSLEE. Dr. Solomon?

Dr. SOLOMON. Yes, I would agree with that.

Mr. INSLEE. And Dr. Borgert?

Mr. BORGERT. Yes, I would agree that it can happen. I would have to disagree though that that is always the case. We don't know of all the factors that might affect that, and in some instances, their habitat alterations for other effects that cause other effects that may lead to the same thing. I don't think we have unraveled the story completely.

Mr. INSLEE. But we don't think it is sunspots, right? I mean we would agree we don't think there are sunspots? That is a rhetorical question.

Mr. BORGERT. I haven't heard sunspots.

Mr. INSLEE. Well, we have heard sunspots blamed for a lot of significant global activity. We just wonder if this is another one of them. Mr. Jones, can you give me sort of a lay answer that I can convey to my constituents on what percentage of chemicals that in the realm of possibility could be considered endocrine disruptors will be adequately tested by X date that we can tell our constituents that will have been receiving an appropriate level of the screening to determine whether or not they present a human health risk? Could you give me percentages by certain dates on the current track that we are on?

Mr. JONES. The current track that we are on will take many years to tell you what that percentage is. The universe of chemicals in front of us include a thousand pesticides, and people throw around the number of 80,000 industrial chemicals. It is probably actually more in the range of 40,000. So we are talking about tens of thousands of compounds. Under current techniques, it will take many years to evaluate them all. We are working very hard with our colleagues in NAHS and some other agencies within the executive branch to develop alternative methods that will allow us to test thousands of chemicals in very short periods of time.

That work, however, is not quite ready up to the task that we are seeking and that you are asking for. So I am hopeful that within the next 5 years those kinds of methods are available which will allow us to test thousands of chemicals in a matter of weeks as opposed to hundreds of chemicals in a matter of years.

But that is still developmental. Under the existing framework that we have, it takes quite a while to even do the screening test, and we are talking about a universe of, as I said, upwards of 40,000 chemicals that you would need to screen to be able to tell you which percentage——

Mr. INSLEE. Very quickly. Probably be a decade before we have 50 percent of these tests——

Mr. JONES. Absolutely.

Mr. INSLEE. —concluded? Thank you.

Mr. MARKEY. The gentleman's time has expired. And just for clarification, Mr. Jones, earlier you told me that BPA was not on the list of chemicals that EPA was using to examine the purposes of setting drinking water standards. But I had asked you why EPA didn't put BPA onto its chemicals of concerns action plan despite the data and the administrator's statements regarding her concerns about the chemical. Can you clarify?

Mr. JONES. Yes, and thank you for asking that. Going back to the CCL list part of my answer.

Mr. MARKEY. What does CCL mean?

Mr. JONES. The chemical contaminant list. That is the list of potential drinking water contaminants for regulation that was released last summer. It is not on that list; however, the work that is going on right now at the Food and Drug Administration, which we are working with them on, could ultimately lead to a different conclusion. So that work will inform future CCL lists.

As it relates to BPA as an industrial chemical as opposed to a drinking water contaminant, the agency is planning on in the not-too-distant future—and the administrator has spoken to this, and I think she actually testified yesterday at the appropriations hearing. That action plan is with the Office of Management and Budget right now going through interagency review, and we are hopeful that it will be publicly released in the very near future. So it could be on that last. Yes, it will be on that list.

Mr. MARKEY. OK, it will be on that list. OK, that is important. OK, so we thank you all for coming here today. It is a very important hearing, and we thank anyone who has been watching this hearing on C–SPAN today. The endocrine system for human beings is really just our computer system. It is just a computer, and like a computer, if someone hacks in to a computer and drops in a new virus, it can cause a tremendous disruption to a computer.

And there is one thing no one wants in America or in the world is for someone to hack in to their computer, for someone to add in a virus that can begin to disrupt it. No matter how small that virus might be, it is a big change in your relationship with the computer.

Well, the endocrine system is the computer system, and that is why we are so concerned about it, that the more that the water, other avenues, that are used in order to disrupt the endocrine system, the computer system for human beings, you start to get these very significant or even minor changes in the body. And it can have very significant changes in the way in which people live.

And so that is why it is so important, and since we are seeing significant changes over the last 30 or 40 years, whether it be, you know, autism or you go down the whole list, we are wondering what is happening? Why are we seeing so much larger identification of these problems in human beings?

And so, you know, scientists are like the detectives. They look around. They see what could have hacked in to the human being. What is different? What is going into human beings that weren't

going into human beings before especially as they affect children because that is when the system is most vulnerable?

That is when a computer is most vulnerable, when it is brand new. You know it hasn't quite developed all of its defenses yet. You haven't added in all of the software packages that can defend, and so it is much more vulnerable to changes, OK.

So that is why we are so concerned about it, and that is why I am concerned about BPA as it affects especially things that are close to children. That is what my legislation would be most concerned with, the kinds of things that children would be putting into their bodies because obviously that would have a more profound effect on the computer system of the body.

So we thank you so much for your testimony here today, and in the weeks and months ahead, we are going to be pursuing this very aggressively. And I want to make sure that the right things are done in order to protect against the things which we think have a higher likelihood of having an impact especially upon children in our country.

So we thank you all for your testimony, and I tell you what I am going to do. I am going to give each of you 1 minute to summarize what it is that you want us to remember about your testimony and would ask you to put it in as simple a language as is possible. And try to use as many monosyllabic words as you can in order to make it possible for us to in 1 minute understand what you are trying to tell us. We will go in reverse order of the opening statements, and Dr. Borgert—I am sorry as you are, I am sure, that Humphrey Bogart ever lived. That your name is constantly mispronounced. But we thank you, sir, for being here. Whenever you are ready, please begin. One minute.

Mr. BORGERT. Well, thank you for that opportunity, sir. I would just leave you with one admonition, and that is to make sure that the information we gather is based on repeatable science, that is based on reliable science, that is based on relevant science, and that the data be evaluated for themselves for the relevance and reliability and repeatability and not merely over what can be suggested or hypothesized from that data, but what the data actually show. And I think that is very important in any decision-making process that will involve regulation because we risk actually imperiling ourselves rather than protecting ourselves with faulty information.

Mr. MARKEY. OK, thank you. Dr. Solomon.

Dr. SOLOMON. Yes, as was the case around the health effects of tobacco, there were many, many years through questions being raised and, you know, claims that the science was not totally clear yet. And it is always easy to do that kind of thing because science is never 100 percent crystal clear. But we do need to act based on the information we have, and major medicine societies such as the Endocrine Society and the American Medical Association have concluded, I actually quote "the evidence for adverse reproductive outcomes in fertility, cancer, malformations, from exposure to endocrine-disrupting chemicals is strong."

So we need to look at the conclusions of these important medical organizations and move to take action to protect human health. Thank you.

Mr. MARKEY. Thank you, Dr. Solomon. Mr. Jones.

Mr. JONES. EPA is very worried about endocrine-disrupting chemicals not only in drinking water but in other media, and we are moving very aggressively in our testing program. Although, we are as frustrated as the committee is and many others of the public about how long it took to develop a testing schematic to evaluate chemicals for endocrine disruption.

We have done that now, and that testing schematic is ready to be deployed. And we will be deploying it aggressively I think as evidenced by the first orders that have gone out in the last three months and our commitment here today to begin using the discretionary authority in the Safe Drinking Water Act to begin screening chemical contaminants in drinking water in the very near future.

Mr. MARKEY. Thank you, Mr. Jones. Dr. Birnbaum.

Ms. BIRNBAUM. Fish, frogs, birds, and mammalian wildlife are our canaries in the coalmine when we talk about endocrine disruption. The doses that are causing these effects when you look in the animals are many times comparable to the effects that we actually are measuring in humans, and we are finding that essentially the entire American population has these chemicals in their body.

These chemicals are not associated with one health effect. They are associated with a multitude of health effects because what the hormones do is integrate everything in our body. They control development, and they control our normal way of life. Thank you.

Mr. MARKEY. Thank you, Dr. Birnbaum, very much. So we thank all of you for being here. I think the lessons that were learned is that in order to ensure that drinking water is safe that we must make sure that the endocrine disruptor screening program robustly and aggressively tests chemicals to see which ones cause endocrine-disrupting health effects and that the screening program adapts its tests to take advantage of new scientific advances and that we move in a way that does so in a very rapid process because the EPA additionally must move forward to regulate known endocrine disruptors without conducting redundant and duplicative tests.

When we have enough information, we are going to have to move because clearly there are families all across the country very concerned about the impacts, especially upon children. And as soon as we reach that level where we have enough evidence, I just think that we should err on the side of caution because some very significant things are happening amongst children in our country that we have not seen in previous generations. And we know it is related to this endocrine-disruptor issue.

So we thank you all so much. We are going to be working very closely with you in the months ahead. This hearing is adjourned.

[Whereupon, at 11:30 a.m., the Subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

Statement of the Honorable Joe Barton
Hearing on Endocrine Disruptors and their Effects in Drinking Water
Subcommittee on Energy and Environment
February 25, 2010

Thank you for recognizing me to provide an opening statement and thank you for calling today's hearing on a topic that is increasingly getting media attention.

Before I get to my remarks on the issue of today's hearing, I want to congratulate you, Mr. Chairman, and express my support for your efforts – in holding this hearing -- to remind certain committees in this Congress which committee has expertise and jurisdiction over drinking water programs. I think we do a pretty good job and we don't need the help of others to make a complicated process disjointed. If any House committee should be telling EPA what to do in the operation of its drinking water or chemicals programs, it should be this committee.

As far as the issue of endocrine disruption goes, I am more than interested to hear about this subject and ferret out what the actual science on this matter is from creative suppositions that sound appealing. We need an environmental policy in this country that is predicated on high quality science, whose results are repeatable, and whose objective is not to answer questions for which we already have decided the

answer. If we are not using science to make decisions, we should be honest and transparent enough to tell the public that opinions and not the actual science are the real pillars behind these decisions.

While I think there is enough data to suggest that there are substances that affect wildlife, I am much more skeptical about the universe of these substances that might translate to humans. I hope we will have a robust discussion to help inform us on that score. Further, if the route of exposure is drinking water, I think we need to be very clear that other actions, including waste and sewage management are appropriately factored into this equation concerning endocrine disrupting substances -- as well as the existing disinfection process used by today's community water systems -- to examine whether doses worthy of concern, not just detection, exist and require action.

We should find out today if public health trade-offs are being made based on decisions to eliminate chemical substances based upon minimal evidence and maximum uncertainty. We must ascertain whether politically popular substances are being focused on in this debate rather than ones – required by the Safe Drinking Water Act – to be addressed

first because they present the greatest health threats and are present or are likely to be present in drinking water.

We need to know that the Federal programs involved in this effort are using the funding we have given them in the most appropriate manner - that money is not being spent just to be spent and that a real plan is in place to obtain high quality results worthy of serious scientific scrutiny. Fundamentally, I think we should find out if these programs are focused on doing their statutory missions well rather than doing a lot of politically expedient things in a mediocre fashion. While I recognize that some are upset that certain Federal agencies haven't served them the results they wanted in the timeline they wanted, the fact is that high quality science takes time and we need to make sure those in charge are not hindered or blinded to ensuring high-quality, objective science answers questions to the best of its ability.

From my work in this committee on the Toy Bill, I am familiar with the claims and counterclaims of what threats are really posed by various chemical substances. We made some decisions in that bill that sounded like a good idea at the time based on some interesting, but not overwhelming science, and the results have turned out to be a nightmare. We need

to make sure that we are more critical in asking questions about science underpinning various regulatory and legal policies before making the same mistakes.

Mr. Chairman, I take this subject seriously. I think there are some substances that pose real problems. I am glad we have an expert panel to educate on this matter because I want to know more about how widespread of a problem we are facing.

I thank you for yielding me this time and yield back the balance of my time.

Congressman Michael C. Burgess, M.D.
Opening Statement
Subcommittee on Energy & Environment
Hearing entitled "Endocrine Disrupting Chemicals in Drinking Water: Risks to Human Health and the Environment"

Thank you, Mr. Chairman.

I think this is an important oversight hearing into the Environmental Protection Agency's process of monitoring and regulating certain chemicals which may be posing risks to human health via our drinking water systems. Having practiced medicine for 25 years before joining Congress, I made it a life-long mission to protect the health of those patients who came to me back home in Texas, and I believe I've continued that mission here.

Chemicals have become a pervasive part of our daily lives the globe over for the past century. Indeed, chemicals have made our lives better in a plethora of ways, responsible for medications and anti-bacterial hand soaps, providing affordable consumer products, and serving as cost

effective pesticides, protecting crops and humans from such things as malaria-causing mosquitoes.

However, the flip-side of any discussion on chemicals is the reality that certain chemicals in certain concentrations can indeed be harmful to human and animal health. We all know this. Utilizing chemicals to make our lives easier and safer comes with risks, and those risks must be balanced and weighed against the benefits the chemicals provide. This cost-benefit analysis can only be done after we are presented with solid, scientific findings as to the full harm any given chemical poses.

The EPA is best positioned to provide us with these scientific findings, and indeed this task falls most squarely within EPA's mission. In 1996, Congress gave EPA the tools to look into which chemicals could be posing harm to our health. Yet here we are, 14 years later, and we all sit behind this dais, scratching our heads and wondering what EPA has been doing for the last decade. It's almost incredible how quickly EPA can make scientific findings on climate change, which to hear some

people tell it, will kill us all in the decades to come, yet has sat on its hands in regards to whether the chemicals we are exposed to in our everyday lives are going to kill us in a matter of months.

I'm happy we are having this hearing, and I hope that shat comes out of it is that EPA will refocus its efforts on the true mission of the agency: protecting Americans in their everyday lives from harmful agents in the environment. EPA should leave saving the world to Congress.

American Water Works Association
The Authoritative Resource on Safe Water SM

Government Affairs Office
1300 Eye Street NW
Suite 701W
Washington, DC 20005-3314
T 202.628.8303
F 202.628.2846

Headquarters Office
6666 West Quincy Avenue
Denver, CO 80235-3098
T 303.794.7711
F 303.347.0804
www.awwa.org

Statement
for the House Subcommittee on Energy and Environment
on Endocrine-Disrupting Compounds in Drinking Water
February 25, 2010

The American Water Works Association (AWWA) would like to offer some comments on the subject of endocrine-disrupting compounds (EDCs) and pharmaceuticals in water. AWWA is the world's oldest and largest association dedicated to safe water. Our utility members serve safe and affordable drinking water to more than 80 percent of the American people.

Contrary to reports that characterize EDCs and pharmaceuticals in water as an entirely new issue, these substances were first reported in US waters by the U.S. Environmental Protection Agency (EPA) in 1975. The fact that more are detected today is a reflection of the increasingly sensitive analytical technology that allows us to identify and quantify diminishingly minute concentrations of these substances in water.

AWWA believes the critical question we must address is not "Do they exist?" but rather, "At what concentration are these compounds harmful to human health?" Only then can we make intelligent, rational decisions that protect the health of this country's municipal water customers.

AWWA is dedicated to protection of public health. Accordingly, we have intensively analyzed available information in the pursuit of ensuring the safety of the nation's water supplies, entirely without a federal mandate. In particular, we point to the research conducted by Dr. Shane Snyder, Research and Development Project Manager for the Southern Nevada Water Authority. The cities that participated in a study conducted by Dr. Snyder -- by submitting water samples for analysis -- did so in the absence of any regulatory requirement, being proactive and going well above and beyond the regulations in the interest of furthering understanding of this issue.

Dr. Snyder's studies have been transparent, and have been published in open literature and frequently presented in public forums. As a scientist, Dr. Snyder strongly cautions that in order to provide meaningful information on EDCs and pharmaceutical compounds in water, scientists need both occurrence data and human health effects information. It is scientifically inadequate to communicate solely on what we can measure at any level without a frame of reference for what that means.

AWWA has frequently been asked about the sources of these substances in our waters. We will not go into it here in detail, but will note that both nonpoint source runoff and sewage effluent from properly operated waste treatment plants may contain minute traces of these compounds. Some minute quantities of these products will pass through animals and humans who use them, and enter the waste stream. They are typically not completely destroyed or removed by waste water treatment processes.

A more central point about our studies is that the few EDCs and pharmaceuticals we did detect in US drinking waters occurred at unfathomably low concentrations. To illustrate that point, consider this: If Dr. Snyder's study had been constrained by the ability to find these compounds at parts-per-billion levels instead of delving into the parts-per-trillion range, none of them—not a single one—would have been found.

This raises the critical question we suggested earlier: are we going to make decisions based upon our ability to find contaminants, or based upon protection of public health? AWWA can say with absolute certainty that, if the country regulates contaminants based upon detection rather than health effects, we are embarking on a futile journey without end. The reason is simple: Decades ago, we could only detect contaminants at parts per million levels. Years ago, we advanced to parts per billion. We are now able to detect compounds at the parts-per-trillion level, and are breaching the parts-per-quadrillion boundary in some cases. The truth is that the concentrations of EDCs and pharmaceuticals found in water supplies are millions of times lower than a medical dose. Consider that the highest concentration of any pharmaceutical Dr. Snyder detected in US drinking waters is approximately 5,000,000 times lower than the therapeutic dose. This concentration is difficult to perceive, so consider these analogies. This concentration is roughly equivalent to ½ of an inch in the distance between the earth and the moon, or in terms of time, this concentration would be equivalent to approximately one second in approximately 750 years. Based upon Dr. Snyder's four-year study of the health relevance of trace EDCs and pharmaceuticals, using the highest concentrations found and the most conservative safety factors to protect susceptible populations such as infants and pregnant women, one could safely consume more than 50,000 eight-ounce glasses of this water per day without any health effects. Dr. Snyder's report, "Toxicological Relevance of EDCs and Pharmaceuticals in Drinking Water," published by the Water Research Foundation, 2008, concluded that the concentrations of EDCs and pharmaceuticals studied are on orders of magnitude lower than would pose a public health threat. We are not suggesting that this is the final, definitive study on this issue; in fact, we urge Congress to support further health effects research.

That said, the Safe Drinking Water Act already has established processes for identifying and regulating drinking water contaminants to protect human health. The Candidate Contaminant List and the Unregulated Contaminant Monitoring Rule are appropriate processes that entail great scientific rigor. We caution against regulating EDCs and pharmaceuticals any differently than the scores of contaminants currently covered by the Safe Drinking Water Act, because in reality they are no different. Our decision as humans to improve and extend our lives by using pharmaceuticals dictates that some infinitely small amount of these products can and will make their way into the environment. The fact that we can detect trace contaminants does not alone imply risk.

With regard to removing these compounds through treatment, Dr. Snyder's team tested the effectiveness of a diverse array of water treatment technologies on removal of pharmaceutical compounds, and to be certain, some technologies are more effective than others. However, back to the pinnacle question: is use of these treatment technologies going to be warranted to protect public health, because there are environmental and societal costs associated with using them. In an age where we are concerned about greenhouse gas emissions and energy efficiency, is it wise to dictate energy-intensive water treatment systems when there is no evidence of public health benefits? Additionally, there is a looming crisis related to aging water infrastructure that will require a vast financial investment by utilities. Should that be set aside so treatment to remove all concentrations of a compound is achieved?

So what should we do? AWWA believes the following steps make sense.

First, this issue does highlight the need to better protect America's sources of drinking water from various sources of contamination.

Second, clearly there is a pressing need for additional research on this issue. We understand there are concerns about the effects such chemicals have within the natural environment, as well as human health. We recommend that we focus on research related to health effects from trace EDCs and pharmaceuticals with a lesser emphasis on occurrence, in order to determine whether there is in fact a problem to solve.

Our additional recommendations are spelled out in more detail below:

1. EPA should work with states, water and wastewater utilities, and the agricultural community to minimize contamination of source waters by EDCs and pharmaceutical products as well as other contaminants.

It is imperative that the nation do a better job of protecting its waters, and especially sources of drinking water, from contamination. We have said previously that there is an imbalance between the enforceable controls on point sources, such as Publicly Owned Treatment Works, and the far less rigorous programs used to limit nonpoint sources of pollution, such as agricultural runoff. Congress may wish to evaluate this issue to assure that all sources of pollution are equitably contributing to the protection of the nation's waters.

2. We urge support for proper pharmaceutical disposal programs to reduce the flushing of pharmaceutical products into sewage systems to the greatest degree possible, while recognizing that this addresses only a small part of the problem.

Although more research would be needed to accurately characterize this issue, we believe it is likely that more pharmaceuticals end up in the environment after passing through animals and humans than after flushing unused products. However, some unused pharmaceutical products are undeniably flushed into waste streams, contributing to the problem but also offering an opportunity to make reductions in the pollutant loading through a "pollution prevention" approach. We urge support for pharmacy "take back" programs that make doing the right thing obvious and convenient for consumers.

3. Elevate EPA's drinking water health effects research budget so that it is at least equivalent to the air pollution health effects research budget. Even though this Subcommittee does not appropriate funds, we ask you to support this increase.

To date, no peer-reviewed published research has found ill effects on humans from EDCs and pharmaceuticals in the environment at the trace levels we have seen in drinking water. However, drinking water providers would like to see more research on this matter, so that we can either take appropriate action to address an actual health risk if there is one, or reassure the public that there is not one. Treatment to completely remove all traces of pharmaceuticals from drinking water will be very expensive, and our customers have a right to expect that we will only undertake the investment necessary to do this – and increase their utility bills to pay this expense - if doing so addresses an actual health risk.

We also specifically support 1) a dedicated authorization in the Research Title of the Agriculture Reauthorization bill for collaborative research between the drinking water community and the agriculture industry on ways to limit contaminants from entering water supplies; and 2) a dedicated research authorization to support decisions on contaminant listing and rulemaking by EPA's Office of Ground Water and Drinking Water. These funds should be used to focus research on priority drinking water areas of concern.

4. We should continue to rely upon EPA's science-driven Contaminant Candidate List (CCL) process to identify candidates for new drinking water standards.

Though at times this process appears to move slowly, a methodical, science-based process is necessary for determining which contaminants need to be regulated, so that we focus on actual risk and on the higher risks first. The standard-setting process detailed in the Safe Drinking Water Act is sound, and setting standards through a science-driven process gives the public confidence that the regulations they pay for are necessary, reasonable, and protect public health. An increase in human health effects research, as mentioned in Item 3 above, would improve this process.

5. We should continue to rely upon the Unregulated Contaminant Monitoring Rule (UCMR) for decisions concerning testing and reporting to customers about contaminants that are not currently regulated.

EPA employs a comprehensive and science-based approach to determining which unregulated contaminants utilities should monitor for, and what utilities should say about these contaminants (if detected) to their customers. It is appropriate to use this kind of science-based process to determine which, if any, additional currently unregulated contaminants utilities should investigate.

AWWA stands ready to work with Congress to improve the country's understanding of these complex issues.

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Contacts:
Tom Curtis
Deputy Executive Director for Government Affairs
202 628-8303

Greg Kail
Director of Public Affairs
303 734-3410

February 25, 2010

The Honorable Edward J. Markey
Chairman, Subcommittee on Energy and Environment
Energy and Commerce Committee
United States House of Representatives
Washington, D.C. 20515

The Honorable Fred Upton
Ranking Member, Subcommittee on Energy and Environment
Energy and Commerce Committee
United States House of Representatives
Washington, D.C. 20515

Dear Chairman Markey and Ranking Member Upton:

The House Subcommittee on Energy and Environment is scheduled to hear testimony today from several witnesses concerning potential risks from "endocrine disruptors" in drinking water. The American Chemistry Council (ACC), a national trade association representing 140 member companies which employ 800,000 workers, requests that ACC's perspectives on this issue be entered into the hearing record.

In 1996, in response to public concern that some substances may interfere with endocrine processes in humans and wildlife, Congress directed the EPA, to develop a screening program, using appropriate validated test systems and other scientifically relevant information, for evaluating the potential of substances to induce hormone-related health effects.[1] The Food Quality Protection Act (FQPA) mandated the screening of pesticide chemicals and gave EPA authority to require screening of certain other substances. It also required EPA to "take action" as appropriate, on substances found to have an endocrine effect on humans, under existing statutory authority available to EPA. Shortly after passing the FQPA, Congress also passed an amendment to the Safe Drinking Water Act (SDWA) that gave EPA authority to test (in accordance with the FQPA provisions) for endocrine effects, substances that may be found in sources of drinking water if EPA determines that a substantial population may be exposed to such substance.[2]

After these laws were enacted, it quickly became apparent, as the result of a stakeholder advisory process conducted by EPA, that the scientific complexity of the endocrine system and the technical difficulties of screening and testing chemicals for endocrine disruption would be major challenges. EPA assessed the current state of the science and found that there were few, if any, scientifically valid screens and tests available to study the potential endocrine activity of chemical substances. Therefore EPA initiated an

[1] Food Quality Protection Act of 1996, 21 U.S.C. 346(a)-§408(p)
[2] Safe Drinking Water Act Amendments of 1996, 42 U.S.C. 300j-17

extensive research and development program, composed of both basic and applied research, to develop, standardize and validate the necessary endocrine test methods for its Endocrine Disruptor Screening Program (EDSP). The EPA has expended over $100 million dollars since 1996 on this joint applied- and basic-research effort.

The American Chemistry Council (ACC) has played a constructive role in the Agency's development of the EDSP. Our goals have been to see the EDSP implemented as quickly and efficiently as possible and in a manner consistent with the law, the science and ACC members' commitment to the safe manufacture, transport, use and disposal of chemicals. To those ends, ACC has consistently supported increased funding for the Agency's research and laboratory studies to develop, standardize and validate the screening and testing methods required for the EDSP. ACC also has sponsored technical studies to supply needed data for endocrine test development and validation, and has participated with the broader scientific and stakeholder communities on EPA's standardization and validation advisory committees. Further, ACC has sponsored scientific research on the endocrine hypothesis through its Long-Range Research Initiative.[3]

These actions demonstrate that with respect to endocrine disruption, as with any potential chemical risks, ACC members take these concerns seriously. We have committed substantial resources and expertise to make sure that there are well established scientifically robust methods for assessing endocrine activity and adverse effects, and that there are well established regulatory processes to act on this scientific information. Having confidence in the scientific information is critical, as this is the necessary foundation for assuring that chemicals and the products of chemistry are used safely and effectively.

A related key principle is that we must harness advances made in science and technology in our laws and regulations. Many emerging technologies like computational toxicology, molecular tools and computer modeling hold great promise for improving how we screen chemicals for endocrine activity. ACC very actively supports the development of these promising techniques. To date, however, they haven't been shown to meet the scientific standards of reliability, sensitivity and specificity. While some emerging technologies may be nearing the point of use, they are not there yet. But as new technologies are proposed to be integrated into EPA's endocrine screening program, they must be appropriately validated so that their results can be relied upon and replicated by different labs. They must be shown to measure what they purport to measure and do so with an acceptable degree of accuracy. Doing so will provide regulatory certainty and ensure protection of human health and the environment.

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[3] http://www.americanchemistry.com/s_acc/sec_lri.asp?CID=1369&DID=5053
http://www.americanchemistry.com/lrisearch/

The importance of basing regulatory decisions on the best science cannot be overstated. Decisions not based on the best science and on established risk assessment and management procedures can misallocate limited resources and limit the use of safe chemicals, and create potentially unnecessary public health concerns. In an attachment to this statement is a more in-depth discussion of three additional science topics that are important in your subcommittee's consideration of the endocrine issue in the context of the Safe Drinking Water Act. These topics address: a) mechanism of action and adverse effects; b) effects mediated by endocrine pathways that are addressed in outcomes from toxicity tests; and c) the "low dose" hypothesis. (See Attachment A.)

EPA has begun issuing endocrine test orders for certain pesticide chemicals and has also been charged by Congress to begin to identify certain drinking water contaminants for endocrine screening. ACC welcomes the opportunity to comment on the Agency's criteria for identifying drinking water contaminants for endocrine screening. We understand that if after screening and testing, EPA finds that certain substances pose adverse effects via endocrine mechanisms, EPA has existing authority to take actions to protect public health. This was the case in 1996 when Congress passed the endocrine screening requirements under the FQPA and the SDWA amendments, and is still the case today.

Finally, it is important to note that ACC supports improvements to the US chemical management framework to ensure the safety of chemicals in commerce today. To that end, ACC is on record calling for Congress to modernize the Toxic Substances Control Act, which is the primary federal law regulating chemicals in commerce, including chemicals that may be found in drinking water. I call your attention to ACC's principles for modernizing TSCA for your information.[4]

ACC and its members look forward to working with you and the entire Committee as discussions around the endocrine issue continues. If we can provide any additional information on ACC's perspectives on this or related topics, please contact me.

Sincerely,

Cal Dooley

Cal Dooley
President and CEO

[4] http://www.americanchemistry.com/s_acc/sec_article_access.asp?CID=2178&DID=9939

Attachment A

Discussion of Additional Scientific Topics
Relevant to Endocrine Disruption Issue

Regulation of Endocrine Disruptors Must Be Based on Adverse Effects: It is important to recognize that the concept of "endocrine disruption" encompasses both an endocrine mechanism of action and adverse health effects. Finding that a chemical may interact with a component of the endocrine system does not necessarily mean that an adverse effect will ensue. Given the right dose and timing of exposure, almost anything – including everyday food – can, and often does, elicit an endocrine system mediated response that can be observed at a mechanistic or biochemical level. It is important to understand that natural variations in hormone levels and reversible or transient changes that are not considered adverse have been well documented. The concept of "endocrine disruption" applies only when two criteria are met: demonstration that 1) the primary biological mechanism of action is via an endocrine system pathway and 2) adverse health effect(s) are directly caused by a substance's interaction with that pathway. Mechanistic information alone is insufficient to evaluate the potential health significance of exposure to chemicals. Certain interactions or responses will be within the range of normal homeostatic response, and these are not adverse effects.

This is why, under the EPA's Endocrine Disruptor Screening Program (EDSP), Tier 1 screening (which will identify the potential for a substance to interact with the endocrine system, i.e. a mechanistic response) cannot be the basis of regulation. The EDSP Tier 2 testing, which determines the potential for adverse effects, and delineates the dose response for such effects, provides the needed data for hazard evaluation. This is a well recognized principle clearly articulated by the EPA's Endocrine Disruptor Screening and Testing Advisory Committee and subsequently codified by EPA in the Agency's EDSP. When hazard data are coupled with exposure data, the ensuing risk assessment provides the quantitative benchmark needed to evaluate the potential health significance of exposures, including exposures via drinking water pathways. This approach is consistent with the well-established scientifically sound procedures for assessing and managing risks that EPA employs under the SDWA to set national health-based standards for drinking water. Regulation should continue to be based on adverse effects, dose response and risk assessment.

Effects Mediated by Endocrine Disruption Pathways Are Covered in Outcomes from Toxicity Tests: It is also important to point out that even if specific endocrine screening has not yet been conducted on certain compounds, hazard identification based on observable outcomes from apical toxicity tests (i.e., outcomes such as pathologic states indicative of disease conditions) covers all modes of action, including endocrine pathways. As noted above, endocrine

disruption is not a distinct toxicological hazard per se, but a mode of action (MoA) of toxicity that could potentially result in a hazard, typically manifesting in the reproductive system.[5]

ACC members are committed to develop, produce and put into the marketplace products that are both beneficial and safe for humans and the environment. Accordingly, science-based evaluations of chemicals are necessary both to determine efficacy and safety for intended uses. In this regard, the toxicity information developed by ACC members as part of the High Production Volume Challenge Program, as well as other programs, is directly relevant to evaluating risks to children's health, including potential effects mediated by endocrine pathways, because it includes: 1) identification and definition of possible hazards upon all major organ systems from both acute and repeated exposures; 2) detection of potential hazards arising from *in utero* exposures; 3) evaluation of potential of a substance to affect reproduction; and 4) evaluation of the potential of a substance to damage DNA. Acute toxicity studies are most critical to assure correct packaging, labeling and handling to prevent poisoning incidents. Developmental and reproductive toxicity studies are most relevant for assessing risks that could affect normal prenatal and postnatal growth, development and maturation. It is these endpoints that are of most concern for endocrine disruption.

For evaluating the potential of a substance to cause adverse effects via endocrine-mediated pathways, a weight of evidence approach is considered to be the best scientific means to assess and integrate the range of available toxicity information. This approach considers not just the EDSP Tier 1 screening assays, but also the results of all other existing, relevant and validated toxicity tests such as subchronic, reproductive toxicity, and developmental studies. With this scientific analysis, in particular the laboratory toxicity studies investigating dose response of adverse health effects, there is assurance that the most relevant and best available science is used as a basis for regulatory decision making and setting health-based environmental standards. In such a weight of evidence evaluation, objective criteria are first employed to determine data quality and study reliability, and then a systematic evaluative process is applied for assessing the overall weight of the evidence for the postulated mode of action and dose response of adverse effects. In this way all relevant toxicity data can be comprehensively reviewed, given appropriate weight, and integrated in a manner that provides a robust, biologically plausible understanding of the potential hazards and health risks that exposures to a substance could pose.

Status of Scientific Debate on the "Low Dose Hypothesis": In the late 1990s, some scientists asserted that environmental exposure to compounds that could mimic hormones were capable of causing effects in lab animals at "low doses" and that these effects had not been detected earlier because the standard toxicology studies had been performed at high doses. This is the so called "low-dose" hypothesis – that low doses produce certain effects that are not seen at high doses.

There has been a considerable number of comprehensive, expert panel, reviews of this hypothesis over the last 10 years. In his comprehensive review of the scientific literature, Dr.

[5] ECETOC report TR106 "Guidance on Identifying Endocrine Disrupting Effects Technical Report No. 106, Brussels, June 2009.

Michael Kamrin, emeritus professor of Michigan State University, reached a clear finding that, "Based on the evidence, it is concluded that these "low dose" effects have yet to be established, that the studies purported to support these cannot be validly extrapolated to humans, and the doses at which the studies have been performed are significantly higher than the levels to which humans are exposed" (*International Journal of Toxicology*, 26:13–23, 2007).

The U.S. EPA in 2002 also carefully considered the entire body of scientific information available on the "low dose" hypothesis and concluded, "Until there is an improved scientific understanding of the low-dose hypothesis, EPA believes that it would be premature to require routine testing of substances for low-dose effects in the Endocrine Disruptor Screening Program. See: http://www.epa.gov/endo/pubs/edmvs/lowdosepolicy.pdf.

The media coverage of the scientific debate around the "low dose" hypothesis has been confusing and has tended to continue to "stir the pot" on this question. Therefore, it's important to clarify that at the present time, a considerable body of credible scientific evidence leans against the "low dose" hypothesis and therefore against changing the way chemicals should be tested in the endocrine program. This is the scientific process at work. The call to stay true to the scientific method and follow the data rather than "strong convictions" was most recently demonstrated in a statement from one of the leading researchers on endocrine disruptors, Dr. Richard Sharpe, on the recent studies published by EPA's lab showing no such "low dose" effects. See: http://toxsci.oxfordjournals.org/cgi/content/full/114/1/1

EPA's endocrine research lab recently published results of their studies focusing on very early stages of life in rodents and that found no such "low dose" effects on the brain, reproduction or development, and concluded that this lack of effects confirms "other robust, well-designed, properly analyzed multigenerational studies" ((Toxicological Sciences 114(1), 133–148 (2010)). This research by EPA scientists has been described in the leading scientific toxicology journal as "unequivocal and robust and are based on a valid and rational scientific foundation" See: http://toxsci.oxfordjournals.org/cgi/content/full/114/1/1

Based on the totality of this information, ACC believes that the overall weight of the scientific evidence clearly indicates there is no need to change the toxicity testing dose-setting approach or risk assessment methods because: 1) the low-dose findings have not been demonstrated consistently across different studies of the same substance in independent laboratories; 2) the findings are not consistent for all substances with similar mechanisms of action; and, 3) the biological significance of the reported low-dose effects is scientifically uncertain, in particular with respect to relevance of such effects, if any, to adverse effects upon health of the organism.

COMMITTEE ON RULES
CHAIRWOMAN

WASHINGTON OFFICE:
2469 RAYBURN BUILDING
WASHINGTON, D.C. 20515-3221
(202) 225-3615

LOUISE M. SLAUGHTER
CONGRESS OF THE UNITED STATES
28TH DISTRICT, NEW YORK

DISTRICT OFFICES:

3120 FEDERAL BUILDING
100 STATE STREET
ROCHESTER, NY 14614
(585) 232-4850

465 MAIN STREET, SUITE 105
BUFFALO, NY 14203
(716) 853-5813

1910 PINE AVENUE
NIAGARA FALLS, NY 14301
(716) 282-1274

WEBSITE: http://www.louise.house.gov

February 25, 2010

The Honorable Louise M. Slaughter

Statement for the Record

Submitted to the Committee on Energy and Commerce

Energy and Environment Subcommittee

"Chemicals in Drinking Water"

Mr. Chairman,

Mr. Chairman and members of the Committee, I would like to thank you for taking the time to hold this hearing on this important subject, as well as for giving me the opportunity to submit my remarks for the record.

A few years ago, I participated in a study conducted by the Environmental Working Group to find out what toxic substances I have been exposed to throughout my life. My stunning test results showed literally hundreds of chemicals pumping through my vital organs every day. These chemicals include PCBs that were banned decades ago, as well as chemicals like Teflon that are currently under federal investigation. The study also tested ten newborn babies and found that on average, each one had some 200 chemicals in their blood at the time of birth. The fact that we have children coming into this world already polluted and at the same time, do not know what the effects of that pollution will be on their mental and physical development, is both bad policy and immoral. We must test chemicals *before* they go onto the market, not *after* they get into our bloodstreams.

Over the last 30 years, the U.S. has seen a steep rise in the occurrence of breast cancer, childhood cancers, testicular cancer, juvenile diabetes, attention deficit disorder, learning disabilities, thyroid disorders, cognitive impairment, autoimmune disorders, and genital deformities. Autism cases alone rose 210 percent between 1987 and 1998. For years, the evidence has mounted that these increases are associated with endocrine disruptors in our water, yet research on this connection remains limited, particularly on the impact of these chemicals on women and on how long-term, low-dose exposure to environmental pollutants impacts children at critical stages of development.

Endocrine disruptors are widely used in agriculture, industry and consumer products. Some also enter the water supply when estrogens in human urine — compounded when a woman is on birth control — pass through sewage systems and then through water treatment plants. These endocrine disruptors have complex effects on the human body, particularly during fetal development of males. In the past several years scientists have began to suspect that the large increases in numbers of genital deformities among newborn boys is being caused by endocrine disruptors. For example, up to 7 percent of boys are now born with undescended testicles, and up to 1 percent of boys in the United States are now born with hypospadias, in which the urethra exits the penis improperly.

Endocrine disruptors can have equally devastating effects on females. It is now well established that DES, a synthetic estrogen that was given to many pregnant women from the 1930s to the 1970s to prevent miscarriages, caused abnormalities in the children. Evidence demonstrataes that girls born to those women have been more likely to develop misshaped sexual organs and cancer. Researchers also suspect that the disruptors can cause early puberty in girls, which greatly increases their likelihood of developing breast cancer as adults. Recent research shows that the risk that a 50-year-old white woman will develop breast cancer has soared to 12 percent today, from 1 percent in 1975, and that younger people also seem to be developing breast cancer. As Nicholas Kristof asked in a recent *New York Times* column, "What if breast cancer in the United States has less to do with insurance or mammograms and more to do with contaminants in our water or air?" This is an alarming prospect that demands immediate congressional attention, and an drastically enhanced research program.

While the Environmental Protection Agency's (EPA) Endocrine Disruptor Screening Program (EDSP) should be commended for their screening of substances found in sources of drinking water for their endocrine disruption potential, research into the specific health effects that endocrine disruption has on human growth and development is still severely limited. To fill this void I have reintroduced H.R. 4160, the Environmental Hormone Disruption Act, which would establish a new research program within the NIH's National Institute of Environmental Health Sciences (NIEHS) focused on how endocrine disruptors influence the development and progression of diseases. The clinical research conducted by the NIEHS would allow for a more comprehensive program investigating the specific health impact of hormone-disrupting chemicals. This research would serve to compliment and supplement the work done by the EPA,

Currently, about 100,000 chemicals are registered for use in the United States, 90 percent of which have never been fully tested for their impact on human health. Without a doubt, it is critical that we act now to identify other endocrine disruptors being ingested every day by pregnant women and young children that could have similarly devastating effects on their growth and development.

Mr. Chairman, thank you again for the opportunity to submit my remarks for the record, and I look forward to working together.

Louise M. Slaughter

QUESTIONS SUBMITTED FOR THE RECORD
HEARING ENTITLED,
"ENDOCRINE DISRUPTING CHEMICALS IN DRINKING WATER:
RISKS TO HUMAN HEALTH AND THE ENVIRONMENT"
SUBCOMMITTEE ON ENERGY AND ENVIRONMENT
COMMITTEE ON ENERGY AND COMMERCE
UNITED STATES HOUSE OF REPRESENTATIVES
FEBRUARY 25, 2010

Linda Birnbaum, Ph.D.
Director, National Institute of Environmental Health Sciences
National Institutes of Health
and Director, National Toxicology Program
U.S. Department of Health and Human Services

Questions for the Record

The Hon. Edward J. Markey

1. *In your testimony you mentioned that the potential health effects of endocrine disrupting chemicals are much broader than just reproductive issues. Could you detail some of these other potential health impacts and what we know about chemical causation?*

Response: The NIEHS has a research program to understand the role of exposures to environmental chemicals during development (in utero and the neonatal period) in the etiology of disease. The data in animal studies at environmentally relevant doses show that developmental exposures to a variety of chemicals with endocrine disrupting activity for just a few days can result in increased susceptibility to numerous diseases later in life, some with latent periods of a year of more. [1][2][3][4][5] Examples of diseases that have been associated with developmental exposures to chemicals, at low environmentally relevant doses in experimental

[1] Miller KP, Gorgeest C, Greenfeld C, et al. In utero effects of chemicals on reproductive tissues in females. Toxicol Appl Pharmacol 2004;198:111-131.

[2] Heindel J: Role of exposure to environmental chemicals in the development of reproductive disease and dysfunction. *Semin Reprod Med* 2005;24:168-177.

[3] Bern B. *The Fragile Fetus.* Colborn TA, ed. Princeton, NJ: Princeton Scientific Publishing Co., 1992

[4] Newbold RR, Heindel JJ. Developmental exposures and implications for early and latent disease. In *Environmental Impacts on Reproductive Health and Fertility,* Woodruff TJ, Lanssen SJ, Guillette LJ, and Guidice LC, eds. Cambridge Press, 2010, pp 92-102

[5] Newbold RR, Heindel JJ, Developmental origins of health and disease: the importance of environmental exposures. In *Early Life Origins of Human Health and Disease,* Newnham JP, Ross MG, eds. Basel, Karger 2009, pp. 41-50

animals, include: weight gain (obesity)[6]; attention deficit hyperactivity disorder (ADHD)[7]; behavior[8 9 10]; allergic diseases and asthma[11 12]; infertility[13]; premature puberty[14]; breast[15], prostate[16] and uterine cancers[17]; cardiovascular[18] diseases. These results are in controlled animal studies, although the mechanism by which the exposure causes the observed result is not clear. It is interesting that in these studies developmental exposures to endocrine disrupting chemicals at environmentally relevant doses in animal models for just a few days during development can

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[6] Newbold RR, Padilla-Banks E, Jefferson WN, Heindel JJ. Effects of endocrine disruptors on obesity. *Int J Androl* 2008;31(2):201-208.

[7] Colborn, T. Neurodevelopment and endocrine disruption. *Environ Health Perspect* 2004;9(112):944-949.

[8] Chung, YW, Nunez AA, Clemens LG. Effects of neonatal polychlorinated biphenyl exposure on female sexual behavior. *Physiol Behav* 2001;74:363-370.

[9] Palanza P, Morellini F, Parmigiani S, vom Saal FS. Prenatal exposure to endocrine disrupting chemicals: effects on behavioral development. *Neuroscience & Behavioral Reviews* 1999 Nov;23(7):1011-1027.

[10] Gioiosa L, Fissore E, Ghirardelli G, parmigiani S, Palanza P. Developmental exposure to low-dose estrogenic endocrine disruptors alters sex differences in exploration and emotional responses in mice. *Horm Behav* 2007 Sep;52(3):307-316.

[11] Narita S, Goldblum RM, Watson CS, Brooks EG, Estes DM, Curran EM, Midoro-Horiuti T. Environmental estrogens induce mast cell degranulation and enhance IgE-mediated release of allergic mediators. *Environ Health Perspect* 2007 Jan;115(1):48-52.

[12] Guo TI, Auttachoat W, Chi RP. Genistein enhancement of respiratory allergen trimetallitic anhydride-induced IgE production by adult B6C3F1 mice following in utero and postnatal exposure. *Toxicol Sci* 2005 Oct;87(2):399-408.

[13] Hung-Shu C, Anway MD, Rekow SS, Skinner MK: Transgenerational epigenetic imprinting of the male germ-line by endocrine disruptor exposure during gonadal sex determination. *Endocrinol* 2006; 147:5524-5541.

[14] Blanck HM, Marcus M, Tolbert PE, Rubin C, Henderson AK, Hertzberg VS, Zhang RH, Cameron L. Age at menarche and tanner stage in girls exposed in utero and postnatally to polybrominated biphenyl. *Epidemiology* 2000 Nov;11(6):641-647.

[15] Durando M, Kass L, Viva J, et al: Prenatal bisphenol A exposures induce preneoplastic lesions in the mammary gland in Wistar rats. *Environ Health Perspect* 2007; 115:80-86.

[16] Prins GS, Tang WY, Belmonte J, Ho SM. Developmental exposure to bisphenol A increases prostate cancer susceptibility in adult rats: epigenetic mode of action is implicated. *Fertil Steril* 2008; 89(Suppl. 2):e41.

[17] Newbold RR, Bullock BC, McLachlan JA. Uterine adenocarcinoma in mice following developmental treatment with estrogens: a model for hormonal carcinogenesis. *Cancer Res* 1990; 50:7677-7681.

[18] Melzer, D, Rice NE, Lewis C, et al. Association of urinary bisphenol A concentration with heart disease: evidence from NHANES 2003/06. *PLOS One* 2010;5(1)e8673:1-9.

increase the incidence of many diseases that have increased in humans in the last 40 years – obesity, ADHD, asthma, and cancer.

We are working to understand the mechanism whereby a chemical can have a latent effect long after the exposure. The data indicate that the developmental time frame is extremely sensitive to alterations in the epigenetic system that controls which genes are turned on and off at particular times in order to form different cells and tissues. Thus, the current hypothesis under study in our research programs is that developmental chemical exposures alter epigenetic programming, leading to altered gene expression, which leads to altered protein expression in cells that persists throughout life, causing increased susceptibility to disease later in life. Most of this work is in animals, but we are also funding some human research, looking at epigenetic changes. If this hypothesis is not disproven, in the future, once we better understand how to translate the results from the animal studies to humans, it may be possible to measure the epigenetic changes and use them as biomarkers of increased susceptibility to disease later in life, which can lead to the development of intervention strategies.

A critical aspect of this work is the hypothesis that disease starts during development and thus can be potentially prevented by reducing exposures during development.[19] [20] This paradigm will help to change the focus from intervention once someone has the disease, to disease prevention, which is more cost effective and supports a healthier population.

At present, much of the data comes from animal studies, but there are a growing number of human studies that show associations of exposures to environmental chemicals during development to childhood diseases like obesity[21], behavioral problems[22], asthma[23], and cancer[2425]. It will take longer to be able to link developmental exposures to adult-onset diseases as the populations need to be followed for many decades.

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[19] Grun F, Blumberg B. Perturbed nuclear receptor signaling by environmental obesogens as emerging factors in the obesity crisis. Rev Endocr Metab Disord 2007;8:161-171

[20] Heindel JJ, vom Saal FS. Role of nutrition and environmental endocrine disrupting chemicals during prenatal period on the aetiology of obesity. Mol Cell Endocrinol. 2009 May 25;304:90-6

[21] Baillie-Hamilton PF. Chemical toxins: a hypothesis to explain the global obesity epidemic. *J Altern Complement Med* 2003;348(16): 1527-1536.

[22] Colborn T. Neurodevelopment and endocrine disruption. *Environ Health Perspect* 2004;112(9):944-949.

[23] Dietert, RR and Zelikoff JT. Early-life environment, developmental immunotoxicology, and the risk of pediatric allergic disease including asthma. *Birth Defects Res (Part B)* 2008;83:547-560.

[24] National Institutes of Health (NIH) DES Research Update, NIH Publication No. 00-4722. Bethesda, MD, 1999

We are currently focusing on exposures to a single agent during development, but in the future we expect to develop initiatives to examine exposures to mixtures of chemicals, which is more similar to the exposures that humans actually experience. All studies noted here use environmentally relevant doses.

2. *There are some scientists that suggest that although endocrine disrupting effects in animals have been demonstrated, humans are better able to deal with the low doses of chemicals without suffering adverse effects. Can you respond to that?*

Response: Certainly, there is widespread agreement that extrapolation of rodent data to humans must be done with caution. There are a variety of factors that influence the effects caused by endocrine disrupting substances: age (e.g., prenatal, postnatal, child); species and strain differences in susceptibility; gender differences; variation in study protocol, endpoints evaluated, and data analysis; and the endocrine disrupting substance being evaluated.

Controlled animal studies show that low doses of endocrine disrupting chemicals can cause adverse effects in rodent models.[26] [27] [28] [29] Since there are numerous variables associated with understanding the levels that cause adverse effects in humans and how humans may or may not vary from rodents in handling endocrine related stresses, additional information is needed to understand how humans are able to deal with low doses of these substances. We do not know how humans compare to animal models in their sensitivity to endocrine disrupting chemicals; however, the suggestion that humans are better able to deal with exposures to endocrine disrupting chemicals has yet to be firmly demonstrated.

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[25] Smith AH, Marshall G, Yuan Y, Ferreccio C, Liaw J, von Ehrenstein OS, Steinmaus C, Bates MN, Selvin S. Increased mortality from lung cancer in young adults following exposure to arsenic in utero and early childhood. Environ Health Perspect 2006;114:1293-1296

[26] Durando M, Kass L, Viva J, et al: Prenatal bisphenol A exposures induce preneoplastic lesions in the mammary gland in Wistar rats. *Environ Health Perspect* 2007; 115:80-86.

[27] Prins GS, Tang WY, Belmonte J, Ho SM. Developmental exposure to bisphenol A increases prostate cancer susceptibility in adult rats: epigenetic mode of action is implicated. *Fertil Steril* 2008; 89(Suppl. 2):e41

[28] Heindel JJ, vom Saal FS. Role of nutrition and environmental endocrine disrupting chemicals during prenatal period on the aetiology of obesity. Mol Cell Endocrinol. 2009 May 25;304:90-6

[29] Smith AH, Marshall G, Yuan Y, Ferreccio C, Liaw J, von Ehrenstein OS, Steinmaus C, Bates MN, Selvin S. Increased mortality from lung cancer in young adults following exposure to arsenic in utero and early childhood. Environ Health Perspect 2006;114:1293-1296

3. *What evidence do we have of the presence of endocrine disruptors in sources of drinking water?*

Response: There are several strong lines of evidence to support the presence of endocrine disruptors in sources of drinking water including direct measurement of compounds and indirect evidence of endocrine disruptor activity provided by biological indicators.

Numerous studies give direct evidence for the presence of endocrine disruptors in sources of drinking water in the U.S.[30] [31] and throughout the world (e.g., Spain[32]; South Korea[33]). A range of precise analytical techniques are required to detect endocrine disruptors in water because the compounds are generally present at trace levels (i.e., nanogram/Liter or below) and have diverse chemical properties that affect analysis[34]. The most common analytical techniques employed to measure endocrine disruptors in water are gas chromatography and liquid chromatography, each coupled with tandem mass spectrometry (LC-MS/MS and GC-MS/MS). For example, Benotti et al. (2009) recently published the results of a survey to detect the presence of 51 compounds (including 25 endocrine disruptors and 20 pharmaceuticals) in both source water and treated drinking water from 19 drinking water treatment plants across the U.S. The most frequently detected endocrine disruptors in the study were atrazine, estrone, nonylphenol, and linuron; all of which were also detected in treated water with the exception of estrone[35]. Government agencies such as the U.S. Geological Survey,[36] as well as local municipalities such as the city of Ann

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[30] Kolpin, D. W., E. T. Furlong, et al. (2002). Pharmaceuticals, hormones, and other organic wastewater contaminants in U.S. streams, 1999-2000: a national reconnaissance. Environ Sci Technol 36(6): 1202-11

[31] Benotti, M. J., R. A. Trenholm, et al. (2009). Pharmaceuticals and endocrine disrupting compounds in U.S. drinking water. Environ Sci Technol 43(3): 597-603

[32] Carballa, M., F. Omil, et al. (2004). Behavior of pharmaceuticals, cosmetics and hormones in a sewage treatment plant. Water Res 38(12): 2918-26

[33] Yoon Y, J. Ryu, et al. (2010). Occurrence of endocrine disrupting compounds, pharmaceuticals, and personal care products in the Han River (Seoul, South Korea). Sci Total Environment 408(3):636-43

[34] Comerton, A. M., R. C. Andrews, et al. (2009). Practical overview of analytical methods for endocrine-disrupting compounds, pharmaceuticals and personal care products in water and wastewater. Philos Transact A Math Phys Eng Sci 367(1904): 3923-39

[35] Benotti *et alia.*, 2009.

[36] Chambers DB, Leiker TJ (2006). A Reconnaissance for Emerging Contaminants in the South Branch Potomac River, Cacapon River, and Williams River Basins, West Virginia, April-October 2004. Accessed at http://pubs.usgs.gov/of/2006/1393/pdf/ofr20061393.pdf on March 26, 2010.

Arbor,[37] have also published studies on the presence of endocrine disruptors in source waters and/or drinking water.

A number of researchers have utilized aquatic animals as biological indicators of the presence of endocrine disruptors. Animals serve as indicators because they have a well characterized biological response to an endocrine compound. These animals can be housed in water to test whether or not the water contains a sufficient quantity of endocrine disruptors to trigger the biological response. The production of vitellogenin (a yolk protein not normally produced by males) in male fish is one biological indicator that has been used in a number of fish studies of endocrine disruptors[38]. Fish and aquatic crustaceans have been used as indicator species because they can be housed directly in water where endocrine disruptors may be a concern, such as in the effluent from waste water treatment plants [3940] for recent examples). Numerous studies demonstrate the presence of endocrine disruptors in sources of drinking water by either direct measurement of compounds or indirect evidence from biological indicators.

4. *In your testimony you mention that some endocrine disrupting chemicals can have profound effects at "sensitive stages of development". Can you please clarify what constitutes a "sensitive stage"?*

Response: Any period of rapid development is sensitive to disruption. The periods when organogenesis (the actual development of the organs) and differentiation (establishing organ function) are occurring are known to be especially sensitive.[41]

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[37] Skadsden JM, Rice BL, Meyering DJ (2004). "The Occurrence and Fate of Pharmaceuticals, Personal Care Products and Endocrine Disrupting Compounds in a Municipal Water Use Cycle: A Case Study in the City of Ann Arbor." Accessed at http://www.a2gov.org/government/publicservices/water_treatment/Documents/EndocrineDisruptors.pdf on March 26, 2010.

[38] Marin, M. G. and V. Matozzo (2004). "Vitellogenin induction as a biomarker of exposure to estrogenic compounds in aquatic environments." Mar Pollut Bull 48(9-10): 835-9.

[39] Barber, L. B., K. E. Lee, et al. (2007). "Reproductive responses of male fathead minnows exposed to wastewater treatment plant effluent, effluent treated with XAD8 resin, and an environmentally relevant mixture of alkylphenol compounds." Aquat Toxicol 82(1): 36-46.

[40] Verslycke, T., A. Ghekiere, et al. (2007). "Mysid crustaceans as standard models for the screening and testing of endocrine-disrupting chemicals." Ecotoxicology 16(1): 205-19.

[41] Reproductive and Developmental Toxicology - ed K.S. Korach, Marcel Dekker, NY, 1998.

5. *In your testimony, you also indicate that some endocrine disruptors have the ability to alter DNA structure. Please describe how this may influence genetic predisposition of certain diseases?*

Response: Epigenetic mechanisms are cellular regulatory processes that influence the expression of genes without affecting DNA base sequences. Thus, while the DNA itself still maintains the genetic coding sequence, other changes such as addition of extra atoms has an effect on whether a set of genes gets turned on or off. Other modifications can occur to the chromatin, which is the highly organized protein package around the DNA in the chromosome; these modifications can also affect gene expression.

For example, a recent study in yellow agouti mice demonstrated that maternal exposure to BPA shifted the coat color of the offspring by decreasing methylation in a controlling portion of the DNA sequence upstream of the coat-color gene.[42] In the same study, maternal dietary supplementation with either folic acid or a phytoestrogen (genistein) inhibited the ability of BPA to reduce DNA methylation in a rodent model. These and other results highlight the importance of this growing area of research for our ability to understand how endocrine disrupting chemicals exert their effects, and how these alterations, which occur during development, may persist into adulthood.

These modifications are independent of the actual DNA sequence of the gene, so they are not equivalent to what we usually think of as "genetic predisposition" which resides in the DNA sequence. However, we are only beginning to scratch the surface in our understanding of how various types of "predispositions" and susceptibilities actually work at the cellular and molecular level.

The Hon. Joe Barton

1. *In your testimony, you state: "chemicals with endocrine disrupting activity are widely dispersed in our environment, often at levels plausibly associated with biological effects; exposure to humans is widespread." Does your use of the word "plausibly" indicate you are unsure and this is an educated guess at best, or has causation been established between the condition and the chemical?*

Response: Causation has been established in the laboratory setting for a wide variety of endocrine disrupting chemicals (EDCs) and consequent biological effects. Since people are

[42] Dolinoy DC, Huang D, Jirtle RL. Maternal nutrient supplementation counteracts bisphenol A-induced DNA hypomethylation in early development. Proc Natl Acad Sci USA 2007 Aug 7;104:13056-61

exposed to many different chemicals in their daily lives, the same certainty of causation is hard to establish for humans, but when you detect in humans a level of exposure which has been reliably demonstrated to cause adverse effects in laboratory animals, I consider it to be plausible that that level of exposure is having an effect on human health as well.

2. *The CDC previously testified that the mere detection of a substance in a bio-monitoring test is not an indication that any disease or other effect will result. Do you agree with the CDC on this point? If not, why?*

Response: I agree that the mere detection of a substance in a bio-monitoring test is not by itself proof that any disease or other effect will result.

3. *Please describe what you consider to be sufficient types of data needed to fairly evaluate chemicals.*

Response: Over the past several decades, our understanding of the effects of environmental chemicals has grown considerably. As our knowledge base grows, the baseline for what constitutes sufficient information also changes. Years ago, toxicity testing evaluated high dose effects and focused on overt toxicity. Animal testing and human epidemiological studies have demonstrated that these early testing strategies are inadequate. This is particularly the case for endocrine disrupting chemicals. For example, test guidelines used in the 1970's and 1980's for developmental endpoints focused on teratogenicity. These studies would not have detected low dose endocrine effects. Even the multigenerational reproductive studies had weak power to evaluate low dose effects[43]. Traditional rodent cancer bioassays start exposures while the animals are adults and are continued for two years.

At a workshop sponsored by the National Toxicology Program, entitled *National Toxicology Program Workshop on Hormonally Induced Reproductive Tumors—Relevance of Rodent Bioassays*, one of the conclusions was that this exposure period is inadequate to evaluate hormonally induced tumors[44]. In response to this workshop, the National Toxicology Program has modified their bioassays to begin exposures *in utero* and continue exposures for two years.

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[43] Hotchkiss AK et al., Fifteen years after "Wingspread"--environmental endocrine disrupters and human and wildlife health: where we are today and where we need to go. Toxicol Sci. 2008 Oct;105(2):235-59.

[44] Thayer KA and Foster PM. Workgroup report: National Toxicology Program workshop on Hormonally Induced Reproductive Tumors - Relevance of Rodent Bioassays. Environ Health Perspect. 2007 Sep;115(9):1351-6.

This new exposure paradigm is consistent with human exposures to environmental chemicals, because, for most environmental chemicals, humans are exposed from "cradle to grave."

In addition, where older bioassays simply tested for the endpoint of cancer, there are a variety of non-cancerous diseases that have rapidly increased over the past several decades including autism, ADHD and metabolic syndrome. Very few chemicals have been evaluated for developmental neurotoxicity and the potential for metabolic syndrome, as the bioassays to conduct the evaluations were not available. For many outcomes, the perfect bioassay has yet to be developed.

With our current understanding of the toxicity of endocrine disruptors and other environmental chemicals, an adequate testing protocol should include "cradle to grave" exposures, to evaluate neurodevelopmental, reproductive, and immunological effects in addition to cancer. It is clear that these tests would have significant cost and time constraints. This is why the National Toxicology Program, in collaboration with the US EPA, is developing a biochemical- and cell-based "high throughput" screening program, called Tox21. It is hoped that this screening program will provide some insights into the potential adverse effects of environmental exposures. The results from these high-throughput screens will lead to more targeted testing of specific environmental chemicals. We envision that this approach would guide our testing to the most appropriate animal model, including the potential use of novel transgenic animals that serve as better models for specific human diseases.

Finally, recent advances in pharmacokinetic studies allow for more accurate species extrapolation of the absorption, distribution, metabolism and elimination of chemicals. Toxicity testing must continue to advance and incorporate new technologies.

4. *Your testimony in support of low dose theory refers to rats that were susceptible to illness at 100 parts per billion of arsenic. Today's Federal drinking water standard is 10 parts per billion, or 1/10th of the rat dosage you cited. Please explain the relevance of your example considering the disparity in subject, weight, and dosage.*

Response: With regard to subject disparity, it is noted that mice and humans show similar arsenic metabolism and biokinetics.[45] [46] [47] In terms of comparing effects between humans and

[45] Carter, D.E., Aposhian, H.V., Gandolfi, A.J., 2003. The metabolism of inorganic arsenic oxides, gallium arsenide, and arsine: a toxicochemical review. Toxicol. Appl. Pharmacol. 193, 309–334.

[46] Styblo, M., Drobna, Z., Jaspers, I., Lin, S., Thomas, D.J., 2002. The role of biomethylation in toxicity and carcinogenicity of arsenic: A research update. Environ. Health Perspect. 110, 767–771.

mice, one study indicates that humans are far more sensitive to arsenic than rodents, making the mouse a conservative model in this one experiment.[48]

To address the disparity in weight between humans and mice, it is important to consider internal dose, i.e., the measure of a chemical in the blood stream. Waalkes reports that mice must consume 100 to 200 times greater inorganic arsenic concentration in drinking water to achieve similar blood levels to that of humans.[49] Although we cannot say at this time how 100 ppb arsenic in drinking water given to mice for 5 weeks directly corresponds quantitatively to a given human exposure, the Waalkes research supports the theory that this applied dosage to a mouse would achieve an internal dose relevant to arsenic exposures at or below the current drinking water standard.

In terms of the relevancy of the applied dose, the internal dose resulting from a 100 ppb dose to a mouse is relevant to possible human exposures to arsenic found in sources of drinking water in the U.S. The US EPA has estimated that the number of US residents who are exposed to excess arsenic in drinking water may be as high as 1.4 million Americans. Higher levels of arsenic tend to be found more in ground water sources than in surface water sources (i.e., lakes and rivers) of drinking water. The demand on ground water from municipal systems and private drinking water wells may cause water levels to drop and release arsenic from rock formations. Compared to the rest of the United States, western states have more systems with arsenic levels greater than EPA's standard of 10 parts per billion (ppb). Parts of the Midwest and New England have some systems whose current arsenic levels are greater than 10 ppb, but more systems with arsenic levels that range from 2-10 ppb. While many systems may not have detected arsenic in their drinking water above 10 ppb, there may be geographic "hot spots" with systems that may have higher levels of arsenic than the predicted occurrence for that area.[50]

In a recent study, researchers at Dartmouth College gave mice drinking water containing 100 ppb arsenic then exposed them to a combination of flu viruses including H1N1. The effects were severe: all arsenic treated mice died while those in the control group recovered. In their next phase of research, they will repeat the in vivo study with lower doses (including the 10 ppb

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[47] Aposhian, H.V., Zakharyan, R.A., Avram, M.D., Sampayo-Reyes, A., Wollenberg, M.L., 2004. A review of the enzymology of arsenic metabolism and a new potential role of hydrogen peroxide in the detoxication of the trivalent arsenic species. Toxicol. Appl. Pharmacol. 198, 327–335.

[48] Waalkes, M. P., Liu, J., and Diwan, B. A.: Transplacental arsenic carcinogenesis in mice. Toxicol. Appl. Pharmacol. 222: 271-280, 2007.

[49] Ibid

[50] EPA Web Site. "Basic Information About Arsenic Regulations" http://water.epa.gov/lawsregs/rulesregs/sdwa/arsenic/Basic-Information.cfm

level).[51] The gene and protein expression studies relating arsenic to endocrine disruption and immune suppression showed marked effects at 0.1 ppb in laboratory based experimental studies.[52] [53] (one-hundredth of the drinking water standard).

5. *In a September 21, 2009 letter to FDA Commissioner Hamburg, a group of researchers led by Dr. R. Thomas Zoeller of the University of Massachusetts-Amherst wrote that they had "serious concerns with the FDA's toxicity studies for BPA" and that it was "troubling that the FDA is proposing to spend such a large amount of money on such a well-researched chemical." The letter additionally called the ongoing National Center for Toxicological research's (NCTR) work with rats "a serious waste of time and money." The group further opined that there was "sufficient research and independent review available for the agency to make a decision." Yet, later that same year, many of the signatories on the Zoeller letter received NIEHS grants to conduct even more studies on the effects of BPA, the very chemical cited by the Zoeller group as needing no further study. Please explain why NIEHS would invest millions of dollars in testing by individuals who have publicly opined no further research is necessary.*

Response: The NIEHS/NTP decision to fund more research on BPA was based on interactions with FDA officials who, notwithstanding the arguments made in the September 21, 2009, letter to FDA Commissioner Hamburg, believed that there were still significant data gaps that needed attention before regulatory action would be appropriate. The NTP/NCTR initiative specifically, and the NIEHS grants program more generally, were designed to fill data gaps that were identified by the NTP and independently by the FDA during the course of their respective reviews of the BPA literature. Research was designed to assess the following: (1) develop information on the comparable amounts of active circulating BPA in the bloodstream of neonatal and adult rats and non-human primates; (2) develop further rodent studies that specifically focused on developmental exposures and diseases later in life; (3) provide more complete dose responses for all experiments, including internal dose measurements of free (active) and

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[51] Kozul, Courtney D., Kenneth H. Ely, Joshua W. Hamilton, and Richard I. Enelow. 2009a. Low-dose arsenic compromises the immune response to influenza A infection *in vivo*. *Environmental Health Perspectives* 117:1441-1447. doi:10.1289/ehp.0900911

[52] Barr, Fiona D., Lori J. Krohmer, Joshua W. Hamilton, and Lynn A. Sheldon. 2009. Disruption of histone modification and CARM1 recruitment by arsenic represses transcription at glucocorticoid receptor-regulated promoters. *PLoS ONE* 4(8):e6766. doi:10.1371/journal.pone.0006766

[53] Davey, J.C., Athena P. Nomikos, M. Wungjiranirun, J. Sherman, L. Ingram, C. Batki, Jean P. Lariviere, and Joshua W. Hamilton. 2008. Arsenic as an endocrine disruptor: arsenic disrupts retinoic acid receptor-and thyroid hormone receptor-mediated gene regulation and thyroid hormone-mediated amphibian tail metamorphosis. *Environmental Health Perspectives* **116**:165-172. doi:10.1289/ehp.10131

conjugated BPA (inactive); (4) in collaboration with academic investigators, examine multiple overlapping endpoints that address actual disease endpoints rather than early predictors of disease or disease susceptibility; (5) use larger number of animals per group (when justified); (6) assess both males and females; and (7) develop more data to support areas with some but insufficient data, including weight gain, behavior, breast and prostate cancer, reproduction, fertility, and puberty.

The NIEHS funded 10 grants from this initiative. At the time of funding the NIEHS was not aware of the letter. However, we fund the best science based on our review system and data needs; thus, this letter would not have affected any funding decisions.

6. *In the section entitled "New Science," your written testimony described the initial results of BPA testing as significant. Is it wise to announce experiment results before the full experiment and analysis is complete?*

Response: The results cited in my testimony were complete and have been announced and published by EPA scientists in a peer reviewed journal.[54] They were referred to as "initial results" because they were the product of the first phase of the ToxCast program. Phase I profiled over 300 well-characterized chemicals (including BPA) in over 400 high-throughput endpoints. "Initial" was not intended to imply "incomplete."

7. *You testified the "NTP is also planning new research relevant specifically to EDCs in drinking water. One set of studies will investigate the potential for mixtures of chemicals known to occur in drinking water to impact pre- and early post-natal development." In the spirit of fiscal restraint and consistent with the President's message of making tough budget choices, do you plan to consult with Dr. Borgert and NAS on their work that has already addressed this matter?*

Response: With regards to drinking water and mixtures, there is little science on which to base an assessment of cumulative risks posed by mixtures of the myriad of substances (pharmaceuticals, disinfection by-products, industrial chemicals) in drinking water that could adversely affect developing organisms. Plans for research on substances nominated to the National Toxicology Program (NTP) are developed by NTP scientists in consultation with a variety of inputs, including both government and non-government scientists.

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[54] Judson RS et al. (2010) *In vitro* screening of environmental chemicals for targeted testing prioritization – the ToxCast project. Environ Health Perspect 118:485-92

In developing its research programs, the NTP works with other federal agencies to ensure its efforts are not duplicative and meet regulatory and public health needs. Once a draft research concept is developed, it is reviewed in a public meeting by the NTP's Board of Scientific Counselors, to ensure that it is scientifically justified, mission-related and appropriate in scope. Comments are solicited via the Federal Register, and any public commenter is afforded time to provide comments on the proposed research plan if they so wish or they may submit written comments if they prefer. It is then subsequently reviewed by members of the NTP executive committee. These reviews are taken into consideration by NTP management when setting both scientific and fiscal priorities for research and testing in subsequent fiscal years. In addition, NTP often sends the draft concepts to additional experts with specific expertise to ensure the most robust review of these concepts. In this case we will ensure that Dr Borgert receive notifications of the meetings where these concepts are being reviewed so that he may have opportunity for comment.

8. *You testified "there was an approximately 42% decrease in sperm count worldwide between 1940 and 1990." Yet, the World Health Organization's comprehensive review of endocrine disruptions concluded that global reductions in human semen quality over time are related to increasing exposure to estrogenic, antiandrogenic (identity unknown), or other as yet unidentified chemicals, during critical phases of testicular development. Based on the weight of evidence WHO concluded:*

> *For outcome, the evidence is judged to be weak. A global trend for declining semen quality is not supported by current data. Some studies show declines in certain regions or cities, whereas others have not found a decline, suggesting there may be regional trends but not a global trend. There is no evidence relating to the strength of the hypothesis because of the lack of exposure data. There are no human data to support an EDC-related mechanism.*

Please explain the basis of your disagreement with the WHO.

Response: There is no substantive disagreement with the WHO. My testimony cited the 1992 paper to justify the research we have done on endocrine disrupting chemicals (EDCs) over the past years. In their 2002 report, WHO states that "a number of studies report a decline (since the 1930's) in human sperm quality in several countries" and that there are important variations in sperm count, although studies are hard to compare and have been retrospective.[55] The 2009

[55]Damstra T, Barlow S, Bergman A, et al., eds, (2002). "Global Assessment of the State-of-the-Science of Endocrine Disruptors." Accessed at http://www.who.int/ipcs/publications/new_issues/endocrine_disruptors/en/index.html on March 26, 2010.

Scientific Statement of the Endocrine Society[56] also refers to reports of declining sperm count in Denmark and other countries contributing to the hypothesis of environmental contaminants being harmful to reproduction. WHO's analysis points out that the lack of data about levels of exposure in humans has made it difficult to judge the strength of the hypothesis of EDC causation – this is distinctly different from stating that there is no effect from EDCs. That is why NIEHS believes this is an important area for research.

9. *Dr. Borgert testified that high-quality science consists of science that is based on: verifiable measurements with sufficiently small error rates; well controlled measurements whose interpretation is not confounded by extraneous influences; and results that are repeatable by independent scientists. Please state whether you agree with this assessment. If you disagree, please explain the basis of your disagreement.*

Response: I agree that the listed items are elements of a good study, but with the understanding that no study involving living organisms can be exactly duplicated and that in human studies (essential to our health and well-being) we can never achieve "well-controlled measurements whose interpretation is not confounded by extraneous influences". High-quality science consists of the results from state-of-the-art studies that build incrementally to a consensus—a consensus that is rarely 100 percent.

[56] Diamanti-Kandarakis et al. (2009) Endocrine-disrupting chemicals: an Endocrine Society scientific statement. Endocrine Reviews, 30(4):293-342

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUN 3 0 2010

OFFICE OF CONGRESSIONAL AND
INTERGOVERNMENTAL RELATIONS

The Honorable Henry A. Waxman
Chairman
Committee on Energy and Commerce
U.S. House of Representatives
Washington, D.C. 20515

Dear Chairman Waxman:

Thank you for the opportunity to respond to questions for the record that followed the February 25 hearing on Endocrine Disrupting Chemicals in Drinking Water. I hope this information will be useful to you and the members of the Committee.

If you have any further questions, please contact me or your staff may contact Christina J. Moody in my office at 202.564.0260.

Sincerely,

Arvin R. Ganesan
Deputy Associate Administrator

Attachment

Endocrine Disrupting Chemicals in Drinking Water:
Risks to Human Health and the Environment
House Committee on Energy and Commerce
February 25, 2010 Hearing Date
Jim Jones' Responses to the
Questions for the Record

Response to the Honorable Edward J. Markey

Markey 1. Do you believe that EPA has the personnel and resources to ensure that the endocrine disruptor screening program can carry out its intended purpose? If not, please elaborate on what resources might be needed.

Markey 1 Response: In the Office of Chemical Safety and Pollution Prevention (OCSPP), EPA currently has enough resources and personnel in the Endocrine Disruptor Screening Program.

Markey 2. In your testimony, you state that the validation of tests ensure that they are based on solid science and that they measure what they are intended to measure.

Markey 2a. It is my understanding that there are some rodent strains that are unusually sensitive to certain endocrine disruptors, and others that are unusually insensitive. When testing for endocrine disruption in animal systems is it necessary to take into consideration variation in sensitivity to endocrine disruptors that occurs in different rodent strains? How would a scientist determine the sensitivity of a rodent strain to a particular hormonal stimulus? Should scientists establish this baseline sensitivity using a known endocrine disruptor prior to testing an unknown compound for endocrine disruption?

Markey 2 and 2a Response: EPA has been concerned for many years about the possibility that rat strains may have different sensitivities to endocrine disruptors. In 2002 it commissioned a comprehensive literature search and report on the effect of strain and species on the mammalian assays being considered for the Tier 1 Battery of the Endocrine Disruptor Screening Program. As part of the preparation of the report, the contractor submitted a draft for review by an external reviewer. The final report and the external reviewer's comments have been on the EDSP Web site since the summer of 2003 (http://www.epa.gov/scipoly/oscpendo/pubs/program/whitepaper.htm).

The conclusion that EPA reached on the basis of this review is that while some strains may be more sensitive than others for individual endpoints, there is no single strain that is most sensitive overall in the assays with multiple endpoints. The external reviewer suggested that several strains be tested simultaneously to provide a better chance of minimizing sensitivity issues. There are problems with this recommendation. First, as the peer reviewer noted, it would take substantial additional research to identify which strains to use. Second, it would be substantially more costly (both in dollars and numbers of live animals) to test multiple strains. While the reviewer suggested that a reduced number of animals of each of multiple strains could be used to keep the total number of animals in the

study manageable, such an approach relies on the assumption that the same dose levels would be appropriate in all of the strains used. Without such an assumption, data could not be pooled across the strains. The assumption is not justifiable due to strain differences in rates of metabolism, sizes, etc.

EPA stated a preference for a particular strain of rat because it has data showing that that strain works correctly and identifies endocrine disruptors. If additional research shows that a different strain or set of strains is consistently more sensitive, the test guidelines may be changed appropriately. The Agency believes it is better to begin testing for endocrine disruptors now with a strain that has repeatedly been demonstrated to be sensitive enough to detect known endocrine disruptors than to wait for an optimal strain or set of strains to be identified.

Markey 2b. Do you specify in your test orders the strain of animal or cell type that must be used in a particular assay to ensure consistency across laboratories? If so, please elaborate, and if not, why not, since using a different strain could lead to widely varying and inconsistent results?

Markey 2b Response: Some test guidelines specify exactly the strain of animal or cell type that must be used. For example, the steroidogenesis assay requires that H295R cells be used. That cell line has characteristics that make it uniquely suitable to evaluate the entire metabolic path of steroidogenesis and without using that particular cell line the assay cannot work. In other assays, however, a preference for an animal strain rather than a strict requirement is given. This is usually because strain is only one of many factors that can affect the outcome of the study, and may not be among the most important variables. Studies using little-known strains or strains known to be inappropriate are likely to be considered "other scientifically relevant information" rather than information from a "validated" assay, and consequently subject to significantly greater scrutiny. If a laboratory presents data showing that the results of a screening assay have not been compromised by use of a non-preferred strain, the study may provide information that can carry significant weight in an overall evaluation of the chemical.

Markey 2c. It is my understanding that certain animal food and housing equipment contain chemicals that can act as endocrine disruptors and can subsequently interfere with assays that are designed to look at a hormonal endpoint. Do you specify in your test orders the type of food and housing procedures that are necessary in order to minimize contamination from these sources and to ensure consistency across laboratories? If so, please elaborate, and if not, why not, since this variability can lead to inconsistent results?

Markey 2c Response: The test guidelines contain provisions to restrict use of materials in feed and housing equipment that may interfere with the ability to detect endocrine disruptors. For example, the use of polycarbonate water bottles for rat studies is prohibited since water in prolonged contact with aged and distressed polycarbonate has been shown to have the potential to be estrogenic. Similarly, the fish and frog assays specify that glass aquaria are to be used. EPA does not restrict use of materials if they were judged not to have any bearing on the outcome of the study. For example, use of polycarbonate cages for rats is not prohibited since the cages are not expected to be in

contact with water for a prolonged period of time. In the case of rat feed, the level of natural plant-based estrogens has been capped at a level that does not interfere with the results of a screening assay. However, EPA recognizes that there may be compounds present in feed and housing equipment that may have endocrine effects but we are simply unaware of them.

Markey 2d. What can you say about the accuracy of a study designed to evaluate whether a certain suspected endocrine disruptor causes adverse health effects in an animal strain if that study chose as its model an animal strain that is considered highly insensitive to hormonal stimuli?

Markey 2d Response: If an animal strain were highly insensitive to hormonal stimuli, weak endocrine disruptors might not be identified correctly by assays that use that strain. However, use of a putatively suboptimal strain might be justifiable if data show that it correctly identifies known weak endocrine disruptors, and if no other strain or set of strains has been shown to be more sensitive. It should be remembered that strain is only one factor among many that affect the outcome of an assay, and may not be the most important one.

Markey 2e. When designing assays for both the Tier 1 and Tier 2 protocols, is a positive relevant hormonal control, such as estrogen or testosterone, used to verify the relevance and responsiveness of the assay? If not, why not?

Markey 2e Response: Positive controls have been used (or are being used) in the validation for the Tier 1 and Tier 2 protocols. In addition, concurrent positive controls are required to be run in parallel with the test chemical in many of the Tier 1 assays. However, positive controls are not required in certain resource-intensive assays that detect multiple potential mechanisms of endocrine activity. For example, running estradiol in the pubertal female assay as a positive control might help ensure that chemicals that act similarly to estradiol would be identified but would not help to ensure that chemicals that are anti-estrogenic, that interfere with steroidogenesis, or that interfere with thyroid hormone activity would be identified. Including positive controls for each of the applicable mechanisms would require several different positive controls to be run simultaneously with a single test chemical. Ideally, a positive control would have to be included for estrogenicity through the estrogen receptor, anti-estrogenicity through the estrogen receptor, androgenicity through the androgen receptor, antiandrogenicity through the androgen receptor, aromatase inhibition, interference with steroidogenesis, and the many mechanisms by which thyroid function could be affected – each time a test chemical is tested. This would add significant cost and use of animals. The Agency believes that the performance criteria included in such complex studies will help to ensure that the study is run correctly.

Markey 2f. How will the results from positive control experiment influence concentrations of test chemicals that are used in the Tier 2 dose response assays?

Markey 2f Response: Results from positive control experiments in Tier 1 assays are not expected to influence concentrations of test chemicals that are used in the Tier 2 dose-

response assays. Appropriate dose levels are almost without exception chemical-specific so it generally is not advisable to set dose levels based on a different chemical (viz., the positive control in a Tier 1 assay). Presumably, a preliminary dose-range study and/or data from the Tier 1 pubertal, fish, and frog assays for each specific chemical would influence the selection of the dose levels for the Tier 2 assays for that chemical.

Markey 3. I recently wrote letters to both FDA and EPA about triclosan, which is used in many consumer products - from hand soap to cutting boards - despite questions about whether it works and potential for endocrine disrupting effects. Triclosan has also been found in nearly 60% of U.S. streams1, and the CDC demonstrated it to be contained in the urine of 75% of Americans2. FDA recently responded to my letter, and stated that it is "FDA's opinion that existing data raise valid concerns about the effect of repetitive daily human exposure to these antiseptic ingredients."

Markey 3a. Do you think triclosan should be screened under the Endocrine Disruptor Screening Program – or do you believe that the existing data could be sufficient to either accelerate the screening process or move straight to consideration for regulation under the Safe Drinking Water Act? Please explain your response.

Markey 3a Response:
The Agency uses its Contaminant Candidate List (CCL) and Regulatory Determinations processes to evaluate unregulated contaminants for potential regulation under SDWA. As noted in the response to your January 5, 2010 letter, EPA published our third CCL (or CCL 3) on October 8, 2009. This list includes unregulated contaminants that are known or anticipated to occur in public water systems and may require regulation under SDWA. In developing CCL3, EPA considered the best available occurrence and health effects data to evaluate a universe of approximately 7,500 contaminants and subsequently identified a list of 116 contaminants that presented the greatest public health concern for drinking water. While EPA evaluated triclosan as part of the universe of 7,500 contaminants, the Agency determined that it did not present as great a public health concern (for drinking water) as other contaminants that were selected for the final CCL 3.

Even if the Agency had listed triclosan on CCL3, in order to determine whether to regulate a contaminant with a national primary drinking water regulation (NPDWR), section 1412(b) of SDWA requires that EPA make an affirmative finding for all three of the following statutory criteria: (1) The contaminant may have an adverse effect on the health of persons; (2) The contaminant is known to occur or there is a substantial likelihood that the contaminant will occur in public water systems with a frequency and at levels of public health concern; and (3) In the sole judgment of the Administrator, regulation of such contaminant presents a meaningful opportunity for health risk reduction for persons served by public water systems. In the case of triclosan, the Agency would not have sufficient information for finished drinking water to address the second and third statutory criteria.

However, EPA is conducting several tests on triclosan as part of its research program. The Agency believes that these data will provide useful information on the potential of triclosan

to affect the endocrine system and believes that the results of this testing will provide the Agency with important information regarding the further testing needs for triclosan. EPA will continue to evaluate unregulated contaminants such as triclosan and will utilize any new, relevant data that might require the Agency to issue an EDSP test order for triclosan or reconsider placing this contaminant on future CCLs and/or future regulation.

Markey 3b. It is estimated that 95% of the uses of triclosan (found in numerous consumer products) are disposed of in residential drains and are consequently found in sources of water.3 When EPA re-evaluated triclosan for use as a pesticide did it take into consideration cumulative exposures that come from products that fall under FDA's jurisdiction? Are EPA's risk assessments based on this total public exposure? If not, why not, since EPA is charged with ensuring that drinking water is safe to drink irrespective of the source of the contamination of the drinking water?

Markey 3b Response: EPA's re-evaluation of triclosan for use as a pesticide considered all potential exposures to the general public resulting from EPA and FDA regulated uses. EPA's risk assessment is based on the total exposure from all uses that may co-occur including any contribution from contaminated drinking water. The total exposures from all sources of triclosan were derived from the National Health and Nutrition Surveys (NHANES) biological monitoring data. NHANES is a nationally representative biological (urine) survey of the general public, capturing their daily routines/exposures such as consumption of drinking water. EPA views the NHANES monitoring data as the most reliable and representative assessment of total exposures that co-occur including daily use products as well as to other sources of triclosan contamination such as drinking water.

Markey 3c. Currently, under EPA regulations products treated with triclosan to protect the product itself – such as a cutting board, for example - are not subject to the law requiring that the products be labeled as containing triclosan. Given the health concerns with triclosan, do you think that the public should be notified when a product contains triclosan, regardless of what type of product it is? Why or why not?

Markey 3c Response: EPA's pesticide regulations exempt "treated articles" from FIFRA requirements. See 40 CFR 152.25(a). A "treated article" is any product which has been treated with an EPA-registered pesticide to protect the product and for which no other pesticidal claims are made. For example, many paints, sealants, paperboard products, and plastic products (e.g., shower curtains) contain pesticides in order to prevent the growth of mold or mildew in or on the products. Before approving a pesticide for such materials preservative use, EPA carefully assesses the potential risks resulting from such use. This assessment includes consideration of the possible exposure a consumer, who uses the product, might experience. The Agency will not approve a pesticide for materials preservative uses if there is a risk to consumers who handle products treated with the pesticide. EPA's assessment of the materials preservative uses of triclosan concluded that except for use in paint as an in-can preservative, they did not pose a risk to consumers who would come into contact with products treated with triclosan, http://www.epa.gov/oppsrrd1/REDs/2340red.pdf. However, EPA determined that there were risks for the material preservative use of triclosan in paint as an in-can preservative.

Therefore, EPA did not re-register the paint use. Had EPA reached a different conclusion for the other material preservative uses, rather than requiring labeling of treated products, we would have disallowed the use of triclosan as a materials preservative. In sum, so long as a pesticide used in consumer products as a materials preservative is registered and its use complies with its EPA-approved directions for use and the treated articles exemption, EPA does not think there is any need to require a separate registration or labeling of products treated with such pesticide. As new information becomes available on the hazards and levels of exposure to triclosan, EPA will work with FDA to evaluate the safety of all uses of triclosan. If there are uses of triclosan as a pesticide that do not meet the safety standard, EPA will take the appropriate regulatory action to prohibit those uses.

Response to the Honorable Joe Barton

Barton 1. Regarding the EPA's endocrine testing program:

Barton 1a. How much has the EPA spent to date?

Barton 1aResponse: The Endocrine Disruptor Screening Program in the Office of Chemical Safety and Pollution Prevention (OCSPP) has total obligations of approximately $88.9M and 189.1 FTE from FY 1999 through the end of second quarter of FY 2010 . Note that this total obligation amount for the Endocrine Disrupter Screening Program of OCSPP does not include funds obligated through EPA's Office of Research and Development for endocrine disruptor research which includes the development of some screening assays.

Barton 1b. Is it true that EPA staff at one point thought chemicals might be screened under the EDSP for as little as $50 per chemical?

Barton 1b Response: We do not believe that the estimate that chemicals could be screened for $50 per chemical came from EPA. There were two sets of hearings held in 1991 and 1993 as a prelude to the passage of the FQPA. Although we have not researched the hearing records, it is our belief that this estimate was provided by one of the witnesses who testified that a single in vitro screen to detect estrogen receptor binding (the E-Screen) could be conducted for $50 per chemical. EDSTAC and other experts did not regard this simple, single assay approach to screening to be scientifically adequate to detect chemicals with the potential to affect the endocrine system.

Barton 1c. Is it true that most estimates currently put the cost of the Tier 1 testing battery at $500,000 to $1 million per chemical?

Barton 1c Response: Two estimates of laboratory costs have been performed, one commissioned by the American Chemistry Council (ACC) in 2003 and one by EPA in 2009. Additional information was submitted by the ACC as comments on the ICR.[1] EPA's study titled "Laboratory Testing of Chemicals for Endocrine Disruption Potential-Analysis of

[1] Borgert CJ. 2008. Comments on EPA's Information Collection Request developed for the Agency's EDSP. Docket No. EPA-HQ-2007-1081-0010.2 and EPA-HQ-2007-1081-0015.2

Market Factors" was designed, in part, to provide contemporary cost estimates from 17 laboratories for conducting the most recent protocols for the 11 screening assays in the EDSP Tier 1 battery.

EPA's study report indicated a median estimated cost to conduct the 11 assays was $532,397 per chemical. Since there was a large variation in the cost estimates among laboratories--EPA's study report indicated a minimum of $243,000 and maximum of $941,750 per chemical-- the median was reported to better convey the information. The highest and lowest cost estimates for all *in vitro* assays were provided by two laboratories.

In addition, in 2007, EPA published calculations for paperwork burden and costs for data generation activities (Information Collection Request, ICR) related to conducting 11 screening assays in the EDSP Tier 1 battery for the first list of 67 chemicals to be screened (Docket # EPA-HQ-OPPT-1081). In Attachment F of the supporting documentation, the average estimated cost to conduct the 11 assays was $404,315 per chemical. The 2003 survey, conducted by Applied Pharmacology and Toxicology, Inc. (APT) and funded by ACC was the basis for EPA's cost estimates for eight of the screening assays in the ICR. The APT survey included 11 laboratories and draft protocols available at the time for ER and AR binding, Steroidogenesis, Aromatase, Uterotrophic (ovariectomized), Hershberger and Female and Male Pubertal assays. EPA adjusted the APT survey cost estimates by an inflation factor of 1.14. Since the Human ER Transcriptional Activation, Amphibian Metamorphosis and Fish Short-term Reproduction screening assays estimates were not included in the initial APT survey, EPA cost estimates were based on professional judgment and the costs the Agency incurred during assay validation (Amphibian Metamorphosis and Fish Short-term Reproduction).

Although median and mean cost estimates from EPA's estimates in 2009 and 2007, respectively, are not directly comparable, the median estimate for the 2009 EPA study was approximately $10,000 to $20,000 higher for most individual assays than the mean estimate for the same assays in the 2007 EPA ICR. Apart from reporting the median versus mean, the discrepancy may be due, in part, to older versus newer versions of the protocols and economic changes between 2007 and 2009.

Barton 1d. If these expense estimates are accurate, in light of that expense, why would EPA not first evaluate existing data before taking other steps?

Barton 1d Response: Recipients of the EDSP Test Orders for the initial screening of chemicals have the option to submit or cite existing data (including citing data previously submitted to the Agency) that they believe is relevant to one or more of the assays specified in the Test Order. The Agency will review this Other Scientifically Relevant Information that may be submitted by either the test order recipient or the public in lieu of the Tier 1 battery. The policies and procedures the Agency adopted for initial screening under the EDSP recommend that the Test Order recipient or other parties, provide an explanation of the relevance of any cited existing data to the test order as well as a rationale for why they believe the information is or is not sufficient to satisfy part or all of the Tier 1 order. These policies and procedures provide for the use of information that is consistent with all or part

of the battery or may also inform the outcomes that the battery seeks to evaluate. In this manner, the Agency will only require needed data.

Barton 2. Dr. Borgert testified that expanding the endocrine testing program before the effectiveness of its testing system can be evaluated would be an inefficient use of taxpayer resources. Please state whether you agree or disagree with this statement.

Barton 2 Response: EPA accepted the recommendation of the 1999 review of the proposed EDSP by a Joint Subcommittee of the Science Advisory Board and FIFRA Scientific Advisory Panel to limit the number of chemicals in the first list to 50-100 chemicals and review the results before issuing a second list. This was a cautious approach and prudent when it appeared that such a list could be issued and data received by 2005. However, the validation of assays has taken far longer than EPA or anyone else anticipated. The current Tier 1 battery was reviewed by the SAP in March 2008 and found to be adequate to detect substances with estrogen, androgen, and thyroid activity. EPA believes the battery will produce sufficiently valuable data and that further delays in testing should not be made.

Barton 3. Do you agree that there are real world consequences that will accompany the results of the endocrine screening battery, and if so, doesn't that make it all the more important that the tests are precise and reliable?

Barton 3 Response: EPA agrees that issuing test orders which require recipients to conduct the endocrine screening battery has real world consequences. We also agree that it is important therefore for the tests that comprise the battery to be scientifically reliable for their intended purpose. Based on the extensive, multi-year effort to validate the assays used in the endocrine screening battery, we concluded that the testing methods we are requiring meet the statutory standard of being "appropriate validated tests systems." The independent, experts on the FIFRA Scientific Advisory Panel who reviewed the battery in March 2008 agreed with EPA's conclusion.

Barton 4. You testified the "first list of chemicals was selected solely on the basis of exposure." Exposure is an important consideration but how many of the selected chemicals are high risk chemicals for the purposes of this program?

Barton 4 Response: EPA is not prepared to identify any of the 67 chemicals on its initial list of substances undergoing EDSP screening as "high risk chemicals." When we began to identify substances for this list, scientists had not developed an approach for setting testing priorities based on the potential of a test substance to be an endocrine disruptor (although we are aware of promising research that may provide priority setting tools in the future). Therefore, EPA used exposure-based criteria to select chemicals for the initial list. We have repeatedly stated that the inclusion of a chemical on the initial list does not indicate that the chemical has the potential to disrupt the endocrine system. Rather, we will use the results of the Tier 1 battery to characterize the potential of substances to interact with the endocrine system, and where appropriate, the results of Tier 2 assays to define the

relationship between dose and response. With such information, EPA can assess the potential risks posed by human exposure to endocrine-disrupting chemicals.

Barton 5. Do the test orders for Tier I consist of a "cookie-cutter" or "one-size-fits-all" approach? If not, why? Could the quality of EPA's results be impacted by this kind of approach?

Barton 5 Response: No, the test orders for the EDSP Tier I assays require that recipients perform all 11 Tier I assays unless the respondent has justification equally informative as that which would be provided by conducting a particular EDSP Tier I assay (in other words, they have other scientifically relevant information that can inform determinations that would be generated through a Tier I assay). It is the responsibility of the respondent to provide significant justification that the Tier I assay has been satisfied in full in order to ensure the data needed to fulfill the Tier I assay requirements.

Barton 6. The statutory language of Section 1457 of the Safe Drinking Water Act requires EPA to test substances that may be in drinking water sources if a substantial population is exposed. Yet, your testimony states that EPA is compiling a list of 100 chemicals pursuant to non-statutory report language.

Barton 6a. Would any of the 100 chemicals not meet the statutory criteria of the Safe Drinking Water Act?

Barton 6a Response: The House Report for H.R. 2996, which accompanied the FY 2010 appropriations, for EPA directs the Agency to "publish within one year of enactment a second list of no less than 100 chemicals for screening that includes drinking water contaminants, such as halogenated organic chemicals, dioxins, flame retardants (PBDEs, PCBs, PFCs), plastics (BPA), pharmaceuticals and personal care products, and issue 25 orders per year for the testing of these chemicals."

EPA has already issued test orders for 67 pesticide chemicals and believes that it is important to continue testing additional substances for potential endocrine disrupting activity. We are currently developing our second list of approximately 100 chemicals and expect to invite public comment on the list within the next several months and begin issuing test orders later this year. Orders requiring testing of additional chemicals must be authorized under our existing statutory authorities, which include section 1457 of the Safe Drinking Water Act (SDWA) and section 408(p) of the Federal, Food, Drug, and Cosmetic Act (FFDCA). Some of the chemicals proposed for the second list will be pesticide ingredients, and we would rely on section 408(p) of FFDCA as the authority to issue test orders for these chemicals. The remaining chemicals proposed for the second list will be drinking water contaminants. For them, we would rely on section 1457 of SDWA, which requires EPA to make certain findings before issuing the test orders.

Barton 6b. Why does EPA intend to include pesticides on a non-statutory list that the agency previously concluded did not meet the minimum concern criteria to merit a listing on CCL3?

Barton 6b Response: As noted above, EPA believes it is important to evaluate chemicals, including pesticides, for potential for endocrine disrupting activity. We have a statutory mandate to screen all pesticide chemicals under section 408(p) of FFDCA. In addition to the initial list of 67 pesticides for which we have already issued test orders, we plan to use our statutory authority under section 408(p) of FFDCA to issue test orders for any other pesticides that are included on our second list. Note that some of the pesticides on the second list may also be drinking water contaminants as well.

Barton 7. Please explain whether much of the problem of the presence of these substances in surface waters could be solved with better waste water treatment techniques.

Barton 7 Response:
The effectiveness of technologies in removing the potentially wide range of chemicals that may be EDCs has not been fully studied. However, generally the more advanced the treatment technology, the greater the removal of chemical contaminants. Many factors impact the type of treatment that is appropriate for a publicly owned waste water treatment works (POTW). These include the source and type of contaminants in the waste stream, the size of the community served by the POTW, and the cost of the treatment technology to the community served. A portion of EPA's endocrine disruptor research budget is devoted to studying the effectiveness of wastewater treatment technologies to remove chemical contaminants.

Barton 8. Hasn't it been EPA's approach to conduct screening of an initial list of chemicals to test the performance of its Tier 1 screening battery? Doesn't EPA need to await the results of that screening before it undertakes additional screening?

Barton 8 Response: The purpose of the screening of chemicals on the initial list is to generate data that will be used to determine whether or not those chemicals have the potential to interact with the endocrine system. It is not specifically designed to test the battery; however, consistent with the 1999 SAB/SAP's recommendation, EPA will conduct an analysis of the data to determine how the different assays worked in concert with each other, compare the results with Part 158 data and with the ToxCast data to determine the correlation of the ToxCast assays with the EDSP results. ToxCast has been developed since 2005. The comparison of ToxCast results with the results of the Tier 1 battery is an important step in determining the potential of ToxCast, and to understand whether the relevant ToxCast assays provide the reliability and reproducibility required for chemical screening. Determining how well the assays work as part of the battery as a whole would allow EPA to optimize the battery by eliminating assays that provide needless redundancy or flag others for improvement or replacement. Ideally, this analysis would be conducted before EPA issued additional test orders.

Barton 9. In 1999, EPA's Science Advisory Board (SAB) and EPA's Science Advisory Panel (SAP) recommended that EPA conduct an initial phase of screening of 50 to 100 substances.

Barton 9a. Please explain the basis for that recommendation, including whether there were concerns that the assays or battery might not perform as hoped. Please further explain the SAP's specific concerns.

Barton 9a Response: The SAP report notes: "The Subcommittee supports the proposal to develop a two-phase program for endocrine disruptor screening and testing (EDST). Further, a formal reevaluation of the screening and testing process at regular intervals should be part of the program. The purposes of this reevaluation process would be to evaluate the effectiveness of the protocols initially adopted for screening and testing and to adopt new protocols in cases where none currently exist for identifying endocrine alterations or the effects of those alterations. Adoption of new screens and tests should also mean the elimination of previous, less useful ones."

Barton 9b. Please state whether EPA has undertaken the SAP-recommended phased approach by ordering screening of an initial list of 67 pesticide chemicals.

Barton 9b Response: As stated in several Federal Register notices, EPA is following the 1999 SAB/SAP's recommendations to screen 50-100 chemicals and review the results. That review is projected to occur in 2013 after all of the data have been submitted and reviewed by the Agency. However, EPA is also following the directive in the Appropriation Committee report that a second list of no less than 100 chemicals be published by October 31, 2010 and that the Agency issue a minimum of 25 orders per year.

Barton 9c. Please state whether EPA believes it may find it necessary to modify some Tier 1 screens and the T1S battery as a result of information it obtains from screening the initial list of chemicals.

Barton 9ci. Please state whether it is possible that the Tier 1 battery may not be effective for determining which chemicals may interact with the endocrine system. Please also explain the basis of EPA's conclusion...

Barton 9ci Response: EPA believes, and the SAP review in 2008 concurred, that the battery will perform its essential function to identify chemicals that interact with the estrogen, androgen and thyroid hormone systems. EPA does not anticipate any serious problems with any of the assays in the battery, but acknowledges that there is always the possibility of unforeseen problems that did not show up during validation. Please note that the validation process has been very rigorous, and EPA has carefully sought to balance the need for validation with the statutory mandate to require testing. EPA is developing potential replacement assays and will phase in newer technologies as they are validated. This is consistent with the SAP recommendations: "In summary, the proposed set of Tier 1 assays are appropriate to begin screening for disruptors of the [estrogen, androgen, and thyroid] EAT axes. However, several assays do not represent the current state of the science, or the proposed screens do not fully address major modes of action and should be updated and extended as soon as possible. The EPA should consider this set of assays to be a work in progress. The Panel expects that the EPA will continue to develop, refine, and review the battery. New endocrine disruptors and new mechanisms of action are likely to

be revealed in the future requiring that the current Tier 1 assays be modified and new ones developed and validated."

Barton 9cii. Please state whether it is possible EPA may find it necessary to significantly modify some assays and the battery.

Barton 9cii Response: Other than replacement of assays with newer technology, EPA does not anticipate significant modifications; however, as noted EPA is prepared to do so if this is warranted. EPA also intends to explore additional areas recommended by the Appropriation Committee such as the adrenal axis. The adrenal axis is the adrenal, the hypothalamus and pituitary glands and their hormones.

Barton 9d. Please state whether EPA drafted flexible implementation policy and procedures (as opposed to a rulemaking) on the basis that the agency might need to modify those policies and procedures in response to information it gathers in implementing the first phase of screening.

Barton 9d Response: EPA chose not to use rulemaking to codify its policies and procedures so that their modification could be more expeditious if warranted by the experience with the first group of 67 chemicals

Barton 9e. Please explain how the benefits of a phased screening approach can be if EPA does not awaits the results of phase 1 screening before undertaking additional screening.

EPA is proceeding with the second list before the analysis of the results from the first list can be conducted; however, what EPA learns from the first and second lists will be reflected into modifications to the EDSP, if appropriate, and applied to subsequent lists. Rather than a rigidly sequential approach, EPA is adopting a rolling approach to improvement of the EDSP.

Barton 9ei. Please state whether EPA has identified all issues that might arise during screening.

Barton 9ei Response: EPA made a good faith effort to identify the most important issues that are likely to arise during screening, and to prepare for them. However, there can be no guarantee that all important issues have been anticipated.

Barton 9eii. Please state if EPA has already determined whether or not it will modify its Tier 1 assays and battery.

Barton 9eii Response: As noted above, EPA plans to evaluate newer technologies that may provide significant advantages over some of the older technologies. However, until validation is complete and the Agency can be certain that such technologies provide equivalent or better information, a decision to modify the existing Tier 1 assays and battery would be inappropriate.

Barton 10. Please state whether, in 1999, the EPA Science Advisory Panel (SAP) stated with respect to Negative Control Agents, "There is a need to define and agree on some negative

control agents for [endocrine disruptor] assay validation. Assay specificity will not be capable of assessment unless such agents can be made available for general study."

Barton 10 Response: The sentences cited appear in the SAP's "Review of the EPA's proposed environmental endocrine disruptor screening program" released in 1999.

Barton 10a. Please state whether EPA has established and run negative control agents in some of the EDSP Tier 1 screening assays.

Barton 10a Response: EPA has established and run negative control agents in some of the EDSP Tier 1 screening assays. For example, in the estrogen receptor binding assay, octyltriethoxysilane has been established as a negative control agent. All of the Tier 1 assays were successfully tested with negative chemicals prior to the issuance of test orders. However, during the validation program, the chemical selected as the negative chemical for the pubertals showed some effects on the endocrine system, i.e., it was not negative. This raised concerns regarding the specificity of these assays.

Barton 10b. Please state whether in March 2008 the SAP told EPA, "A negative control substance(s) has not been identified for the pubertal assays and this stands as a major limitation to the Tier 1 battery."

Barton 10b Response: In SAP Minutes No. 2008-03 "A set of scientific issues being considered by the Environmental Protection Agency regarding: the Endocrine Disruptor Screening Program (EDSP) proposed tier 1 Screening Battery" transmitted to EPA in June of 2008 the SAP wrote as follows: "Although the Panel found that the battery of assays presented would serve as an adequate screen for estrogenic, androgenic and thyroid hormone disruptors, a number of recommendations were made for modifications of the assays and for further research. Among those are the following: ... 7. A negative control substance(s) has not been identified for the pubertal assays. This stands as a major limitation to the Tier 1 battery and more compounds should be tested. ..."

The follow-up to this concern was stated in the response to question 10a.

Barton 10c. Please state whether the Agency has released for independent peer, as well as public, review studies of a non-endocrine active, negative control agent in these pubertal assays.

Barton 10c Response: As of March 22, 2010 the Agency has not yet released for independent peer review its evidence that a chemical that has non-endocrine toxicity does not necessarily have effects on the endocrine system. The study, which has been completed, is actively being prepared for submission to a peer-reviewed journal.

Barton 10d. Please state whether the Agency has neglected to heed the advice of the SAP, and if so, please explain why.

Barton 10d Response: The Agency has not neglected to heed the advice of the SAP. The SAP called for additional research. EPA is preparing for publication the results of a

research study which addresses the SAP's concern about the lack of a negative control in the pubertal assays.

EPA also notes the difficulty of finding a chemical that is already "known" to be negative and that can be used to test whether the pubertal assays give the "correct" (negative) response, when no validated endocrine assays that test the breadth of endocrine mechanisms covered by the pubertal assays are available. That is, there is no accepted assay to compare the results of the pubertal assays to. Certainly there are chemicals which are known to be negative for specific mechanisms such as estrogen receptor binding or aromatase inhibition, but the pubertal assays test for effects that might be due to any of several different mechanisms and that may be modified by the complexities and possible interactions across multiple pathways of a living organism. Thus the negative control chemicals that are used in mechanism-specific assays and test-tube assays cannot be said to be "known" to be negative for all endocrine pathways tested by the pubertal assays.

Barton 10e. Please state the reasoning behind EPA's decision to require these assays despite the need for specificity as one of the core elements of establishing a scientifically valid assay.

Barton 10e Response: Since there are no compounds that are "known" to be negative for all of the endocrine mechanisms tested by the pubertal assays in a complex living organism and that could, thus, serve as chemicals to test the specificity of the pubertal assays, EPA has relied on the fact that certain chemicals are negative for one mechanism or another to show that the pubertal assays are specific. A thyroid-active compound could reasonably be expected to be negative for estrogenic or androgenic effects (although there is some cross-talk among the systems), and vice versa and indeed this is shown to be true when using the pubertal assays. Propylthiouracil, for example, showed clear effects on the thyroid in the pubertal female assay at a dose level that did not have an effect on the reproductive axis. Conversely, ethynyl estradiol showed clear effects on the reproductive axis but no effect on the thyroid system. The pubertal assays clearly do not give positive results for all endpoints for all chemicals, as might be expected if the pubertal assays responded to general stress rather than to endocrine-specific mechanisms and it was on this basis that EPA decided to include the pubertal assays in the battery proposed to the SAP. As noted above, EPA's Office of Research and Development continued to search for a chemical that would be generally toxic but devoid of all effects on the endocrine system.

Barton 10f. Please state the rationale for EPA's decision not to follow the SAP recommendations. Please explain why assays which may not be able to distinguish endocrine activity from other types of toxicity should be included in the endocrine screening battery if the purpose of that battery is to identify substances with the potential to interact with components of the endocrine system.

Barton 10f Response: As explained above, EPA has followed the SAP recommendations. . The fish screening assay contains apical endpoints such as fecundity which has caused some concern among stakeholders who argue that the screens should only measure endpoints specific to endocrine disruption. However, consistent with the recommendations of its advisory committees, EPA decided to include some apical endpoints as not all endocrine

modes of action can be captured without them. While other types of toxicity may also affect fecundity, the battery as a whole can be used to distinguish effects that are endocrine related from those arising from other modes of action.

NATURAL RESOURCES DEFENSE COUNCIL

March 31, 2010

Committee on Energy and Commerce
2125 Rayburn House Office Building
Washington, DC 20515-6115

Dear Chairman Markey, Rep. Barton, and Members of the Committee:

I am pleased to respond to the additional written questions posed by Chairman Markey and Representative Barton in follow-up to my testimony before the Subcommittee on Energy and Environment on February 25, 2010. My original testimony focused on "Endocrine Disrupting Chemicals in Drinking Water: Risks to Human Health and the Environment". I expressed serious concerns about the documented presence of chemical contaminants in source water in the United States. The decade-long delay in the implementation of the EPA Endocrine Disruptor Screening Program (EDSP) has resulted in a huge backlog of chemicals that have not been tested for endocrine disrupting effects, including many common drinking water contaminants. Furthermore, EPA has failed to take regulatory action under the Safe Drinking Water Act (SDWA) to protect the public from chemicals that have been tested and found to be endocrine disruptors, and that are known to be contaminants in drinking water. In my testimony, I offered a number of recommendations to help address these problems, including:

- Implementing testing under the endocrine disruptor screening program for priority drinking water contaminants, including all chemicals on the CCL3, as well as other chemicals in pharmaceuticals and personal care products that have been detected by USGS in surface or groundwater.
- Implementing aspects of the EDSTAC report that have been ignored, such as creating the Endocrine Disruptor Priority Setting Database, integrating the High-Throughput Pre-Screen (or ToxCast) into the program for priority-setting, screening common mixtures, and inviting public nominations for testing;
- Evaluating and identifying wastewater and drinking water treatment practices for removing endocrine disrupting chemicals, including pharmaceuticals;
- Preventing or limiting the use of hormones in agriculture.
- Requiring EPA to prioritize and screen chemicals in drinking water, including mixtures, for endocrine disrupting effects;
- Restoring adequate funding for the USGS Toxic Substances Hydrology Program and the USGS National Water Quality Assessment Program (NAWQA), so more data are available on contaminants in source water and drinking water; NAWQA

started with 500 sites in 1991, and has now been reduced to 113, of which only 12 are monitored annually. 86 sites are monitored only once every four years;

- Reforming the Toxic Substances Control Act (TSCA) to require testing of chemicals for toxicity, and require EPA action to promptly regulate hazardous chemicals.

Responses to follow-up questions from Chairman Markey are presented below.

1. *In your testimony, you state that certain endocrine disrupting chemicals are present in our water supply, albeit at low levels.*

   a. Are there documented health effects associated with low dose exposures to endocrine disrupting chemicals? If so, can you describe them?

Yes, peer-reviewed scientific publications have found health effects from low dose exposures to endocrine disrupting chemicals. "Low doses" are defined here as exposures that are occurring at or below current levels of exposure in the human population. Endocrine disrupting compounds such as bisphenol A[1], phthalates[2], and some pesticides[3,4] have been associated with a wide array of adverse health effects after low dose exposures. Many of these studies have been done in laboratory animals, but emerging research has found evidence of similar harm in non-human primates and humans.

Low doses of bisphenol A (BPA) have been associated with precancerous lesions in the prostate and mammary gland (breast), alterations in brain development causing behavioral abnormalities, reproductive harm including earlier onset of puberty, uterine fibroids, and abnormal numbers of chromosomes in oocytes (female eggs)[5]. Recent studies in non-human primates and human epidemiological studies have found effects similar to those seen in animal studies after low dose BPA exposure. These include interference with the treatment and progression of breast cancer[6,7], prostate cancer[8], altered development of the brain causing changes in behavior[9,10], alterations in hormone signaling in fat tissue[11,12] and cardiovascular disease[13]. Low doses of phthalates have been associated with allergic responses,[14] worsening of asthma, altered development of male genitals[15], impaired semen quality[16], and alterations in toddler behavior[17]. Finally, mixtures of phthalates and other anti-androgenic chemicals including some pesticides, have been found to have additive effects such that exposures to the mixture cause harm where exposures to the individual chemicals at the same doses cause no harm[18].

   b. Why is the dose-response for endocrine disrupting chemicals different than other toxic chemicals?

It is a well-recognized and accepted physiological phenomenon that hormones naturally occurring in the human body (endogenous hormones), are regulated by feedback loops which respond to small changes in circulating hormone levels, receptor binding, and metabolism or breakdown of hormones. Therefore, low levels of endogenous hormones have very different, and sometimes opposite, effects than high levels of a hormone. These

feedback loops respond to very small changes in concentration, in the parts-per-trillion to part-per-billion range, but are potent enough to bring about ovulation and other physical changes each month in a women's reproductive cycle and the profound changes that occur during puberty. Therefore, it is not surprising that chemicals in the environment that interfere with the endogenous hormones in a human body can have differing effects at low versus high levels of exposure. Furthermore, laboratory studies which rely on dosing animals with high doses of an endocrine disrupting chemical, will not adequately predict the effects of low doses of exposure.

c. If endocrine disruptors exert their effects at what are considered minute dosages, can a dose that is low enough to be considered safe ever be determined?

Risk assessments currently done by federal agencies such as the EPA do not adequately address endocrine disruptors because they do not consider mixtures, low dose effects, or background exposures, and therefore have not been adequately protective of the most susceptible populations. The National Academy of Sciences (NAS) recently issued two important reports which called on EPA to consider mixtures, background exposures and susceptible populations for improvements in chemical risk assessments – especially for endocrine disrupting chemicals.[19][20] The NAS also recommended that EPA move away from the assumption that there is a threshold for non-cancer adverse effects.

Although endocrine disruptors pose a challenge to risk assessment, the NAS clearly communicated that the challenge can be met with updates and improvements to the current risk assessment process. In some cases, there may be no safe level of exposure to a chemical or group of chemicals, but these chemicals can also be addressed using existing approaches. For example, there is a broad scientific consensus that there is no safe level of exposure to lead, so there has been a decades-long effort to reduce or eliminate sources of lead exposure. As a result of exposure reduction efforts, CDC biomonitoring data have documented a dramatic reduction in blood lead levels in the U.S. over the past few decades. Endocrine disruptors – like lead – are chemicals that can have health effects at low doses. Regulatory approaches to assess population risks and to reduce exposures as much as feasible can successfully protect human health and the environment from these chemicals.

d. What do we know about the effects of being simultaneously exposed to low doses of several different endocrine disruptors?

Mixtures of phthalates and other anti-androgenic chemicals including some pesticides have been found to have additive effects such that exposures to the individual chemicals at doses shown to cause no harm have been found to cause harm when combined in a mixture[21]. Furthermore, there are a number of environmental chemicals which mimic thyroid hormone and also can be expected to exert additive or synergistic effects when combined in a mixture.[22] The National Academy of Sciences (NAS) recently issued a report underscoring the importance of evaluating groups of chemicals that cause the same adverse outcome, such as altered male genital development caused by mixtures of anti-androgens including phthalates, or neurodevelopmental harm caused by thyroid hormone

disrupting chemicals. [23] The NAS stated that basing chemical safety evaluations on just one chemical at a time or ignoring other modes of action which contribute to the same outcome "may lead to considerable underestimation of risks to the developing fetus."

2. In your testimony, you state that you served on EPA's Endocrine Disruptor Screening and Testing Advisory Committee. The committee submitted its final report to EPA in August 1998 with a number of recommendations.

a. Which of these recommendations did EPA fail to implement?

1) EPA failed to implement the "high-throughput pre-screen (HTPS)" for estrogen and androgen receptor binding and transcriptional activation. This rapid screen was envisioned as important for priority-setting, and for rapid detection of chemicals that may be endocrine disruptors via a receptor-based mechanism. The EDSTAC envisioned using the HTPS to screen 10,000 chemicals per year.
2) EPA has not yet validated the "tier 2" tests, so it is possible that chemicals which test positive in the current round of testing may still not have sufficient data for regulatory action even after the testing is done.
3) EPA never created the Endocrine Disruptor Priority Setting Database which was envisioned as a way for the information on exposure and potential endocrine hazard of chemicals to be gathered together in one place in a publicly accessible format.
4) EPA has not developed a strategy for screening mixtures of chemicals for endocrine effects, including the six priority mixtures identified by the EDSTAC. Two of the EDSTAC priority mixtures related to drinking water: common pesticide/fertilizer mixtures found in surface water, and disinfection byproducts commonly found in drinking water.
5) EPA has not yet implemented the recommended nominations process to allow members of the public to recommend chemicals for priority testing.
6) EPA has not proposed testing chemicals other than pesticides and pesticide inerts, even though the EDSTAC explicitly recommended that all chemicals be prioritized for potential screening.

b. Which of the recommendations listed in question 2a do you think EPA should still incorporate into the screening program?

The public nominations process, and screening of priority mixtures are still very important and should be implemented. The most important recommendation that still remains to be implemented, however, is the recommendation to prioritize, screen, and test a broader universe of chemicals than just pesticides. For example, drinking water contaminants should also be tested under the EDSP.

c. What additional recommendations do you have to improve the Endocrine Disruptor Screening Program?

The ToxCast program is implementing approaches similar to the HTPS. EPA should integrate endocrine disruptor screening approaches from the ToxCast and Tox21 efforts

with the EDSP to improve prioritization and expand the number of chemicals screened. EPA should also create a public database that contains endocrine-related data – as well as data gaps – on a broad universe of chemicals.

3. Over a decade ago, the EPA adopted a battery of validated experimental assays (called Tier 1) for the endocrine disruptor screening program.

a. Do you think the EPA should regularly update its screening assays to incorporate advances in sensitivity, accuracy, reliability, reproducibility, or efficiency?

Yes, EPA should regularly update its screening assays to incorporate advances in testing approaches and also to pursue four major objectives outlined by the National Research Council: (1) to increase 'throughput' so more chemicals can be screened, (2) to enhance the depth of information for risk assessment by incorporating more endocrine effects and a broader range of doses, (3) to reduce animal use, and (4) to reduce cost.[24] Newer techniques are being developed that allow screening of chemicals using in-vitro methods and non-mammalian approaches. These should be run in parallel with the current EDSP screens until it is clear that they are reliable enough to replace some or all of the current screens. This will allow continuous improvement in the program without further delaying implementation of the EDSP.

b. What recommendations do you have to ensure that the adopted screening protocols are scientifically valid?

The National Research Council, in their report entitled "Toxicity Testing for the 21st Century," recommended running newer assays in parallel with current testing methods until there is sufficient experience with the newer assays, and sufficient confidence using these results in priority-setting and risk assessment, that the newer assays can smoothly replace the older ones.[25]

4. Are there chemicals that have been listed on any of EPA's Candidate Contaminant Lists, for which you believe there is enough information about their endocrine disrupting effects that further Tier 1 screening under EDSP is not necessary? If so, which ones? Are the health effects associated with any of these chemicals sufficiently well-understood such that Tier 2 screening under EDSP is also unnecessary? If so, which ones?

Several important veterinary steroids that have been detected in drinking water are on the CCL3, including estriol, estrone, ethinyl estradiol, and mestranol. Some of these are also breakdown products of human pharmaceuticals. Perchlorate is also on the CCL3. The CCL1 and CCL2 list contain several additional well-understood endocrine disruptors including linuron, triazine herbicides, and organotin compounds. These are chemicals whose endocrine disrupting effects are well-characterized. There is no need for additional screening or testing of these chemicals. In my opinion, regulatory determinations for these chemicals can (and should) be made based on currently-available toxicity and pharmacological information.

Responses to follow-up questions from Rep. Barton are presented below.

1. You are critical on (sic) the speed at which EPA has moved the Endocrine Screening Program along. Please tell me what is the exact amount of time that it takes to produce high-quality science?

Congress gave EPA a reasonable timeline for creation and implementation of the EDSP: two years to create the program and an additional year for implementation. EPA met the deadline for creation of the program, but missed the implementation deadline by more than a decade. The explanation the Agency offered for failure to meet the Congressional deadline was that the validation process was ongoing. It is puzzling to many scientists and to the members of the Endocrine Disruption Screening and Testing Advisory Committee (EDSTAC) that validation of these particular assays took so long. The EDSTAC envisioned that EPA could complete the validation within the allotted year. Most of the assays used in the EDSP are ones that have been in widespread scientific use and have achieved broad scientific acceptance for many decades. For example, the receptor binding assays and the Hershberger assay have all been in common scientific use since the early 1970's, and the uterotrophic assay had been in broad scientific use for more than 80 years at the time of the EDSTAC report. These assays were not new science, and represented well-established and well-understood scientific tests for hormonal effects. For such assays, a decade-long validation process makes no scientific sense.

2. You testified that an "unsavory mix" of such substances like pharmaceuticals, hormones, pesticides, flame retardants, and plasticizers have been found in the nation's waterways. Many of these substances are not just vital to human health- like pharmaceuticals and often hormones- but many are mandated by law for safety. How do you respond?

As a physician I am distressed at the implication that because some pharmaceuticals and hormones may be prescribed to some individuals to treat specific diseases, widespread exposure to the entire population might somehow be "vital to human health". I have never prescribed a drug to a patient who doesn't need it. To do so would be malpractice, and could result in serious harm. For drugs such as antibiotics, overuse and resulting environmental contamination has been linked to the very dangerous problem of antibiotic resistant bacteria. In fact, the CDC has an ongoing campaign to prevent antibiotic resistance and has highlighted numerous dangerous human diseases that have been linked to this problem.[26] The problem is not limited to antibiotics. Synthetic hormones that might benefit some adults at some times in their lives are known to harm developing infants. Many pesticides, flame retardants, and plasticizers have well-documented adverse health effects. I am not aware that any of these chemicals are "mandated by law for safety" in drinking water.

3. While it is a good goal to reduce toxic exposures in the environment, should the U.S. Government stop requiring the use of flame retardants in consumer products like

mattresses, furniture, and clothing? In the absence of alternatives, should we stop mandating the use of the chemicals that make our cars safer and more impact resistant and our children's bike helmets more protective and shatter-proof?

To my knowledge, the U.S. Government does not require the use of toxic flame retardants, nor does it mandate the use of any specific chemicals to make cars and bike helmets safer. Instead, there are flame retardancy standards and safety standards for some consumer products. These standards can be met in various ways, such as through the use of naturally flame-resistant materials or design changes. For example, Apple was the first electronics manufacturer to announce a commitment to remove all chlorinated and brominated chemicals, including flame retardants, from their products and as one example of a design change has replaced the polycarbonate housing of its laptop computers with an aluminum alloy. As a result of these and many other design changes, many Apple products such as the iPhones and iPods, as well as their computers, are free of brominated flame retardants.[27] Seagate, the largest disk drive manufacturer in the U.S. has eliminated chlorine and bromine-based chemicals from a line of new disk drives. Furniture companies such as Herman Miller and IKEA also have pledged to replace toxic flame retardants with safer alternatives.[28]

I certainly hope that my testimony did not imply that consumer safety protections should be eliminated. Instead, the goal is to eliminate contamination – such as of our drinking water supply – and to encourage innovation in the chemical industry to adopt "green chemistry" approaches. It is certainly within the range of modern science to ensure product safety without needing to use toxic chemicals or produce environmental contamination.

4. Your testimony of (sic) is highly critical of BPA. If BPA is so dangerous, why have countries like Israel and the EU reversed their bans on the substance, stating unequivocally that its use is perfectly safe?

Neither Israel nor the EU have ever temporarily banned BPA or reversed a ban on BPA. The Israeli Health Ministry advises parents to throw away baby bottles that have been in use for over a year and those that have cracks or scratches. The Israeli Health Ministry has said that it is watching recommendations on BPA from relevant organizations abroad and is working with the Israel Standards Institution to produce a standard for baby bottles and related plastic products.[29] An extensive search failed to find any documentation of the alleged statement that "unequivocally… its use is perfectly safe". I would be very interested in seeing documentation of this statement.

In Europe, the French Food Safety Agency (AFSSA) is pursuing a new safety assessment of BPA with the European Food Safety Authority (EFSA).[30] Meanwhile, the French government is moving to ban BPA in baby bottles.[31] A spokesman for the French environmental health research institute Réseau Environnement Santé, said the French Senate had taken "a big step forward" by voting in favor of the ban. He called for it to "go a step further and vote to ban BPA from all food containers used by mothers that could cause foetuses and breastfed babies to be contaminated by the chemical".[32] On Feb.

9, 2010, the Danish Parliament voted to ban bisphenol A in products aimed at children under three years old and called on the Danish government to press for a European Union-wide moratorium on the use and sale of food contact materials with BPA. The resolution urges the government to ask other member-states to implement national bans and support an EU-wide ban.

The Canadian Ministry of Health has determined BPA is a "chemical of concern" and has banned the use of BPA in baby bottles and is restricting use in formula cans.[33] In addition, the U.S. FDA has recently changed its opinion on the safety of BPA in our food supply and has expressed "some concern" for the impacts of developmental exposure to BPA. FDA is encouraging the development of safer alternatives and has public information on its website about how to avoid BPA exposure.

5. You cite studies that allegedly show exposure to BPA is so dangerous that it is linked to cancer and brain abnormalities.

a. What was the route of exposure for the BPA dosage?

Laboratory studies that have found evidence of a predisposition to cancer or brain and behavioral abnormalities have dosed the animals via subcutaneous injection during critical windows of development such as in the womb (prenatal) or early in life (neonatal). Independent peer-reviewed research has demonstrated that during these critical windows of development, the capacity to breakdown or metabolize BPA is not developed and therefore, the route of administration has not been found to change circulating levels of BPA.[34]

In the 2008 report of the National Toxicology Program's (NTP) Center for Evaluation of Risks to Human Reproduction on BPA, the NTP wrote the following regarding route of administration of BPA in animal studies:

> "Taken together these data indicate that, compared to adults at a given dose, neonatal rats (and presumably mice) metabolize bisphenol A more slowly and suggest that differences in circulating levels of free bisphenol A arising from oral and subcutaneous routes of administration as a result of "first-pass metabolism" are reduced in fetal or infant animals compared to adults." and "While more research in this area is warranted, data from studies where bisphenol A was given by subcutaneous injection were considered as useful in the NTP evaluation as oral administration when treatment occurred during infancy when the capacity to metabolize bisphenol A is low."[35]

b. Assuming the animal tested is identical in form and substance to a human, is that a normal route of exposure for BPA?

For fetuses in the womb the route of exposure will be through BPA transferred from the mother's blood. Administration of BPA in laboratory animals via the subcutaneous route of exposure to the mother will result in identical transplacental exposure to the fetus.

c. Generally speaking, are there studies that suggest that BPA is not harmful?

Most industry-funded studies have not found evidence of harm. These studies have had flaws, including not looking at endpoints that have been described for BPA toxicity such as precancerous lesions in prostate tissue or behavioral abnormalities and the studies reportedly contained inconsistencies in the reporting of animal data.[36] One new study by US EPA scientists has also found no evidence of harm in laboratory rats.[37] However, this study has also been criticized for using a strain of rat that is relatively insensitive to estrogen and estrogen-mimicking chemicals such as BPA.[38]

d. If so, what is the ratio of studies that allegedly demonstrate danger to those studies that support its safe use? 10 percent to 90 percent that it is unsafe? 25 to 75 percent unsafe? 50-50? 90 percent to 10 percent?

In an analysis of the BPA literature published in 2005, there were 115 published studies concerning low-dose effects of BPA. Ninety-four of these (about 82 percent) reported significant effects.[39] Since this publication, there have been many more research studies on BPA and the overwhelming weight of evidence continues to demonstrate that BPA causes a wide array of adverse effects in a number of animal models, including non-human primates. In addition, there is an emerging body of research in humans which is consistent with the evidence of harm seen in the animal studies.

6. Dr. Robert David Utiger, one of the leading thyroid doctors in the country, testified last Congress that Americans live in an iodine sufficient country. He further testified that "there is a potent mechanism – increased TSH secretion by the pituitary gland – to compensate for thyroid hormone deficiency"; that supplementing the human diet with iodized salt was a cheap and easy way of adding enough compensatory iodine to the diet for iodine deficient persons; and that prenatal vitamins should include iodine. This testimony was consistent with the findings of the National Academy of Sciences and the American Thyroid Association, both of which preceded and postdated the CDC study cited in your testimony. Please explain your contradictory conclusion that a regulatory solution is necessary to address iodine deficiency.

Among women of reproductive age in the United States, the median urine iodide (UI) level was 139 microg/L according to the 2003-2004 National Health and Nutrition Examination Survey. 15 percent of women had a UI level <50 microg/L, and Non-Hispanic blacks in this group had a lower UI level than other racial/ethnic groups.[40] In contrast, the World Health Organization (WHO) considers that a median urinary iodine (UI) concentration of 150-249 microg/L indicates adequate iodine intake in pregnant women.[41] Therefore, according to WHO criteria, the median iodine intake in U.S. women is low and 15% of U.S. women have outright iodine insufficiency. I agree that iodized salt is a positive public health measure and also agree that pregnant women may sometimes require supplementation (although excessive iodine can also be a health hazard so this approach would need to be employed with caution). None of this, however, should be used to countenance contamination of drinking water with industrial chemicals that are known to interfere with normal thyroid function. The widespread contamination

of drinking water in the U.S. with a chemical – perchlorate – that is known to block the thyroid gland, is reckless and dangerous to health. Additional iodine supplementation, if indeed it were pursued in a widespread manner, would not obviate the need to control human exposure to a chemical such as perchlorate.

7. Your testimony was very critical of the Toxic Substances Control Act. You stated that we need more testing and that we do not know anything about new chemicals.

> *a. Please provide specific examples of how section 5 of TSCA has been a failure.*

Section 5 of TSCA deals with new chemicals that are entering the market. The EPA Office of Inspector General (OIG) reported in February of this year on EPA's implementation of TSCA.[42] The report concluded that:

> "EPA does not have integrated procedures and measures in place to ensure that new chemicals entering commerce do not pose an unreasonable risk to human health and the environment. We found that EPA's New Chemicals Program had limitations in three processes intended to identify and mitigate new risks – assessment, oversight, and transparency. The program is limited by an absence of test data and a reliance on modeling because TSCA does not require upfront testing as part of a Premanufacture Notice (PMN) submission."

Specifically, according to EPA data, 67% of PMNs contain no test data, 85% of PMNs contain no health data, and more than 95% of PMNs contain no ecotoxicity data. Because manufacturers are not required to provide such data under Section 5 of TSCA, EPA does not have the information it needs to determine if new chemicals are safe.[43]

> *b. Many observers believe EPA's ChAMP program made progress in plugging information gaps. Please state whether you agree with this statement, and if not, why not.*

EPA's Chemical Assessment and Management Program (ChAMP) was created to implement commitments that the United States made at the Security and Prosperity Partnership of North America (SPP) Leaders Summit, in August 2007. The United States agreed to complete screening-level chemical prioritizations and initiate action as appropriate by 2012 on an estimated 6,750 chemicals. The chemicals include High Production Volume (HPV) chemicals, and Medium Volume Production (MPV) chemicals – in other words, all chemicals manufactured or imported at over 25,000 pounds per year. The program had potential for generating important hazard data on thousands of chemicals. Unfortunately, it came up short.

Serious concerns have emerged over both the quality and completeness of data for many HPV chemicals. EPA's own accounting indicates that data gaps remain in about 30% of the supposedly final HPV submissions it has reviewed, and an analysis by the Environmental Defense Fund identified even more.[44] The foundation of the HPV Challenge was that companies were to provide a hazard data set specified through an international consensus process as the minimum amount of data needed to conduct a

screening-level hazard assessment for a chemical. The fact that serious data gaps remain call into question EPA's ability to characterize hazards of these chemicals even at a screening level.

ChAMP generated flawed risk decisions that prematurely exonerated hundreds of chemicals, despite inadequate data on exposure and hazard. It also caused EPA to fail to meet its promise to characterize the hazards of all sponsored HPV chemicals in a timely manner – and to clearly identify gaps in the quality and completeness of the data received under its voluntary program. It is one thing for EPA to identify as high-hazard those chemicals where, despite the data gaps, available data demonstrate high toxicity. It's quite another for EPA to effectively exonerate chemicals as low-hazard or low-priority when not even a bare-minimum data set is available for them.[45]

ChAMP has been superseded by the comprehensive approach to enhancing the Agency's current chemicals management program announced by Administrator Lisa Jackson on September 29, 2009.

c. Please explain why the EPA should not wait for the results of the initial screen of certain chemicals before imposing massive new testing requirements on these and other chemicals?

Over the past half-century, tens of thousands of chemicals have been introduced onto the market and many of these have become widespread in our environment. As a physician, I frequently see patients who are exposed at work or in their community to chemical contaminants and who have health concerns that may (or may not) be linked to those exposures. I frequently seek information on the toxicology of these chemicals and very often find that the information I am seeking does not exist. It is difficult or impossible for a physician to advise a patient about potential links between their illness and chemical exposures if there are no data on which to base the advice. I cannot, in good conscience, tell a patient that there is no harm associated with a chemical that has not been tested. On the other hand, I cannot, in good conscience, advise them to change their lifestyle, change their job, or move out of their home without a solid basis for doing so. That is one reason why I believe that chemicals that are in our environment, homes, products, and workplaces should be tested for safety. My experience is but one example of how having public access to good data on all chemicals in commerce is of use, not only to EPA, but to many other sectors of our society, including companies seeking to make better-informed choices about the chemicals and products they make, use, sell or buy

I hope that this additional information is useful to the Committee as it continues its deliberations on these important public health issues.

Sincerely,

Gina M. Solomon, M.D., M.P.H.
Senior Scientist

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The Honorable Edward J. Markey

1. In limine, LLC has you listed as a scientific and technical advisor for health and exposure based litigation claims.

a. What is the nature of your work for In limine, LLC?

b. In the course of your work of In limine, LLC, have you done work for any companies that have been sued for exposing people to endocrine disruptors or other toxic substances that resulted in an out of court settlement or case dismissal? Please list all such companies. How much have you been compensated for your work for these companies?

c. Have you ever testified in court as an expert witness for a defendant in a product liability claim involving endocrine disruptors or other toxic substances? Please list all such companies. How much have you been compensated for your testimony for such companies?

Dear Chairman Markey:

Thank you for your follow-up questions. Your questions signal an interest, and perhaps a familiarity with my writings on the subject of conflict of interest in scientific discourse (Borgert, 2007a, 2007b). Your question raises an issue of great importance, and one on which Congress could demonstrate real leadership if they so choose.

As you know, absolutely alien to the precepts of good science, participation in peer-review panels for the US. EPA and other federal agencies now requires disclosure of compensated and non-compensated employment, consulting, grants, expert witness testimony, stocks, bonds, real estate, business interests, patents, trademarks, royalties, and financial liabilities, for the reviewer, spouse and dependent children, meaning that the worthiness of individuals to publish in most journals or to participate in the government agency peer-review process is being judged on the basis of affiliations, sources of funding, and the financial assets of one's family rather than on actual scientific merit.

I believe you should know, this cuts at the epistemological foundation of scientific reasoning and at the very precept that distinguishes science from any other form of inquiry in the quest of factual knowledge. The reasons are abundantly clear to anyone who knows the difference between scientific methods and political consensus. Science elevates observation over the observer, but outside of science no objective method exists for judging observations, and so the observer becomes of paramount interest. Outside of science, professional and personal affiliations, funding, experience, employment, and social status establish credibility and fitness to participate, to opine, and to proclaim. Outside of science, consensus is achieved subjectively through the dialectic persuasiveness of the participants, by compromise, by vote, and even by the diktat of strident minorities.

In stark contrast, the observing scientist is only an accessory in the acquisition of scientific evidence, where the facts are asked to first speak for themselves in order to enhance objectivity. The method of science randomizes, double-blinds the identity of treatments, measures, controls for biases and confounders, tests probabilities, and replicates in order to remove the individual observer as far as possible from the process of observation and interpretation. In science, provisional consensus is achieved only as the range of interpretations narrows, consistent with an increasingly broad and probative data set; compromise and vote are anathema. By these precepts science has proved itself time and again, accruing myriad benefits to lifestyles, public health, and the environment.

Admittedly, complete removal of bias from the observer – in effect, a completely controlled experiment or interpretation – is impossible. In fact, the central, and perhaps the only argument of scientific discussion is about how well controlled the measurements and experimental conditions might be, and how thoroughly and unequivocally the interpretations are supported by the data.

To this end, information technology now enables unprecedented transparency of the scientific process: the details of experimental design, data collection, methods of analysis, and criteria for interpretation. Laboratory notebooks, raw data, and the statistics used can be posted online for thorough review and replication by anyone. Similarly, peer-reviews for governmental agencies and testimony before Congress could be conducted according to guidelines for systematic review, with all details posted online. Such transparency is bound to thwart bias far better and more honorably than any conflict of interest or financial disclosures. Data transparency would definitely enhance the scientific merit of any report, peer review process or testimony. Conversely, experimental data and scientific interpretations cannot be factually improved or weakened by irrelevant disclosures of political and financial affiliation.

I urge Congress to take this opportunity to improve the science used in regulatory decision-making by advocating transparency of the scientific process and the data rather than irrelevant disclosures about the scientist, and by insisting that government agencies do the same. To do otherwise is to accede to the invidious doctrine of anti-science interests, bent on deciding issues by ad hominem arguments rather than by testable facts. Journals, funding agencies, peer-review bodies, and especially Congress, should abandon demands that focus the debate more on the politics of the science or scientists and instead embrace accessible and verifiable data and transparent methods as the exclusive determinants of scientific merit.

I am concerned that to do otherwise may pave a wide road to corrupting science into a process where personalities are prominent, data are relegated to rhetorical sound bites, subjectively derived consensus is praised, and the loudest voices rule. I believe the progress of valid science and its ability to offer improvements to public health and the environment depend upon these choices.

To the specific details of your question, a) the purpose of In Limine, LLC is to explain to the Courts the very fundamental tenets of science that I explained to your Subcommittee both verbally and in my written testimony. b) In Limine, LLC has not been retained to do any work for any entity, and thus, no income has been received. c) I have testified in court approximately 30 times in my career. A list of these is attached. Some of these, but not all, involved product liability issues; some, but not all, involved industrial chemicals or pesticides; many involved prescription medications. I do not recall testifying with respect to a specific claim of "endocrine disruption." I cannot be more specific because I do not maintain a list of the companies involved, other than would appear in the style of the case, nor whether I was retained by the defense or the plaintiff, nor do I track my income according to the nature of the projects.

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The Honorable Joe Barton

1. Dr. Birnbaum testified there are four aspects of exposure to endocrine disruption. In these four aspects, she relates what could be "plausible." Please state your opinion on whether this is a good way to conduct science or make regulatory determinations.

The concept of biological plausibility involves the application of deductive and inductive reasoning to biological data. Biologically plausible conclusions are, in essence, reasonable speculations based on available data, but this is an inherently subjective process and should not be confused with objectively verifiable scientific facts. A set of objectively verifiable scientific facts typically invites further hypothesis generation such that the blurring of scientific fact with further hypothesis generation enjoys an easy relationship in basic research. Within the research context, however, it must be kept in mind that most hypotheses turn out to be wrong. Even hypotheses that are not completely rejected upon rigorous testing must typically undergo tortuous corrections and refinements in order to remain viable. This is a healthy process for basic research, but in my opinion, it is a wasteful and potentially dangerous way to make regulatory determinations. The lack of biological plausibility can substantially weaken a scientific hypothesis or conclusion, but should not be used to imply that a particular hypothesis or conclusion is established or even likely to be correct. Rather than react in a regulatory setting to biologically plausible speculation, I would prefer to know that the risks being regulated are real, and therefore, that their mitigation will produce measurable improvements to public health and the environment.

2. Please state whether in your opinion there is enough high-quality science to justify a "low dose" theory of regulation.

Unequivocally, there is insufficient valid science to justify a "low dose" theory of regulation. In fact, the so-called 'low-dose' theory has not been formulated with sufficient clarity to even be scientifically testable. Many different concepts have been used, in a confused and inconsistent fashion, to advance the so-called "low-dose" theory, some of which are inconsistent with one another and perhaps even contradictory. What can be said with certainty is that toxic effects produced by chemicals at high doses may be very different from the effects, if any, produced at lower doses, and that the subtle effects produced at low doses may not be toxic effects but rather adaptive and compensatory responses of the organism.

3. Modern science and technology allows us to more easily detect increasingly subtle changes in the human body. Please explain whether a subtle change in human functioning based on external factors necessarily means something negative has happened.

As mentioned in answering the previous question, subtle effects produced at low doses may not be toxic effects but rather adaptive and compensatory responses of the organism. To expand briefly, the great challenge to toxicology as I see it is to discover the fundamental differences between subtle adverse effects and responses that merely reflect a successful compensation or adaption to the presence of an external factor. So that the concepts can be understood in the broader biological context, please indulge a non-chemical example. Bacterial and viral infections can adversely affect humans in many ways and are a significant cause of morbidity and mortality, even in advanced societies. However, we have learned in recent decades that some exposure to infectious bacteria and viruses are actually necessary for normal development of a healthy and resilient immune system. Some research even suggests that a very low exposure to infectious agents in early life might weaken the immune system in its important role in preventing cancer. Clearly, all immunological responses in a child do not lead to harm; the challenge is to understand more clearly which responses signal that the immune system is responding normally to bacterial and viral exposures versus those that portend illness. This is not to suggest that exposures to environmental chemicals is necessary for normal development. However, just as not all immunological responses portend illness, all responses to chemical exposures do not portend toxicity.

Among the various biological systems, the endocrine system best exemplifies this principle. Because the endocrine system is one of the body's principal homeostatic systems, enabling the body to maintain a consistent internal environment in the face of ever-changing external influences, it by design responds to exposures in the environment from chemicals, light, sound, heat, and a myriad of other social and external factors. These endocrine responses are not mostly adverse; instead, they indicate that the endocrine system is detecting external influences and is responding appropriately to maintain an internally consistent environment. The challenge for endocrine toxicology, and thus, for the EPA's EDSP, is to properly differentiate endocrine responses that are adaptive and compensatory from those that are adverse. Failure to do so increases the likelihood that regulatory actions based on a presumption of precaution will be as ill-informed, ineffective, and potentially damaging to public health as they are well-intentioned.

4. You testified EPA "conducted the minimum validation work that might satisfy the Congressional mandate." Please explain this comment.

In the 1996 Food Quality Protection Act (FQPA), Congress required EPA to use "validated test systems" in screening chemicals for the ability to cause estrogen-like effects in humans. I believe the stipulation to use validated test systems was wise and apparently intended to avoid potentially unreliable and ineffective screening. The FQPA, however, gave the Administrator of EPA discretion to screen for additional hormonal activity beyond estrogen. Rather than develop a screening program that would satisfy the explicit mandate of FQPA, EPA took a much broader view and devised a screening battery to include three hormones and their antagonists. This could be seen as a six-fold expansion of the explicit requirement, and it necessitated EPA proposing to use some assays that were relatively little known and untested for screening purposes. Validation of such a screening battery was sure to be more expensive, more complex, and require much more time than had EPA focused on meeting the explicit requirement of FQPA as rapidly as possible in the most scientifically rigorous way. Interestingly, many who exhorted EPA to be expansive in its screening program subsequently criticized the

Agency for failure to rapidly issue test orders to screen. The pressure to implement clashed with the requirement to validate the assays, and so EPA did the best they could to respond to both pressures. In truth, many scientists acknowledge that adequate validation of the Endocrine Screening Battery (ESB) awaits results for the first 67 chemicals placed under test order, as EPA has simply not been given sufficient time to develop a full validation data set prior to issuing these current test orders.

5. Please state whether you believe the minimum validation work for the EDSP would satisfy most scientists. Please also state whether the minimum validation work provides a good discriminator for what should move on to the next level.

I cannot credibly say what most scientists would find satisfactory, but having served on the peer-review panel for the OECD validation program for the uterotrophic assay - one of the key assays in the ESB - I know that some scientists who are quite knowledgeable about validation procedures consider the level of validation for the EDSP assays to be inadequate.

I discussed three tenets of scientific validity in my testimony; using those tenets as a guide, the validation results for the various EDSP assays reveals a varied degree of validation. We can verify what we are measuring within a defined degree of precision for most of the eleven EDSP assays, and for many, we have identified and can control the confounding factors that influence the measurements. For some of the assays, we have reasonably sufficient data to know how consistently results from these assays can be replicated by independent scientists, in other words, we have data on inter-laboratory variability. However, for other assays, none of those tenets are particularly well characterized. The battery as a unit has not been subjected to a round of overall validation. Thus, no one can say how effectively the battery discriminates between chemicals that actually show adverse endocrine effects on further testing versus those that do not. Furthermore, EPA has not yet defined the criteria for interpreting the screening battery so that it is effective and efficient in making this discrimination. Since more extensive, tier-2-level data have already been generated under current pesticide regulations for the first 67 chemicals now undergoing endocrine screening, it is hoped that the performance of the screening battery can be evaluated once the screens are completed. This will involve comparing the screening results with the already-available tier-2-level testing data to determine interpretive criteria will allow adequate prediction of tier 2 results.

6. You testified the endocrine screening program detects potentially weak hormonal activity for certain chemicals.

a. Please state whether the reliability of this method concerns you given that most of the assays were intended for potent hormonal activity.

The 11-assay screening battery is intended to be able to detect even weak hormonal activity. Some of the types of assays included in the battery have a history of reliable use in screening for potential new pharmaceuticals, but this purpose, of course, seeks to identify compounds that have high potency. This does not mean that the screening assays will be useless for detecting compounds that have weak potency, but neither does it assure us the assays are reliable for that purpose. It does, however, underscore the importance of validating the assays and determining their specificity, sensitivity, and predictive value. In my view, EPA should be given the time, resources, and encouragement to complete this process before insisting that more chemicals be screened using a battery that is as yet uncharacterized.

b. Please explain what the significance of "weak hormonal activity" is for human health and the environment.

Medical science has not yet determined the significance of weak hormonal activity for human health. As was heard during the subject Congressional hearing, there is much speculation that serious human diseases and malformations arise because of exposure to weak hormonal activity. Even though some are firmly convinced of these speculations, and choose to state their views as if the science were settled, it is far from settled. The science on this issue is in the hypothesis-generation phase, and it must be recognized that the hypotheses on this subject have been shifting for about two decades without definitive confirmation that any chemical, or mixture of chemicals with weak hormonal activity causes disease in humans at environmentally relevant levels of exposure. In my view, there are overwhelming data that call into question the endocrine disruption hypothesis, particularly regarding chemicals with weak hormonal activity, but the science is not completely settled in the negative either, as it is nearly impossible to establish a negative premise.

c. Please state the rate of false positives from this type of screening.

This is indeed a critical question, but it cannot be answered with available data. The answer awaits data emerging from the results of the first 67 chemicals to be screened. Without those data, one can only speculate that the incidence of false positives will be very high. A few simple statistical concepts illustrate how high it could be.

In most biological assays, we find it acceptable if no more than 5% of the observed responses are positive due to chance alone, i.e., a false positive rate of 5%. The probability of observing at least one false positive result among several independent assays rises with the number of assays according to the following simple statistical formula: $1-(1-\rho)^n$, where ρ is the false positive rate for each individual assay and n is the number of assays to be conducted. Thus, even if each assay in the endocrine screening tier has a false positive rate of only 5%, the probability that at least one assay the 11-assay endocrine screening battery will give a false positive result would be expected to be about 43%. Some assays in the ESB measure several independent endpoints, so the true probability of at least one assay in the battery giving a false positive result could be even higher. Thus, if a positive result in any of the assays is deemed to render the endocrine screening battery positive for that chemical, then half or more of the chemicals screened would be expected to give a false positive result.

Furthermore, because two of the assays have failed to yield a clear negative result for any chemical, it is unclear whether anything will be deemed negative, and so all substances screened could be declared candidates for further testing. This is why it is critical to complete the validation exercise that will allow EPA to establish a set of interpretive criteria that provide a reasonable level of discrimination.

7. Isn't the real concern here dosage? Even water can be fatal in high enough dosages. Don't you think it's important that we take the time to understand if these chemicals can have an adverse affect on humans, and at what dosages before we make sweeping and potentially damaging, Federal regulations?

Yes, dosage is the critical issue for any toxic effect, and yes, at what dosage chemicals might have an adverse effect on humans is the critical issue for regulation of chemicals to which humans may be exposed. It is important to recognize, however, that our current regulatory testing paradigm does not require that a real risk to human health is ever demonstrated in order

for EPA to impose regulations. Instead, human risk is inferred from any adverse effect in a rodent or other mammalian test species, unless that adverse effect can be demonstrated to be irrelevant for human physiology. i.e., that the physiological differences between humans and the test species are understood in such detail that it is clear the effect could not occur in humans. This is a very conservative approach in that many risks to humans are assumed without any actual human evidence, but this is the prevailing policy based on prioritizing precaution over accuracy. My statements are not meant to disparage that policy, but merely to point out that the policy is conservative and must not be confused with actual scientifically demonstrable risks.

EPA has rightly and consistently stated its intent to make a determination of adverse endocrine effects and dose-response on the basis of tier 2 testing, and explicitly not on the basis of tier 1 screening. If this intent can be realized, then the screening program, once fully validated, might serve its intended purpose. Unfortunately, regardless of how well-intentioned EPA might be, inaccurate publicity regarding the purpose and predictive power of endocrine screening can result in products being displaced from the market on the basis of public perception rather than fact. A review of the video of the Subcommittee Hearing gives testament to this phenomenon: even though Mr. Jones and I clarified that the endocrine screening battery cannot identify endocrine disruptors, and that the determination of adverse effects will be made after tier 2 testing, other witnesses and members of the subcommittee continually made reference to 'endocrine disruptors' being identified by the 'endocrine screening battery'.

8. Please describe the importance of potency of a substance in relation to its presence or dose. Please explain whether the EPA's tests appropriately consider this factor in your opinion.

Potency refers to the strength of a chemical for producing a particular biological effect. For example, the greater the potency of a pain-reducing drug, the less of it is required to eliminate the sensation of pain. The endocrine screening battery is not designed to determine the potency of a chemical, but simply to determine whether at any achievable dose, the chemical might interact with a component of the endocrine system. Some of the screening assays are performed in test-tube systems utilizing just one component of the endocrine system - either a hormone receptor or a particular enzyme - while others measure changes in specific tissues or hormone levels in a test species, either rats, frogs, or fish. The effects measured in these endocrine screens are not necessarily adverse effects. Thus, potency for producing adverse endocrine effects is not measured by the endocrine screening assays, but will be determined in tier 2, where adverse effects in test species are measured. This two-tiered screening and testing program would appropriately consider potency for single chemicals if conducted as it was designed (see answer to previous question).

Cumulative risk assessment is the area in which EPA procedures may not appropriately consider potency. Please refer to question #13.

9. You testified that we risk replacing relatively safe chemicals with riskier ones. Please describe with what other chemicals or in what other circumstances you have seen this occur.

As I explained during my testimony, the concept behind this statement is that we often attempt to eliminate all risks irrespective of whether they are demonstrable risks or only theoretical risks, and we suffer an increasing tendency for failing to distinguish between real and hypothetical risks and benefits. Consequently, our proclivity for precaution may render us vulnerable to real adverse health consequences, or resistant to real health benefits, in order to avoid theoretical risks. During my oral statements, I used the example of eliminating all fats from our diets just a

few decades ago on the mistaken belief that all dietary fat contributed to the risk of coronary artery disease. We now know that some fats are actually beneficial, and many doctors now advise patients to consume supplements containing fish oil and other omega fatty acids. The examples are too numerous to list, but two prominent examples illustrate the concepts.

In the 1990s, Peru suffered new outbreaks of cholera. In many locations, poorly sanitized water became a vector for the disease. Thousands of people died and many more were hospitalized. Many of these infections, and some deaths were likely preventable had public health authorities not feared theoretical cancer risks posed by chlorine disinfection of water supplies, and based on that fear of a hypothetical risk, increased risks of contracting cholera and its very real adverse health consequences. An article by Fred Reiff, extracted from the American Chemistry Council website <http://www.americanchemistry.com/s_chlorine/sec_content.asp?CID=1195&DID=4489&CTYPEID=107>, explains the details.

The Precautionary Principle Under Fire: Detractors Continue to Challenge Chlorination as a Safe Water Solution for Developing Nations

By Fred Reiff

Former PAHO official, Fred Reiff, recounts his experiences battling chlorine misinformation during the Latin American cholera epidemic of the 1990s.

Despite data supporting chlorine's highly beneficial impact on clean water supplies and public health, claims persist that the potential risks of chlorination outweigh the public health value of water disinfection. To me this is comparable to watching the third sequel of a grade Z science fiction movie about a monster that won't die. A case in point is a Greenpeace report currently posted on the organization's website asserting that DBP concerns had no bearing on the spread of disease during the 1991 cholera epidemic that began in Peru and was propagated to almost all countries of Latin America. From personal experience I can confirm that these claims are utter nonsense. I am concerned that such disinformation and half truths might be accepted as fact, resulting in otherwise avoidable disease, suffering, death, and economic impact on the poor people of developing countries.

Why am I qualified to respond? From 1981 through most of 1995, I was an official in the Pan American Health Organization/World Health Organization (PAHO) in a position that offered a very unique vantage point. During this period I was responsible for disseminating the WHO drinking water quality guidelines and fomenting the adoption or updating of national drinking water quality standards. I also was responsible for managing the United Nations Global Environmental Monitoring Programs for Water (for the Americas), the development and promulgation of environmental interventions in disaster preparedness and relief, and the development of appropriate technology for treatment of both potable and waste water. I also served on PAHO's management task force that was formed for the prevention and control of cholera. This level of involvement provided many opportunities for both overall and close-up monitoring of the status of water supply disinfection and its effectiveness as a public health measure in prevention and control of waterborne diseases in all Latin American and the Caribbean countries before, during, and after the introduction of cholera in Peru in 1991.

For many years prior to the cholera outbreak, PAHO had been promoting the disinfection of community water distribution systems and other delivery systems for water for human consumption. Primarily through its Center for Sanitary Engineering and Environmental Science (CEPIS) in Lima, Peru, PAHO collaborated in pilot and demonstration projects for virtually all disinfection methodologies in various countries to ascertain their relative disinfection efficiency, cost effectiveness, and practicality for various cultural and economic situations. Some of them worked well and others were failures. Everything considered, chlorination was almost always found to the most reliable and cost effective.

Until the cholera outbreak erupted in Peru in January-February of 1991, the acute and deadly diarrheal disease had not been prevalent in the Americas since the early 1900's. Immediately upon verification of its presence, PAHO began organizing workshops to inform the appropriate officials of the countries of Latin America (and later Caribbean countries) of the seriousness of this disease and its potential to become an epidemic. We shared the most effective and advanced technologies to detect the pathogen, how to diagnose and treat the disease, the tried and proven methodologies that have been used to prevent cholera, public education strategies, and the epidemiological efforts and methodologies to track and understand the propagation of the disease.

Simultaneously, PAHO headquarters directed each of the PAHO Country Offices to advise health and water agencies to take measures to continuously chlorinate all water distribution and delivery systems. For the population not connected to public water systems, special programs were developed to promote the disinfection of water at the household level. In addition, treatment of the waste products of cholera victims with lime was recommended before its discharge to the sewer systems or the environment, and a list of all preventive measures to be taken by officials and individuals were provided to all appropriate officials. Chlorination was recommended, not only because all of the countries were familiar with this technology, but also because chlorine products were readily available and chlorination was the least costly of the disinfection methodologies. And, most importantly, chlorine is very effective in killing or inactivating Vibrio cholerae, the pathogen of this disease as well as pathogens associated with almost all other waterborne diseases.

Shortly after this directive was issued, I was surprised to learn that some local PAHO officials were encountering pockets of resistance to chlorination from a number of health officials, both in Peru and in other countries. I was specifically told that the reason was their concern for chlorination by-products, especially trihalomethanes. This concern had its origin in press releases and published scientific studies widely disseminated by environmental agencies in the developed countries. I traveled to Peru and other countries and personally met with the health officials and even heads of water agencies who expressed their concern directly to me; some even believed that they might be subjected to a lawsuit if they chlorinated or raised the level of chlorine in their water supplies. I also met other concerned health officials in various cholera workshops and symposiums sponsored by PAHO. Most surprising of all was the discovery that even officials in small towns were aware of disinfection by-products and their alleged negative health effects. It was pointed out to all that when the cholera pathogen is present in a water supply, the risk of contracting the disease is immediate, and that a resulting epidemic could cause thousands of deaths. In contrast, the hypothetical health risk posed by trihalomethanes in levels in excess of

those recommended by WHO (and EPA) was one extra death per 100,000 persons exposed for a period of 70 years. Unfortunately, some of these well-meaning, but ill-informed officials had to experience the immense proportional difference in risk before accepting this reality.

Debates over the relative significance of the drinking water pathway for cholera in comparison to other pathways also impeded the rapid implementation of drinking water chlorination. Routes that can be taken by cholera include food, beverage, and ice that have been processed or prepared with contaminated water, unhygienic food handlers, produce that is eaten raw but which has been irrigated with cholera contaminated water, filter feeding shellfish harvested in sewage contaminated water, and casual person-to-person contact. Both practical experience and studies have proven that even if cholera is initially introduced through a pathway other than drinking water, the waterborne pathway will soon be activated unless drinking water is disinfected continuously with an adequate level of disinfectant and measures are taken to prevent recontamination before its consumption. A cholera contaminated distribution system is without doubt the most efficient way to transmit this disease.

It should be noted that throughout the first four years of this epidemic the countries with the highest percentage of continuously and adequately chlorinated water systems had no secondary transmission of cholera, even though the disease was introduced into these countries. Also countries that quickly implemented chlorination were able to bring the epidemic under control. There was also an obvious inverse correlation between the percentage of the population receiving chlorinated water and the incidence of new cases of cholera. In one country with excellent long-term epidemiological surveillance in place, it was found that after implementation of measures to prevent cholera, there was also a significant reduction in typhoid fever and infectious hepatitis.

Conversely, those countries that were not able (for whatever reason) to implement chlorination of water supplies on a timely basis, suffered recurring annual epidemics until a sufficient percentage of the population had developed immunity, preventing further epidemic propagation of the disease. Typically there were a number of reasons for delay in implementing widespread chlorination of drinking water supplies. However, no obstacle was harder to overcome than the incorrect perception of risks posed by disinfection by-products relative to the very real and deadly threat of cholera.

To reduce the spread of cholera in areas of abject poverty where household were not connected to water distribution systems PAHO worked in concert with the U.S. Centers for Disease Control and Prevention (CDC) and the University of North Carolina to develop, test, and microbiologically and epidemiologically monitor the results of a methodology to purify the available water at the household level. The end result was chlorination of the household water in containers that were specifically designed to preclude subsequent contamination during storage and use. The annual cost of this intervention was found to be less than $2.00 per family, the major cost being the container. The annual cost of the calcium hypochlorite was less than fifty cents per family. Not only did this prove effective for Latin America but it also led to global health organizations adopting this or similar programs as a viable interim health measure for developing countries in Africa and Asia.

Since the cholera outbreak of 1991, many nations have embraced what is known as the "Precautionary Principle", a protocol acknowledging that uncertainty is inherent in managing emerging risks. The thrust of public health management in the principle is to take steps to reduce potential harm, even when uncertainties remain. Yet a true precautionary approach also means that you do not do away with a proven health intervention. This concept was clearly stated by Dr. Carlyle Macedo, Director of PAHO in his address to the 1992 International Conference on the Safety of Water Disinfection, Balancing the Chemical & Microbiological Risks sponsored by the International Life Sciences Institute.

"In developing countries, the primary public health concern for water supplies should remain preventing them from becoming an efficient vehicle for the widespread transmission of enteric diseases. This concern should not be overshadowed in any way in our efforts to also address the tertiary concern of minimizing the relatively small risk stemming from disinfection by-products...

The high incidence of diseases that are related to water supply and sanitation are primarily a reflection of the social and economic inequities and marginalization that unfortunately still exist in our hemisphere. Basically the people that suffer the most from these diseases have so few economic resources that all but the simplest and least expensive of interventions to reduce their risk of exposure to the many waterborne pathogens are beyond their means. Under such circumstances the disinfection of drinking water with chlorine at the household level, is usually the most viable and cost-effective public health intervention available. To cause these people to abandon chlorination is not only unwise, but cruel, if the alternative is beyond their economic and technical means. Unless there is a simple alternative at an affordable cost, these people should not be frightened away from chlorinating their water. This will only increase their suffering and decrease their life expectancy."

To protect public health, particularly in developing regions, applying the precautionary principle requires use of practical, affordable technologies and a realistic balancing of known and uncertain risks.

Fred M. Reiff, an engineer, is a former official of the Pan American Health Organization/World Health Organization. He retired from that organization in 1995 but continues to serve as an independent international consultant.

To read the Greenpeace report "Cholera and Chlorine" please refer to the following link: http://archive.greenpeace.org/toxics/reports/cholerachlorine.pdf

A second example comes from my own publications. One of the recurring concerns of modern mothers is whether it is safe to breast feed their infants. Given the enormous public attention given to synthetic chemical contaminants that can be detected in our bodies, it is not surprising that some women have avoided breast-feeding because of the theoretical risks from these chemicals. Some of these chemicals are putative endocrine disruptors. Despite the theoretical health effects of putative endocrine disrupting chemicals that may be present in human milk, the epidemiological and clinical data reveal clear benefits of breast feeding. In a paper published in Environmental Health Perspectives, a journal of the National Institute of Environmental Health Sciences (Environmental Health Perspectives, 111(8): 1020-1036.), I and co-authors wrote:

> *Clinical data currently available indicate a health benefit to offspring for 6 weeks of breast- feeding. At present, there is no evidence that infants breast-fed for more than 6 weeks suffer more adverse health effects, hormonally medi- ated or otherwise, than infants receiving infant formulas or other sources of nutrition. Effects similar to those observed following high-dose exposure to potent estrogens—e.g., in utero exposure to DES—to the best of our knowledge, have not been associated with breast-feeding or other sources of infant nutrition. Thus, the epidemiologic and clinical studies con- ducted to date suggest that breast-fed infants suffer no adverse estrogen-related health effects. Given that much of the data on breast-fed infants was collected several decades ago when levels of persistent contaminants in humans were likely higher than at present, particularly in countries such as the United States where the use/release of many of these chemicals has been banned or restricted (LaKind et al. 2001; Westphal 1986), estrogenic risks to infants from consumption of human milk should be considered de minimis.*

Furthermore, in a publication summarizing the conclusions of an expert panel on human milk surveillance convened at the Milton S. Hershey Medical Center, Pennsylvania State University College of Medicine, Hershey, PA (Journal of Toxicology & Environmental Health Part A, 65: 1929-35), my co-authors and I wrote:

> *The panel strongly supports the scientific and public health value of studies on environmental chemicals in human milk. However, it is even more strongly emphasized that the mere presence of an environmental chemical in human milk does not necessarily indicate that a health risk exists for breast-fed infants. The accumulated data overwhelmingly supports the positive health value of breast-feeding infants.*

10. You testified the "performance of the battery as a whole has been left unaddressed." Please explain this statement and its implications.

The ESB was intended to be conducted and interpreted as a battery of assays, not as a set of single, independent assays. To date, validation exercises have focused on the performance of the individual assays. Although a necessary step, validating the individual assays does not answer whether the battery as a whole is useful for discriminating between chemicals that need further testing because they exhibit real potential to interact with the endocrine system versus those that do not. Ultimately, some combination(s) of results among the various assays may be discriminative, but we will not know what the interpretive criteria must be until more data is available. It is hoped that the information necessary to develop such criteria will emerge from results of the first 67 chemicals to undergo screening. Until we know whether the battery can be interpreted in a way that produces an effective screen, i.e., a means of separating the chemicals that need no further analysis from those that do, we have no idea whether the ESB is effective, If the ESB improves neither the sensitivity nor the efficiency of testing chemicals, then it is merely a burdensome process for both industry and EPA, and ultimately the public.

11. You testified the criteria for interpreting ambiguous results was modified so that such results could be interpreted as negative. Please describe how the criteria were modified and the significance of those modifications.

My statement relates to the way a maximum tolerated dose was defined for the pubertal assays As background, it is important to appreciate that endocrine tissues and organs can be affected in some of the endocrine screening assays by pathways that are not endocrine-related. Therefore, correct interpretation of the results relies on discerning effects that occur via endocrine activity from those that are secondary to other effects. For example, a small change in body weight is known to affect the weights of endocrine tissues measured as indicators of an endocrine effect in these assays.

EPA typically requires reproductive toxicity assays and assays for other specific effects to be run at a 'maximum tolerated dose' (MTD), which is defined as the highest dose that fails to produce general toxicity and which fails to alter terminal body weights by 10 percent or more. EPA initially selected 2-chloronitrobenzene, but the initial results were positive for endocrine activity and it was obvious that a new negative control compound would be needed. At this time, EPA had done several studies with hydroxyatrazine. Interestingly, the EPA found hydroxyatrazine positive in an early pilot study with the female pubertal assay in 2003 (Laws et al., 2003. Toxicological Sciences 76, 190–200). One of the primary effects of hydroxyatrazine is kidney histopathology, which is not a typical MTD endpoint. These endpoints (kidney histopathology and clinical chemistry values) were not included as MTD targets in the EPA's inter-laboratory validation studies for the pubertal assays, which were reported in 2005-2006. However, in their Integrated Summary Reports for the pubertal assays, EPA identified kidney histopathology and changes in clinical chemistry values as potential endpoints for determining the MTD in the pubertal assays, and in 2008, carried these endpoints into the test guideline. To the best of my knowledge, EPA's Integrated Summary Reports for the pubertal assays are the first mention of these endpoints as possible MTD targets. EPA's current hydroxyatrazine negative control data set from the pubertal assays the are not publicly available, however, it is my understanding that a manuscript is in preparation and will be submitted for publication soon.

12. You testified that a positive result in the endocrine screening battery is not necessarily indicative of adverse effects. Please describe other instances, if any, where the presence of a substance has not been proven to have an impact.

The examples of chemicals that can be present in the human without portending adverse consequences are too numerous to begin to list, but a few examples illustrate the general principle. Human physiology itself gives numerous examples of chemicals whose presence alone poses no toxic risk at all. Chromium and magnesium are metals used industrially, are toxic pollutants, and are normally found in humans. Their mere presence in humans does not portend adverse effects. In fact, small amounts of magnesium and chromium are necessary for normal physiological functioning, and recently, concern has been raised that modern diets may provide insufficient levels of chromium. Even arsenic is believed to be necessary in trace amounts in the human diet; larger amounts have been used medicinally to cure infections, though with toxic side effects; higher doses are lethal and have been used as poison. Organic chemicals may also be present without implying adverse effects. Ethanol is the type of alcohol contained in alcoholic beverages and is known to be toxic and lethal at sufficient doses. Yet, low levels of ethanol are detectable in healthy, non-drinking subjects as a by-product of normal metabolism and these low levels have no toxicologic or medical significance. Formaldehyde is produced in the human liver as a product of normal metabolism and is found in the blood in low levels, yet at high concentrations in the air, formaldehyde is toxic and corrosive to the respiratory tract.

13. You referred to your presentation to the NAS concerning mixtures of chemicals in drinking water and their potential effects on human health and the environment. Please explain the significance of your assessment of the valid science on this matter.

My presentation to the NAS[1] explained the scientific basis for my evaluation of methods used in assessing risks of mixtures in drinking water, also known as assessing risks for cumulative toxicity, or cumulative risk assessment. That basis included the three fundamental tenets of valid scientific evidence I explained in my testimony to this subcommittee. I further explained that current recommendations for performing cumulative risk assessment make the assumption that all chemicals capable of producing a particular effect, irrespective of their potency, will add together in producing that effect. This assumption relies on extrapolating data collected at relatively high doses, where effects are observable and where toxicity from multiple chemicals may be cumulative, to doses below which any measurable effect occurs and at which the concept of cumulative toxicity is questionable speculation, at best. Such approaches also rely on the assumption that the mechanisms by which chemicals produce effects at high doses also occur at much lower doses, but simply produce a lesser magnitude of effect. Current approaches ignore the substantial evidence that contradicts these questionable assumptions, which I explained in my presentation.

The general concept can be explained by an analogy to density, mass, and buoyancy, where density is analogous to potency, mass to dose, and buoyancy to whether or not a particular biological effect occurs in a human. Although one can weigh a ton of closed cell foam on the same scales as one can weigh a ton of iron, their weights will not be additive when put to sea. In fact, the iron will sink but the foam will float, irrespective of the mass weighed, and closed cell foam will counteract the sinking of iron if placed in the same vessel.

During my oral comments to this subcommittee, I gave the example of testosterone, the principal male sex hormone, activating the human estrogen receptor with a potency similar to that reported for some putative environmental estrogens including the synthetic chemicals bisphenol A and methoxychlor, among others. Yet, no serious endocrinologist would decry the estrogenic risks of testosterone; although testosterone truly possesses the ability to activate the estrogen receptor, its potency at the estrogen receptor is too low to have an estrogenic impact in the presence of estradiol, the principal female sex hormone.

14. Please state whether in your opinion the screening tests are faulty because of the minimum validation. Please also state whether Congress should prohibit minimum validation testing or otherwise mandate what validation standards must be met for future regulatory assessment.

Validation is a process that helps to ensure that an assay or test is not faulty. Since validation of the endocrine screening battery is incomplete, it would be premature for me to say that it is faulty. I believe that mandating extensive testing before the battery of assays has been fully validated is a faulty process.

Regarding validation standards, I believe it was wise of Congress to require validated tests systems for the endocrine screening battery, and this should be a routine requirement for

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[1] *Considerations for Single Chemical Versus Mixture Risk Assessment: Concepts and Caveats.* National Academies of Science, National Research Council, Board on Environmental Studies & Toxicology, Workshop on Pharmaceuticals in Drinking Water, December 11-12, 2008. Washington, DC.

assays used in regulatory decision making. Although it may be difficult for Congress to mandate detailed validation requirements that would apply in all circumstances, the three tenets I described in my testimony could be used as a general guide, as these apply to all areas of scientific inquiry. To briefly reiterate, 1) the identity and authenticity of scientific measurements and observations must be verifiable within a defined range of precision and relevant to the question at hand; 2) the measurements and observations must not be confounded by extraneous factors and influences known to corrupt their accuracy and precision; and, 3) the measurements and observations must be replicable in independent hands. Technical details for fulfilling these simple requirements could be left to the appropriate Agency, but this would help to standardize and enforce the use of high quality science in regulatory activities.

15. Please state your opinion on whether the screening test results for the 67 chemicals currently undergoing the endocrine screening battery should be validated before moving forward with a second set of test orders.

Yes; I believe it is essential to provide EPA the time and resources it needs to fulfill validation for the individual endocrine screening assays as well as the endocrine screening battery as a unit before more test orders are issued. Here, it is important for Congress to appreciate that scientific investigation, including assay validation, cannot be placed on a time schedule and that particular outcomes cannot be dictated. Congress may desire that a new set of assays be proved valid and that the validation be accomplished within a particular time frame, but the data that emerge may support both, only one, or neither objective.

16. You testified that some of the assays used in the endocrine screening program are used in "novel" ways. Please explain this statement.

My statement referred primarily to the fact that many of the assays in the ESB have a long history of reliable use to screen for chemicals that have high endocrine potency. EPA's endocrine screening battery utilized these assays to detect chemical that may have very low endocrine potency. Whether all of these assays are useful for discriminating chemicals with low versus no potency remains to be determined.

17. Please explain whether or not children are always more sensitive to chemicals and drugs.

Children are not always more sensitive to drugs and chemicals than adults, however, they may be more sensitive to some drugs and chemicals. The oft-quoted phenomenon of critical windows of sensitivity is real, especially during development, but this does not apply to all chemicals or drugs, nor to all effects of chemicals and drugs. Whether or not a child is more sensitive than adults depends on a variety of factors, including the age of the child at issue, the tissues and pathways affected by the drug or chemical, the way the drug or chemical is absorbed into the body, the way the drug or chemical is metabolized by the body, the way the drug or chemical and its metabolites are distributed in the body, the way the drug or chemical is eliminated from the body, and other factors.

18. You testified that the endocrine screening program will not identify endocrine disruptors. Please explain this statement. Please also define what an endocrine disruptor is.

As a Plenary member of EDSTAC (Endocrine Disruptor Screening and Testing Advisory Committee), the the Federal Advisory Committee convened by the U.S. Environmental Protection Agency to provide advice in meeting the endocrine screening mandates of the 1996 Food Quality Protection Act (FQPA) and the 1996 amendments to the Safe Drinking Water Act (SWDA), I argued a common-sense definition of "Endocrine Disruptor' in response to the Assistant Administrator of EPA's proposed definition of the term. Her definition was as follows:

> *"The EDSTAC defines an endocrine disruptor as an exogenous chemical substance or mixture that alters the function(s) of the endocrine system and thereby causes effects at the level of the organism, its progeny, and populations or subpopulations of organisms. The EDSTAC considers endocrine disruption to reflect mechanisms of action which (among others) may lead to adverse outcomes including, for example, carcinogenic, reproductive, or developmental effects that need to be routinely considered in reaching regulatory decisions."*

I argued:

> *1. The literature held out as support for the endocrine disruptor hypothesis is unfailing in its assertion that endocrine disruption is an adverse effect. Especially the writings of those individuals who now insist that "adverse" NOT be included in the definition are precisely the publications that warn most strongly that endocrine disruption IS adverse. I cannot fathom why Congress would have mandated screening and testing unless they were led to believe that endocrine disruptors were producing adverse effects in wildlife and humans. Certainly, I would not have spent the time and effort I have spent serving on this committee and on two of its workgroups had I believed that our charge was to design a screening and testing program for effects that might be merely adaptive and compensatory.*
>
> *2. Surely, whoever coined the term "endocrine disruptor" was aware that "disruption" is a "morphologic defect":*
>
> *disruption: a morphologic defect resulting from the extrinsic breakdown of, or intereference with, an originally normal developmental process. [Dorland's Illustrated Medical Dictionary, 27th Edition, 1988. W.B. Saunders Company, Philadelphia.]*
>
> *disruptive: bursting apart; rending. [Dorland's Illustrated Medical Dictionary, 27th Edition, 1988. W.B. Saunders Company, Philadelphia.]*
>
> *I could find no reference to "adaptive" or "compensatory" changes in any definition of any form of the word "disrupt" in any dictionary I consulted.*
>
> *3.. Therefore, to define an "endocrine disruptor" as a chemical that produces anything other than defects or adverse effects would make the EDSTAC appear to be contradictory and perhaps, intellectually dishonest. I fear that if such a definition emerges with consensus, the credibility of this committee becomes immediately suspect. I will not sign-on to such a definition.*

Please remember that while the committee has made considerable progress without a firm consensus definition of endocrine disruptor (Tim Mealey, stated 49 times since October, 1997), 'the definition of what we are addressing ultimately sets the standard against which our report will be judged.' If we have not addressed a meaningful subject, or if our screens and tests do not match our definition, then we will not fare well in either the peer or public review.

4. The argument was made that the EDSTAC's draft definition does include the word "adverse", and so my concerns are met. This is thoroughly unconvincing to me. One has only to read and reason clearly to see that the EDSTAC's draft definition does not specify that endocrine disruption is an adverse effect; rather, the draft definition merely allows that endocrine disruption MAY lead to adverse effects. The EDSTAC must have a definition that requires the effect to be both endocrine mediated and adverse; otherwise, we must also state clearly that endocrine disruptive effects may as likely be meaningless to human health and the environment. The draft definition gives one the option to be intellectually honest and consistent, but does not require it. Perhaps that makes grade in Washington D.C., but it's not my standard, and I hope it is not the EDSTAC's.

5. While it may be difficult to determine that an observed effect is clearly adverse, this should not confuse our definition of endocrine disruptor (the section on Weight Of Evidence is the appropriate place for discussion of this difficulty). When it is unclear whether or not a specific effect is adverse, this is due to limitations of scientific knowledge rather than an inability to know what we are looking for. An analogy is cancer: there is no question that cancer is an abnormal and unhealthy population of cells; sometimes, however, a pathologist may be uncertain as to whether or not a particular cell is abnormal. This has not confused the field of oncology into defining cancer as a loose collection of mechanisms or as simply an effect that either may or may not be abnormal and unhealthy.

6. The consistent and intellectually honest thing for the EDSTAC to do is to define endocrine disruptor as a chemical that produces adverse effects or defects through endocrine mechanisms (I'm paraphrasing). The Europeans have thought clearly and accurately on the term "disruptor", despite the fact that English is not the first language of many Europeans. I would be embarrassed to concede that we are unable to do as well. The following definition is similar to the European definition, but puts endocrine function first to convey emphasis, and is close to an earlier definition the EDSTAC considered. I propose that the EDSTAC adopt the following definition:

"An endocrine disruptor is an exogenous substance that changes endocrine function and causes adverse effects in an intact organism or its progeny, or in populations or subpopulations of organisms."

Please note that the I use "adverse effect" instead of "morphologic defect" because the latter term may imply to some an excessively restrictive

meaning. In the spirit of compromise, I can accept that "adverse effect" is a broader term that would include and is consistent with "defect", even though the medical definition of "disruption" specifies "morphologic defect".

I stand by this analysis today, and I believe my arguments have been upheld by the OECD and in general by the scientific community. Therefore, identifying "Endocrine Disruptors" requires demonstrating adverse effects produced by an endocrine mechanism.

The benefit of an additional decade of research since EDSTAC substantiates that the most accurate, complete, and clear definition of "endocrine disruptor" is "*a chemical or other factor that causes adverse effects in an organism or its progeny as a consequence of altering endocrine function.*"

EPA has consistently stated, as was emphasized by Mr. Jones at the February hearing before this subcommittee, that adverse effects are not determined in tier 1 (endocrine screening), but in tier 2 (definitive testing). The screening tier was intended to identify interaction of a chemical with components of the endocrine system; it was not designed to determine whether that interaction results in any deleterious change in the animal. Many of the endocrine screens are in vitro ('test tube') assays that do not necessarily reflect what will occur in an organism. Thus, it is erroneous to state or imply that endocrine screening will identify endocrine disruptors

19. Please state whether the risks of additive or synergistic estrogenic effects in humans from drinking water have been evaluated, and if so, what those risks are.

Humans may be exposed to estrogenic substances in drinking water that are natural estrogens excreted by humans and other animals and from plant materials, or that are synthetic estrogens from medications and other products. By far the most potent of these are the natural estrogenic hormones and estrogen medications. Human risks of additive estrogenic effects have recently been evaluated in a study authored by scientists from the pharmaceutical industry (Caldwell et al., 2010) and published in Environmental Health Perspectives, the journal of the National Institutes of Environmental Health Sciences. This study compared the potential doses of natural, synthetic and total estrogens from drinking water to normal dietary intake of estrogens and to four independent estimates of the acceptable daily intake of estrogens derived from toxicology studies.

The acceptable daily intake is a level at which there is no reasonable concern for adverse human health effects. Calculating the ratio of different received doses gives the 'margin of exposure' for the exposures to various classes of estrogen. The ratio of a received dose to the acceptable daily intake dose gives the 'margin of safety' indicating how much difference exists between the received dose and the dose that would raise no reasonable concern for adverse health effects. The margins of exposure and safety calculated for the various classes of estrogens in the Caldwell et al. study are additive because comparisons to the acceptable daily intake levels were made on the basis of the total doses of natural estrogens, synthetic estrogens, and total natural and synthetic estrogens, rather than on a chemical-by-chemical basis.

The results of this comparison indicate that children's exposures to synthetic estrogens from drinking water are from 730 to 480,000 times lower that their exposure to background levels of naturally occurring estrogens in milk, and a child's total estrogen exposures from drinking water

are about 150 times lower than exposures from milk. Adult margins of exposure from estrogens in drinking water compared to total natural dietary estrogen intake are about 2-fold less than for children based on natural estrogens in milk. Margins of safety for of an adult's exposure to total prescribed estrogens in drinking water vary from about 135 to greater than 17,000 depending on the acceptable daily intake used in the comparison. Margins of safety for total estrogens in drinking water are approximately 2-fold lower than for prescribed estrogens, indicating the increased estrogenic load in drinking water that is contributed by natural sources of estrogen. For young children, margins of exposure range from 28 to 5,120 for total estrogens, including both prescribed and naturally occurring sources in drinking water depending on the acceptable daily intake used in the comparison. In sum, the consistently large margins of exposure and margins of safety strongly suggest that prescribed and total estrogens that may potentially be present in drinking water in the United States are not causing adverse health effects in children or adults.

The potential for synergistic effects cannot be estimated directly because synergistic effects are, by definition, effects produced by a mixture of chemicals that exceed the effects that would be expected based on the individual chemicals. In other words, it is not possible to predict the unpredictable. Nonetheless, the fact that no credible demonstration of significant synergistic estrogenic effects has been published in the peer-reviewed literature suggests that such effects are highly unlikely. The single example of a significant estrogenic synergy, published just a few months before passage of the 1996 Food Quality Protection Act, was retracted due to lack of reproducibility, and was ultimately believed to involve scientific fraud. The study was not funded or in any way connected with industry; rather, the authors had ties to large universities and the National Institutes of Environmental Health Sciences.

20. You testified that you do not believe the scientific evidence warrants a ban on bisphenol-A. Please provide information to support this conclusion. Please also state whether BPA has been tested for endocrine disruption, and if so, please identify the results.

The conclusion that scientific evidence does not support a ban on BPA is not simply my belief: Regulatory agencies around the world have extensively assessed the science on BPA and concluded that BPA is safe for use in currently approved applications. Not a single one of the eleven regulatory agencies that have examined the science on BPA concludes that it there should be an "across the board" ban on BPA; indeed they have determined that BPA is safe for use in food contact products:

- U.S. Food and Drug Administration (August 2008, February 2009, January 2010)
- European Food Safety Authority (January 2007, July 2008, October 2008)
- European Commission Risk Assessment (June 2008)
- Swiss Federal Office of Public Health (February 2009)
- French Food Safety Authority (November 2008)
- Dutch Food and Consumer Product Safety Authority (November 2008)
- Danish Environmental Protection Agency (October 2008)
- German Federal Institute for Risk Assessment (January 2010)
- Food Standards Australia and New Zealand (January 2010)
- Japanese National Institute of Advanced Industrial Science and Technology (November 2005)
- Health Canada (October 2008, July 2009) - A 2008 proposal to ban polycarbonate baby bottles in Canada was based on precaution; the Canadian scientific assessment concluded that exposure is below levels that pose a risk

Even Health Canada acknowledges that, despite its precautionary ban on baby bottles, the low levels of BPA to which humans are exposed are well below those that could cause health effects. In its October 2008 announcement of the conclusion of a screening risk assessment on BPA, the Canadian government noted: "The current research tells us that the general public need not be concerned. In general, most Canadians are exposed to very low levels of bisphenol A, therefore, it does not pose a health risk."

Clearly, my conclusion that the scientific evidence does not support a ban on BPA is consistent with conclusions reached by numerous independent global regulatory agencies that have extensively assessed the full body of scientific research and determined that human exposure to BPA is low and that BPA is safe for use in current applications.
With respect to the question whether BPA has been tested to determine whether it is an endocrine disruptor, the answer is yes. Tests have been performed and the results show that BPA is not an endocrine disrupter. As you know, there are a range of screening assessments and tests that EPA is proposing under the EDSP program. Under a screening assay, such as the utertrophic assay, BPA is weakly estrogenic (about 10,000 times less potent than ethinyl estradiol); however, when tested for adverse effects on endocrine modulated endpoints such as reproduction, development and sexually dimorphic behavior, BPA has not shown effects.
With respect to reproduction and development, there are three statistically powerful, multigeneration reproduction and development studies that have been conducted in rats and mice under protocols validated by the OECD and EPA. The three studies independently show that BPA does not adversely affect reproduction or development; collectively they provide very strong corroboration that BPA does not disrupt the endocrine modulated functions of reproduction or development. Tyl et al. (2002b); Tyl et al. (2008b) and Ema et al. (2001)
With respect to neurobehavioral effects, such as sexually dimorphic behavior, two recent high-quality, robust and statistically powerful studies provide scientific evidence that there are no low dose neurobehavioral effects with BPA and no evidence of non-monotonic dose-response curves.

One study – Ryan et al. (2009) funded and conducted by the United States Environmental Protection Agency -- examined whether maternal exposure to low oral doses of ethinyl estradiol and BPA would affect the age of puberty, reproductive function or sexually differentiated behaviors. The study showed that while the oral contraceptive ethinyl estradiol altered reproduction, development and behavioral endpoints, BPA did not affect any of those functions. The lack of effect of BPA on female and male rat offspring after oral exposure to low doses in the EPA study is consistent with the lack of adverse effects on growth, vaginal opening, fertility and fecundity of low doses in several other robust, well-designed, high quality multigenerational studies (Cagen et. Al. 1999; Ema et al. 2001; Tinwell et al. 2002; Tyl et al. 2002).

The second study, Stump et al. (2010), which exposed pregnant rodents to a wide range of BPA dietary doses from low to high, concluded that BPA had no effects on brain development or behavior in their offspring that had been exposed to BPA in utero throughout development. The study was funded by industry and conducted by a highly qualified independent third-party laboratory.

In addition to the high-quality scientific studies noted, as discussed more fully in my answer to question 21, there are multiple comprehensive reviews of the scientific literature on BPA, which conclude that the weight of the scientific evidence does not support the low dose hypothesis. For example, Goodman et al. (2008), an extensive, comprehensive review of the science on reproductive and developmental toxicology, concluded: "The weight of evidence does not support the hypothesis that low oral doses of BPA adversely affect human reproductive and developmental health."

21. You testified that well-qualified scientific panels have evaluated the low dose theory of bisphenol-A and potential risks to humans from its use in products, and that these panels have determined that no unreasonable risk is posed. Please explain those reviews and provide relevant documentation. Please also state whether foreign governments have assessed BPA as an endocrine disrupter.

As stated in my testimony, a number of well-qualified panels, both in the United States and in foreign countries, have evaluated the low dose hypothesis as it relates to claims that BPA has endocrine effects at doses far below levels previously determined to be safe using well-established toxicological procedures and principles. The panels have also examined the low-dose hypothesis claim that the dose-response relationship is "non-monotonic", which means that health effects may only be observed at low doses while much higher doses result in no effects. This theory is contrary to a fundamental principle of toxicology - "the dose makes the poison." As detailed further below, all these well-qualified panels have determined that the low-dose hypothesis is not proven and that no unreasonable risk is posed by BPA.

Panels in the United States

U.S. National Toxicology Program Low Dose Endocrine Review

In 2000, the U.S. National Toxicology Program (NTP), U.S. Environmental Protection Agency and the U.S. National Institute of Environmental Health Sciences cosponsored an independent scientific peer review of the evidence for and against "low-dose endocrine disruptor" effects. The peer review included both a Statistics Subpanel, which evaluated the experimental design, data analysis and interpretation of results, and a Bisphenol A Subpanel, which reviewed the then available studies on BPA. The Bisphenol A Subpanel found that low dose effects from

BPA were not demonstrated:

> *"As a group these studies are very consistent, the conclusions are supported by appropriate statistical analyses, and the Statistics Subpanel confirmed the lack of BPA effects for the studies..." and "Collectively, these studies found no evidence for a low-dose effect of BPA, despite the considerable strength and statistical power they represent, which the subpanel considered especially noteworthy."*

The Bisphenol A Subpanel's overall conclusion stated:

> *"There is credible evidence that low doses of BPA can cause effects on specific endpoints. However, due to the inability of other credible studies in several different laboratories to observe low dose effects of BPA, and the consistency of these negative studies, the Subpanel is not persuaded that a low dose effect of BPA has been conclusively established as a general or reproducible finding. In addition, for those studies in which low dose effects have been observed, the mechanism(s) is uncertain (i.e., hormone related or otherwise) and the biological relevance is unclear."*

Based on its review of the NTP's report the U.S. Environmental Protection Agency, issued a statement that they viewed low-dose as still a "hypothesis" that had not been proven. As a result, EPA further stated, "it would be premature to require routine testing of substances for low-dose effects."

Harvard Center for Risk Analysis

In 2004, the Harvard Center for Risk Analysis impanelled a group of 8 experts to review the scientific literature and to evaluate whether the studies supported a conclusion that BPA

produces low dose developmental or reproductive effects. *"The panel found no consistent affirmative evidence of low-dose BPA effects for any endpoint."* Gray *et al.* 2004, in Human and Ecological Risk Assessment.

Subsequently, a subset of the same scientists were brought together in 2006 and again in 2008, in an 8 expert panel to review the scientific studies that had been published subsequent to the initial review. They considered the rigor, power, corroboration, universality, proximity, relevance and coherence within and among the studies to weigh the evidence. The 8 experts collectively found in 2008 that:

> *"Thus, the weight of the evidence does not support the hypothesis that low doses of BPA are associated with developmental or reproductive effects in humans."* See Goodman *et al.* 2008 in Critical Reviews in Toxicology; see also Goodman *et al.* 2006 in Critical Reviews in Toxicology.

National Toxicology Program/Center for Evaluation of Risks to Human Reproduction Report (September 3, 2008)

In 2008, the CERHR 12 member, independent panel conducted a comprehensive study-by-study review of all available literature on BPA. (Relevant literature was identified by search of the PubMed (Medline) and Toxline databases through February 2007.) In their overall conclusions, the CERHR panel noted that it spent considerable time and effort *"to interpret and understand the inconsistent findings reported in the "low dose" literature for bisphenol A."* They went on to say that:

> *"Every chemical that produces low dose cellular and molecular alteration of endocrine function also produces a cascade of effects increasing in severity resulting in clearly adverse alterations at higher doses, albeit the effects can be different from those seen at low doses. With these endocrine disrupters, but not BPA, the low dose effects are often causally linked to the high-dose adverse effects of the chemical. . . .*
> ***Hence, the failure of BPA to produce reproducible adverse effects via a relevant route of exposure, coupled with the lack of robustness of the many of the low dose studies (sample size, dose range, statistical analyses and experimental design, GLP and the inability to reproduce may of these effects [or] any adverse effect strains the credibility of some of these study results****. . . . The lack of reproducibility of the low dose effects, the absence of toxicity in these low-dose-affected tissues at high-doses, and the uncertain adversity of the reported effects lead the panel to express "minimal" concern for reproductive effects." (CERHR report, Chapin et al. 2008 at 382).*

NTP/CERHR said that for neural and development endpoints the evidence was insufficient to reach a conclusion and that "it is not clear that the reported effects constitute an adverse toxicological response." Two recent studies, Ryan et al. 2009 and Stump et al. 2010, provide additional evidence to show that BPA does not have low dose effects on neural or development endpoints.

Ryan *et al.* 2009, a recent study by EPA researchers further confirms that claims of low dose endocrine effects from BPA are not proven.

> *"The National Toxicology Program rated the potential effects of low doses of BPA on behavior and central nervous system (CNS) as an area of "some concern," whereas most effects were rated as of "negligible" or "minimal" concern. However, the number of robust studies in this area was limited. The current study was designed to determine if*

> *maternal exposure to relatively low oral doses of EE2 or BPA in utero and during lactation would alter the expression of well-characterized sexually dimorphic behaviors or alter the age of puberty or reproductive function in the female Long-Evans rat offspring. . . . . The lack of effect of BPA on female and male rat offspring after oral exposure to low doses in our studies is consistent with the lack of adverse effects on growth, VO, fertility, and fecundity of low doses of BPA in several other robust, well-designed, properly analyzed multigenerational studies (Cagen et al., 1999; Ema et al., 2001; Tinwell et al., 2002; Tyl et al., 2002).*" Ryan et al. 2010 in Toxicological Sciences.

Ryan et al. 2010 and the low dose hypothesis was the subject of a recent commentary in Toxicological Sciences by Richard M. Sharpe of The Queen's Medical Research Institute in Edinburgh, UK. Dr. Sharpe stated:

> *"Ryan et al (2009) and other similarly detailed studies in rodents more or less close the door on the possibility that bisphenol A is an environmental chemical to be concerned about because of its ER-mediated estrogenic activity. . . . I recognize that this statement will run counter to the strong convictions of some, but I base it on objective, scientific principles of evaluation. Bisphenol A has put one of these principles firmly under the spotlight, namely, the almost complete inability for different laboratories to reproduce the same results. . . If an earlier result cannot be reproduced in a huge study conducted in a scientifically rigorous manner, as exemplified by Ryan et al. (2009), then the original result fails one of the golden rules that govern scientific research. When that happens repeatedly, as is the case with bisphenol A, then there can be no logical, scientifically based reason for continuing to espouse that the original results are the only ones that are correct, rather the converse." R.M. Sharpe, "Is It Time to End Concerns over the Estrogenic Effects of Bisphenol A?,"* in Toxicological Sciences (2010)

CA Proposition 65

On July 15, 2009, the eight member Developmental And Reproductive Toxicant (Dart) Identification Committee examined the low dose studies and unanimously determined that BPA does not meet the criteria for developmental or reproductive effects under CA Proposition 65.

Food and Drug Administration

The Food and Drug Administration August 14, 2008 a Draft Assessment of Bisphenol A for Use in Food Contact Applications represents the collective views of the FDA scientists who reviewed 250 references, including those that claimed to show low dose effects. FDA noted that *"based on all available evidence, the present consensus among regulatory agencies in the United States, Canada, Europe, and Japan is that current levels of exposure to BPA through food packaging do not pose an immediate health risk to the general population, including infants and children."*

Panels in Europe

EC Scientific Committee for Toxicity, Ecotoxicity and the Environment

The European Commission completed a comprehensive risk assessment on BPA, in 2003, which was updated in 2008. The EU Risk Assessment includes a review of evidence for and against low-dose effects and which concludes that the low doses of BPA to which humans are exposed are not a risk to human health. See http://ecb.jrc.ec.europa.eu/home.php?CONTENU=/DOCUMENTS/Existing-Chemicals/RISK_ASSESSMENT/ADDENDUM

The European Commission's Scientific Committee on Toxicity, Ecotoxicity and the Environment, independently reviewed the 2003 Risk Assessment Report (June 19, 2002) and stated:

> *"[A] number of studies using non-standard protocols have reported effects of bisphenol A administration on development using substantially lower doses than the studies performed according to testing guidelines. The RAR critically describes the many weaknesses (lack of repeatability, problems with experimental design and statistical evaluation, poor reporting) of the low dose studies. The CSTEE agrees with the conclusion of the RAR that there is no convincing evidence that low doses of bisphenol A have effects on developmental parameters in offspring and remarks that effects observed are not adverse." See* http://ec.europa.eu/health/ph_risk/committees/sct/sct_opinions_en.htm

The CSTEE further remarked, *"a number of high quality studies on the reproductive and developmental effects of bisphenol A are already available and do not support low-dose effects." Ibid*

European Food Safety Authority

The European Food Safety Authority Panel on Food Additives, Flavourings, Processing Aids and Materials in Contact with Food (EFSA), which is made up of 21 independent scientific experts from across the EU, comprehensively evaluated the studies on toxicity, metabolism and pharmacokinetics, and dietary exposure in 2006 and updated its evaluation in 2008. EFSA "considered that low-dose effects of BPA in rodents have not been demonstrated in a robust and reproducible way, such that they could be used as pivotal studies for the risk assessment."

Panels in Canada

Health Canada

Similar to other agencies that have reviewed the evidence, Health Canada chose the multigeneration studies in rats and mice as the basis for their overall conclusions. Health Canada's views on low dose studies, in particular on neurodvelopmental and behavior studies, also are similar to the views of other government agencies and expert panels.

> *"While collectively these studies provide evidence that exposure to bisphenol-A during gestation and early postnatal life may be affecting neural development and some aspects of behavior in rodents, the overall weight of the evidence was considered limited from the perspective or rigour (e.g. study design limitations such as conduct of behavioral assessments as a single time point), corroboration/consistency (limited consistency of studies) and biological plausibility (e.g. certain studies involve use of a single dose, lack of dose response relationship). These limitations make it difficult to determined actual significance of findings to human health risk assessment."* See Screening Assessment for the Challenge, Phenol, 4,4" –(1-methylethylidene)bis-(Bisphenol A), Health Canada 2008 at p. 73.

Panels in Japan

Japanese Ministry of Economy, Trade and Industry

In 2002, the Japanese Ministry of Economy, Trade and Industry released a hazard assessment of BPA conducted by its experts. In regard to low dose effects, the Ministry stated:

> *"Though it is necessary to collect further information on so-called 'low dose effects' represented by BPA from academic point of view, it seems unnecessary to take any specific measure other than the above, considering the view expressed by NTP Low*

Dose Effect Panel that the low dose effect of BPA at present is a phenomenon observed under considerably limited experimental conditions and it is hardly considered to be the general phenomenon."

Japanese Ministry of Health, Labor and Welfare
The Japanese Ministry of Health, Labor and Welfare has also recently released a report from an expert review committee that has been evaluating the potential risks of endocrine disrupting substances (MHLW, 2002). After evaluating experimental reports on low-dose endocrine disruption, the expert committee concluded, "no reproducible experimental results have been obtained, and at this point of time, it is doubtful whether we can conclude that there are endocrine disrupting effects in the low dose range."

Conclusion
In conclusion, the hypothesis that BPA has endocrine effects at low doses that are not seen in traditional high dose studies has been thoroughly tested with a series of comprehensive, carefully conducted studies, all of which have been repeatedly reviewed by various expert panels – both government and independent. Those review show that the low dose studies have not been replicated and that the large-scale studies validated protocol studies, which have examined a range of doses from low to high, do not show low dose effects. The weight of scientific evidence provided by these studies and reviews by scientific experts clearly supports the safety of BPA and provides strong assurance that exposure to low doses of BPA does not raise human health concerns.

22. Are pesticides and other chemicals currently evaluated for endocrine disruption, or does that type of evaluation only occur if the chemical is included in the EPA's endocrine screening program?

Many chemicals are evaluated for potential endocrine activity irrespective of the EPA's endocrine screening battery, and irrespective of regulatory requirements per se. The high production volume chemical (HPV) program in the U.S. and the REACH initiative in Europe include toxicity tests that capture certain endocrine-mediated effects. EPA's more established Series 870 OPPTS test guidelines, which are required for all pesticides marketed in the U.S., include evaluations in multiple mammalian and non-mammalian studies that provide both direct and indirect data on ability of a pesticide to cause adverse endocrine-mediated effects. These studies are conducted according to well-validated and well-documented protocols and conform to the EPA's Good Laboratory Practice Standards (GLP). In a paper published in 1997 entitled "FIFRA Subdivision F testing Guidelines: are these tests adequate to detect potential hormonal activity for crop protection chemicals? Federal Insecticide, Fungicide, and Rodenticide Act" Stevens and co-authors addressed the applicability of other tests required under FIFRA to provide data meeting the objectives of the EDSP Tier 1 screening battery. Their analysis is consistent with the view that potential endocrine disruption is well characterized for pesticides irrespective of the endocrine screening battery.

FIFRA-required tests include sub-chronic and chronic toxicity studies in rats, mice and dogs, developmental toxicity studies in rats and rabbits, and reproduction studies in rats. Such studies evaluate a wide array of estrogen-, androgen- and/or thyroid-sensitive tissues and evaluate potential endocrine-mediated responses such as reproductive parameters (e.g. mating, fertility, and gestational indices), estrous cyclicity, sperm parameters, and histological alterations in a variety of endocrine controlled tissues, (e.g. epididymides, testes, ovaries, uteri, thyroid, adrenals, pituitary). Many of these endpoints are the same or very similar to those required in the endocrine screening assays, but they are evaluated over a much longer time frame. Over and above what the endocrine screening assays assess, these other FIFRA requirements

include evaluation of fetal and pup development assessed by measuring endpoints related to growth, survival, and sexual development, and many studies include additional endpoints such as hormone levels. Endocrine-related effects are also evaluated in representative wildlife species, including fish and birds. Metabolism studies in rats, poultry, ruminant animals and fish characterize the absorption and excretion of the pesticide over time and help to identify any metabolites of concern. In short, the extensive toxicity profile generated on pesticides to meet the FIFRA requirements provides more complete and definitive information about a pesticide's potential to interfere with the endocrine system than the endocrine screening battery is able to provide.

23. You mentioned during the hearing that male fish can produce the female protein vitellogenin in response to human estrogen in the water. Can you characterize the relative importance of chemical endocrine disruptors compared to human estrogens in causing this effect? Does this effect prevent the fish from reproducing?

I acknowledged that the egg protein vitellogenin, normally expressed in female fish, can be produced in male fish exposed to estrogenic chemicals in the water. However, in contrast to the other witnesses who testified at the hearing, I noted that vitellogenin in male fish is not necessarily an indication of exposure to endocrine disrupting synthetic chemicals in the water, but can more likely indicate exposure to estradiol from human urine in the water. Furthermore, and in contrast to other witnesses, I noted that vitellogenin in male fish was not specific for exposure to estrogens and might reflect habitat factors or factors other than endocrine disruption. The presence of vitellogenin in male fish does not portend impaired reproductive capacity and does not prevent fish from reproducing. More detail substantiating these and other points are provided below.

First, as I stated during the hearing, early speculation by researchers in the United Kingdom that synthetic chemicals (detergents and other industrial chemicals) were responsible for the presence of vitellogenin in male fish captured downstream of sewage treatment plants turned out to be incorrect. These same researchers later found that the estrogenic activity was due to hormones in human urine. Human hormones are the most abundant and among the most potent estrogens found in water supplies, therefore, human hormones are indeed of highest relative importance generally (see answer to question #19).

As I further noted during the hearing, the critical question is whether adverse effects are produced, not whether vitellogenin is found in male fish. Summarizing their study, Mills et al. (Environ Health Perspect. 2003 Jan;111(1):93-100)" reported:

> *The gene for vitellogenin, an egg yolk protein precursor, is usually silent in male fish but can be induced by estrogen exposure. For this reason, vitellogenin production in male fish has become a widely used indicator of exposure to exogenous estrogens or estrogen mimics in the aquatic environment. The utility of this indicator to predict impacts on fish reproductive success is unclear because information on the relationship between male plasma vitellogenin and reproductive end points in male and female fish is limited. In the research reported in this article, we investigated whether the presence of male plasma vitellogenin is a reliable indicator of decreased reproductive success in mature fish. ... Results suggest that male plasma vitellogenin expression is not a reliable indicator of male reproductive dysfunction in adult cunner exposed to estrogens for 2–8 weeks during their*

> *reproductive season, at least in relation to capacity to produce motile sperm or fertilize eggs.* [emphasis added]

Furthermore, as I stated during my testimony, the science on endocrine disruption is not settled, as other witnesses implied, but remains hypothetical. A summary of the critical review by Mills and Chichester (Review of evidence: are endocrine-disrupting chemicals in the aquatic environment impacting fish populations? Sci Total Environ. 2005 May 1;343(1-3):1-34) supports my contentions:

> *In this paper, evidence from the current literature is presented that addresses either of two questions: 1) do EDCs in the aquatic environment have the potential to impact the reproductive health and survival of various fish species, and 2) are EDCs in the aquatic environment actually impacting the reproductive health and sustainability of indigenous populations of fish? Overall, data from laboratory experiments support the hypothesis that EDCs in the aquatic environment can impact the reproductive health of various fish species, but evidence that EDCs in the aquatic environment are actually impacting the reproductive health and sustainability of indigenous fish populations is less convincing. The scarcity of evidence linking impacts of environmental EDCs with changes in reproductive success of indigenous fish populations may reflect a critical need for a dependable method or indicator to assess reproduction of fish in situ. In addition, more studies that investigate whether fish populations routinely exposed to EDCs in situ are experiencing changes in population structure are needed. Linking endocrine disruption and reproductive impairment with an ecologically relevant impact on the sustainability of real fish populations remains, with few exceptions, an open challenge.* [emphasis added]

Finally, results of even more recent research substantiate my contention that habitat and other factors are potential causes of supposed endocrine disruption in fish (Trubiroha et al.: Naturally-induced endocrine disruption by the parasite Ligula intestinalis (Cestoda) in roach (Rutilus rutilus). Gen Comp Endocrinol. 2010 Apr 1;166(2):234-40), but that these other factors are rarely researched because it is easier to sensationalize effects of chemicals.

> *Fish represent the most frequently used vertebrate class for the investigation of endocrine disruption (ED) in wildlife. However, field studies are complicated by exposure scenarios involving a variety of anthropogenic and natural influences interfering with the endocrine system. One natural aspect rarely considered in ecotoxicological studies is how parasites modulate host physiology. Therefore, investigations were carried out to characterise the impacts of the parasitic tapeworm Ligula intestinalis on plasma sex steroid levels and expression of key genes associated with the reproduction in roach (Rutilus rutilus), a sentinel species for wildlife ED research. ... In summary, the present results provide basic knowledge of the endocrine system in L. intestinalis-infected roach and clearly demonstrate that parasites can cause ED in fish.* [emphasis added]

These researchers also note that vitellogenin (VTG) production in male fish is not always an indication of exposure to estrogenic chemicals, but may have a normal physiological role in immunity.

VTG has generally been claimed to be a female-specific protein but, nevertheless, an increasing amount of data show that VTG or its mRNA is also present at low levels in male fish which were not exposed to oestrogenic compounds (Bowman et al., 2000; Rod- gers-Gray et al., 2001). As Lake Mueggelsee is located upstream of sewage discharging areas (Massmann et al., 2004), it seems very unlikely that the levels of VTG mRNA detected in male roach are caused by anthropogenic pollution. In addition, samplings of several hundreds of roach from Lake Mueggelsee (2006–2009) re- vealed only a negligible incidence of testicular oocytes (unpublished data). Since in roach, the occurrence of intersex phenomena has been demonstrated to be the best predictor of exposure to oestrogenic compounds (Jobling et al., 2006), this further confirms that low levels of hepatic VTG mRNA are constitutively expressed in male roach even at unpolluted sites. Recent findings show that in fish, VTG functions as a pattern recognition receptor and exhibits opsonic activity, suggesting that VTG plays a role in innate immunity of oviparous vertebrates independent of gender (Li et al., 2008; Liu et al., 2009).

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