FOUR "WITNESS" DOCUMENTS PRESENTED ON FEBRUARY 25, 2010, AT THE U.S. SUBCOMMITTEE ON ENERGY AND THE ENVIRONMENT HEARING:

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

AND CHAIRMAN MARKEY'S CONCLUDING COMMENTS

The Subcommittee on Energy and Environment held a hearing entitled, "Endocrine Disrupting Chemicals in Drinking Water: Risks to Human Health and the Environment," on Thursday, February 25, 2010, at 9:30 a.m. in room 2123 of the Rayburn House Office Building (Washington, D.C.). This hearing examined the science and regulation of endocrine disruptors that may be found in sources of drinking water.

Witnesses

- Jim Jones, Deputy Assistant Administrator, Office of Prevention, Pesticides and Toxic Substances, Environmental Protection Agency
- Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S., Director, National Institutes of Environmental Health Sciences
- Gina Solomon, M.D., M.P.H., Senior Scientist, Natural Resources Defense Council
- Christopher J. Borgert, Ph.D., President and Principal Scientist, Applied Pharmacology and Toxicology, Inc.

CAUTIONARY NOTES:

Though not specifically mentioned on the hearing date, this hearing relates to public concerns about the contamination of hydraulic fracturing (fracking) by the oil & gas industry in the United States.

The following written presentations should be read in conjunction with viewing the video of the committee members and the witnesses testimonies (or, alternatively, in the full hearing transcript) during the Hearing of February 25, 2010 (video link found on the subcommittee web page, http://energycommerce.house.gov/index.php?option=com_content&view=article&id=1908:endocrine-disrupting-chemicals-in-drinking-water-risks-to-human-health-and-the-environment&catid=130:subcommittee-on-energy-and-the-environment&Itemid=71).

The Sub-Committee Hearing video does not begin right away, but 13 minutes, and 40 seconds in, so don't be alarmed if nothing seemingly appears. Just scroll ahead to 13:40.

Energy and Environment Subcommittee Chair, Congressman Ed Markey

At the beginning of the 111th Congress, Rep. Markey became the Chair of the House Energy and Commerce Committee's Energy and Environment Subcommittee, which combines the Energy and Air Quality and the Environment and Hazardous Materials Subcommittees. Markey continues to serve as the Chair of the Select Committee on Energy Independence and Global Warming, and as a member of the House Natural Resources Committee. The Energy and Environment Subcommittee is one of the most powerful Subcommittees in the House, with jurisdiction over national energy policy, and is the principal authorizing Subcommittee for DOE, NRC, FERC, NHTSA, and the EPA. It has jurisdiction over the electric utility industry, the oil and natural gas industry, the Clean Air Act, the Superfund Act, and hazardous waste disposal. (Source: Markey's website)

Markey Video Transcript (end of Hearing, 2:01:56 - 2:10:30)**:**

Markey: We thank you all for coming here today for a very important hearing. And, we thank anyone who has been watching this hearing on Seaspan today.

The endocrine system for human beings is really just our computer system, it's just a computer. And, like a computer, if someone hacks into a computer, and drops in a new virus, it can cause a tremendous disruption to the computer. And, there is one thing no one wants in America, or in the world, is for someone to hack into their computer, for someone to add in a virus that can begin to disrupt it. No matter how small that virus might be it's a big change in your relationship with the computer.

Well, the endocrine system is the computer system and that's why we're so concerned about it. That the more that the water and other avenues that are used in order to ... disrupts 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. That's why it's so important, in the sense that we have seen significant changes over the last 30 or 40 years, whether it would be autism, or you go down the whole list. We're wondering what's happening? Why are we seeing so much larger identification of these problems in human beings.

And so, scientists are like detectives. They look around. They see what could have hacked in to the human being, what's different, what's going into human beings that wasn't going into human beings before, especially as they effect children, because that's when this system is most vulnerable, that's when a computer is most vulnerable. It's brand new, it hasn't quite developed all of its defences yet. You haven't added in all the software packages that can defend. And, it is so much more vulnerable to changes. That's why we are so concerned about it. That's why I'm concerned about EPA, especially things that are exposed to children. That's what my legislation would be most concerned with, the kinds of things children would be putting into their bodies, because, obviously, that would have a more profound effect upon the computer system of the body.

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

I'm going to give you at least one minute to summarize what it is 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 mono-syllabic words as you can in order to make it possible for us to, in one minute, to understand what you are trying to tell us. We'll go in reverse order of the opening statements, and Dr. Borgert ... whenever you are ready.

Dr. Borgert: 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 reputable science, that is based on reliable science, that is based on relevant science, and that the data be evaluated for themselves, for their 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 setting any decision-making process that will involve regulation because we risk actually imperilling ourselves, rather than protecting ourselves, with faulty information.

Markey: Thank you. Dr. Solomon.

Solomon: As was the case around the health effects with tobacco, there were many, many years through questions being raised, claims that the science was not totally clear yet. And, it's always easy to do that kind of thing because science is never one hundred percent crystal clear. But we do need to act based on the information we have. And major medical 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.

Markey: Mr. Jones.

Jones: The 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, in 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 our, the first orders that have gone out in the last three months, and our commitment here today to begin using the Discretionary Order in the *Safe Drinking Water Act* to begin screening chemical contaminants in the drinking water in the very near future.

Markey: Dr. Birnbaum.

Dr. Birnbaum: Fish, frogs, birds and mammalian wildlife are our canaries in the coal mine 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.

Markey: We thank all of you for being here. I think the lessons that we have 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, when we have enough evidence, I just think 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.

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

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

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 largescale 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 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.

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
Expected at 9:30 a.m.
February 25, 2010

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 ofthe 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; [2] 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; [3] the incidence of cryptorchidism (undescended testicles) doubled in the U.K. between 1960 and the mid 1980s; [4] and there was an approximately 42% decrease in sperm count worldwide between 1940 and 1990. [5]

These observations, set against the numerous observations of abnormalities of sexual development in amphibians and fish [6] and the widespread detection of chemicals with endocrine disrupting properties in our bodies, [7] 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 [8] 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, 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,

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

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 [9] 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. [10] 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. [11]

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 nuclear receptors for thyroid honnone and retinoic acid. [12] 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. [13] They found that mice that were exposed to 100 ppb arsenic in drinking water had a significantly compromised response to HINI influenza infection. [14]

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

[9] See http://www.cdc.gov/exposurereport/pdf/FourthReport.pdffor most recent version of the report.
[10] Sheehan DM et al., Environ Health Perspect 1999 Feb; 1 07(2): 155-9
[11] Richter CA et al., Reprod Toxicol24 (2007) pp. 199-224
[12] Davey IC et al. Environ Health Perspect (2008)116:165-172.
[13] Kozul CD et ai. Environ Health Perspect (2009)117(7):1108-15.
[14] Kozul CD et ai. Environ Health Perspect (2009)117:1441-1447.

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. [15] 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, [16] genistein and diethylstilbestrol [17] 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 BP A exposure. BP A 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 [18]), which in turn built on the earlier consensus statement report from the expert panel workshop convened by the NIEHS. [19] While much of the exposure to BP A in humans occurs through the diet, other sources of exposure include air, dust, and water. NIEHS invested approximately $20M in FY2009 to study health effects ofBPA 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 BP A 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 BP A 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. [20] 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.

[15] Diamanti-Kandarakis et aI., Endocrine Reviews (2009) Iune;30(4):293-342
[16] Grun F, Blumberg B. Endocrinology (2006) 147:S50-S55
[17] Newbold RR et ai. Mol Cell Endocrinol (2009) May 25;304(1-2):84-89
[18] http://www.niehs.nih.gov/news/medialquestions/sya-bpa.cfm
[19] vom Saal et ai. Reprod Toxicol (2007)24:l31-l38
[20] Diamanti-Kandarakis et alia, Endocrine Reviews (2009) June;30(4):293-342

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. [21] 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. [22] 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 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. [23]

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. [24] 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). [25] 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. [26] 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.

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[21] Engel SM et al. Environ Health Perspect 2010 Jan 8 [Epub ahead of print]
[22] Herbstman JB et al. Environ Health Perspect 2010 Jan 4 [Epub ahead of print]
[23] WolffMS et al. Environ Health Perspect 2007, 115(1):116-121
[24] R21ES017176 PI: Susan Pinney, Univ of Cincinnati. Exposure biomarkers of poly flu oro alkyl compounds in persons living in the Ohio River valley.
[25] PI: Matthew Longnecker, NIEHS. Perfluorinated alkyls and fecundability.
[26] http://ntp.niehs.nih.gov/filesIPFOAConcept.pdf

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, [27] 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. [28]

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 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, [29] used to make certain industrial polymers; butylparaben, [30] a preservative used in cosmetics; oxybenzone, [31] a sunscreen ingredient; and triclosan. [32] 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.

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[27] http://ntp.niehs.nih.gov/go/28213
[28] http://www.epa.gov/ncct/practice community/category priority.html
[29] http://ntp.niehs.nih.gov/index.cfm?objectid=F609B028-F IF6-97 5E-715EE7E97E4CCB 16
[30] http://ntp.niehs.nih.gov/fileslButylparabenConcept.pdf
[31] http://ntp.niehs.nih.gov/index.cfm?objectid=OnCEB9A-A49B-F6AA-91 E25964528B914A
[32] http://ntp.niehs.nih.gov/index.cfm?objectid=F61 OE7F7 -F 1 F6-975E-76E92BCOB5CC47B3

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 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.

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, [33] 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 fmding 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). [34] 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. [35] 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. [36] 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." [37] 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

[33] Jobling S, Nolan M, Tyler CR, Brighty GC, Sumpter JP. Widespread sexual disruption in wild fish. Environ Sci Tech. 1998;32(17):2498-2506.
[34] 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.
[35] Skelly DK, Benard MF. Mystery unsolved: missing limbs in deformed amphibians. J Exp Zool B Mol Dev Evol. 2009 Nov 30. [Epub ahead of print]
[36] Guillette LJ Jr, Gunderson MP. Alterations in development of reproductive and endocrine systems of wildlife populations exposed to endocrine-disrupting contaminants. Reproduction. 2001 Dec;122(6):857-64.
[37] Based on Kavlock RJ, Daston GP, DeRosa C, Fenner-Crisp P, Gray LE, Kaattari S, Lucier G, Luster M, Mac MJ, Maczka C, Miller R, Moore J, Rolland R, Scott G, Sheehan DM, Sinks T, Tilson HA. Research needs for the risk assessment of health and environmental effects of endocrine disruptors: A report of the U.S. EPA-sponsored workshop. Environ. Health Perspect. 104 Suppl 4:715-740 (1996).

groundwater we rely on for drinking, and in our drinking water itself. [38] [39] [40] 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. [41] 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. [42]

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)." [43]

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

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[38] 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):1202-1l.

[39] Barnes KK, Kolpin DW, Furlong ET, Zaugg SD, Meyer MT, Barber LB. A national reconnaissance of pharmaceuticals and other organic wastewater contaminants in the United States--I) groundwater. Sci Total Environ. 2008 Sep 1;402(2-3):192-200. Epub 2008 Jun 16.

[40] Focazio MJ, Kolpin DW, Bames 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.

[41] Centers for Disease Control and Prevention. National Report on Human Exposure to Environmental Chemicals. Fourth Report, 2009. http://www.cdc.gov/exposurereport/.

[42] Diamanti-Kandarakis E et aI. 2009 Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement. Endocrine Reviews 30(4):293-342. http://www.endosociety. org/journals/scientificstatements/uploadledc_scientific_statement.pdf (Visited February 22, 2010).

[43] http://portal.acs.org/portal/PublicWebSite/policy/publicpolicies/promote/endocrinedisruptors/CNBP _23441 (Visited February 22, 2010).

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. [44] Over a period of20 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 EDST AC 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.

[44] http://www.epa.gov/endo/pubs/edspoverview/finalrpt.htm (Visited February 21, 2010).

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. [45] 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 (FQP A) 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. [46] 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.

[45] http://www.epa.gov/endo/pubs/edsp_orders_status_021610.pdf (Visited February 21, 2010).
[46] EPA Office of the Inspector General. EPA Needs a Coordinated Plan to Oversee Its Toxic Substances Control Act Responsibilities. Report No. 10-P-0066 February 17,2010. http://www.epa.gov/oig/reports/2010/20100217-10-P-0066.pdf (Visited February 21, 2010).

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. 1'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 SDW A 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 ofCCLl and then CCL2 in 2005. CCLl 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 CCL 1. CCL2 consisted of a subset of the chemical contaminants listed on CCL 1; 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 honnones. 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 SDW A - 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.

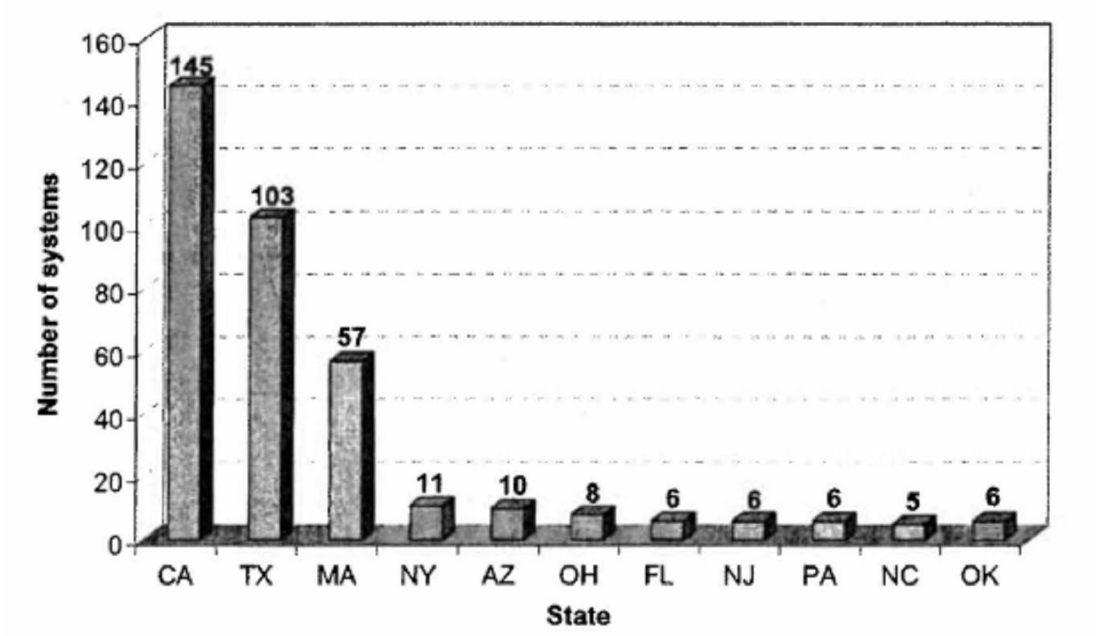
Perchlorate is a contaminant that comes from rocket fuel, fireworks, road flares, fertilizer, and other sources. It is known to interfere with the nonnaI function of the thyroid gland. [47] Iodine is needed by the thyroid in order to create thyroid hormones. Nonnally, iodine is transported into the thyroid 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.

[47] Benjamin C. Blount, James L. Pirkle, John D. Osterloh, Liza Valentin-Blasini, and Kathleen L. Caldwell. Urinary Perchlorate and Thyroid Hormone Levels in Adolescent and Adult Men and Women Living in the United States. Environmental Health Perspectives Volume 114, Number 12, December 2006.

A decrease in circulating thyroid hormone during gestation or the first year of life can result in neurodevelopmental abnormalities leading to permanent brain dysfunction. [48] 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. [49]

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). [50] 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.



[48] Zoeller RT. Thyroid toxicology and brain development: should we think differently? Environ Health Perspect. 2003 Sep; 111(12):A628.

[49] 17 Pop VJ, Kuijpens JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, Vulsma T, Wiersinga WM, Drexhage HA, Vader HL. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol (Oxf). 1999 Feb;50(2): 149-55.

[50] Arizona Department of Environmental Quality (ADEQ), *Perchlorate in Arizona: Occurrence Study of 2004, Revised* (December 2004); California Department of Health Services, *California Drinking Water Data* (April 2005); Massachusetts DEP, Perchlorate monitoring results [data provided by Drinking Water Program] (March 2005); U.S. Army Corps of Engineers (USACOE), *Washington Aqueduct Perchlorate Data* (2004); U.S. Environmental Protection Agency (U.S. EPA) *Unregulated Contaminant Monitoring Data* (January 2005); U.S. Government Accountability Office (GAO), *Perchlorate: A System to Track Sampling and Cleanup Results Is Needed*, (2005); and various Water Quality Reports (or Consumer Confidence Reports) and news articles for the City of Edmond, OK; City of Georgetown, TX; Las Vegas Valley Water District; New Mexico American Water Company; and Shreveport [Louisiana] Department of Operational Services.

The 402 systems that have found perchlorate serve 40.8 million people. [51] 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. [52] 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. [53] [54] [55] Their effects in animal studies are well recognized and include lower testosterone levels, decreased sperm counts and lower sperm quality. Exposure to

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[51] U.S. EPA, *Safe Drinking Water Information System* (SDWIS).

[52] California Environmental Protection Agency State Water Resources Control Board, and Department of Toxic Substances Control, *Joint Geotracker SWRCB and DTSC Perchlorate Confirmed Contaminant Site Data* (2005); U.S. Department of Defense, *DoD Perchlorate Occurrence Survey* (2003); U.S. EPA, *Known or Suspected Perchlorate Manufacturers/Users in US* (April 2003); U.S. EPA, *Known Perchlorate Releases in the US*. (September 23, 2004; and December 10,2004); U.S. EPA, Hazardous Waste Clean-up Information (CLU-IN) [citing Mayer, 2003], *Occurrence and Potential Sources of Perchlorate Releases to the Environment as of April, 2003*; U.S. EPA, STORET [database]; U.S. Government Accountability Office (GAO), *Perchlorate: A System to Track Sampling and Cleanup Results Is Needed* (2005); W.A. Jackson et al., *Distribution and Potential Sources of Perchlorate in the High Plains Region of Texas: Final Report* (2004) Texas Tech University Water Resources Center, prepared for Texas Commission on Environmental Quality.

[53] Kavlock, R., et al. (2002). "NTP Center for the Evaluation of Risks to Human Reproduction: phthalates expert panel report on the reproductive and developmental toxicity of butyl benzyl phthalate." Reprod Toxicol 16(5): 453-87.

[54] Kavlock, R., et a1. (2002). "NTP Center for the Evaluation of Risks to Human Reproduction: phthalates expert panel report on the reproductive and developmental toxicity of di-n-butyl phthalate." Reprod Toxicol 16(5): 489-527.

[55] Kavlock, R., et a!. (2006). "NTP-CERHR Expert Panel Update on the Reproductive and Developmental Toxicity of di(2-ethylhexyl) phthalate." Reprod Toxicol 22(3): 291-399.

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. [56] [57]

National monitoring studies have found one or more phthalates in over 10 percent of streams sampled. [58] 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.

BP A, or bisphenol A, is a hormone-disrupting chemical used in making plastics and epoxy resins. BP A 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. BP A is also found in some dental sealants and fillings, medical devices, paints, epoxy adhesives and cash register receipts.

In animal studies, BP A 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. [59] 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. [60] It also has been associated with obesity and insulin resistancea condition that commonly precedes the development of diabetes. [61]

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. [62] The researchers in this study planned to determine if these widespread detections represented contamination from the laboratory, or contamination in the

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[56] Main, K. M., et al. (2006). "Human breast milk contamination with phthalates and alterations of endogenous reproductive hormones in infants three months of age." Environ Health Perspect 114(2): 270-6.
[57] Swan, S., et al. (2005). "Decrease in Anogenital Distance Among Male fufants with Prenatal Phthalate Exposure." Environ Health Perspect 113: 1056-1061.
[58] 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):1202-1l.
[59] National Toxicology Program, Center For The Evaluation of Risks To Human Reproduction, Reproductive and Developmental Effects of Bisphenol A. September 2008 NIH Publication No. 08 - 5994. Available on line http://cerhr.niehs.nih.gov/chemicalslbisphenollbispheno1.pdf.
[60] vom Saal, F. S., et al. (2007). "Chapel Hill bisphenol A expert panel consensus statement: integration of mechanisms, effects in animals and potential to impact human health at current levels of exposure." Reprod Toxicol 24(2): 131-8.
[61] Newbold, R., et al. (2009). "Environmental estrogens and obesity." Molecular and Cellular Endocrinology 304(1-2): 84-89.
[62] Zhang S, Zhang Q, Darisaw S, Ehie O, Wang G. Simultaneous quantification of polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), and pharmaceuticals and personal care products (PPCPs) in Mississippi river water, in New Orleans, Louisiana, USA. Chemosphere. 2007 Jan;66(6):1057-69.

drinking water; no definitive results are available. [63] National groundwater sampling reported BP A in about 30 percent of groundwater samples. [64]

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. [65] Despite sophisticated wastewater treatment, these chemicals were detected in treated waters discharged into the Bay and have also been detected in the Bay itself. [66] 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.

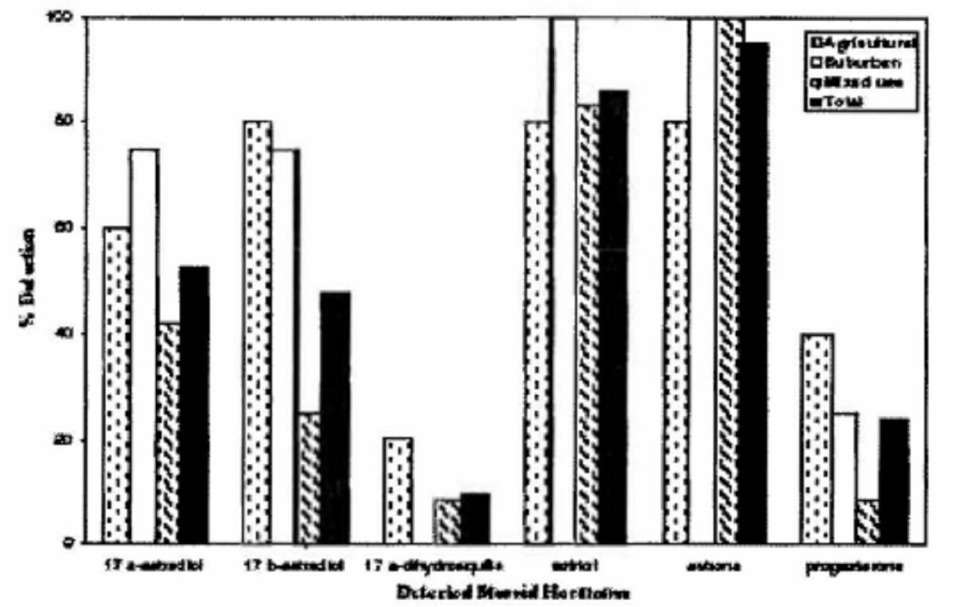
There is no EPA drinking water standard for bisphenol A, even though it is a known endocrine disruptor and a known water contaminant. Unfortunately this chemical is not even on the CCL3, so the likelihood of any appropriate EPA action to protect consumers from this chemical in drinking water appears 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). [67] Potential sources of the hormones include municipal wastewater discharges, septic tanks, and animal manure.

[63] Boyd GR, Reemtsma H, Grimm DA, Mitra S. Pharmaceuticals and personal care products (PPCPs) in surface and treated waters of Louisiana, USA and Ontario, Canada. Sci Total Environ. 2003 Jul 20;311(1-3): 135-49.
[64] Barnes KK, Kolpin DW, Furlong ET, Zaugg SD, Meyer MT, Barber LB. A national reconnaissance of pharmaceuticals and other organic wastewater contaminants in the United States--I) groundwater. Sci Total Environ. 2008 Sep 1;402(2-3):192-200. Epub 2008 Jun 16.
[65] http://www.ewg.org/water/downthedrain (Accessed February 22, 2010).
[66] Oros DR. 2002. Identification and Evaluation of Previously Unknown Organic Contaminants in the San Francisco Estuary (1999-2001). RMP Technical Report: SFEI Contribution 75. Oakland, CA: San Francisco Estuary Institute.
[67] Velicu M, Suri R. Presence of steroid hormones and antibiotics in surface water of agricultural, suburban and mixed-use areas. Environmental monitoring and assessment. Volume 154 issue: 1-4 page: 349 -59, 2009.

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. [68] 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. [69] 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 (CAPOs; also known as "factory farms") are largescale 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.

[68] Durhan EJ, et al. Identification of metabolites of trenbolone acetate in androgenic runoff from a beef feedlot. Environ Health Perspect. 2006 Apr;114 Suppl 1 :65-8.
[69] Durhan EJ, et al. Identification of metabolites of trenbolone acetate in androgenic runoff from a beef feedlot. Environ Health Perspect. 2006 Apr;114 Suppl 1 :65-8.

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 EDST AC 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

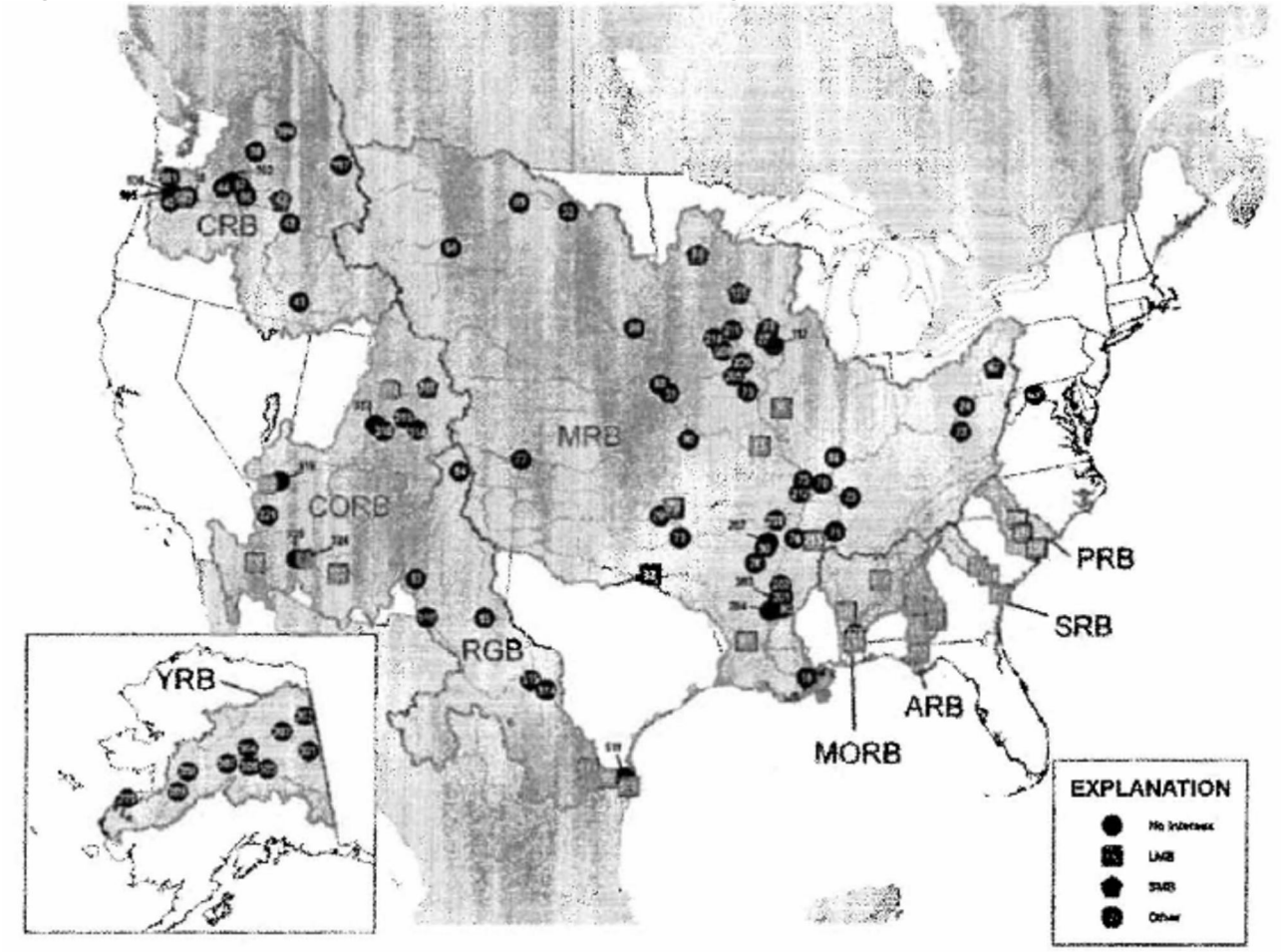
Of the 16 fish species researchers examined from 1995 to 2004, intersex was most common by far in smallmouth and largemouth bass: a third of all male smallmouth bass and a fifth of all male largemouth bass were intersex (Figure 3). This condition is primarily revealed in male fish that have immature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

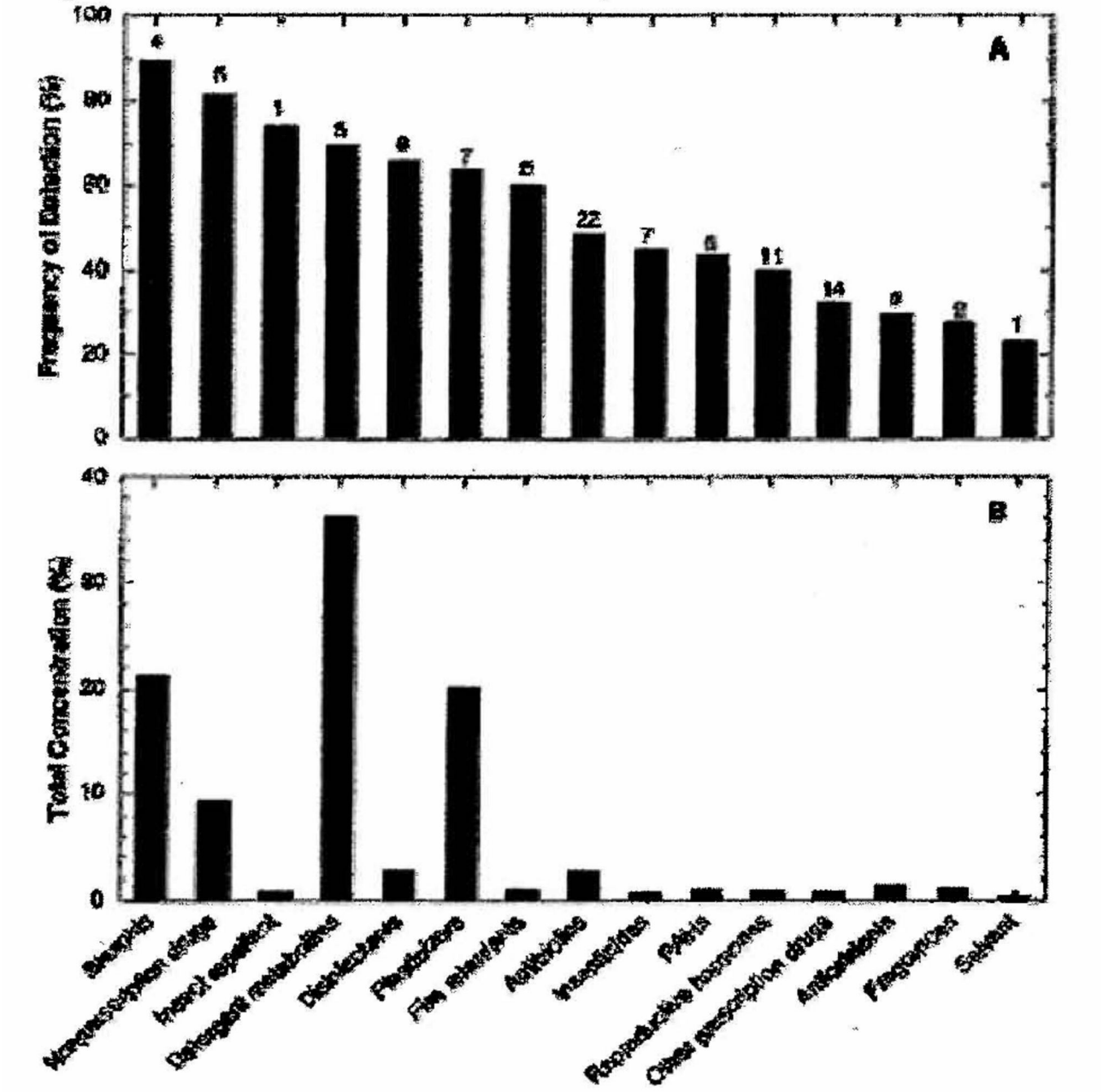


Source: Hinck JE, Blazer VS, Schmitt CJ, Papoulias DM, Tillitt DE. Widespread occurrence of intersex in black basses (Micropterus spp.) from u.s. rivers. 1995-2004. Aquat Toxicol. 2009 Oct 19;95(1):60-70.

Appendix 2
Contaminants in Source Water in the United States

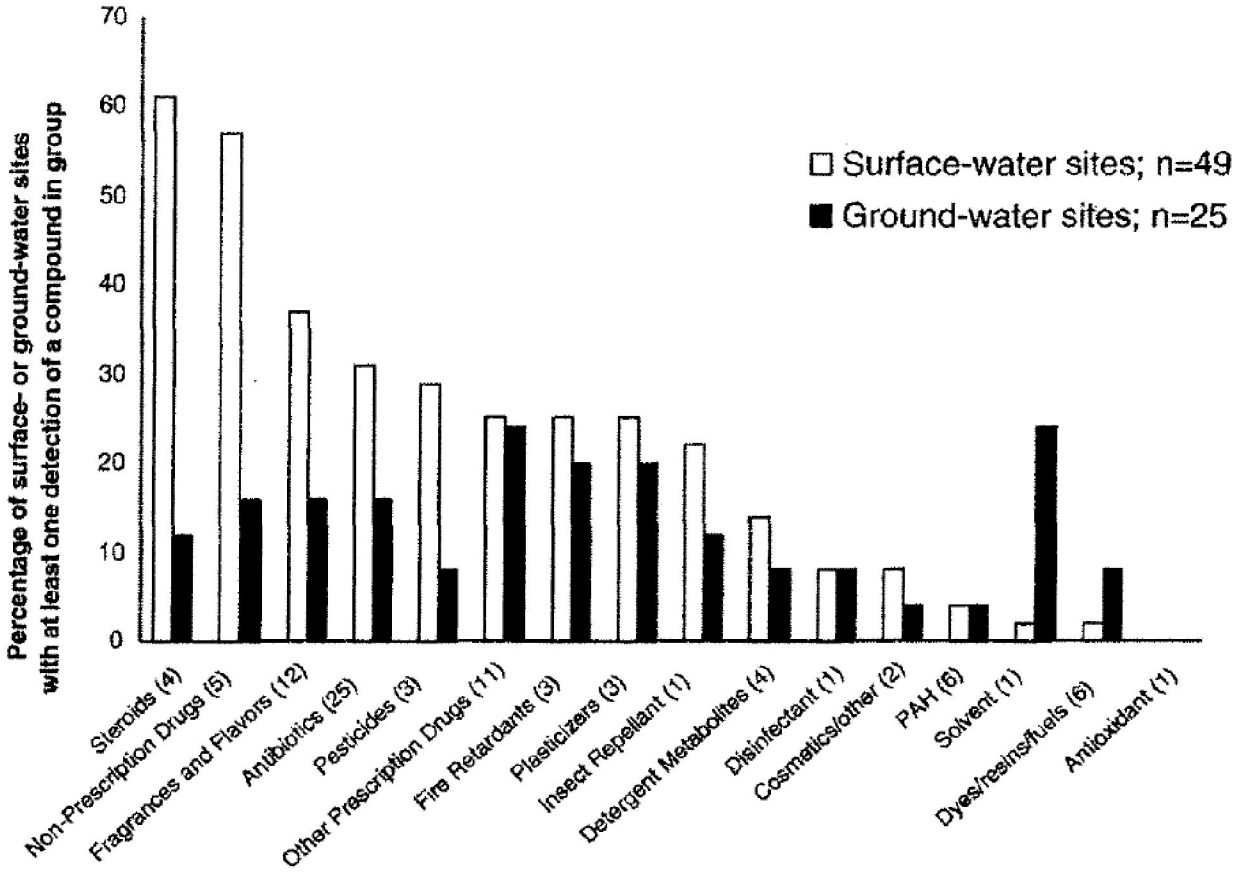
The most common unregulated contaminants detected in surface water include steroid honnones, nonprescription drugs, insect repellent, detergent chemicals, disinfectants, and plasticizers; all of these chemicals were detected at 70 percent or more of sites tested. The concentrations of the steroids, detergents, 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 honnones 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, ftre 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.

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. In doing so, 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 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.