Public Comments
Report to the Legislature on DPR
Deadline:10/25/16 12:00 noon

RRWPC

Russian River Watershed Protection Committee
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SWRCB Clerk

Jeanine Townsend, Clerk to the Board
State Water Resources Control Board

Sent via Email to: commentletters@waterboards.ca.gov
October 23, 2016

COMMENT LETTER-REPORT TO LEGISLATURE ON DPR

Dear Ms. Townsend:

The purpose of this letter is to provide comments on the Report to the Legislature on the *Feasibility of Developing Uniform Water Recycling Criteria for Direct Potable Reuse* and recommendations from expert and advisory panels on that topic. We appreciate the opportunity to comment on this report.

RRWPC Background….

Russian River Watershed Protection Committee (RRWPC) is a nonprofit, public benefit corporation founded in 1980. For about the last eight years, we have been tracking and commenting on the issue of wastewater reuse (specifically regarding tertiary wastewater irrigation) to both your Board and the Regional Water Quality Control Board. During that time, RRWPC has submitted comments and attachments on the *Recycled Water Policy* and the *Policy Amendment*, the *General Waste Discharge Requirements for Landscape Irrigation Users of Municipal Recycled Water (General Permit)*, the *General Order for Recycled Water Use* (2014 and 2016), The *North Coast Basin Plan Amendment for Recycled Water Use*, etc. We include via link RRWPC Comments and Attachments on the *General Order for Recycled Water Use* (2016) for this record: http://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/comments/general_order/)

RRWPC represents hundreds of lower Russian River residents, property and business owners, recreationists, etc. who are concerned about water quality and flows, along with clean drinking water, in the lower Russian River, one of the most popular summer vacation destinations of the Bay Area. For years, our area was the recipient of Santa

Rosa's treated wastewater discharges into our river. For fifteen years we battled this problem and they ultimately built a 40-mile pipeline to take their wastewater to the Geysers steam fields. This has sensitized our community to the problems of allowing toxic materials into our waterways and we are deeply concerned about DPR.

We are concerned that little is known about the toxic substances in our river and we have always wondered what unregulated remnant toxins enter the river through other wastewater discharges, agricultural and irrigation runoff. While the SWAMP program has been conducting some tests on river toxicity, we have not seen any results as yet. The specter of DPR may be enough to drive people to the bottle, the water bottle that is, as some urban water districts promote, "Take it from the tap".

We are aware that the purpose of these comments is to address the feasibility of developing water recycling criteria for DPR to inform the Legislature, and that it is highly unlikely that DPR would become a reality for Northern California anytime soon. We are nonetheless very concerned about the prospect of having statewide regulations developed at this time for direct potable reuse. While we do not claim to be experts in the field of wastewater technology, especially at its highest level of constituent removal, we do know enough about some of the vulnerabilities and issues connected with this possibility that we wish to have our concerns about public health and background information about endocrine disruption entered into the record.

DPR may be infeasible.....

What we do know is that, if done with full consideration of all potential health risks, making the adaptations needed for DPR will be very expensive, may involve higher energy use and potentially increased carbon releases (contrary to current goals to reduce carbon emissions). As with all infrastructure projects, it will ultimately be subject to human failure (with associated higher risk to the public), natural disaster, deterioration with age, not to mention unknown environmental side effects of the technology that may be difficult and expensive to address. These documents provided far more detail on the technical toxin removal aspects of DPR, but left the critical and complex health risk analyses to some vague future studies.

Our growing concerns about endocrine disruption impacts, sometimes caused by the chemical soup of unregulated chemicals bought together by wastewater treatment processes, motivate us to keep commenting on this issue. A woman acquaintance from Santa Cruz, Jude Todd PhD, has authorized me to submit her 27-page analysis of the issue, written to address reuse in the Santa Cruz area and attached to this submission. We share many of the same concerns and I am grateful for her input.

Dr. Todd has comprehensively detailed the issues with wastewater reuse and CECs with specific focus on endocrine disruption. (Attachment #1) She also addresses indirect potable reuse on page 13 of her document, expressing significant concerns about the very limited monitoring of only six constituents out of the many thousand toxins of concern. On page 14 she makes the astute observation that,

Generally speaking, regulatory toxicologists are not on the same page with endocrinologists, developmental biologists, molecular biologists, geneticists, epidemiologists, and other independent scientists who understand how endocrine disruptors and other CECs impact living organisms. As Andrea Gore, editor of Endocrinology, puts it, "There are fundamental differences between *regulatory toxicologists and what I refer to as 'people who understand the endocrine science.'" (qtd. in Brown and Grossman 2015)".*

Although her focus is mostly on wastewater irrigation, the issues Dr. Todd delineates in her paper are every bit as important and relevant to DPR, and perhaps even more so. She also provides an extensive list of scientific resources that should be of value to your staff and the Legislature. I urge you to read this important paper. Can you even consider taking steps to put wastewater into the drinking water supply while ignoring the scientific work of so many experts working in the field of endocrine disruption?

Need for full disclosure on extent of effort and potential impacts....

I'm concerned that Water Board staff and their panels have not defined the extent of the problem of endocrine disruption in the report to the Legislature. Perhaps the quote immediately above explains why. In your staff responses to RRWPC comments on the *General Order for Recycled Water Use,* it states on page 30, *"The Science Advisory Panel acknowledged that the science regarding endocrine disrupting chemicals is incomplete, especially regarding mixtures of CECs."*

Rather than acknowledging all the scientific work that has already been done, the Panel mostly ignores the vast amount of research conducted by the many professionals noted above, along with environmental health organizations and publications such as Environmental Health Perspectives, San Francisco Medical Society Journal, Environmental Health News, The Endocrine Society, Environmental Working Group, USGS, and many more noted in our Endocrine Resource List (Attachment #2) in Canada, Europe, and other advanced countries. While the knowledge in this field continues to evolve, and many more scientific breakthroughs will no doubt occur, it is a travesty to pretend that nothing worthy of note has been accomplished as of this time. (Our lists could be much longer; resources provided in this letter are the tip of the ice berg.)

Why is there no mention of Dr. John Peterson Myers (Pete Myers), who for 25 years, along with Theo Colborn, Lou Guillette and numerous others, lead the field of endocrine disruption and its effects on human health and wildlife? Unfortunately, Dr. Colborn died almost two years ago and is greatly missed; but we wonder why has her name or Dr. Myer's never appeared in any of your documents? (We attach an obituary of Theo telling of her accomplishments over 25 years (Attachment #3) and a prestigious National Institute of Environmental Health Sciences, (part of NIH) recent award to Dr. Myers (Attachment #4).)

The work of Pete Myers and Theo Colborn resulted in the book, *Stolen Future* that was published in the mid-90's. Subsequently it triggered the release of hundreds of millions of dollars for endocrine research (especially from NIH) which in turn brought forth much of the progress in this field over the years since. And their names and their work and the studies they generated don't seem to even be worthy of a mention in any of your documents. Why is that? (I again attach my list of references containing these and other quality scientific references. (Attachment #4)

Laura Vandenberg, PhD, who was a lead writer among 12 scientists, including Dr. Colborn and Dr. Myers, had submitted a comment letter on the Recycled Water Policy Amendment stating that there is no safe dose of endocrine disrupting chemicals. She also emphasized that this is not controversial and that The Endocrine Society, with hundreds of member endocrinologists from around the globe, supports this view completely. (Attachment #5) The link to the study, published in March, 2012, and documents about 800 studies on endocrine disruption, is:

- Vandenberg, L.N., et al., *Hormones and endocrine disrupting chemicals: low dose effects and non-monotonic dose responses.* Endocrine Reviews, 2012. **33**(3): p. 378-455, http://www.ncbi.nlm.nih.gov/pubmed/22419778

The Endocrine Disruption Exchange (TEDX) is Dr. Colborn's website and contained a concise one-page fact sheet with the important basics on this topic. I am placing it in the body of this letter because it is so very important to this topic. (Her website also contains a wealth of information that can be easily understood by most.)

Endocrine Disruption Fact Sheet
The Endocrine Disruption Exchange (TEDX): www.endocrinedisruption.org
Nov. 7, 2011

What are endocrine disrupting chemicals?
The endocrine system is involved in every stage of life, including conception, development in the womb and from birth throughout early life, puberty, adulthood and senescence. It does this through control of the other vital systems that orchestrate metabolism, immune function, reproduction, intelligence and behavior, etc.

The endocrine system acts through signaling molecules, including hormones such as estrogens, androgens, thyroid hormones, and insulin, as well as brain neurotransmitters and immune cytokines (which are also hormones) and other signaling molecules in the body.

How are humans exposed to endocrine disrupting chemicals?
We breathe, eat, drink, and touch EDCs every day. Some can be persistent and remain in the environment for centuries and can build up in the body. Other non-persistent EDCs can be so ubiquitous they are found in nearly every human tested. EDCs include components of plastics, pesticides, flame retardants, fragrances and more. They are found in our homes, schools and work places, toys, clothing, cosmetics, sunscreens, electronics, furniture, cleaning products, lawn care products, automobiles, building materials, food, and food packaging.

How do endocrine disrupting chemicals affect our health?
A vast body of scientific literature exists on the health impacts of some EDCs, while for others there is very little research. Laboratory studies and human epidemiological studies confirm that EDCs have a wide array of effects on the body. Effects of EDCs have been found in animals at tissue concentrations below those measured in humans. In the US, the cost of treating health conditions for which EDC exposure is implicated is over $1 trillion a year.

What distinguishes EDCs from other chemicals of concern?
Dose: *a central feature of endocrine disruption is that effects are found using very low chemical concentrations. Effects of EDCs at very low concentrations can be different from effects of the same chemical at higher concentrations.*

Timing: *there are many periods of vulnerability during which exposure to EDCs can be particularly harmful. The most well studied critical periods are prenatal and early postnatal development. Effects of early life exposure may not manifest until much later in life. Effects in one generation may be transmitted to future generations through mechanisms involved in programming gene activity, referred to as epigenetic changes.*

Endocrine disrupting chemicals (EDCs) interfere with hormone signaling in a variety of ways depending on the chemical and the hormone system. Biomonitoring of chemicals in human blood and urine has shown that 100% of the people tested have EDCs in their bodies. EDCs have been implicated in neurological diseases, reproductive disorders, thyroid dysfunction, immune and metabolic disorders and more. ***Traditional approaches to determining safe exposure levels (for example, chemical risk assessments) do not work with EDCs.*** *(emphasis added)*

The low dose problem……

Chemical risk assessment has always assumed that "…*the dose makes the poison.*" Over-simplifed, high doses are considered bad and low doses generally good and toxic risk levels are expected to correspond. But all of that is turned on its head with endocrine disruption. Dr. Pete Myers, along with Wendy Hessler define it well in their article, "*Does the dose make the poison*?" http://www.ourstolenfuture.org/newscience/lowdose/2007/2007-0525nmdrc.html

They explain that sometimes they see effects at low doses that they don't see with large and that is counter intuitive to most scientists conducting risk assessments. The authors express concern that this anomaly sometimes leads to health standards that are too weak.

Dr. Myers explains, "*In standard toxicology, as the dose increases, so does the effect. Conversely as dose decreases, so does its impact. This relationship is called a monotonic dose-response curve because effects are either increasing or decreasing…. Non-monotonic curves, in contrast, change direction. Over part of the curve, response increases with dose, while over another portion it decreases as dose increases…. While toxicologists have traditionally assumed that the dose makes the poison, endocrinologists --scientists who study the action of hormones-- have long known that hormones can have different effects at different doses.*"

Marla Cone, Editor in Chief of Environmental Health News explains the low dose effect this way: http://www.environmentalhealthnews.org/ehs/news/2012/low-doses-big-effects (see article)

With chronic diseases, risk is difficult to define….

Can anyone identify specific cases where wastewater is known to have caused a specific cancer incidence or that of any other chronic disease? The truth is, when it comes to chronic conditions, generally people may suspect a cause, but can seldom definitely and specifically point to the precise time and place an illness was initiated. And perhaps that is why Public Health Departments focus on pathogenic illness and seldom, if ever, address more mysterious, but common problems.

Dr. Todd quotes Linda Birnbaum, toxicologist in charge of the National Toxicology Program and the National Institute of Environmental Health Services that, ***"…an ED is anything that affects the synthesis of a hormone, the breakdown of a hormone or how the hormone functions."*** And then she continues…

"We used to think it had to bind with a hormone receptor but endocrine disruptors can perturb hormone action at other stages in the process" (qtd. in Borrell 2012, emphasis added). Such perturbations in hormone function can have wide-ranging impacts on our bodies. As the Environmental Working Group, an independent health research organization, explains: There is no end to the tricks that endocrine disruptors can play on our bodies: increasing production of certain hormones; decreasing production of others; imitating hormones; turning one hormone

into another; interfering with hormone signaling; telling cells to die prematurely; competing with essential nutrients; binding to essential hormones; accumulating in organs that produce hormones. (Environmental Working Group 2013)

Given this list of ways that EDs can stymie our normal bodily functions, we can begin to see how they can precipitate childhood leukemia and other cancers, allergies, asthma and other respiratory problems, genital malformations in baby boys, early puberty in girls, ADHD, diminished IQ, autism, obesity, diabetes, cardio-pulmonary diseases, immune-system dysfunction, and Parkinsonism; evidence is mounting that endocrine disruptors may also play a role in development of Alzheimer's disease and other mental illnesses."

Finally, April, 2016 issue of *Environmental Health Perspectives,* (#6) Linda S. Birnbaum et.al. state in the article, "Informing 21st Century Risk Assessments with 21st-Century Science, "*The majority of regulatory frameworks guide risk assessment from the perspective of a single chemical or single component of a project formulation and often do not account for multiple chemical exposures and mixtures. Furthermore, most chemical risk assessments of potential human health effects rely on testing in animal models using exposures that are typically higher than those experienced by humans. This testing model requires the assessor to extrapolate to lower doses and across species, and it provides limited consideration of variability within species. All of these factors undermine confidence that current risk assessments are protective of human health, particularly for the most vulnerable individuals, communities, and life stages."*

Conservation slipping as reuse grows extensively….

With all this, we wish to acknowledge the State's legitimate concerns about developing adequate water supplies under all scenarios for the entire state. First and foremost, the emphasis on conservation needs to be continually emphasized. Unfortunately, many California areas have significantly increased water use in the last year after winter rain eased the drought. In our area, water contractors are now up to about half way between 2013 use and 2015 conservation accomplishments. Local contractors are relieved that they can now get more income from water sales and they point to our full three-year reservoir as an adequate supply (Lake Sonoma).

For instance, Sonoma County Water Agency contractors' water sales in July, August, September of 2015 were 9371.1 acre feet, and in 2016, they were 11,204.6 AF. This was almost a 20% increase. In an article entitled *'Weaker water conservation numbers prompt fears that California is going back to its old bad habits'* author Matt Steven (The Times 10-15-16) (Attachment #7) states that, "*Californians' water conservation slipped for the third consecutive month in August, prompting new alarm from regulators about whether relaxed water restrictions may be causing residents to revert to old habits as the state enters its sixth year of severe drought.*" Isn't full time conservation a much cheaper and healthier route to increasing water supplies than encouraging big infrastructure projects that grow old, they fail, and massive pollution results, as is happening now with water pipes leaching lead?

Wouldn't it be cheaper and healthier in the long run to charge much more for water and build less infrastructure (including wastewater treatment plants)? Is it possible that users may come to appreciate it more and treat it with more respect? To constantly advocate for more growth is slow but steady suicide where drinking water is concerned.

While not wanting to explore another issue in greater detail, something must be done about the wanton use of water in many agricultural areas. It is said that 80% of California's water is used by agriculture, yet regulations of that use have been minimal or non-existent. The passage of the new SGMA groundwater law will help, and we hope serious management of our dwindling resource occurs, although we won't hold our breath. What good does it do if we have adequate almonds to eat and no clean or even less clean water to drink? (Calling attention to the crop that it is said uses one gallon per nut to grow.)

Public perception and DPR…

The City of Santa Rosa has changed the name of their Water and Wastewater Utilities Department to *Water Department*, to convey to the public that all water is the same, but the reverse of that famous quote, *"A rose by any other name would smell as sweet…."*, if true, belies their intention.

Some of the State's Advisory Committee meeting notes on this issue expressed a big concern about public perception of DPR. The group spent time focusing on messaging and emphasizing that the wastewater would be *purified* and totally safe to drink. Public opinion consultants were hired and surveys were taken regarding public perception of augmenting water supplies with 'purified' wastewater. When those surveyed were told that it was done in other places and that no one got sick from it, they thought it must be okay. Of course, no one mentioned the difficulties of assessing causes of chronic illnesses and the inability to prove that no one got sick.

It's unclear how one would really determine the complete safety of drinking water that contains treated wastewater, even when highly treated. Of course no scientific studies have been conducted to test cause and effect ratios of toxic exposure in relation to human disease, nor will they be. Reliance on epidemiological studies are the norm where appropriate, but it is unlikely one can be found that replicates the conditions that will be utilized for DPR. Public health departments have great expertise assessing and controlling pathogens, and many precautions have been effectively imposed to prevent many acute diseases and illnesses.

But when it comes to chronic diseases such as cancer, developmental problems such as autism, neurological and reproductive birth defects, and many other health problems that are associated with exposures to endocrine disrupting chemicals, little is known about the exact pathway of disease in terms of lifestyle, toxic exposure, heredity, etc. that lead to initiation of the condition and/or illness, although more and more studies link toxic exposures to these and many other adverse health conditions.

Unregulated toxins are everywhere; they are in our food, our water, our clothing, our furniture and mattresses, our house cleaning and personal care products, our autos, and much more. And those that get washed into the waste stream to our treatment plants are a toxic stew of pharmaceuticals, industrial and combustion by-products, heavy metals, pesticides, and more. But even more than that, not only does a vast array exist in the wastewater collection process, and in our households, but much of it actually accumulates in our bodies, and may or may not trigger a disease process. You see, we all have different vulnerabilities and our stage in life, and our health history may compound the impacts of various exposures.

Environmental Working Group

Recently an article described how clothing particles .... Organophosphate pesticides and PBDE flame retardants, lead and mercury are all found to be prime examples of neuro-developmentally toxic chemicals according to July, 2016 issue of Environmental Health Perspectives Article, *"Project TENDR: Targeting Environmental Neuro-Developmental Risks.* (Attachment #8) *The TENDR Consensus Statement"*. The project was a call to address the role of common exposures to toxic substances. They state, *"The TENDR authors agree that widespread exposures to toxic chemicals in our air, water, food, soil, and consumer products can increase the risks for cognitive, behavioral, or social impairment, as well as specific neurodevelopmental disorders such as autism and attention deficit hyperactivity disorder (ADHD)."*

Further on it states, *"Many toxic chemicals can interfere with healthy brain development, some at extremely low levels of exposure." Critical windows of development have been identified up through puberty whereby, "....toxic chemical exposures may cause lasting harm to the brain that interferes with a child's ability to reach his or her full potential."*

Another issue mentioned was that health studies never look at multiple exposures of toxic substances and in fact, multiple exposures are very common in our everyday life. We seldom use just one chemical to clean our bathrooms, and in fact, almost everything we do on a daily basis brings together multiple toxic exposures at a time. All of these chemicals that end up going down the drain must be 100% removed from the waste stream at all times if they are to merge with the drinking water supply, even non-toxic chemicals which can combine to form toxic substances, if you are to assure the safety of drinking water. Further, it behooves you to assure that all vulnerable populations must be protected before you put the treated wastewater into the drinking water supply.

In the expert panel's Final Report, they state in their recommendations on page 5 of Executive Summary that the Expert Panel, *".... recommends monitoring the literature on potential health risks that could present serious harm to health over short durations of exposure to compounds likely to be present in recycled water. Of specific concern are chemicals that adversely affect the development of fetuses and children....This activity could be initiated concurrently with the development of DPR regulations and continued as an ongoing effort."*

It is a serious concern of ours that rather than talking about the extensive existing literature on the issue, as we have tried to demonstrate in our comments, that they are going to set up a committee to look at it. Why have they not been looking at it before producing this report that substantially fails to define the problem? How can they begin the process of writing DPR regulations before that occurs?

In any case, this effort gives the impression that the State only has a cursory interest in the topic of the impact of chemicals on public health. It does not feel like a serious effort that should move forward. First the information should be gathered, and then the regulations can proceed. Please prioritize the health of Californians before dumping wastewater in the drinking water supply!

Thank you for the opportunity to address this very serious issue.

Sincerely,

Brenda Adelman

ATTACHMENTS:

1. Jude Todd, PhD, *Statement Regarding Use of Recycled Municipal Wastewater in Santa Cruz*, Nov. 18, 2015

2. RRWPC, List of *References on Endocrine Disruption,* Fall, 2014

3. Carol F. Kwiatkowski, et. al., *Twenty-five years of Endocrine Disruption Science: Remembering Theo Colborn*, Environmental Health Perspectives, DOI: 10.1289/EHP746

4. Environmental Health News staff report, *EHN founder honored as environmental health champ*, (re Pete Myers), Oct. 10, 2016

5. Laura Vandenberg, *Comment Letter (to State Water Board)-Amendment to Recycled Water Policy*, June 27, 2012

6. Linda S. Birnbaum, et.al. *Informing 21st- Century Risk Assessments with 21st-Century Science,* Environmental Health Perspectives, April 2016 DOI:10.1289/ehp.1511135

7. Matt Stevens, *Weaker water conservation numbers prompt fears that California is going back to its old bad habits,* LA Times, Oct. 5, 2016

8. Deborah Bennett, PhD, et.al., *Project TENDR: Targeting Environmental Neuro-Developmental Risks. The TENDR Consensus Statement*, Environmental Health Perspectives, July, 2016, DOI:10.1289/EHP358

Statement Regarding Use of Recycled Municipal Wastewater in Santa Cruz

Rev. November 18, 2015 Jude Todd, PhD

I. INTRODUCTION

A. Purpose

Recycled wastewater use is growing rapidly in California and other western states, largely in response to drought-inspired worries about water supply security. Growing concerns about the impacts of wastewater pollution on receiving waters also factor into the water-reuse equation in many communities. This is true in Santa Cruz as we explore ways to fortify our water supply. But important questions need to be carefully considered and satisfactorily answered before adopting any uses of recycled municipal wastewater water here in Santa Cruz, including:

-- What else besides water do the various types of recycled wastewater contain?

-- What are the possible human and environmental health impacts of proposals to use recycled municipal wastewater for food crop irrigation or for potable reuse?

-- How should we go about discerning between safe, beneficial uses of recycled municipal wastewater and those that pose more risks than benefits to environmental and public health?

This statement, endorsed by People Against Unsafe Wastewater Reuse and other community members, aims to provide information for policymakers regarding these challenging questions. After discussing problems posed by contaminants of emerging concern (CECs) in recycled municipal wastewater, it reviews California State regulations and policy regarding recycled wastewater and examines the two categories of uses that seem particularly problematic (food-crop irrigation and potable reuse). It then briefly explores two more general categories (landscape irrigation and commercial/industrial uses) as including promising candidates for safe, appropriate application of recycled municipal wastewater.

B. Scope of Discussion

Recycled municipal wastewater refers to water that is treated and recycled from the sewer system -- not to greywater or other decentralized wastewater recycling systems. Santa Cruz municipal wastewater comes from sinks, tubs, floor drains, showers, and toilets in homes, business and industrial establishments, hospitals (both human and veterinary), and other institutions such as research laboratories, schools (including college and university science labs), assisted-living communities, long-term care facilities, the county jail, and the morgue. The Santa Cruz wastewater treatment plant processes this sewer water from "the City of Santa Cruz and the Santa Cruz County Sanitation District (includes Live Oak, Capitola, Soquel and Aptos)" (City of Santa Cruz 2015).

Recycled municipal wastewater use is divided into four categories:

-- potable reuse (including both indirect potable reuse (IPR) and direct potable reuse (DPR))

-- agricultural irrigation

-- landscape irrigation (e.g., irrigation of parks, playgrounds, golf courses, cemeteries, and other landscapes)

-- commercial and industrial purposes (e.g., flushing commercial toilets, controlling dust on roads or streets, mixing concrete, and many other possible uses).

C. The Precautionary Principle

In all cases, our assessments should be guided by the Precautionary Principle. While there are many versions of the Precautionary Principle, it has three commonly accepted components:

(1) Where there is reliable scientific evidence that a product or practice may cause serious harm to either humans or the environment, the product or practice should not be used unless or until there is proof of its safety.

(2) Those who advocate adopting the product or practice bear the burden of proof to demonstrate that it is safe before it is put on the market or adopted for use. This second component is important because so many products, including those made with endocrine-disrupting chemicals or engineered nanoparticles, have been unleashed into the environment without adequate safety testing, leaving it up to those who are concerned about public and environmental welfare to spend years appealing to the EPA, FDA, or other agencies to appropriately regulate the product.

(3) The Precautionary Principle also requires democratic public participation as well as full transparency on the part of governing agencies regarding scientific evidence that informs a policy decision.

II. CONTAMINANTS OF EMERGING CONCERN (CECs) IN RECYCLED MUNICIPAL WASTEWATER

Use of the Precautionary Principle is important because of increasing scientific evidence of contaminants heretofore unidentified or unregulated in recycled wastewater that pose health concerns. These "contaminants of emerging concern" (CECs) in recycled municipal wastewater include personal care products, household cleaners, pharmaceuticals, industrial and agricultural chemicals, pathogenic agents, engineered nanomaterials, and byproducts of any of the above that are not regulated but that are now known or strongly suspected to cause harm to either humans or wildlife. So, for example, DDT is not a contaminant of emerging concern because we already know that it is toxic. An itemized list of substances that scientific evidence indicates might be harmful in recycled wastewater would be too long to assemble, but characteristics of some types of CECs, including those that can disrupt endocrine systems, are summarized below to provide a brief documentation of the nature of that concern.

A. Number of Synthetic Chemicals

Over 100,000 synthetic chemicals have been registered in the U.S. including "more than 84,000 industrial chemicals, 9,000 food additives, 3,000 cosmetic ingredients, 1,000 pesticide active ingredients, and 3,000 pharmaceutical drugs" (Regional Monitoring 2013:49).[1]

B. Trace Amounts of CECs Remain in Treated Municipal Wastewater

Currently, there is no wastewater treatment train, including those using reverse osmosis, that can remove all contaminants of emerging concern; **trace levels – i.e., amounts in the parts per billion or parts per trillion levels** -- of many CECs, including endocrine disruptors and an array of disinfection byproducts, **remain in the effluent** (Asano et al. 2007:113; see also WEF and AWWA 2008:1-6; Raghav et al. 2013:4,7; Schnoor 2014:12A).

C. Health Impacts of Endocrine Disruptors (EDs)

Our dependence on synthetic chemicals is problematic because, as endocrinologists, developmental biologists, and other independent scientists have shown, many such chemicals -- especially those that disrupt the endocrine systems of humans and other animals – are implicated in the etiology of diseases that now plague people all over the planet. As the term suggests, endocrine disruptors (EDs) can impact all the complex and delicate endocrine systems, including the pituitary gland, hypothalamus, thyroid, cardiovascular system, mammary glands, pancreas, adrenal glands, ovaries, uterus, prostate, and testes, as well as the brain and adipose (fat) tissue (Diamanti-Kandarakis et al. 2009:4). EDs can impact an organism by either mimicking or antagonizing (or sometimes both) the animal's innate hormones, thus binding with hormone receptors. So, e.g., an ED that mimics estrogen can interfere with the functioning of both male and female reproductive organs; an ED that mimics insulin can throw off the delicate balance maintained by the pancreas; an ED that mimics or antagonizes thyroxin can unbalance the thyroid.

But mimicking or antagonizing endogenous hormones[2] is not the only mode of action for EDs. As Linda Birnbaum, the toxicologist who heads up both the National Toxicology Program and the National Institute of Environmental Health Services, explained in a recent interview, **an ED is "anything**

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[1] Fullbrook (2013) estimates the total number of industrial chemicals alone at "143,000, and rising."

[2] "Endogenous hormones" are those produced within an organism. Exogenous hormones are those produced outside the organism itself.

that affects the synthesis of a hormone, the breakdown of a hormone or how the hormone functions. We used to think it had to bind with a hormone receptor but endocrine disruptors can perturb hormone action at other stages in the process" (qtd. in Borrell 2012, emphasis added). Such perturbations in hormone function can have wide-ranging impacts on our bodies. As the Environmental Working Group, an independent health research organization, explains:

> There is no end to the tricks that endocrine disruptors can play on our bodies: increasing production of certain hormones; decreasing production of others; imitating hormones; turning one hormone into another; interfering with hormone signaling; telling cells to die prematurely; competing with essential nutrients; binding to essential hormones; accumulating in organs that produce hormones. (Environmental Working Group 2013)

Given this list of ways that EDs can stymie our normal bodily functions, we can begin to see how they can precipitate childhood leukemia and other cancers, allergies, asthma and other respiratory problems, genital malformations in baby boys, early puberty in girls, ADHD, diminished IQ, autism, obesity, diabetes, cardio-pulmonary diseases, immune-system dysfunction, and Parkinsonism; evidence is mounting that endocrine disruptors may also play a role in development of Alzheimer's disease and other mental illnesses (Alonso-Magdalena 2006; Grandjean et al. 2007; Diamanti-Kandarakis et al. 2009; Birnbaum 2010; Burkardt-Holm 2010; Landrigan 2010; Soto and Sonnenschein 2010; Karoutsou and Polymeris 2012; Sargis et al. 2012; UNEP/WHO 2012; Weiss 2012; Zoeller et al. 2012; Birnbaum 2013; Carpenter 2013; Welshons 2013; Blaszczak-Boxe 2014; Grandjean and Landrigan 2014; Hamblin 2014; Richardson et al. 2014; Schiffer et al. 2014; Abdolmaleky, Zhou, and Thiagalingam 2015; Bellanger et al. 2015; Konkel 2014a,b, 2015; Genuis and Kelln 2015; Gore et al. 2015; Grossman 2015; Legler et al. 2015; Scutti 2015; Trasande et al. 2015).

D. Trace Quantities of Endocrine Disruptors and the Developmental Basis of Disease

Endocrine disruptors in only trace amounts -- the same amounts present in recycled sewer water -- are especially dangerous for fetuses, infants, and small children. As American Water Resources Association researchers David Norris and Alan Vajda write in their article "Endocrine Active Chemicals (EACs) in Wastewater: Effects on Health of Wildlife and Humans," "**...ample evidence of endocrine disruption of reproduction related to nano-quantities (parts per billion and parts per trillion) of human-based xenoestrogens in wastewater effluents appeared in the late 1980s and early 1990s**" (Norris and Vajda 2007:15, emphasis added).[3] Since that time, evidence of the impacts of EDs on health of both wildlife and humans has grown substantially.

Those health impacts are more likely when the organism is exposed to the ED during the early stages of development. Illnesses triggered by chemicals during those vulnerable formative years are often irreversible (Zoeller et al. 2012:4101; UNEP/WHO 2012:12). When present in the body of a pregnant woman, endocrine disruptors can be passed on via the placenta to the fetus and via breast milk to the infant. Maternal transmission of EDs is particularly important because, as explained in the Endocrine Society's comprehensive review and analysis, *Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement,* the age at which one is exposed to these chemicals can make the health impacts more or less significant, and fetal and early postnatal-infant stages are developmental periods when mammals are most vulnerable (Diamanti-Kandarakis et al. 2009). The brain and nervous system, immune system, reproductive system, heart, lungs, and all other crucial organs are being developed at those times; illnesses due to malfunction of those systems and organs that are precipitated during those early months and years may not become apparent until years or even decades later (Diamanti-Kandarakis et al. 2009:3; see also Colborn, vom Saal, and Soto 1993; Colborn 1997, 2004a; Shapley 2009; Burkhardt-Holm 2010; Landrigan and

[3] The analogy commonly used to illustrate one "part per trillion," or one nanogram per liter, is that it is like one drop of water diluted into 20 Olympic-sized swimming pools. "Xenoestrogens" are chemical compounds, such as those in some pesticides, drugs, and industrial products like plasticizers, that mimic estrogen and can thus disrupt the endocrine system.

Goldman 2011; UNEP/WHO 2012; Zoeller et al. 2012; Williams 2013/2014; Braun 2014; Grandjean and Landrigan 2014; Hanson and Gluckman 2014; Haugen et al. 2014; Vaiserman 2014; Whyatt et al. 2014; Di Renzo et al. 2015; Gore et al. 2015; Heindel and Vandenberg 2015).

Among the many scientific articles demonstrating greater susceptibility to endocrine disruptors by fetuses and children is Philip J. Landrigan and Lynn R. Goldman's (2011) study, "Children's Vulnerability to Toxic Chemicals: A Challenge and Opportunity to Strengthen Health and Environmental Policy." Landrigan, a pediatrician and epidemiologist, is dean of global health and a professor of preventive medicine and pediatrics at the Mount Sinai School of Medicine; Goldman is dean of the School of Public Health and professor of environmental and occupational health at George Washington University. Their review article on this topic explains that children are more susceptible than adults to health impairments from chemical exposure for four reasons:

> First, children have greater exposures to toxic chemicals for their body weight than adults. **A six-month-old infant drinks seven times more water per pound than an adult**....Children's hand-to-mouth behavior and play on the ground further magnify their exposures.
>
> Second, children's metabolic pathways are immature, and a child's ability to metabolize toxic chemicals is different from an adult's.... **[Children] lack the enzymes needed to break down and remove toxic chemicals from the body.**
>
> Third, children's early developmental processes are easily disrupted. Rapid, complex, and highly choreographed development takes place in prenatal life and in the first years after birth... In the brain, for example, billions of cells must form, move to their assigned positions, and establish trillions of precise interconnections.... [4] **[Exposures to chemicals during crucial "windows of vulnerability"] can disrupt organ formation and cause lifelong functional impairments....**
>
> Fourth, children have more time than adults to develop chronic diseases. **Many diseases triggered by toxic chemicals, such as cancer and neurodegenerative diseases [including dyslexia, mental retardation, attention deficit hyperactivity disorder [ADHD], and autism],...evolve through multistage, multiyear processes that may be initiated by exposures in infancy [or in utero].** (Landrigan and Goldman 2011:843, emphasis added)

Chemical-induced diseases set in motion during gestation or infancy often do not show up until years or even decades after exposure. **This "long delay between the time point of exposure and measurable effects" makes tracing causative factors for particular instances of cancer, Parkinsonism, Alzheimer's Disease, or other diseases that appear in later years very challenging** (Burkhardt-Holm 2010, emphasis added).

E. Transgenerational Epigenetic Inheritance of Disease

The long delay between exposure to harmful chemicals and their health consequences is turning out to be even longer than once thought. **Research in the last couple of decades has indicated that in some instances harms inflicted by endocrine disruptors and some other chemicals may be passed on to subsequent generations via a process known as transgenerational epigenetic inheritance** (Edwards and Myers 2007; Grandjean et al. 2007; Diamanti-Kandarakis et al. 2009:4,7-8; Burkhardt-Holm 2010:484-487; Birmbaum 2010; Daughton 2010:54-55; Birnbaum and Jung 2011; Francis 2011; Guerrero-Bosagna and Skinner 2012; UNEP/WHO 2012:13; Martin 2013; Hanson and Gluckman 2014; Haugen et al. 2014; Head 2014; Janesick, Shioda, and Blumberg 2014; Tollefsbol 2014; Dietert 2015; Gore et al. 2015; Heindel and Vandenberg 2015; Stel and Legler 2015; Xin, Susiarjoa, and Bartolomeia 2015).

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[4] As Lauren K. Wolff (2014), writing for the *Chemical and Engineering News*, explains, "**Nerve cells** grow and connect, sometimes **forming 40,000 new junctures [synapses] per second, until a baby reaches about two years of age**" (Wolff 2014, emphasis added).

The concept of transgenerational epigenetic inheritance can seem puzzling at first, but it is not as strange as it might initially seem. We are familiar with the "nature vs. nurture" debate, which most scientists readily resolve by saying that health is a result of both nature (our genes) and nurture (factors in our environment). Most people would likely agree that environmental influences (e.g., diet, exercise, exposure to toxic substances) interact with genetics to influence health.[5] The term "epigenetics" refers to those environmental factors – factors outside the genome itself -- that influence gene expression without causing a genetic mutation. Sometimes those environmental factors, particularly exposure to chemicals such as endocrine disruptors, can result in "methylation" of one or more genes, and that, in turn, influences gene expression.[6] Gene methylation is one of several epigenetic mechanisms by which exposure to endocrine disruptors and other chemicals can alter genetic expression, sometimes resulting in disease or diminished capacity.[7]

"Transgenerational epigenetics" – the newer and more surprising concept -- refers to **heritable** changes in gene expression that are **not due to a genetic mutation**. As Jessica Head, with the University of Michigan School of Natural Resources and Environment in Ann Arbor, explains:

> Epigenetics is not a newly discovered phenomenon; we have known about the role of DNA methylation in regulating gene expression for over 35 years.... What is new is our developing epigenetic perspective on how **early life experiences can have lasting impacts on health that may even be inherited by future generations.... With epigenetic modes of action, level of exposure to contaminants, intermediary sub-clinical responses, and the overt toxic response may be temporarily separated throughout an individual's lifetime, or even between generations, a possibility that most risk assessment does not take into account.** (Head 2014:83-84, emphasis added)

Linda Birnbaum, Director of the National Institute of Environmental Health Sciences (NIEHS) and National Toxicology Program, shares Head's concern about the shortfall of risk assessment and outdated toxicological methods in evaluating the ways that endocrine disruptors and other synthetic chemicals can impact health (Birnbaum 2010). Birnbaum and her colleague Paul Jung, chief of staff at NIEHS, explain transgenerational epigenetics as follows:

> ...we're born with our genes, but epigenetic changes occur because of environmental influences during development and throughout life. Epigenetics thus provides a measurable "imprint" on DNA expression that may be useful as a biomarker for disease susceptibility. And these imprints can be carried and expressed across generations. (Birnbaum and Jung 2011:818)

It would thus seem advisable for people considering the possible health impacts of trace amounts of drugs and other chemicals in recycled wastewater to attend to epigenetics, but the topic is rarely addressed in the water-reuse literature.

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[5] Stephen Rappaport and Martyn Smith, with the UC Berkeley School of Public Health, sum up the relative proportion of chronic disease attributable to genes vs. environment as follows: "Although the risks of developing chronic diseases are attributed to both genetic and environmental factors, **70 to 90% of disease risks are probably due to differences in environments**" (Rappoprt and Smith 2012:460, emphasis added).

[6] Methylation is a chemical reaction in which a carbon atom and three hydrogen atoms, known in organic chemistry as a methyl group, attach to a molecule.

[7] Other mechanisms include histone modification, nucleosome repositioning, misregulation of chromatin, and interference in transcription of both microRNA and long non-coding RNA (Dietert 2014:243).

One exception is the comprehensive review study by C. G. Daughton (2010), "Pharmaceutical Ingredients in Drinking Water: Overview of Occurrence and Significance of Human Exposure." Daughton, who is the U.S. EPA Chief of the Environmental Chemistry Branch at the National Exposure Research Laboratory, explains epigenetics as follows:

> Unlike the genome, the epigenome is plastic, dynamic, extraordinarily complex, and varies across tissues and individuals.... **[E]pigenetic alterations can accumulate, resulting in delayed-onset outcomes that can persist long after exposure has ceased – <u>even across several generations</u>.** (Daughton 2010:54, emphasis added)

Daughton also comments on the dearth of attention to the health implications of epigenetics when considering drugs as drinking-water contaminants:

> Given the thousands of publications devoted to APIs [active pharmaceutical ingredients] as environmental pollutants, few address the possible role of epigenetics in human (or even aquatic) health. Epigenetics has been mentioned only in passing in perhaps a dozen or so of the thousands of published works; most of these have been published since 2006. (Daughton 2010:54)

Transgenerational epigenetic effects of trace pharmaceuticals and other chemicals of emerging concern in recycled municipal wastewater should be receiving – but, to date, have not received – serious attention from both the water-reuse industry and its regulators.

F. Nonmonotonicity and Lack of a Threshold Dose

While most synthetic chemicals remaining in the effluent of state-of-the art wastewater treatment plants may be present only in "trace" amounts (parts per billion or parts per trillion), such low doses do not protect people or other animals who drink or bathe in it. As we've seen, chemicals that can disrupt endocrine systems are bioactive in the parts per billion or parts per trillion levels, and in some cases even less (Norris and Vajda 2007:15; Myers and Hessler 2007:3; Vandenberg et al. 2012; Welshons 2013; Cobb 2015). As surprising as this may seem, there is abundant scientific evidence demonstrating that endocrine disruptors can be even more harmful in miniscule amounts than in slightly larger amounts, depending on the target organism and age at time of contact with the chemical; this phenomenon, known as nonmonotonicity, is evidenced by the chemical's nonmonotonic dosage-response curve (Sheehan 2006; Myers and Hessler 2007; Diamanti-Kandarakis et al. 2009:4; Fagin 2012; Schettler et al. 2012; UNEP/WHO 2012:Vandenberg et al. 2012; Welshons 2013; Birnbaum and Jung 2014:816-818; Vandenberg 2014; Gore et al. 2015; Xin, Susiarjoa, and Bartolomeia 2015).

Nonmonotonicity seems counter-intuitive. Traditional toxicologists and the regulators whom they advise tend to operate according to the more "common sense" maxim, coined by Paracelsus, the 16th-century Father of Toxicology, that "The dose makes the poison." However, endocrinologists and other independent scientists in the 20th and 21st centuries have shown that this "common sense" maxim does not always hold true. In their article, "Does 'The Dose Make the Poison?' Extensive Results Challenge a Core Assumption in Toxicology," Myers and Hessler (2007) explain that some chemicals, including endocrine disruptors,

> ...cause different effects at different levels, including impacts at low levels that do not occur at high doses.... **Because all regulatory testing has been designed assuming that 'the dose makes the poison,' it is highly likely to have missed low dose effects, and led to *health standards that are too weak*.** (Myers and Hessler 2007:1, emphasis added)

In fact, there may be no "threshold dose" (an amount below which the chemical causes no harm) for some chemicals, especially for fetuses, infants, and children, as explained in the preceding section (Sheehan

2006; Grandjean et al. 2007; Vandenberg, Zoeller, and Myers 2012; Zoeller 2012; Birnbaum and Jung 2014:817-818; Gore et al. 2015).

Laura Vandenberg, PhD, molecular and developmental biologist with the Division of Environmental Health Sciences, University of Massachusetts, Amhert, and eleven other independent scientists whose research has demonstrated nonmonotonicity conclude their review of the topic with the following assessment:

> We understand that [our findings of nonmonotonic dosage-response curves for endocrine-disrupting chemicals] challenge risk assessment dogma, but **society's tendency to maintain the *status quo* is insufficient as an argument to rebut scientific data**.... [T]here is...much evidence within the field of endocrinology to support the interpretation that low doses exert adverse effects on the human population. **Data must trump theories, hypotheses, models and assumptions, and not the reverse.** (Vandenberg et al. 2012:16, emphasis added)

In other words, ideologies or other cherished beliefs -- whether that belief is that "the dose makes the poison" or that "only genetic information can be passed on to future generations" -- should be trumped by scientific evidence produced by independent researchers, particularly when public health is at stake.

G. Mixture Effects

The numbers of various chemicals in sewer water at any given time that can potentially interact with each other (out of the possible tens of thousands) are incalculable. Moreover, when trace amounts of some of those chemicals are ingested, inhaled, or absorbed through the skin and find their way into our bloodstream and on to our hearts, thyroids, brains, and other endocrine-sensitive glands and organs, they mix with our endogenous hormones and whatever other exogenous chemicals they encounter. What happens when trace amounts of the drugs and other chemicals discharged from hospitals, industries, residences, veterinary clinics, long-term-care facilities, or chem labs combine in our bloodstream? What are the physiological effects of these chemical mixtures?

Insufficient research has been done to address such vexing questions, but the research that has been done demonstrates that chemicals – even those that may pose little or no threat individually – can be more hazardous when mixed with other chemicals (Yang 1994; Biello 2006; Sheehan 2006; Kortenkamp 2007, 2008; Backhaus, Sumpter, and Blanck 2008; Diamanti-Kandarakis et al. 2009; Payne-Sturges et al. 2009; Birnbaum and Jung 2011; UNEP/WHO 2012:15; Haugen et al. 2014; Brown and Grossman 2015). The **effects of mixing several chemicals** that have a similar physiological effect (e.g., estrogenic) can be **additive, antagonistic,** or **synergistic** (Rajapaske, Silva, and Kortenkamp 2002). Andreas Kortenkamp, with the School of Pharmacy at the University of London, has been studying the problem of mixture effects, particularly in estrogenic chemicals, for many years. He explains that, "In toxicology, 'additivity' describes the case in which chemicals 'act together' to produce effects without enhancing or diminishing each other's action..." (Kortenkamp 2007:98). "Synergism" refers to effects greater than additive, while antagonistic effects are those that are less than additive (Kortenkamp 2007:99).

Traditional toxicological methods used to develop "maximum contaminant levels" (MCLs) for regulatory purposes **ignore these mixture effects, relying instead on testing one chemical at a time.** Studying antibiotics in wastewater treatment plants, Sungpyo Kim and Diana S. Aga, chemists at the State University of New York at Buffalo, note:

> Although a few environmental risk assessment studies suggest that the levels of pharmaceuticals in the environment, including antibiotics, are not a major threat to human health...,**the chronic effects of mixtures of these microcontaminants remain unknown. Typical health risk calculations are based on a single drug exposure in a lifetime. The synergistic and antagonistic effects of pharmaceutical mixtures on human[s] and ecology cannot be ruled**

> **out, and need to be addressed in risk assessment.** For instance, it was demonstrated that a mixture of ibuprofen, prozac, and ciprofloxacin produced 10- to 200-fold higher toxicity in plankton, aquatic plants, and fish .... These results imply that a more sophisticated approach for the risk assessment of antibiotics... might be necessary to obtain a more accurate assessment of health and ecological risks associated with antibiotics in the environment. (Kim and Aga 2007:568-570, emphasis added)

Research done by endocrinologists, chemists, and many other independent scientists who have considered this issue indicates the need for "a more sophisticated approach for the risk assessment" not only for drugs but also for personal care products, household chemicals, pesticides, and industrial chemicals that find their way into sewer water, small amounts of which can remain in treatment plants' effluent. The recent review study by Endocrine Society researchers on the dangers and characteristics of endocrine-disrupting chemicals makes several key recommendations for research over the next five years, including "testing mixtures of EDCs [endocrine-disrupting chemicals] based on their structural or activity homology..." rather than just individually (Gore et al. 2015).

H. Drug Metabolites and Transformation Byproducts

Some consumed drugs may pass through our bodies into sewers largely unchanged. For example, "Most antibiotics are poorly metabolized after administration.... Thus, relatively high fractions of the drug are excreted" (Jjemba 2008:172). However, many other drugs create ***metabolic byproducts*** after consumption, further complicating risk assessment of chemicals – and chemical mixtures – in recycled municipal wastewater. For example, the anticonvulsant drug carbamazepine is often found in wastewater treatment plant effluents, though its several metabolites are usually not included in assessments of wastewater plant efficacy. One exception is the study by Miao et al. (2005), which examined wastewater samples for caffeine, carbamazepine, and five of its known 33 metabolites, at least one of which "has been shown to possess similar anti-epileptic properties [to carbamazepine], and it may cause neurotoxic effects" (Miao et al. 2005:7470; see also La Farre et al. 2008). The authors found the treatment process to be effective in removing caffeine but not in removing the carbamazepine metabolites (Miao et al. 2005:7474). This result is significant because **if a treatment plant's efficacy is assessed looking only for the original drug and not its metabolites, then the analysis could overestimate the plant's treatment efficacy.**

Complicating matters further, "some excreted metabolites can also be transformed back into the parent compound" (Jjemba 2008:172; see also Escher and Fenner 2011). A recent study by Qu et al. (2013) on metabolites of the steroid trenbolone indicates that some drugs are transformed into other compounds by light but then revert to the parent drug in darkness. That study, "Product-to-Parent Reversion of Trenbolone: Unrecognized Risks for Endocrine Disruption," found that, while light breaks down trenbolone (TBA) metabolites, the **phototransformation products re-convert to the parent compounds in dark conditions;** this process "results in the enhanced persistence of TBA metabolites via a dynamic exposure regime that defies current fate models and ecotoxicology study designs" (Qu et al. 2013:350). The authors explain the implications:

> This product-to-parent reversion mechanism results in diurnal cycling and substantial regeneration of TBA metabolites at rates that are strongly temperature- and pH-dependent. Photoproducts can also react to produce structural analogs of TBA metabolites. **These reactions also occur in structurally similar steroids, including human pharmaceuticals, which suggests that predictive fate models and regulatory risk assessment paradigms must account for transformation products of high-risk environmental contaminants such as endocrine-disrupting steroids.** (Qu et al. 2013:347, emphasis added)

The ability of some endocrine disruptors' transformation products to revert to the original chemical in darkness has implications for proposals to inject treated wastewater into aquifers. If testing for these revertible chemicals were done only under light conditions, that **could lead to underestimation of the amount of drugs being introduced into aquifers**, which are pretty dark places.

Similar studies need to be undertaken for a wide range of pharmaceuticals that may remain even in trace amounts in recycled municipal wastewater, which contains every type of drug taken by people in the community: statins, beta blockers, antidepressants, radiotherapeutic agents, sedatives, anesthetics, bronchodilators, antibiotics, diuretics, cytotoxic and cytostatic cancer drugs, anti-psychotics, antibiotics, analgesics, narcotics, drugs to facilitate gender changes, drugs to address erectile dysfunction, "recreational" drugs, etc. Some research has been done on transformation byproducts of X-ray contrast media (Schulz et al. 2008; Kormos, Schultz, and Ternes 2011). Chemotherapeutic cancer drugs have also received some attention (Kosjek and Heath 2011; Zhang et al. 2013).

Other chemicals besides drugs also undergo changes during wastewater treatment (Cwiertny et al. 2014; Ortiz de Garcia et al. 2014; Evgenidou, Konstantinou, and Lambropoulou 2015). While not much is known about the fate of chemical transformation byproducts in wastewater treatment plants, enough is known to conclude that this phenomenon contributes to the problem of mixture effects discussed in Section G above. But this area of metabolites and transformation byproducts needs much more research – and much more attention from the water-reuse industry and the agencies that regulate it.

I. Engineered Nanoparticles

Unimaginable numbers of engineered nanoparticles, particles with at least one dimension smaller than 100 nanometers, are present in our sewer water. Without regulation by the EPA or any other regulatory agency, the use of nanoparticles – especially the antibiotic nanosilver -- has spread widely and rapidly. Engineered nanoparticles are now used in some personal care products (e.g., toothpaste, sunscreens, baby wipes), clothing (e.g., socks, shoe insoles, underwear), kitchen utensils (e.g., knives, cutting boards, ceramic-coated pots and pans), and other products. When those products are washed, nanoparticles can get flushed down drains into sewers. Nanoparticles are also used in drugs and even in diet drinks, allowing them to be excreted into sewers (Reed et al. 2014).

Furthermore, some washing machines use nanosilver to eliminate mold. One such washer, made by Samsung, releases 100 quadrillion silver nanoparticles (that's 100,000,000,000,000,000 of them) into sewers with each wash (Feder 2007).

Engineered nanoparticles, another contaminant of emerging concern, pose a problem for potable reuse of sewer water because they **are potentially harmful to humans** (Gwinn and Vallyathan 2006; Birnbaum and Jung 2011; Abbott Chalew and Schwab 2013), and **their presence in the effluent of wastewater treatment plants has not been adequately studied.** Consequently, we do not know the extent to which various treatment trains remove nanoparticles. As R. Rhodes Trussell et al. (2013) write in *Potable Reuse: State of the Science Report and Equivalency Criteria for Treatment Trains*, "only a limited number of studies have been performed in this research area, but the preliminary data indicate that this may be an important issue to consider in potable reuse applications" (39). Trussell and colleagues express concern about the type of washing machine discussed above, as well as other sources of nanoparticles in sewer water, and they acknowledge the "potential for nanoparticles to persist through [advanced wastewater treatment] trains" (39). They conclude that "There is currently little evidence to determine whether nanoparticles pose a significant public health threat in potable reuse applications. The reuse community would be wise to keep a watchful eye on this issue in the future" (Trussell et al. (2013:39).

Bottom line: Given the inadequate study of the health effects of drinking and bathing with recycled municipal wastewater that may contain unknown numbers of nanoparticles, EDs, and other CECs; studies that suggest harmful effects of many CECs on human health; and the absence of evidence that any wastewater treatment train can effectively remove these contaminants to levels that are safe for fetuses, infants, and children,[8] the Precautionary Principle requires that we in Santa Cruz not use recycled municipal wastewater for drinking or bathing.

III. STATE REGULATIONS AND POLICY REGARDING RECYCLED WASTEWATER

Given the known presence of trace amounts of chemical contaminants in even the most advanced municipal wastewater treatment systems as discussed above and the scientific evidence of potentially serious health impacts, how is it possible that the State permits potable reuse of such water? And how is it possible that less thoroughly treated sewer water can be used to irrigate food crops, including organic produce? As briefly explained below, the State overlooked sound scientific evidence when they wrote Title 22 regulations for non-potable reuse and again when they formulated the 2013 *Recycled Water Policy*, which addresses indirect potable reuse (IPR) via aquifer recharge. This section also explains why Governor Brown's efforts to fast-track regulations for direct potable reuse (DPR) appear likely to repeat the State's history of ignoring important scientific evidence regarding the potential health effects of emerging contaminants in recycled municipal wastewater.

A. Title 22 Regulation of Recycled Wastewater for Food-Crop Irrigation

There are no federal regulations of recycled municipal wastewater. That task is left up to the states. Here, non-potable uses of recycled sewer water are governed by "Title 22: California Recycling Criteria." Title 22 governs irrigation for all agricultural purposes, including ornamental plants, pasture for milk animals, fodder and fiber crops for animals, etc. This paper focuses on the portions of Title 22 that regulate food-crop irrigation.

Title 22 permits irrigating food crops, including organic crops, with either secondary- or tertiary-treated recycled wastewater, depending upon the type of crop and the method of irrigation. However, **the Precautionary Principle rules out irrigating food crops with recycled sewer water for the following reasons:**

1. Uptake of Chemicals

Both secondary- and tertiary-treated wastewater contain small amounts of synthetic chemicals, including endocrine disruptors. It is well known that plants can and do take various synthetic chemicals up into their roots, stems, leaves, and fruits (Schneider 2008; Calderón-Preciado, Matamoros, and Bayona 2011; Malchi et al. 2014). When children and adults, including pregnant women, eat the plants, they would also ingest small amounts of these potentially harmful chemicals. As noted above, endocrine disruptors are especially hazardous for fetuses, infants, and children. Such risk of serious harm to future generations is unacceptable; instead, farmers could use drip irrigation and employ other conservation methods, including considering crop choices that make sense in a drought-prone region.

2. Engineered Nanoparticles

Both secondary- and tertiary-treated wastewater would also likely contain high quantities of engineered nanoparticles, including antimicrobials such as nanosilver, which is known to harm soil

[8] This caution also applies regarding members of other "sensitive populations" not addressed here, including adolescents, the elderly, people who are chemically sensitive, and people in ill health.

organisms and suspected of causing health problems for higher animals, including humans (Navarro et al. 2008; Gajjar et al. 2009; Birnbaum and Jung 2011; Abbot Chalew and Schwab 2013).

3. Antibiotic Resistance Genes

It is well known that antibiotic-resistant bacteria (ARB), such as methicillin-resistant *Staphylococcus aureus* (MRSA) -- which alone kills about 19,000 people in the U.S. annually – are on the rise and pose a serious health threat, particularly in hospitals (Krasner et al. 2006). Such dangerous bacteria are killed by disinfectants, including those used in hospitals and homes as well as chlorine and all other types of wastewater disinfection. Disinfection of recycled sewer water is, of course, essential. However, researchers have now demonstrated that killing the ARB permits the bacteria's antibiotic-resistance genes (ARGs) to be released into the wastewater. By a process known as ***horizontal gene transfer***, these ARGs can be taken up by other living bacteria, causing those bacteria to become antibiotic resistant (Jjemba 2008:171-179; Dodd 2012; McKinney and Pruden 2012; Fahrenfeld et al. 2013; Fatta-Kasinos and Michael 2013; Pruden et al. 2013; Hong et al. 2014; Mole 2014). Consequently, wastewater disinfection, which leads to production of "approximately 600-700" chemical byproducts (Krasner et al. 2006), also contributes to the spread of antibiotic resistance. As medical geo-hydrologist Edo McGowan, M.D., explains, "Pathogens that in nature might never get together for gene exchange are thrust into each other in a sewer plant" (McGowan, posted in Olena 2013).

In his December 2010 comments to the SWRCB regarding CEC monitoring for recycled wastewater, McGowan explains at length how horizontal transfer of ARGs into the human intestine can result in development of antibiotic resistance, why this is dangerous, and why the source of the problem would be untraceable (California State Water Recourses Control Board 2011).

4. Title 22 Regulations of Non-Potable Reuse Ignore Important Scientific Evidence

How is it possible that food-crop irrigation is this fraught with problems? One might assume that California regulations would be sufficiently protective. However, those regulations do not take into account scientific evidence available at the time.

In the year 2000, when the Title 22 regulations of recycled wastewater were put in place, synthetic chemicals were disregarded, even though prior to that year, there was already reliable scientific evidence that endocrine disruptors (EDs) can harm wildlife and can lead to an array of serious illnesses in humans, including infertility, genital abnormalities, breast cancer, and other health problems, as discussed above (Colborn, vom Saal, and Soto 1993; Jobling 1996; Sharpe et al. 1996; Kelce and Wilson 1997; Daugton and Ternes 1999).

As noted earlier, Norris and Vajda (2007) have pointed out that there was already "ample evidence of endocrine disruption of reproduction related to nano-quantities (parts per billion and parts per trillion) of human-based xenoextrogens in wastewater effluents... in the late 1980s and early 1990s" (Norris and Vajda 2007:15, emphasis added). A study by Bitman and Cecil (1970) on polychlorinated biphenols and chemicals like DDT demonstrated estrogenic activity even three decades prior to enactment of Title 22's regulations of recycled wastewater.

Although Title 22 permits use of recycled wastewater on food crops, prior to enactment of the recycled wastewater regulation, it was already known that plants can take synthetic chemicals up into their roots, stems, leaves, and fruits (Briggs, Bromilow, and Evans 1982; Ryan et al. 1988; Hsu, Marxmiller, and Yang 1990; Paterson et al. 1990; Simonich and Hites 1995; Sicbaldi et al. 1997; Burken and Schnoor 1998; Wilson 1998).

The fact that chemical mixtures can have additive, antagonistic, or synergistic effects, as discussed earlier, was also known prior to enactment of recycled wastewater regulations in Title 22 -- even as early as 1939 (Bliss 1939; Calabrese 1991; Yang 1994).

Even the fact that some endocrine disruptors have nonmonotonic dosage-response curves was also recognized prior to enactment of the Title 22 regulations of recycled wastewater (Mehendale 1994; Svendsgaard and Hertzbert 1994; vom Sal and Sheehan 1998; Nawaz et al. 1999).

Bottom line: California Title 22 regulations for non-potable reuse of recycled wastewater are inadequate to protect the health of both humans and other organisms because regulators ignored sound science that warned about health impacts of endocrine disruptors and other contaminants of emerging concern. The potential for irrigation with treated wastewater to spread antibiotic resistance has come to light more recently, as have problems with nanoparticles, adding to the concerns about this practice, especially in irrigation of food crops.

B. Recycled Municipal Wastewater for Potable Reuse

Potable reuse of wastewater is divided into two types: indirect and direct. While exact definitions vary, currently in California, **indirect potable reuse (IPR)** refers to treated municipal wastewater that is sent to an aquifer, either by direct injection or by surface spreading.[9] The recycled wastewater gradually mixes with the rest of the water in the aquifer; it is subsequently drawn out and processed in the drinking-water treatment plant before being sent to people's taps. **Direct potable reuse (DPR)**, which is not yet permitted in California, refers to treated wastewater that is sent from an advanced wastewater treatment facility directly to either the municipal water treatment plant (where it undergoes the usual treatment for drinking water) or directly into the distribution system that supplies tap water. In either scenario, DPR differs from IPR in that there is no intermediate step where the treated water is first put into an aquifer.

There are no federal regulations of recycled municipal wastewater for potable reuse. However, drinking water is federally regulated via the Safe Drinking Water Act. The State of California has somewhat stricter drinking-water standards than the federal government requires. The combined Federal and State regulation of potable reuse are inadequate to protect public health. The number of synthetic chemicals regulated under the Federal Safe Drinking Water Act plus those added to the list by the California EPA add up to just 60, plus an additional 11 disinfection byproducts (California Department of Health 2014). That still leaves more than 100,000 other man-made chemicals unregulated, and thus largely untested, in drinking-water treatment plants.[10] **Thus, when recycled wastewater advocates assert that a treatment plant's effluent "meets or exceeds" all Federal and State drinking-water requirements, the claim may sound reassuring, but it is hollow.**

C. State Policy Regarding Indirect Potable Reuse

Thirteen years after the Title 22 regulations of non-potable reuse were enacted, the State Water Resources Control Board (SWRCB) published its ***Policy for Water Quality Control for Recycled Water***

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[9] At this time, the State has no regulations for IPR involving a reservoir rather than an aquifer, although the City of San Diego was permitted by the CDPH to test this alternative in a demonstration plant using microfiltration, RO, UV, and hydrogen peroxide (Gerrity et al. 2013:332). Regulations for reservoir augmentation with treated municipal wastewater may be developed pending the 2016 recommendations of an expert panel (California State Water Resources Control Board 2014).

[10] EPA and other government agencies have some programs for occasional additional testing of drinking water and sources for some other contaminants such as EPA's Contaminant Candidate List Program http://www2.epa.gov/ccl/basic-information-ccl-and-regulatory-determination and the USDA Pesticide Data Program, which studied the Santa Cruz municipal water system in 2012-2013.

(Recycled Water Policy), 2013. This policy, intended to "streamline" the permitting process for non-potable uses as well as for indirect potable reuse (IPR), purports to address the contamination of recycled wastewater by CECs. However, this 2013 policy, like the Title 22 regulations before it, fails to adequately protect environmental and public health.

In spite of scientific evidence of potential harms to humans and other organisms posed by CECs, the 2013 *Recycled Water Policy* permits recycled wastewater for indirect potable reuse with minimal monitoring of CECs to indicate treatment-plant efficacy. That policy requires monitoring **only eight chemicals out of the tens of thousands** of the drugs, personal care products, food additives, pesticides, industrial chemicals, disinfection byproducts, and household chemicals that may be present in tertiary-treated wastewater used to replenish aquifers by surface spreading. For direct injection of advance-treated wastewater into aquifers using reverse osmosis, **only six** of those chemicals must be monitored.

Like the Title 22 regulations described earlier, this 2013 policy still relies on **traditional approaches to toxicology:** test one chemical at a time on lab animals, looking for <u>acute</u> toxic reactions, then reduce the dosage downward with each round of testing to the point where the "no observable adverse effect level" (NOAEL) is found; then extrapolate from those animal studies, using "uncertainty factors," to determine the "safe" dosage for humans.

-- This **traditional toxicological** approach:

-- **ignores additive, antagonistic, and synergistic mixture effects;**

-- **ignores epigenetic transgenerational inheritance**;

-- **ignores nonmonotonic dose-response curves**;

-- **ignores** the corollary **that there often is <u>no threshold dose for EDs and some other chemicals</u>**;

-- **ignores scientists' warnings that ingesting <u>trace amounts (parts per trillion or even less)</u> of EDs and other CECs can have serious health consequences, <u>especially for fetuses, infants, and children</u>.**

This neglect of substantial bodies of scientific evidence regarding the characteristics and potential health impacts of endocrine disruptors and other CECs raises the question: Why would the State set aside scientific evidence in formulating the 2013 *Recycled Water Policy*?

Generally speaking, regulatory toxicologists are not on the same page with endocrinologists, developmental biologists, molecular biologists, geneticists, epidemiologists, and other independent scientists who understand how endocrine disruptors and other CECs impact living organisms. As Andrea Gore, editor of *Endocrinology*, puts it, "There are fundamental differences between regulatory toxicologists and what I refer to as 'people who understand the endocrine science.'" (qtd. in Brown and Grossman 2015).

Sometimes there are also **conflicts of interest** at play. In the case of the *2013 Recycled Water Policy*, the California State Water Resources Control Board gave too much credence to the report of six "blue ribbon" panelists who were appointed in 2009 by the Southern California Coastal Water Research Project to advise the SWRCB on how to address CECs in recycled wastewater (Anderson et al. 2010). The only expert in human toxicology on that panel, Paul Anderson, a traditional toxicologist, had co-authored at least three industry-funded, industry-informed studies concluding that there are no health concerns from pharmaceuticals in drinking water (Schwab et al. 2005; Hannah et al. 2009; Caldwell et al. 2010). At the time of his appointment to the "blue ribbon" panel, Anderson was also employed by ARCADIS U.S., a southern-California company that sells water-reuse services and technologies (ARCADIS U.S. 2014). This apparent **conflict of interest** was overlooked by the SWRCB.

The "blue ribbon" panel's guidelines recommend monitoring just eight indicator chemicals for tertiary-treated recycled wastewater that would be surface-spread to replenish aquifers. Those eight indicators for monitoring chemicals in wastewater used in surface application for groundwater recharge are N-nitrosodimethylalamine (NDMA, a disinfection byproduct), 17beta-estradiol, caffeine, triclosan, DEET, gemfibrozil, iopromide, and sucralose (Anderson et al. 2010:66). For advance-treated wastewater directly injected into aquifers, the two pharmaceuticals, gemfibrozil and iopromide, were removed from the list of indicator chemicals, leaving only six indicators for subsurface injection of treated sewer water into aquifers.

Prior to the State's acceptance of the expert panel's recommendations, the list of indicators was questioned by Dr. Andrew Eaton, Technical Director of MWH Laboratories in Monrovia, California, which specializes in testing for CECs in water (Eaton 2010). In his comments for the public hearing on the topic held December 15, 2010, Eaton notes that caffeine "is detected in only about 50% of effluent samples ... and is subject to extensive biodegradation," so it is "potentially a poor indicator" (Eaton 2010). Similarly, because gemfibrozil only turns up in about 40% of the effluents, "using this compound as an indicator of treatment performance would run the risk of measuring a compound that was frequently not present at all..." (Eaton 2010). Eaton also lists iopromide as a poor indicator because "it is not commonly used as an X-ray contrast medium. Instead iohexol ... occurs much more frequently and at higher concentrations" (Eaton 2010). In each instance, **using the indicator chemicals recommended by Anderson et al. (2010) could lead to false-negative conclusions about the existence of CECs in a treatment plant's effluent.** Given that Eaton's lab is "the largest in the U.S. that is focused solely on water analysis, specifically CECs in water" (Eaton 2010), his comments regarding the panel's choice of indicators suggest that their research into that topic may not have been sufficiently careful.[11]

The SWRCB set aside Eaton's comments on the choice of indicator chemicals, McGowan's warnings about antibiotic resistance genes, and other letters raising scientifically grounded concerns with the "blue ribbon" panel's recommendations. The SWRCB adopted the panel's recommendations into the 2013 *Recycled Water Policy.*

D. The Next Wave: Direct Potable Reuse (DPR)

Governor Brown's intent to use ever more recycled wastewater prompted a provision in SB 322 to form another expert panel to advise the CA Department of Public Health (CDPH)[12] on developing guidelines for both indirect and direct potable reuse (DPR). The charge to this new expert panel was described on the SWRCB website, as of February 23, 2015, as follows:

1. Assess what, if any, additional areas of research are needed to be able to establish uniform water recycling criteria for direct potable reuse;
2. Advise on public health issues and scientific and technical matters regarding development of uniform water recycling criteria for indirect potable reuse through surface water augmentation; and
3. Advise on public health issues and scientific and technical matters regarding the feasibility of developing uniform water recycling criteria for direct potable reuse. (California State Water Resources Control Board 2015)

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[11] See also Eaton's more recent co-authored studies, "The List of Lists – Are We Measuring the Best PPCPs for Detecting Wastewater Impact on a Receiving Water?" (Eaton and Haghani 2012) and "How Reliable Is the Recycled Water Monitoring List?" (Eaton and Wilson 2013). Those publications **recommend that a very different and much longer list of indicators be used instead of those few identified in the SWRCB's *Recycled Water Policy.***

[12] On July 1, 2014, the Drinking Water Program transferred from CDPH to the State Water Resources Control Board (http://www.waterboards.ca.gov/drinking_water/programs/DW_PreJuly2014.shtml Accessed January 15, 2015). The wording of the expert panel's charge was edited to reflect that change.

Given that two of the three tasks include offering advice regarding "public health issues," one might expect the panel to include several experts in public health, such as people with advanced degrees in that field, endocrinologists, developmental biologists, epidemiologists, and others who understand the potential health impacts of contact with the EDs and other CECs remaining in trace levels in potable-reuse wastewater. Such is not the case. About half of the panelists are engineers. There is only one epidemiologist (Tim Wade). While another panelist, Joan Rose, has much-needed expertise in water pathogens, she is not an expert in chemical contaminants. **Absent from the panel are endocrinologists and other independent scientists with expertise in the public-health implications of EDs' nonmonotonic dose-response curves, likely absence of a threshold dose, or the transgenerational epigenetic consequences of early-life exposure to pesticides, pharmaceuticals, unregulated industrial chemicals, and other contaminants.**

On the contrary, the panel includes Richard Bull, of MoBull Consulting, who, with James Crook (fellow panelist) and two others, wrote an extensive defense of using "therapeutic dose" as the point of departure for determining safe levels of drugs in drinking water (Bull et al. 2010). Bull and Crook argue that risk assessors should use the dose of a drug intended for a patient who needs that drug as the basis for calculating the amount of that drug that would be safe for members of the public to consume in drinking water.[13] Subsequently, Bull, Crook, and the same colleagues authored *Health Effects Concerns of Water Reuse with Research Recommendations,* published by the WateReuse Foundation (Cotruvo et al. 2012). In both publications, they write: "it is difficult to articulate a [human]-health-based concern that would even require municipal wastewater to be treated to remove drugs" (Bull et al. 2010:16; Cotruvo et al. 2012:xx). Crook and Bull's statement might baffle endocrinologists and other independent scientists familiar with the ways EDs impact health. But endocrinologists and other scientists with expertise to challenge Crook and Bull's views are not on the State's panel charged with evaluating potable reuse.

In their more recent monograph, Crook, Bull, and colleagues describe "the very low concentrations of" pharmaceuticals and personal care products (PPCPs) in recycled municipal wastewater as follows:

> These chemicals do not necessarily pose a significant health hazard at concentrations found in [recycled] drinking water, but they serve as reminders of where the water comes from.... [Therefore] the issue **may not be a need for health research, but a need for the regulatory agency to make a formal judgment** on whether the levels even approach those at which adverse health effects would be expected with an adequate margin of safety. (Cotruvo et al. 2012:7, emphasis added)

Crook and Bull's statement implies that a regulatory agency simply needs to *write* that the water "is safe," and it shall be so. Bizarre as that idea sounds, that same approach – determine that a recycled-wastewater process "is safe" by fiat rather than by unbiased scientific investigation – would not be new, since it was used for the State's Title 22 regulations of non-potable recycled wastewater and for the 2013 *Recycled Water Policy.*

Since **both Crook and Bull are on the panel that will recommend the new (2016) State policy regarding both IPR and DPR** – in fact, **Crook is now the panel's co-chair** -- it appears that wastewater-reuse regulators may again ignore the warnings of many members of the Endocrine Society and other prominent scientists whose work demonstrates that even trace amounts – the amounts of some

[13] Using therapeutic dose as the point of departure for determining safe daily consumption levels for people who do not need those drugs flies in the face of all the evidence regarding characteristics of EDs discussed in this paper. For a critique of the many questionable assumptions inherent in this practice, see C. G. Daughton (2010:49-51).

CECs found in advance-treated municipal wastewater -- of drugs, cosmetics, pesticides, plasticizers, and other EDs can have serious, long-term health effects, especially for fetuses, infants, and children.

Bottom line: Unless and until there is much more rigorous, science-based regulation of contaminants of emerging concern in recycled wastewater destined for potable reuse, whether as IPR or DPR, we cannot rely on either Federal or State regulations to protect people who would be drinking and bathing in it.

IV. OTHER USES FOR RECYCLED MUNICIPAL WASTEWATER

Although reliable scientific evidence indicates that using recycled municipal wastewater for food-crop irrigation or for drinking is not worth the health risks, there are other possible uses of this water that may not pose undue risk to humans or other organisms. This section looks very briefly at some examples of reuse in landscape irrigation and for commercial or industrial purposes.

A. Landscape Irrigation

Each proposal for using recycled sewer water for landscape irrigation should be carefully studied in light of the Precautionary Principle. In each case, possible impacts on the health of humans, other animals, plants, insects, and soil microorganisms should be considered, along with any pertinent issues relating to run-off or penetration of the effluent into aquifers. **In light of the heightened vulnerability of fetuses, infants, and children to endocrine disruptors and other contaminants of emerging concern, particular attention should be given to potential exposure of children and pregnant women to recycled municipal wastewater.** Accordingly, although specific conclusions about the advisability of any particular application would depend on information about the treatment train, the effluent quality, the irrigation site, and other parameters of application, it seems likely that irrigation of freeway landscaping might be a more appropriate use of recycled wastewater than would irrigation of children's playgrounds. Applying the Precautionary Principle and studying specific features of each proposal on a case-by-case basis is a sensible way to proceed.

B. Commercial and Industrial Uses

Other possible uses for recycled sewer water include flushing commercial toilets, mixing concrete, fire-fighting, settling road dust, etc. To briefly explore a few examples: Assuming proper protection of workers and others who might potentially contact the recycled wastewater were put in place, it seems that using recycled wastewater to flush sanitary sewers would be a good application, and using it to flush commercial toilets and mix concrete might also be promising candidates for using recycled sewer water. However, using it to settle dust on roads or streets might be more problematic (depending on the setting) due to contaminant accumulation and potential runoff into a sensitive stream or other habitat. Particularly in populated areas, the nanoparticles, antibiotic resistance genes, and some chemical contaminants could also become a future airborne health threat if the dust were not adequately controlled. However, these hypothetical scenarios are just general sketches, and decisions would need to be made in light of the Precautionary Principle and factors specific to each proposal.

V. CONCLUSION

To summarize: Given that current wastewater treatment technology leaves trace amounts of endocrine disruptors and other contaminants of emerging concern in the effluent; that some of those trace contaminants are now recognized as especially hazardous for fetuses, infants, and children; that existing regulations fail to adequately protect public health from such contaminants; and that using recycled municipal wastewater for either food-crop irrigation or for drinking is not aligned with the Precautionary

Principle, both of those ways of using recycled sewer water should be avoided. For all other purposes, including landscape irrigation and commercial/industrial uses, policymakers should apply the Precautionary Principle to each proposal on a case-by-case basis, taking into account the specific parameters of the proposed application.

There are alternatives: There are viable alternatives that our local policymaking bodies have an obligation to pursue before resorting to recycled municipal wastewater for drinking or other contact uses. Currently, the most important example is that instead of potable reuse of recycled municipal wastewater, Santa Cruz should adopt the Water Supply Advisory Committee's recommendations. These include (1) conservation strategies that aim for 200-250 million gallons per year reduction in projected demand by 2035, (2) water transfers among neighboring districts using treated surplus river water (conjunctive use, or in-lieu recharge), and (3) using treated surplus river water for aquifer storage and recovery via injection wells. These approaches would not only require far less energy than would potable reuse, but they would also expose the community to far fewer endocrine-disrupting chemicals and other contaminants of emerging concern.

The big picture: Toxic chemicals are ubiquitous in contemporary environments. Drinking clean water is one of the few ways our bodies have to eliminate such chemicals once ingested, so increasing both the *numbers* of different chemicals and the *quantities* of them in our diets by regularly bathing in and consuming recycled wastewater is a step in the wrong direction. Instead, we should be working to reduce both the numbers and amounts of man-made chemicals in our homes and in the environment.

VI. REFERENCES

Abbott Chalew, Talia E. and Kellogg J. Schwab. (2013) Toxicity of Commercially Available Engineered Nanoparticles to Caco-2 and SW 480 Human Intestinal Epithelial Cells. *Cell Biology and Toxicology*. 29:101-116.

Abdolmaleky, Hamid Mostafavi, Jin-Rong Zhou, and Sam Thiagalingam. (2015) An Update on the Epigenetics of Psychotic Diseases and Autism. *Epigenomics*. 7(3):427–449.

Alonso-Magdalena, Paloma et al. (2006) The Estrogenic Effect of Bisphenol A Disrupts Pancreatic β-Cell Function In Vivo and Induces Insulin Resistance. *Environmental Health Perspectives*. 114(1):106-112.

Anderson, Paul et al. (2010) *Monitoring Strategies for Chemicals of Emerging Concern (CECs) in Recycled Water: Recommendations of a Science Advisory Panel, Final Report.* Sacramento: California State Water Resources Control Board.

ARCADIS U.S. website. (2014) http://wwww.arcadis-us.com/Water_Reuse.aspx and http://www.arcadis-us.com/Services_Drinking_Water.aspx Both accessed February 6, 2014.

Asano, Takashi et al. (2007) *Water Reuse: Issues, Technologies, and Applications.* NY: McGraw Hill.

Backhaus, T., J. Sumpter, and H. Blanck. (2008) On the Ecotoxicology of Pharmaceutical Mixtures. Chapter 16 in *Pharmaceuticals in the Environment: Sources, Fate, Effects, and Risks*. 3rd ed. Ed. by Klaus Kummerer. NY: Springer.

Bellanger, Martine et al. (2015) Neurobehavioral Deficits, Diseases and Associated Costs of Exposure to Endocrine Disrupting Chemicals in the European Union. *Journal of Clinical Endocrinology and Metabolism*. Early release; accepted March 1. 1-12.

Biello, David. (2006) Mixing It Up: Harmless Levels of Chemicals Prove Toxic Together. *Scientific American.* May 10. http://www.scientificamerican.com/article.cfm?id=mixing-it-up Accessed January 3, 2014.

Birnbaum, Linda S. (2010) *Statement on the Environment and Human Health: The Role of HHS*, before the Committee on Energy and Commerce, Subcommittee on Health, U.S. House of Representatives. April 22.

__________. (2012) Environmental Chemicals: Evaluating Low-Dose Effects. *Environmental Health Perspectives*. April. 120(4):a143–a144.

__________. (2013) State of the Science of Endocrine Disruptors. *Environmental Health Perspectives*. April. 121(4):A107.

Birnbaum, Linda S. and Paul Jung. (2011) From Endocrine Disruptors to Nanomaterials: Advancing Our Understanding of Environmental Health to Protect Public Health. *Health Affairs*. May. 30(5):814-822.

Bitman, Joel and Helene C. Cecil. (1970) Estrogenic Activity of DDT Analogs and Polychlorinated Biphenols. *Journal of Agriculture and Food Chemistry*. 18(6):1108-1112.

Blaszczak-Boxe, Agata. (2014) Prenatal Exposure to Common Chemicals Linked to Lower IQ in Kids. *Live Science*. December 10. http://www.livescience.com/49087-phthalates-exposure-lower-iq-kids.html Accessed December 11, 2014.

Bliss, C. I. (1939) The Toxicity of Poisons Applied Jointly. *Annals of Applied Biology*. August. 26(3):585-615.

Borell, Brendan. (2012) Chemical "Soup" Clouds Connection between Toxins and Poor Health. *Nature*. November 23. http://www.nature.com/news/chemical-soup-clouds-connection-between-toxins-and-poor-health-1.11881 Accessed March 8, 2014.

Braun, JM et al. (2014) Gestational Exposure to Endocrine-Disrupting Chemicals and Reciprocal Social, Repetitive, and Stereotypic Behaviors in 4- and 5-Year-Old Children: The HOME Study. *Environmental Health Perspectives*. March 12. http://ehp.niehs.nih.gov/1307261/ Accessed March 20, 2014.

Briggs, G. G., R. H. Bromilow, and A. A. Evans. (1982) Relationships between Lipophilicity and Root Uptake and Translocation of Non-Ionised Chemicals by Barley. *Pesticide Science*. 13(5):495-504.

Brown, Valerie and Elizabeth Grossman. (2015) Why the United States Leaves Deadly Chemicals on the Market. *In These Times*. November 2.
http://inthesetimes.com/article/18504/epa_government_scientists_and_chemical_industry_links_influence_regulations Accessed November 16, 2015.

Bull, Richard J. et al. (2011) Therapeutic Dose as the Point of Departure in Assessing Potential Health Hazards from Drugs in Drinking Water and Recycled Municipal Water. *Regulatory Toxicology and Pharmacology*. 60:1-19.

Burken, J. G. and J. L. Schnoor. (1998) Predictive Relationships for Uptake of Organic Contaminants by Hybrid Poplar Trees. *Environmental Science and Technology*. 32:3379-3385.

Burkhardt-Holm, Patricia. (2010) Endocrine Disruptors and Water Quality: A State-of-the-Art Review. *Water Resources Development*. 26(3):477-493.

Calabrese, E. J. (1991) *Multiple Chemical Interactions*. Chelsea, Michigan: Lewis Publishers.

Calderon-Preciado, Diana, Victor Matamoros, and Joseph M. Bayona. (2011) Occurrence and Potential Crop Uptake of Emerging Contaminants and Related Compounds in an Agricultural Irrigation Network. *Science of the Total Environment*. 412-413:14-19.

Caldwell, Daniel et al. (2010) An Assessment of Potential Exposure and Risk from Estrogens in Drinking Water. *Environmental Health Perspectives*. March. 118(3):338-344.

California Code of Regulations, Title 22, Division 4, Chapter 3, Water Recycling Criteria
http://ca.eregulations.us/code/t.22_d.4_ch.3 March 7, 2015.

California Department of Health. (2014) MCLs, DLRs, and PHGs for Regulated Drinking Water Contaminants. Updated March.
http://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/MCLsandPHGs.shtml Accessed January 19, 2015.

California State Water Resources Control Board website. (2011)
http://www.waterboards.ca.gov/water_issues/programs/water_recycling_policy/comments_cec011011.shtml
Accessed December 12, 2014.

California State Water Resources Control Board. (2013) *Policy for Water Quality Control for Recycled Water (Recycled Water Policy).* Resolution No. 2013-0003. Rev. January 22, 2013. Effective April 25, 2013. Sacramento: SWRCB.

__________. (2015) Recycled Water - Expert Panel to Advise on Developing Uniform Recycling Criteria for Indirect Potable Reuse via Surface Water Augmentation and on the Feasibility of Developing Such Criteria for Direct Potable Reuse. February 23.
http://www.waterboards.ca.gov/drinking_water/certlic/drinkingwater/RW_SWA_DPRexpertpanel.shtml Accessed March 4, 2015.

Carey, Nessa. (2012) *The Epigenetics Revolution: How Modern Biology Is Rewriting our Understanding of Genetics, Disease, and Inheritance.* NY: Columbia University Press.

Carpenter, David O., ed. (2013) *Effects of Persistent and Bioactive Organic Pollutants on Human Health.* NY: Wiley.

City of Santa Cruz. (2015) *Wastewater Treatment Facility.* http://www.cityofsantacruz.com/departments/public-works/wastewater-treatment-facility Accessed February 18, 2015.

Cobb, Kurt. (2015) Public Health, Endocrine Disruption and the Precautionary Principle. *Resource Insights.* October 24. http://resourceinsights.blogspot.com/2015/10/public-health-endocrine-disruption-and.html Accessed October 25, 2015.

Colborn, Theo. (1997) *Our Stolen Future: Are We Threatening Our Fertility, Intelligence, and Survival?--A Scientific Detective Story.* New York: Plume.

__________. (2004a) Neurodevelopment and Endocrine Disruption. *Environmental Health Perspectives.* June. 112(9):944-949.

__________. (2004b) Setting Aside Tradition When Dealing with Endocrine Disruptors. *ILAR Journal.* 45(4)394-400.

Colborn, Theo, Frederick S. vom Saal, and Ana M. Soto. (1993) Developmental Effects of Endocrine-Disrupting Chemicals in Wildlife and Humans. *Environmental Health Perspectives.* October. 101(5):378-384.

Collignon, Peter. (2011) Recycling Water from Sewage into Drinking Water: A "High Level" Health Risk We Should Only Take as a "Last Resort." May 23. Woden, Australia. http://www.pc.gov.au/inquiries/completed/urban-water/submissions/subdr098.pdf Accessed July 1, 2015.

Cotruvo, Joseph A. et al. (2012) *Health Effects Concerns of Water Reuse with Research Recommendations.* Alexandria, VA: WateReuse Research Foundation.

Cwiertny, David M. et al. (2014) Environmental Designer Drugs: When Transformation May Not Eliminate Risk. *Environmental Science & Technology.* September 12. 48:11737-11745.

Daughton, C. G. (2010) Pharmaceutical Ingredients in Drinking Water: Overview of Occurrence and Significance of Human Exposure. In: *Contaminants of Emerging Concern in the Environment: Ecological and Human Health Considerations.* Ed. by Rolf U. Halden. Washington D.C.: American Chemical Society, 9-68.

Daughton, Christian G. and Thomas A. Ternes. (1999) Pharmaceuticals and Personal Care Products in the Environment: Agents of Subtle Change? *Environmental Health Perspectives*. 107(6):907-938.

Di Renzo, Gian Carlo et al. (2015) International Federation of Gynecology and Obstetrics Opinion on Reproductive Health Impacts of Exposure to Toxic Environmental Chemicals. *International Journal of Gynecology and Obstetrics*. Article in press.

Diamanti-Kandarakis, Evantia, et al. (2009) *Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement.* Chevy Chase, MD: The Endocrine Society.

Dietert, Rodney R. (2014) Transgenerational Epigenetics of Endocrine-Disrupting Chemicals. In: *Transgenerational Epigenetics.* Ed. by Trygve Tollefsbol. San Diego: Academic Press, 239-254.

Dodd, Michael C. (2012) Potential Impacts of Disinfection Processes on Elimination and Deactivation of Antibiotic Resistance Genes During Water and Wastewater Treatment. *Journal of Environmental Monitoring*. 14:1754-1771.

Eaton, Andrew. (2010) Constituents of Emerging Concern (CEC) Monitoring for Recycled Water. Comment Letter for CA State Water Resources Control Board, Public Hearing, December 15, 2010. http://www.waterboards.ca.gov/water_issues/programs/water_recycling_policy/comments_cec011011.shtml Accessed June 14, 2014.

Eaton, Andrew and Ali Haghani. (2012) The List of Lists – Are We Measuring the Best PPCPs for Detecting Wastewater Impact on a Receiving Water? *Water Practice & Technology*. 7(4). http://www.iwaponline.com/wpt/007/0069/0070069.pdf Accessed October 2, 2014.

Eaton, Andrew and Ed Wilson. (2013) How Reliable Is the Recycled Water Monitoring List? Paper presented at the California WateReuse Conference, April 2013, Los Angeles.

Edwards, Thea M. and John Peterson Myers. Environmental Exposures and Gene Regulation in Disease Etiology -- Review. (2007) *Environmental Health Perspectives*. September. 115:1264-1270.

Environmental Working Group. (2013) *Dirty Dozen List of Endocrine Disruptors*. http://www.ewg.org/research/dirty-dozen-list-endocrine-disruptors Accessed January 24, 2014.

Evgenidou, Eleni N., Ioannis K. Konstantinou, and Dimitra A. Lambropoulou (2015) Occurrence and Removal of Transformation Products of PPCPs and Illicit Drugs in Wastewaters: Review. *Science of the Total Environment*. 505:905-926.

Escher, Beate I. and Kathrin Fenner. (2011) Recent Advances in Environmental Risk Assessment of Transformation Products. *Environmental Science & Technology*. April 7. 45:3835-3847.

Fagin, Dan. (2012) The Learning Curve. *Nature*. October 25. 490:462-465.

Fahrenfeld, Nicole et al. (2013) Reclaimed Water as a Reservoir of Resistance Genes; Distribution System and Irrigation Implications. *Frontiers in Microbiology*. May 28. 4:Article 130, 1-11.

Fatta-Kassinos, Despo and Costas Michael. (2013) Wastewater Reuse Applications and Contaminants of Emerging Concern. *Environmental Science and Pollution Research*. 20:3493-3495.

Feder, Barnaby J. (2007) Samsung's Nanotech Washer Must Follow Bug-Spray Rules. *New York Times*. September 26. http://bits.blogs.nytimes.com/2007/09/26/samsungs-washers-regulated-as-a-pesticide/?_php=true&_type=blogs&_r=0 Accessed March 30, 2014.

Francis, Richard C. (2011) *Epi-Genetics: The Ultimate Mystery of Inheritance.* NY: Norton.

Freeman, Gregory, Myasnik Poghosyan, and Matthew Lee. (2008) *Where Will We Get the Water? Assessing Southern California's Future Water Strategies.* Revised August 14. Los Angeles. http://www.mwdh2o.com/BlueRibbon/pdfs/Water_SoCalWaterStrategies.pdf Accessed January 30, 2015.

Fullbrook, David. (2013) How Much Do Man-Made Chemicals Affect Our Health? *South China Morning Post.* March 20.
http://www.scmp.com/comment/insight-opinion/article/1194779/how-much-do-man-made-chemicals-affect-our-health Accessed October 25, 2015.

Gajjar, Priyanka et al. (2009) Antimicrobial Activities of Commercial Nanoparaticles Against an Environmental Soil Microbe, *Pseudomonas putida* KT2440. *Journal of Biological Engineering*. 3(9):1-13.

Genuis, Stephen J. and Kasie L. Kelln. (2015) Toxicant Exposure and Bioaccumulation: A Common and Potentially Reversible Cause of Cognitive Dysfunction and Dementia: Review Article. *Behavioural Neurology*. 2015:1-10.

Gerrity, Daniel et al. (2013) Potable Reuse Treatment Trains throughout the World. *Journal of Water Supply Research and Technology—AQUA*. 62(6):321-335.

Gore, A. C. et al. (2015) Executive Summary to EDC-2: The Endocrine Society's Second Scientific Statemet on Endocrine-Disrupting Chemicals. *Endocrine Reviews*. 36. (Early release)

Grandjean, Philippe. (2013) *Only One Chance: How Environmental Pollution Impairs Brain Development – And How to Protect the Brains of the Next Generation*. NY: Oxford UP.

Grandjean, Philippe and Philip J. Landrigan. (2014) Neurobehavioural Effects of Developmental Toxicity: Review. *Lancet Neurology*. 13:330–338.

Grandjean, Philippe et al. (2015) Life-Long Implications of Developmental Exposure to Environmental Stressors: New Perspectives: Mini-review. *Endocrinology*. Early release, August http://press.endocrine.org/doi/pdf/10.1210/EN.2015-1350 Accessed August 5, 2015.

__________. (2007) The Faroes Statement: Human Health Effects of Developmental Exposure to Chemicals in Our Environment. *Basic & Clinical Pharmacology & Toxicology*. 102:73-75.

Grossman, Elizabeth. (2014) Banned in Europe, Safe in the U.S. *Ensia.* June 9. http://ensia.com/features/banned-in-europe-safe-in-the-u-s/ Accessed June 10, 2014.

__________. (2015) Chemical Exposure Linked to Billions in Health Care Costs. *National Geographic*. March 5. http://news.nationalgeographic.com/news/2015/03/150305-chemicals-endocrine-disruptors-diabetes-toxic-environment-ngfood/Accessed March 5, 2015.

Guerrero-Bosagna, Carlos and Michael K. Skinner. (2012) Environmentally Induced Epigenetic Transgenerational Inheritance of Phenotype and Disease. *Molecular and Cellular Endocrinology*. 354:3-8.

Gwinn, Maureen R. and Val Vallyathan. (2006) Nanoparticles: Health Effects -- Pros and Cons. *Environmental Health Perspectives*. December. 114(12):1818-1825.

Hamblin, James. (2014) The Toxins That Threaten Our Brains. *The Atlantic*. March 18. http://www.theatlantic.com/features/archive/2014/03/the-toxins-that-threaten-our-brains/284466/ Accessed March 18, 2014.

Hannah, Robert et al. (2009) Exposure Assessment of 17alpha-ethninylestradiol in Surface Waters of the United States and Europe. *Environmental Toxicology and Chemistry*. 24(12):2725-2732.

Hanson, M. A. and P. D. Gluckman. (2014) Early Developmental Conditioning of Later health and Disease: Physiology or Pathophysiology? *Physiological Review*. 94:1027-1076.

Haugen, A. C. et al. (2014) Evolution of DOHaD: The Impact of Environmental Health Sciences. *Journal of Developmental Origins of Health and Disease*. 6(2):55–64.

Head, Jessica. (2014) Patterns of DNA Methylation in Animals: An Ecotoxicological Perspective. *Integrative and Comparative Biology*. 54(1):77-86.

Heindel, Jerold J. and Laura N. Vandenberg. (2015) Developmental Origins of Health and Disease: A Paradigm for Understanding Disease Cause and Prevention – Review. www.co-pediatrics.com. 27(2):248-253.

Hong, Pei-Ying et al. (2014) Environmental and Public Health Implications of Water Reuse: Antibiotics, Antibiotic Resistant Bacteria, and Antibiotic Resistance Genes. *Antibiotics*. 2:367-399.

Hsu, F. C., R. L. Marxmiller, and A. Y. Yang. (1990) Study of Root Uptake and Xylem Translocation of Cinmethylin and Related Compounds in Detopped Soybeans Roots Using a Pressure Chamber Technique. *Plant Physiology*. 93(4):1573-1578.

Janesick, Amanda S., Toshihiro Shioda, Bruce Blumberg. (2014) Transgenerational Inheritance of Prenatal Obesogen Exposure. *Molecular and Cellular Endocrinology*. 398:31-35.

Jensen, Genon K. and Lisette van Vliet. (2012) The European Example: What Have We Learned about Health and the Environment? *San Francisco Medicine*. June. 85(5):28-29. http://issuu.com/sfmedsociety/docs/june2012/1?e=3533752/5898094 Accessed July 18, 2014.

Jjemba, Patrick K. (2008) *Pharma-Ecology: The Occurrence and Fate of Pharmaceuticals and Personal Care Products in the Environment.* Hoboken, NJ: Wiley.

Jobling, Susan et al. (1996) A Variety of Environmentally Persistent Chemicals, Including Some Phthalate Plasticizers, Are Weakly Estrogenic. *Environmental Health Perspectives*. June. 103(6): 582-587.

Karoutsou, E. and A. Polymeris. (2012) Environmental Endocrine Disruptors and Obesity. *Endocrine Regulations*. 46:37-46.

Kelce, William R. and Elizabeth M. Wilson. (1997) Environmental Antiandrogens: Developmental Effects, Molecular Mechanisms, and Clinical Implications. *Journal of Molecular Medicine*. 75:198-207.

Kim, Sungpyo and Diana S. Aga. (2007) Potential Ecological and Human Health Impacts of Antibiotics and Antibiotic-Resistant Bacteria from Wastewater Treatment Plants. *Journal of Toxicology and Environmental Health, Part B*. 10:559-573.

Konkel, Lindsey. (2014a) Kids Exposed in the Womb to Plasticizers More Likely to Have Asthma. *Environmental Health News*. September 17. http://www.environmentalhealthnews.org/ehs/news/2014/sep/child-asthma-phthalates Accessed September 17, 2014.

__________. (2014b) Plastics Chemical Linked to Changes in Baby Boys' Genitals. *Environmental Health News*. October 29. http://www.environmentalhealthnews.org/ehs/news/2014/oct/plastics-chemical-and-boys-genitals Accessed October 29, 2014.

__________. (2015) Chemical in Plastics May Alter Boys' Genitals Before Birth. *Live Science*. February 19. http://m.livescience.com/49870-phthalates-chemical-plastics-boys-genital-development.html Accessed February 19, 2015.

Kormos, Jennifer Lynne, Manoj Schulz, and Thomas A. Ternes. (2011) Occurrence of Iodinated X-ray Contrast Media and Their Biotransformation Products in the Urban Water Cycle. *Environmental Science & Technology*. 45:8723–8732.

Kortenkamp, Andreas. (2007) Ten Years of Mixing Cocktails: A Review of Combination Effects of Endocrine-Disrupting Chemicals. *Environmental Health Perspectives*. December. 115(Supp. 1):98-105.

__________. (2008) Low Dose Mixture Effects of Endocrine Disruptors: Implications for Risk Assessment and Epidemiology. *International Journal of Andrology*. 31:233-40.

Kortenkamp, Andreas et al. (2011) *State of the Art Assessment of Endocrine Disrupters: Final Report*. December 12. Commissioned by the EU. Project Contract Number 070307/2009/550687/SER/D3.

Kosjek, Tina and Ester Heath. (2011) Occurrence, Fate and Determination of Cytostatic Pharmaceuticals in the Environment. *Trends in Analytical Chemistry*. 30(7):1065-1086.

Krasner, Stuart W. et al. (2006) Occurrence of a New Generation of Disinfection Byproducts. *Environmental Science & Technology*. 40:7175-7185.

La Farre, Marinel et al. (2008) Fate and Toxicity of Emerging Pollutants, Their Metabolites and Transformation Products in the Aquatic Environment. *Trends in Analytical Chemistry*. 27(11):991-1007.

Landrigan, Philip J. (2010) What Causes Autism? Exploring the Environmental Contribution. *Current Opinion in Pediatrics*. 22:219-225.

Landrigan, Philip J. and Lynn R. Goldman. (2011) Children's Vulnerability to Toxic Chemicals: A Challenge and Opportunity to Strengthen Health and Environmental Policy. *Health Affairs*. May. 30(5):842-850.

Legler, Juliette et al. (2015) Obesity, Diabetes, and Associated Costs of Exposure to Endocrine-Disrupting Chemicals in the European Union. *Journal of Clinical Endocrinology and Metabolism*. April. 100(4):1278-1288.

Malchi, Tomer et al. (2014) Irrigation of Root Vegetables with Treated Wastewater: Evaluating Uptake of Pharmaceuticals and the Associated Human Health Risks. *Environmental Science & Technology*. 48(16):9325-9333.

Manikkam, Mohan et al. (2012) Pesticide and Insect Repellent Mixture (Permethrin and DEET) Induces Epigenetic Transgenerational Inheritance of Disease and Sperm Epimutations. *Reproductive Toxicology*. 34:708-719.

Martin, Francis L. (2013) Review Article: Epigenetic Influences in the Aetiology of Cancers Arising from Breast and Prostate: A Hypothesised Transgenerational Evolution in Chromatin Accessibility. *ISRN Oncology*. 2013:1-13.

McKinney, Chad W. and Amy Pruden. (2012) Ultraviolet Disinfection of Antibiotic Resistant Bacteria and Their Antibiotic Resistance Genes in Water and Wastewater. *Environmental Science & Technology*. 46:13393-13400.

Mehendale, Harihara M. (1994) Mechanism of the Interactive Amplification of Halomethane Hepatotoxicity and Lethality by Other Chemicals. In: *Toxicology of Chemical Mixtures: Case Studies, Mechanisms, and Novel Approaches*. Ed. by Raymond S. H. Yang. NY: Academic Press, 299-334.

Miao, Xiu-Seng, Jian-Jun Yan, and Chris D. Metcalfe. (2005) Carbamazepine and Its Metabolites in Wastewater and in Biosolids in a Municipal Wastewater Treatment Plant. *Environmental Science & Technology*. 38(19):7469-7475.

Mole, Beth. (2014) Recycled Water May Flood Urban Parks with Dangerous Germs: With Irrigation, Drug Resistance Genes Swamp the Soil. *Science News*. July 30. https://www.sciencenews.org/article/recycled-water-may-flood-urban-parks-dangerous-germs Accessed July 31, 2014.

Myers, Pete and Wendy Hessler. (2007) Does "The Dose Make the Poison?" Extensive Results Challenge a Core Assumption in Toxicology. *Environmental Health News*. April 30. http://www.ourstolenfuture.org/NewScience/lowdose/2007/2007-0525nmdrc.html Accessed July 11, 2014.

Navarro, Enrique et al. (2008) Environmental Behavior and Ecotoxicity of Engineered Nanoparticles to Algae, Plants, Fungi. *Ecotoxicology* 17:372-386.

Nawaz, Z. et al. (1999) Proteasome-Dependent Degradation of the Human Estrogen Receptor. *Proceedings of the National Academy of Sciences, U.S.A.* 96:1858-1862.

Norris, David O. and Alan M. Vajda. (2007) Endocrine Active Chemicals (EACs) in Wastewater: Effects on Health of Wildlife and Humans. *Water Resources IMPACT.* 9(3):15-16. http://www.awra.org/impact/issues/0705impact.pdf Accessed July 8, 2014.

Olena, Abby (2013) Birds Carry Resistant Bacteria. *The Scientist.* November 11. http://www.the-scientist.com/?articles.view/articleNo/38254/title/Birds-Carry-Resistant-Bacteria/ Accessed December 14, 2014.

Ortiz de Garcia, Sheyla Andrea et al. (2014) Ecotoxicity and Environmental Risk Assessment of Pharmaceuticals and Personal Care Products in Aquatic Environments and Wastewater Treatment Plants. *Ecotoxicology.* 23:1517-1533.

Paterson, S. et al. (1990) Uptake of Organic Chemicals by Plants: A Review of Processes, Correlations and Models. *Chemosphere.* 21(3):297-331.

Payne-Sturges, Devon et al. (2009) Evaluating Cumulative Organophosphorus Pesticide Body Burden of Children: A National Case Study. *Environmental Science and Technology.* 43:7924-7930.

Pruden, Amy et al. (2013) Management Options for Reducing the Release of Antibiotics and Antibiotic Resistance Genes to the Environment – Review. *Environmental Health Perspectives.* 121(8):878-885.

Qu, Shen et al. (2013) Endocrine Disruption Product-to-Parent Reversion of Trenbolone: Unrecognized Risks for Endocrine Disruption. *Science.* 342:347-351.

Raghav, Madhumitha et al. (2013) Contaminants of Emerging Concern in Water. *Arroyo.* 1-12.

Rajapaske, Nissanka, Elisabete Silva, and Andreas Kortenkamp. (2002) Combining Xenoestrogens at Levels below Individual No-Observed-Effect Concentrations Dramatically Enhances Steroid Hormone Action. *Environmental Health Perspectives.* 110(9):917-921.

Rappaport, Stephen M. and Martyn T. Smith. (2010) Environment and Disease Risks. *Science.* 330(6003):460-461.

Regional Monitoring Program for Water Quality in San Francisco Bay. (2013) *The Pulse of the Bay: Contaminants of Emerging Concern.* Richmond: San Francisco Estuary Institute.

Richardson, Jason R. et al. (2014) Elevated Serum Pesticide Levels and Risk for Alzheimer Disease. *JAMA Neurology.* 71(3):284-290

Ryan, J.A. et al. (1988) Plant Uptake of Non-Ionic Organic Chemicals from Soils. *Chemosphere.* 17:2299-2323.

Sargis, Robert M. et al. (2012) The Diabetes Epidemic: Environmental Chemical Exposure in Etiology and Treatment. *San Francisco Medicine.* June. 85(5):18-19. http://issuu.com/sfmedsociety/docs/june2012/1?e=3533752/5898094 Accessed July 18, 2014.

Schettler, Ted at al. (2012) Assessing Toxin Risk: Improvements Needed to Protect Human Health from Chemicals. *San Francisco Medicine.* June. 85(5):26-27. http://issuu.com/sfmedsociety/docs/june2012/1?e=3533752/5898094 Accessed July 18, 2014.

Schiffer, Christian et al. (2014) Direct Action of Endocrine Disrupting Chemicals on Human Sperm. *EMBO Reports.* July. 15(7):758-765.

Schneider, Rudolf J. (2008) Plant Uptake of Pharmaceuticals from Soil: Determined by ELISA. In *Fate of Pharmaceuticals in the Environment and in Water Treatment Systems*, Ed. by Diana S. Aga, 179-198.

Schnoor, Jerald L. (2014) Re-Emergence of Emerging Contaminants. *Environmental Science and Technology*. September 12:A-B.

Schulz, Manoj et al. (2008) Transformation of the X-ray Contrast Medium Iopromide in Soil and Biological Wastewater Treatment. *Environmental Science & Technology*. 42:7207-7217.

Schwab, B. W. et al. (2005) Human Pharmaceuticals in US Surface Waters: A Human Health Risk Assessment. *Regulatory Toxicology and Pharmacology*. 42(3):296-312.

Scutti, Susan. (2015) Puberty Comes Earlier and Earlier for Girls. *Newsweek*. January 26. http://www.newsweek.com/2015/02/06/puberty-comes-earlier-and-earlier-girls-301920.html Accessed January 27, 2015.

Sharma, Abhay. (2013) Transgenerational Epigenetic Inheritance: Focus on Soma to Germline Information Transfer. *Progress in Biophysics and Molecular Biology*. 113:439-446.

Sharpe, Richard M. et al. (1996). Effects on Testicular Development and Function. *10th International Congress of Endocrinologists*. S23-4.

Sheehan, Daniel M. (2006) No-Threshold Dose-Response Curves for Nongenotoxic Chemicals: Findings and Applications for Risk Assessment. *Environmental Research*. 100:93-99.

Sicbaldi, F. et al. (1997) Root Uptake and Xylem Translocation of Pesticides from Different Chemical Classes. *Pesticide Science*. 50:111-119.

Silva, Elisabete, Nissanka Rajapaske, and Andreas Kortenkamp. (2002) Something from "Nothing" – Eight Weak Estrogenic Chemicals Combined at Concentrations below NOECs Produce Significant Mixture Effects. *Environmental Science & Technology*. 36:1751-1756.

Simonich, Staci L. and Ronald A. Hites. (1995) Organic Pollutant Accumulation in Vegetation. *Environmental Science and Technology*. 29(12):2905-2914.

Sonnenschein, Carlos and Ana M. Soto. (1998) An Updated Review of Environmental Estrogen and Androgen Mimics and Antagonists. *Journal of Steroid Biochemistry and Molecular Biology*. 65(1):143-150.

Soto, Ana M. and Carolos Sonnenschein. (2010) Environmental Causes of Cancer: Endocrine Disruptors as Carcinogens – Review. *Nature Reviews*. July 6:363-370.

Stel, Jente and Juliette Legler. (2015) The Role of Epigenetics in the Latent Effects of Early Life Exposure to Obesogenic Endocrine Disrupting Chemicals. *Endocrinology*. October. 156(10):3466-3472.

Svendsgaard, David J. and Richard C. Hertzberg. (1994) Statistical Methods for the Toxicological Evaluation of the Additivity Assumption as Used in the Environmental Protection Agency Chemical Mixure Risk Assessment Guidelines. In: *Toxicology of Chemical Mixtures: Case Studies, Mechanisms, and Novel Approaches.* Ed. by Raymond S. H. Yang. NY: Academic Press, 640-642.

Tollefsbol, Trygve, ed. (2014) *Transgenerational Epigenetics*. San Diego: Academic Press.

Trasanade, Leonardo et al. (2015) Estimating Burden and Disease Costs of Exposure to Endocrine-Disrupting Chemicals in the European Union. *Journal of Clinical Endocrinology and Metabolism*. Early release; accepted February 9. 1-11.

Trussel, R. Rhodes et al. (2013) *Potable Reuse: State of the Science Report and Equivalency Criteria for Treatment Trains.* Alexandria, VA: WateReuse Research Foundation. http://www.watereuse.org/product/11-02-2

UNEP/WHO (2012). *State of the Science of Endocrine Disrupting Chemicals—2012*. Geneva, Switzerland: United Nations Environment Programme/World Health Organization.

Vaiserman, Alexander. (2014) Early-Life Exposure to Endocrine Disrupting Chemicals and Later-Life Health Outcomes: An Epigenetic Bridge? Review. *Aging and Disease*. December. 5(6):419-429.

Vandenberg, Laura N. (2014) Non-Monotonic Dose Responses in Studies of Endocrine Disrupting Chemicals: Bisphenol A as a Case Study. *Dose Response*. 12:259-276.

Vandenberg, Laura N. et al. (2012) Hormones and Endocrine-Disrupting Chemicals: Low-Dose Effects and Nonmonotonic Dose Responses. *Endocrine Reviews*. June. 33(3):378-455.

Vandenberg, Laura N., Thomas Zoeller, and J.P. Myers. (2012) Environmental Chemicals: Large Effects from Low Doses. *San Francisco Medicine*. June. 85(5):15-16. http://issuu.com/sfmedsociety/docs/june2012/1?e=3533752/5898094 Accessed July 18, 2014.

vom Saal, Frederick S. and Daniel M. Sheehan. (1998) Challenging Risk Assessment. *Forum for Applied Research and Public Policy*. Fall. 13:11-18.

WEF and AWWA. (2008) *Using Reclaimed Water to Augment Potable Water Resources: A Special Publication*. 2nd ed. Water Environment Federation and American Water Works Association. Alexandria, VA.

Weiss, Bernard. (2012) The Intersection of Neurotoxicology and Endocrine Disruption. Neurotoxicology. December. 33(6):1410–1419.

Welshons, W. V. et al. (2013) Large Effects from Small Exposures. 1. Mechanisms for Endocrine-Disrupting Chemicals with Estrogenic Activity. *Environmental Health Perspectives*. 111:994-1006.

Whyatt, Robin M. et al. (2014) Asthma in Inner-City Children at 5-11 Years of Age and Prenatal Exposure to Phthalates: The Columbia Center for Children's Environmental Health Cohort. *Environmental Health Perspectives*. Advance publication: September 17. http://ehp.niehs.nih.gov/wp-content/uploads/advpub/2014/9/ehp.1307670.pdf Accessed September 17, 2014.

Williams, Florence. (2013/2014) Generation ToXic. *OnEarth*. Winter. 29-37.

Wilson, Duff. (1998) Wasteland. *Amicus Journal*. Spring. 20(1):34-38.

Wolf, Lauren K. (2014) The Crimes of Lead. *Chemical & Engineering News*. 92(5):27-29. http://cen.acs.org/articles/92/i5/Crimes-Lead.html Accessed February 3, 2014.

Xin, Frances, Martha Susiarjoa, and Marisa S. Bartolomeia (2015) Multigenerational and Transgenerational Effects of Endocrine Disrupting Chemicals: A Role for Altered Epigenetic Regulation? Review. *Seminars in Cell & Developmental Biology*. Article in pres. http://dx.doi.org/10.1016/j.semcdb.2015.05.008 Accessed October 9, 2015.

Yang, Raymond S. H., ed. (1994) *Toxicology of Chemical Mixtures: Case Studies, Mechanisms, and Novel Approaches*. San Diego: Academic Press.

Zhang, Jiefeng et al. (2013) Removal of Cytostatic Drugs from Aquatic Environment: A Review. *Science of the Total Environment*. 445–446:281–298.

Zoeller, R. Thomas et al. (2012) Endocrine-Disrupting Chemicals and Public Health Protection: A Statement of Principles from the Endocrine Society. *Endocrinology*. September. 153(9):4097-4110.

List of References on Endocrine Disruption

Websites & List Serves:

- The Endocrine Disruption Exchange (TEDX): http://endocrinedisruption.org/
    - TEDX: Endocrine Disruption: Overview: http://endocrinedisruption.org/endocrine-disruption/introduction/overview
    - List of Potential Endocrine Disruptors: http://endocrinedisruption.org/endocrine-disruption/tedx-list-of-potential-endocrine-disruptors/overview
    - Prenatal Origins of Endocrine Disruption: http://endocrinedisruption.org/prenatal-origins-of-endocrine-disruption/introduction
    - Pesticides: http://endocrinedisruption.org/pesticides/introduction

- San Francisco Medical Society Journal: http://www.sfms.org/NewsPublication/SanFranciscoMedicine.aspx
- Collaborative on Health and the Environment (CHE): http://www.healthandenvironment.org/ (talks and articles on health and the environment)
- Environmental Health Perspectives: National Institute of Environmental Health Sciences: http://ehp.niehs.nih.gov/
- *Above the Fold*: free daily list serve of nationwide articles on environmental health: Contact following to be put on list: Compiled by Environmental Health News: □A project of *Environmental Health Sciences*□ 421 Park Street, Suite 4□ Charlottesville, VA 22902 □EnvironmentalHealthNews.org□feedback@EnvironmentalHealthNews.org you may subscribe here

Studies:

- Vandenberg, L.N., et al., *Hormones and endocrine disrupting chemicals: low dose effects and non-monotonic dose responses.* Endocrine Reviews, 2012. **33**(3): p. 378- 455, http://www.ncbi.nlm.nih.gov/pubmed/22419778
- Pharmaceuticals in the Environment: A growing threat to our tap water and wildlife, http://www.chemtrust.org.uk/wp-content/uploads/CHEM-Trust-Pharma-Dec14.pdf

- Anway, Matthew D., and Michael K. Skinner, *Epigenetic Transgenerational Actions of Endocrine Disruptors*, Endocrinology: The Endocrine Society may 11, 2006, http://press.endocrine.org/doi/abs/10.1210/en.2005-1058

Articles & Publications:

- Edited by Ake Bergman et. al., *State of the Science of Endocrine Disrupting Chemicals-2012*, World Health Organization: ISBN: 978 92 4 150503 1)
  Link to report and summary:
  http://www.who.int/ceh/publications/endocrine/en/
- World Health Organization: *Endocrine disruptors and child health*: 2012 ISBN: 978 92 4 150376 1,
  http://www.who.int/ceh/publications/endocrine_disrupters_child/en/
- **CHEMTrust:**
  - **CHEMTrust overview of Key Scientific Statements on Endocrine Disrupting Chemicals (EDCs) 1991-2013, as of January 2014.**
    (This document contains about 35 major scientific reports and statements over 22 years that each contain many references and resources on endocrine disruption.)
- Endocrine Society: *Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement*; Apr. 17, 2009 (also in CHEMTrust list above)
- Zoeller, R.T., et al., *Endocrine-disrupting chemicals and public health protection: a statement of principles from the Endocrine Society.* Endocrinology, 2012. **Epub June 25, 2012**: p. en.2012-1422, http://www.ncbi.nlm.nih.gov/pubmed/22733974
- Melnick, R., et al., *Summary of the National Toxicology Program's report of the endocrine disruptors low-dose peer review.* Environ Health Perspectives, 2002. **110**(4): p. 427-31, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1240807/
- Birnbaum, L.S., *Environmental chemicals: evaluating low-dose effects.* Environ Health Perspect, 2012. **120**(4): p. A143-4 online 14 March 2012
  http://ehp.niehs.nih.gov/1205179/
- Birnbaum, Linda S., *Endocrine Disrupting Chemicals in Drinking Water: Risks to Human Health and the Environment* before Committee on Energy and Commerce, Feb. 25, 2010, http://www.hhs.gov/asl/testify/2010/02/t20100225a.html
- Charles W. Schmidt, *Uncertain Inheritance: Transgenerational Effects of Environmental Exposures*, Environmental Health Perspectives, Vol. 121, #10, October 2013, http://ehp.niehs.nih.gov/121-a298/
- Maria Hegstad, *Condemning EPA Endocrine Review, NAS Urges Redo of Draft Risk Paper*, Inside Washington Publishers, 5-3-14
- Janet Raloff, *Weed Killer in the Crosshairs*, Science News, Feb. 27, 2010 (atrazine), http://onlinelibrary.wiley.com/doi/10.1002/scin.5591770520/
- Nikita Naik, *Wastewater Irrigation on Farms Contaminates Food*, Pesticides and You, Vol. 34, #3, Fall 2014 p.19-p.23,

http://www.beyondpesticides.org/infoservices/pesticidesandyou/documents/WastewaterFall2014.pdf

The Tufts Center
FOR REGENERATIVE AND
DEVELOPMENTAL BIOLOGY

June 27, 2012

Jeanine Townsend, Clerk to the Board
State Water Resources Control Board
1001 I Street, 24th floor
Sacramento, CA 95814

RE: Comment letter-Amendment to the Recycled Water Policy

Dear Members of the State Water Resources Control Board,

I am an academic scientist who has worked for nine years on issues related to endocrine disruptors, including assessments of human exposures, meta-analyses of published literature, and benchwork assessing the effects of chemicals on development, behavior, reproduction, and other endpoints in rodents and aquatic animals. My PhD is in Cell, Molecular and Developmental Biology, although my work is also well recognized in the field of Environmental Health Science. I have published more than 25 peer-reviewed studies and two book chapters and have served on expert scientific and risk assessment panels in the EU and the US. I was also the lead author on the most comprehensive review to date on low dose exposures to endocrine disrupting chemicals (EDCs; discussed in more detail below).

I am writing to challenge the assertion that "monitoring of individual CECs is not [necessary] for recycled water used for landscape irrigation." I encourage you to consider the extensive peer-reviewed scientific literature on the effects of low doses of EDCs before making decisions about chemical safety in the water supply. Although your scientific board, and many toxicologists around the world, conclude that "the dose makes the poison" when it comes to environmental toxicants, this statement is simply not supported by fact when the chemical in question is a hormone, hormone mimic, or hormone blocker.

In 2001-2002, the National Toxicology Program (NTP) addressed whether there was sufficient evidence to conclude that EDCs act at low doses, i.e. at the doses that humans encounter in their everyday lives. As you are likely well aware, humans encounter EDCs in their food, water, air, dust, as well as household products like detergents, upholstery, solvents, etc. Although typical humans are exposed to low levels of these chemicals (often in the nanogram per kilogram body weight range), the US FDA has identified more than 1000 EDCs in current use, a significant percentage of the over 80,000 chemicals currently in commerce (see http://www.fda.gov/scienceresearch/bioinformaticstools/endocrinedisruptorknowledgebase/default.htm). In 2002, the NTP addressed whether there was significant support in the scientific literature for *The Low Dose Hypothesis,* the scientific hypothesis that EDCs could affect development and reproduction of animals *in the range that humans typically experience, i.e. the*

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low dose range. Although the NTP was hindered at that time by a relative paucity of data, they did conclude that there was evidence for low dose effects for several EDCs including DES, genistein, nonylphenol and methoxychlor [1].

In 2009, I began working with a group of 11 experts in the fields of endocrinology, cancer biology, ecology, developmental biology, and epidemiology on re-assessing scientific support for The Low Dose Hypothesis. These experts are at the forefront of their fields, have served on expert panels around the world, testified before the US Congress, and are collectively the authors of more than 1000 papers on environmental chemicals. Most of these scientists have been working on this issue for decades.

It took us three years to review over 800 published papers from the endocrinology and toxicology literature. Looking at this body of evidence as a whole, we concluded that there was clear and consistent evidence that a large number of EDCs have effects at low doses [2]. In fact, for every chemical where we could identify a low-dose cut-off and low dose studies had been performed, there were low dose effects. These chemicals include herbicides, insecticides, fungicides, preservatives, industrial chemicals, surfactants, plasticizers, pharmaceuticals, flame retardants and anti-bacterial agents, among others. We also identified hundreds of examples of non-monotonic dose response curves, i.e. those where the dose *does not* make the poison. Not only did we identify these types of responses in cultured cells and laboratory animals, but they were also observed in human populations.

Our analysis indicates that low dose effects and non-monotonic dose responses are common for EDCs, and in fact may be *the expected* type of biological response for this large class of chemicals. Most importantly, we have a great understanding of the mechanisms behind these types of effects; hormones act in the body at exceedingly low concentrations, i.e. in the part per trillion or part per billion range. The endocrine system is tuned to respond to these low doses. Thus, low doses of chemicals that mimic hormones follow the same "rules" as the natural compounds. Additionally, while these low levels of hormones can have reversible actions in adults (i.e. an adult female taking pharmaceutical estrogens [birth control pills] will have reduced fertility due to ovulation inhibition, but cessation of pharmaceutical treatment restores her fertility), hormones are known to change the development and differentiation of tissues in embryos, fetuses, and even neonates. These effects will be permanent and irreversible.

The concept of low dose effects and non-monotonic dose responses **is not at the fringe of science**. The Endocrine Society, the world's largest professional association of clinical and research endocrinologists, has released two recent statements regarding EDCs, and has repeatedly reiterated the conclusion that low doses of EDCs are harmful to humans and wildlife [3, 4]. This conclusion has widespread acceptance in the field of endocrinology due to the strength of the published data. Additionally, following the publication of our review [2], Dr. Linda Birnbaum, Director of the National Institutes of Environmental Health Science (NIH) and one of the world's leading toxicologists wrote an editorial stating: "the question is no longer whether nonmonotonic dose responses are 'real' and occur frequently enough to be a concern; clearly these are common phenomena with well-understood mechanisms...It is time to start the conversation between environmental health scientists, toxicologists, and risk assessors to determine how our understanding of low-dose effects and nonmonotonic dose responses influence the way risk assessments are performed for chemicals with endocrine-disrupting activities. Together, we can take appropriate actions to protect human and wildlife populations from these harmful chemicals and facilitate better regulatory decision making." [5]

On page 13 of your revised policy, it is stated that "Regulatory requirements for recycled water shall be based on the best available peer-reviewed science." The low dose literature that we reviewed in our recent analysis was all peer-reviewed science, and our analysis was peer reviewed as well. Yet this vast body of science has not been considered or addressed by the board. Thus, I respectfully ask this committee to reconsider suggestions that exposure of human and wildlife populations to EDCs, including pharmaceuticals, should not be concerning if the concentrations of these chemicals are "low". Clearly, relying on the centuries old adage that "the dose makes the poison" is not sufficient to protect public health.

Sincerely,

Laura N. Vandenberg, Ph.D.
Tufts University Center for Regenerative & Developmental Biology

References Cited

1. Melnick, R., et al., *Summary of the National Toxicology Program's report of the endocrine disruptors low-dose peer review.* Environ Health Perspect, 2002. **110**(4): p. 427-31.
2. Vandenberg, L.N., et al., *Hormones and endocrine disrupting chemicals: low dose effects and non-monotonic dose responses.* Endocrine Reviews, 2012. **33**(3): p. 378-455.
3. Diamanti-Kandarakis, E., et al., *Endocrine-disrupting chemical: an Endocrine Society scientific statement.* Endocr Rev, 2009. **30**: p. 293-342.
4. Zoeller, R.T., et al., *Endocrine-disrupting chemicals and public health protection: a statement of principles from the Endocrine Society.* Endocrinology, 2012. **Epub June 25, 2012**: p. en.2012-1422.
5. Birnbaum, L.S., *Environmental chemicals: evaluating low-dose effects.* Environ Health Perspect, 2012. **120**(4): p. A143-4.

ENVIRONMENTAL CHEMICALS

Large Effects from Low Doses

Laura N. Vandenberg, PhD; R. Thomas Zoeller, PhD; J.P. Myers, PhD

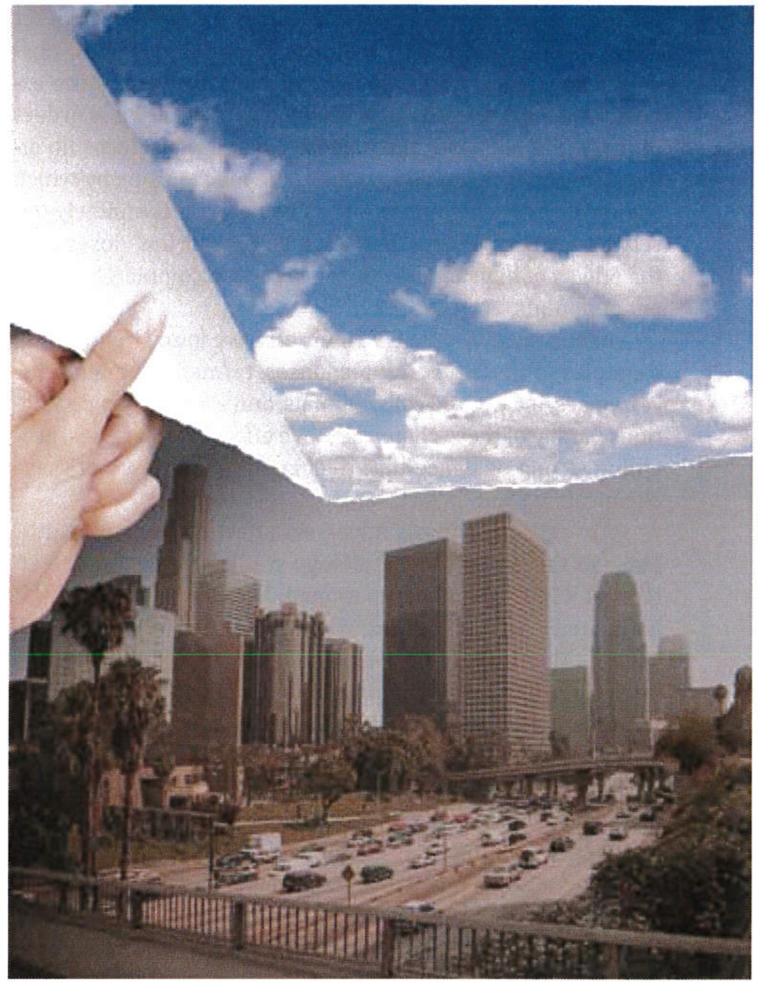
Virtually all safety standards for chemical exposures are determined through a process that assumes that high-dose testing will reveal relevant risks because "the dose makes the poison." For many well-studied contaminants this is a reasonable assumption, but for compounds that behave like hormones, it is demonstrably false.[1] The public health implications of this conclusion are enormous, because it means that many—likely dozens, plausibly hundreds, possibly thousands—of today's chemical safety standards are too weak by orders of magnitude.

The basis for this conclusion derives from endocrinology. In endocrinology, it is well established that the impacts of hormones (such as estrogen) at high doses can differ from those in the "physiological range" of normal circulating levels of hormones in serum; it is at these concentrations that hormones interact with their receptors to cause physiological and developmental changes by altering gene expression. Indeed, hormones at abnormally high doses are often overtly toxic, through mechanisms that have nothing to do with receptor action.

As research has expanded into the effects of endocrine-disrupting chemicals (EDCs), it has been shown that they follow the same rules that hormones follow.[1] Unfortunately, this runs counter to the core assumption that forms the basis for all toxicological testing done to establish regulatory standards: High-dose testing will be informative about low-dose impacts.

The EPA defines an EDC as "an exogenous agent that interferes with the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body that are responsible for the maintenance of homeostasis, reproduction, development, and/or behavior."[2] Although Rachel Carson examined the effects of many environmental chemicals on health and reproduction in her landmark book *Silent Spring*,[3] work on EDCs really took shape in 1991, when a group of scientists met at the Wingspread Conference Center in Racine, Wisconsin, to discuss research on the effects of environmental chemicals on sexual development. The Wingspread attendees produced a consensus statement stating, "We are certain of the following: A large number of man-made chemicals that have been released into the environment, as well as a few natural ones, have the potential to disrupt the endocrine system of animals, including humans."[4]

EDCs are now understood to be any chemicals that interact with the endocrine system, including chemicals that act as agonists and antagonists of hormone receptors, including estrogen, androgen, thyroid, glucocorticoid, retinoid, and others. To determine the mode of action of these chemicals, both



in vivo (animal) and in vitro (cell culture) assays have been developed. While most chemicals on the market today have never been tested for safety, much less for endocrine disruption, these assays could be used to test new chemicals for hormonal activity prior to their entry into the environment through the food supply, packaging materials, or as waste; they are also widely used to test for their hormonal activity many chemicals that are already in use. Chemicals with a wide range of uses, including detergents, plastics, cosmetics, pesticides, pharmaceuticals, and flame retardants, among others, have been shown to have endocrine-disruptor activities.

In 2002, the National Toxicology Program (NTP) examined evidence for what has been termed "the low-dose hypothesis," i.e., the theory that EDCs could have actions at low doses.[5] What is meant by "low doses"? Typically, these are doses in the range of what humans experience in their every-

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day lives—residues on food, in the air, in dust, and in drinking water. Low doses are often within the range that traditional toxicological testing has determined to be "safe."

The question is whether EDCs are safe at the doses the typical person experiences. To determine what doses are safe, regulatory toxicology usually starts by administering large doses of a chemical to animals, identifying the highest dose at which no effect is found, and then extrapolating downward to calculate a safe dose. Those "safe" doses are rarely tested. Yet EDCs, like hormones, defy the toxicological dogma: Low doses can have effects that are not expected from high-dose exposures. In fact, these effects can be observed at doses orders of magnitude beneath the highest dose that produces no effect using traditional approaches. The mechanisms by which chemicals cause high-dose effects usually are completely unrelated to mechanisms that EDCs employ at low doses, and the effects of high and low doses can be on completely different endpoints.

In our review of the EDC literature, we found hundreds of examples of these types of responses, termed nonmonotonic responses, in cultured cells, animals, and even human populations.[1] Many of these chemicals have effects at low doses, providing strong evidence that calculated "safe" doses of these chemicals are not, in fact, safe.[1]

Are these chemicals adversely affecting human health? Many of the earliest epidemiology studies examining the effects of EDCs studied occupationally or accidentally exposed individuals, i.e., people who were exposed to relatively high doses, either acutely or over longer periods of time. Now a large number of epidemiology studies have focused on environmentally exposed individuals, i.e., people who are exposed to EDCs from everyday life. These studies show that many of the effects observed in cultured cells and controlled animal experiments accurately predict what epidemiologists are observing in human populations: associations between human exposures and disease endpoints consistent with the "low-dose hypothesis."

So where do we go from here? As scientists, these findings suggest for us that EDCs, as a chemical class, act very similarly to the hormones they mimic or block: They act at low doses, with effects that are more pronounced when exposures occur during critical periods of development. Just as hormones have nonmonotonic relationships between dose and effect, nonmonotonic effects of EDCs are expected. This means that high-dose testing is insufficient to establish the safety of low doses. In our review,[1] we propose some changes to the way risk assessors determine safety of EDCs: 1) "safe" doses of chemicals, and chemicals in the range of human exposures, should be tested; 2) regulators should assume that EDCs produce nonmonotonic dose responses; 3) more sensitive endpoints should be included in chemical testing.

What can the average person, or patient, do to reduce EDC exposures? This is, of course, an important issue for health care practitioners and others invested in improving public health. Several studies suggest that making small lifestyle changes can have dramatic effects on exposure levels.[6] Patients should be encouraged to make lifestyle choices that reduce known EDC exposures. However, the lessons learned from the published literature seem to be clear: Even low doses, including reduced exposures from changes in consumer behavior, cannot be considered safe. Thus, widespread changes to chemical safety regulations are likely to have the widest effects on human health.

We encourage physicians, nurses, public health administrators, and others working in the medical field to read our recent review and to get involved with the many scientific societies that support new approaches to chemical regulation that better reflect current scientific understanding than do standard toxicological procedures.[7] Your expertise provides an important voice to help the risk assessment community develop new approaches to chemical risk assessment, especially as it pertains to EDCs. Hormones are important signaling molecules that dictate the health of individuals throughout the life course, and therefore the effects of EDCs simply cannot be ignored.

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References

1. Vandenberg LN, Colborn T, Hayes TB, Heindel JJ, Jacobs DR, Lee D-H, Shioda T, Soto AM, Vom Saal FS, Welshons WV, et al. (2012). Hormones and endocrine disrupting chemicals: Low dose effects and non-monotonic dose responses. 2012. *Endocrine Reviews.* Online 2012 Mar 14.

2. Kavlock RJ, Daston GP, DeRosa C, Fenner-Crisp P, Gray LE, Kaattari S, Lucier G, Luster M, Mac MJ, Maczka C, et al. Research needs for the risk assessment of health and environmental effects of endocrine disruptors: A report of the U.S. EPA-sponsored workshop. 1996. *Environ Health Perspect.* 104;715-740.

3. Carson R. *Silent Spring: 25th Anniversary Edition.* 1987. New York: Houghton Mifflin Co.

4. Wingspread Consensus Statement. In *Chemically Induced Alterations in Sexual and Functional Development: The Human/Wildlife Connection.* T. Colborn and C. Clement, eds. 1992. Princeton: Princeton Scientific Publishing, pp. 1-8.

5. Melnick R, Lucier G, Wolfe M, Hall R, Stancel G, Prins G, Gallo M, Reuhl K, Ho SM, Brown T, et al. Summary of the National Toxicology Program's report of the endocrine disruptors low-dose peer review. *Environ Health Perspect.* 2002. 110;427-431.

6. Rudel RA, Gray JM, Engel CL, Rawsthorne TW, Dodson RE, Ackerman JM, Rizzo J, Nudelman JL, Brody JG. Food packaging and bisphenol A and bis(2-ethylhexyl) phthalate exposure: Findings from a dietary intervention. *Environ Health Perspect.* 2011. 119;914-920.

7. Hunt PA. Assessing chemical risk: Societies offer expertise. *Science.* 2011. 331;1136.

Weaker water conservation numbers prompt fears that California is going back to its old bad habits

Sprinklers water the front lawn of a house on Zelzah Avenue in Encino earlier this year. (Michael Owen Baker / For The Times)

Matt Stevens

Californians' water conservation slipped for the third consecutive month in August, prompting new alarm from regulators about whether relaxed water restrictions may be causing residents to revert to old habits as the state enters its sixth year of severe drought.

The trend raises new questions about Californians' willingness to continue austere conservation after spending the last two years dramatically reducing their water use by ripping out lawns, installing water-sipping appliances and shortening their showers.

Conservation numbers varied widely across the state, with some places actually saving more water compared with 2015 levels. But other communities are turning the spigot back on, and state data show that several of the worst offenders are the affluent cities that previously have been criticized for heavy consumption.

Regulators on Wednesday singled out Malibu as one example of a city returning to profligate water use. The water district that serves the city saw its water-savings drop from 20.4% in August 2015 to just 7.9% in August 2016. The 22,000 residents served by the district used about 300 gallons per person per day, according to state data. By contrast, Los Angeles residents used an average of only 84 gallons per day in August.

The Santa Fe Irrigation District, which serves upscale pockets of northern San Diego County, including Rancho Santa Fe, saw its residents use about 525 gallons per person per day. The district had ramped up conservation efforts after being tagged as one of the state's heaviest water users and had managed to save 36.6% in August 2015. But this August, the savings fell to 14%.

As cities get warmer, their trees lose some of their ability to take carbon out of the atmosphere

Beverly Hills, long a target of regulators' scorn, actually increased its water savings in August by about two percentage points compared with the same month in 2015.

"Everybody liked to pick on Beverly Hills in the beginning, but Beverly Hills is using less than half of what Malibu is," State Water Resources Control Board Chairwoman Felicia Marcus said.

Statewide, people in cities and towns cut their water use by just 17.7% in August, compared with the same month in 2013, state board staff members said. That's a dip from August 2015, when Californians reduced their consumption by 27%, beating the target of a 25% reduction set by Gov. Jerry Brown.

"We're at yellow alert," Marcus said. "I'm not ready to go to red alert until we see the details."

Regulators lifted mandatory conservation for the vast majority of the state's water suppliers beginning in June. That month, water savings fell sharply to 21.5%, and conservation has continued to flag each month since.

Water board members have defended their decision to ease the rules, saying that while a 25% statewide reduction in urban water use was necessary for a time, it could not continue indefinitely. They cite significant rains and snow in Northern California, which replenished some reservoirs, as helping reduce the need for conservation.

But faced with lower conservation numbers, officials on Wednesday acknowledged that easing the restrictions may have contributed to increased water consumption.

"There are some communities back over 500 gallons [per person] per day," Marcus said. "I'm not going to say, 'What's the story there?' But that's a question. ... Did they stop messaging, or what's happening?"

Mark Gold, UCLA's associate vice chancellor for environment and sustainability, called the August numbers "completely predictable."

"This is what we've come to expect when there are strong messages from Sacramento that the crisis isn't as bad as we thought it was," Gold said. "People, on their own, in a voluntary way, don't do as much to conserve."

The High Sierra forest is dying, and you can't count the loss in dead trees

California is broken down into 10 so-called hydrologic regions, and in every one, residents used more water per person per day in August 2016 than they did during the same month in 2015.

On average, Southern Californians used about 104 gallons per person per day, about 10 gallons more than they had the year prior, making them the fourth-lowest users among the 10 regions.

In April 2015, Brown ordered a 25% statewide reduction in urban water use, which the board tried to achieve by assigning conservation "standards" to each of the state's urban suppliers. Some were told to slash their usage by as much as 36%; others could cut as little as 4% and remain in compliance.

The suppliers were required to hit their targets beginning in June 2015. In the 15 months since, Californians have cumulatively cut their consumption by about 23%, state officials said. They have saved almost 660 billion gallons of water over that period — enough to provide water for 10 million residents for a year.

Some water officials were more optimistic than others about the August conservation numbers. Rob Hunter, general manager of the Municipal Water District of Orange County, noted that this August was two degrees warmer than August 2013, the baseline against which water savings was measured. So an 18% statewide reduction is something "we should be congratulating people for, not castigating people for," he said.

“That’s an incredible achievement,” Hunter said. “There was some concern there would be zero conservation, that everybody would start using more,” he added. “That’s not happening.”

But water board staff members also said conservation efforts tend to start sliding around this time of year, as the temperatures cool and water use dips. As urban Californians use less water, there is less savings to be had, officials say.

When the water year ended last week, forecasters and water officials warned that it will be hard to predict whether this winter will bring the rain and snow the state so desperately needs. And if a sixth year of drought is on the horizon, regulators have warned that they could return to mandatory conservation.

“While last year’s rain and snow brought a respite for urban California, we are still in drought, and we can’t know what this winter will bring,” Marcus said in a statement released later Wednesday. “What we do know is that climate change will continue to make our water years even more unpredictable, so we need to retain our conservation habits for the long term, rain or shine, drought or no drought.”

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Twenty-Five Years of Endocrine Disruption Science: Remembering Theo Colborn

Carol F. Kwiatkowski,[1,2] Ashley L. Bolden,[1] Richard A. Liroff,[3] Johanna R. Rochester,[1] and John G. Vandenbergh[4]

- For nearly 30 years, Dr. Theo Colborn (1927–2014) dedicated herself to studying the harmful effects of endocrine-disrupting chemicals on wildlife, humans, and the environment. More recently, she extended this effort to address the health impacts of unconventional oil and gas development. Colborn was a visionary leader who excelled at synthesizing scientific findings across disciplines. Using her unique insights and strong moral convictions, she changed the face of toxicological research, influenced chemical regulatory policy, and educated the public. In 2003, Colborn started a nonprofit organization—The Endocrine Disruption Exchange (TEDX). As we celebrate the 25th anniversary of endocrine disruption science, TEDX continues her legacy of analyzing the extensive body of environmental health research and developing unique educational resources to support public policy and education. Among other tools, TEDX currently uses the systematic review framework developed by the National Toxicology Program at the National Institute of Environmental Health Sciences, to answer research questions of pressing concern. In this article, we pay homage to the tenacious woman and the exemplary contribution she made to the field of environmental health. Recommendations for the future of the field are drawn from her wisdom.

Introduction

The field of endocrine disruption is widely recognized as having formally begun in 1991 with the historic meeting at the Wingspread Conference Center in Racine, Wisconsin. This year, the National Institute of Environmental Health Sciences (NIEHS) celebrates the 25th anniversary of endocrine disruption science with an open meeting to explore past lessons and future directions (http://tools.niehs.nih.gov/conference/endocrine_2016/index.cfm). This anniversary provides an opportunity to reflect on the role of Theo Colborn, the woman who many referred to as "the mother of endocrine disruption." In 1988, she saw the devastation of wildlife in the form of eggshell thinning, poor chick rearing, and the failure of offspring to thrive, and she feared for the health of humans. Prescient, tenacious, and passionate about the cause, she gathered the science and marched it to Washington, DC. When that was not enough, she rallied the masses with a hugely popular scientific detective story (Colborn et al. 1996). Although the development of the endocrine disruption movement was brought about by the contributions of many people (Schug et al. 2016), Theo Colborn was a seminal leader in the field (Grossman et al. 2015). In this article, we briefly chronicle her unique contribution, visionary leadership, and relentless voice for the health of future generations.

Early Discoveries and Regulatory Response

The story of endocrine disruption began with research on the health of wildlife in and around the Great Lakes of North America, which had been accumulating industrial pollutants for decades (Canada-United States Collaboration for Great Lakes Water Quality 2012). Although the lakes had been intensely studied by world-renowned scientists, few understood the significance of the research as a whole. This changed in 1987 when Colborn joined a bi-national "State of the Great Lakes" environmental project (Colborn et al. 1990; Musil 2014).

Colborn brought to this task an intense curiosity and appetite for multidisciplinary learning. Only a few years earlier, in a striking career change at the age of 58, she earned a Ph.D. in zoology with minors in epidemiology, toxicology, and water chemistry. Before this career change, she was a pharmacist in New Jersey in the 1950s and then a sheep rancher in western Colorado, where she raised her four children. Her life's wisdom combined with the enthusiasm of a new graduate gave her a unique perspective as she reviewed thousands of studies for the Great Lakes project. Not only did she voraciously consume the scientific literature, but she also networked with the many scientists whose studies she was reading—of which a handful had begun to sense the larger story. This rich cross-disciplinary conversation helped her connect patterns of health impacts that no scientist had previously made.

The result was what she would later label "that little grid that changed the world" (http://endocrinedisruption.org/about-tedx/theo-colborn). The grid featured 11 columns of health effects and 15 rows of wildlife species, with entries in the matrix denoting reported effects in each species. From bald eagles to beluga whales, mink to osprey, she showed the varying effects on reproduction, metabolism, and target organs. They were not all classic toxicological effects and were often only evident in the young. It became clear that chemicals were making their way up the food web, posing a threat not only to the health of the Great Lakes wildlife, but to people eating contaminated fish (Mehlman 1992).

To explore the research further, Colborn invited a small, carefully selected group of scientists to talk with each other face to face about their findings. In addition to wildlife biologists, she invited laboratory scientists, human health scientists, and others from 16 different disciplines, including endocrinology, toxicology, ecology, pharmacology, and anthropology. The meeting was held at the Wingspread Conference Center in Racine, Wisconsin, in July 1991. After several days of presenting their findings, the participants all agreed: "Many compounds introduced into the environment by human activity are capable of disrupting the endocrine system of animals, including fish, wildlife, and humans. The consequences of such disruption can be profound because of the crucial role hormones play in controlling development" (Mehlman 1992). It was at this meeting that the term "endocrine disruption" was coined. Perhaps more astonishing than such rapid cross-disciplinary consensus was that within five years of publication of what is now known as "The Wingspread Statement," laws were being drafted to identify endocrine-disrupting chemicals (U.S. EPA 1998). Such was the power of the woman referred to as "the little old lady in tennis shoes" who was storming the halls of Congress in the early 1990s.

One of her demands was a shift in the emphasis in government chemical risk assessments from end points related solely to cancer to functional end points relevant to the endocrine system (Colborn 1995). This led to the creation, in 1996, of the Endocrine Disruptor Screening and Testing Advisory Committee, a group of multiple stakeholders tasked with advising the U.S. Environmental Protection Agency (U.S. EPA) on creating a new chemical risk evaluation process that would address the health outcomes resulting from exposure to endocrine disruptors.

Unfortunately, the scope of the tasks of the resulting Endocrine Disruptor Screening Program would prove to be impossible to execute because of the meager funds and short time frame allotted. In 2014, Colborn was still bemoaning the lack of appropriate government intervention to address what science had discovered to be numerous disorders associated with exposure to endocrine-disrupting chemicals.

Educating the Public

Meanwhile, in 1996, Colborn and others were working to spread the word about endocrine disruption to a broader audience, beyond readers of scientific journals and academic texts. Colborn teamed with Dr. John Peterson Myers, director of the W. Alton Jones Foundation, and Dianne Dumanoski, an award-winning science journalist, to write *Our Stolen Future: Are We Threatening Our Fertility, Intelligence, and Survival? A Scientific Detective Story* (Colborn et al. 1996). In a forward by former Vice President Al Gore, he described it as a sequel to Rachel Carson's *Silent Spring* (Carson 1962); the story drew worldwide attention and has since been translated into at least 14 languages.

After the publication of *Our Stolen Future,* Colborn dedicated the rest of her life to educating the public about endocrine disruption. In 2003, she moved back to western Colorado when health concerns forced her to retire from the pressures of working in Washington, DC. This move was far from a retirement: At the age of 76, Colborn started a nonprofit organization, naming it The Endocrine Disruption Exchange (TEDX). It seemed fitting that the first three letters of the acronym TEDX were the initials of her birth name.

During this time, the chemical bisphenol A (BPA) was rapidly emerging as a chemical of concern due to its estrogenic properties. Colborn immediately went to work reviewing hundreds of studies. She and her staff compiled the data on the adverse health impacts of exposure to low concentrations of BPA in laboratory animals (http://endocrinedisruption.org/endocrine-disruption/bisphenol-a/overview). They made the results publicly available in a spreadsheet that categorized the findings and presented summary statistics with very little interpretation so that readers could examine and utilize the data as needed.

Another visionary concept of Colborn's that has become popular among scientists, academics, and students is referred to as "Critical Windows of Development" (http://endocrinedisruption.org/prenatal-origins-of-endocrine-disruption/critical-windows-of-development/overview). This interactive web page displays a timeline of the 38 weeks of human prenatal development. Superimposed on the timeline are studies indicating the disruptive effects of chemicals in laboratory animals. Thus, timing of normal developmental events in humans, such as the development of external genitalia, are chronologically aligned with the timing of chemical exposure in laboratory animals that leads to disruption, such as altered testes development. In addition to BPA, the effects of chlorpyrifos, dioxin, phthalates, and perfluorinated compounds are displayed on the timeline. A companion learning tool developed by TEDX is also available for college classroom exercises and discussion.

Colborn's second major area of investigation arrived in the form of threats to the health of citizens in western Colorado from rapid expansion of hydraulic fracturing, a fossil fuel extraction process now commonly known as fracking. Again, her first response was to survey the literature and compile the data on the potential health impacts of chemicals used by the industry. At the time, there was little concern about the process or the use of chemicals in such close proximity to residences. Colborn's commitment to public education drove her to travel the state of Colorado (then in her 80s) using an environmental justice grant from the U.S. Environmental Protection Agency (EPA) to give presentations to local communities about the process and potential harms from natural gas production in their neighborhoods. As with endocrine disruption, the issue quickly became political on a national scale.

In the eastern United States, exploration of the Marcellus Shale formation brought concerns for the safety of the water supply to New York City. TEDX was called upon to provide scientific information on the chemicals likely to be used and their potential health impacts. The New York City Water Board's Impact Assessment, citing "potentially catastrophic consequences" reverberated throughout the state and led to an eventual moratorium on hydraulic fracturing in New York (New York Department of Environmental Protection and Hazen and Sawyer Environmental Engineers and Scientists 2009). Colborn also published two peer-reviewed papers on the subject: a review of the public health implications (Colborn et al. 2011) and a primary research investigation of air quality in a western Colorado community heavily impacted by oil and gas development (Colborn et al. 2014). These efforts had a tremendous impact on the field and helped mobilize community efforts to bring the issues to the attention of federal and state agencies.

Continuing Colborn's Legacy

On December 14, 2014, Theo Colborn died peacefully in her home at the age of 87. She worked steadfastly and passionately until the day she died. In an "In Memoriam" in the journal *Environmental Health Perspectives*, her significance to the field was lauded, with Linda S. Birnbaum, the director of NIEHS, among the co-authors (Grossman et al. 2015). TEDX provided an on-line forum for her many friends and colleagues to post comments on her influence on their lives. Eighty stories from around the world remain posted (http://endocrinedisruption.org/about-tedx/theo-colborn).

The synthesis of research continues to drive the efforts of TEDX to engage scientists, regulatory agencies, and the public. In 2013, moving beyond data compilation and narrative reviews, TEDX began using systematic review methods derived from a framework developed by the NIEHS, National Toxicology Program (NTP), Office of Health Assessment and Translation (OHAT).

OHAT's approach provides a thorough and transparent framework for identifying literature, evaluating risk of bias of research studies (i.e., internal validity), and combining data from epidemiological, *in vivo* animal models, and *in vitro* studies to determine whether a chemical poses a hazard to human health (NTP 2015). In addition, TEDX has advanced beyond the simple tools Colborn had at her disposal and is using custom systematic review software, including machine-learning, text-mining, and data extraction tools, to allow more rapid and comprehensive assessment of relevant literature. The organization is also conducting meta-analyses to provide quantitative estimates of effects.

Aspects of the systematic review were integrated into a TEDX review of the connections between BPA exposure and human health conditions (Rochester 2013). More than 90 peer-reviewed studies were included, attesting to the contribution of BPA to reproductive disorders, adverse birth outcomes, altered behavior in children, asthma, and metabolic disorders. The review also discussed the various mechanistic pathways that might support the biological plausibility of such findings in humans. In 2015, TEDX published a systematic review of the physiological impacts of two BPA analogs: bisphenol F (BPF) and bisphenol S (BPS). These chemicals are commonly used as substitutes for BPA, which is being phased out of some products due to the evidence of endocrine disruption. TEDX's synthesis of the BPS and BPF studies have shown that these analogs are also endocrine disruptors that interact with the endocrine system via mechanisms similar to BPA (Rochester and Bolden 2015).

Systematic review methods were also used to assess potential endocrine disruptors for the International Chemical Secretariat's Substitute It Now (SIN) List, which urges the business community to replace chemicals in their products that are likely to be regulated under Europe's REACH legislation (http://chemsec.org/business-tool/sin-list/). The European Union is moving forward to adopt legally binding criteria to identify and regulate chemicals as endocrine disruptors. TEDX has contributed to such efforts by maintaining a publicly available list of potential endocrine disruptors (http://endocrinedisruption.org/endocrine-disruption/tedx-list-of-potential-endocrine-disruptors/overview) that has been used by many organizations, including the Joint Research Center of the European Commission and the NIEHS.

TEDX continues to address chemical exposure related to hydraulic fracturing. For example, it published a review of benzene, toluene, ethylbenzene, and xylenes (BTEX), which are products of oil and gas development. Exposure also comes from vehicular emissions and off-gassing of consumer products. The review concluded that BTEX may contribute to a variety of common health conditions including sperm abnormalities, reduced fetal growth, cardiovascular disease, respiratory dysfunction, asthma, and sensitization to common antigens (Bolden et al. 2015). Possible endocrine mechanisms were explored in the review. Notably, health effects of BTEX exposure were found at concentrations well below reference concentrations (i.e., safe levels) set by the U.S. EPA (Bolden et al. 2015). TEDX is also conducting a project to help prioritize chemicals that may be leading to endocrine, reproductive, birth, and long-term health effects in residents living near oil and gas development. This topic will be of continuing national concern as the Mancos Shale in western Colorado and eastern Utah was just determined to have the second largest reserve of technically recoverable gas after the Marcellus Shale formation in the eastern United States (Hawkins et al. 2016).

In addition to publishing in the peer-reviewed literature, TEDX also works to educate the general public. For example, TEDX organizes and hosts teleconference calls in which scientists present their findings and answer questions from the audience. These calls are recorded and available for listening at any time (http://endocrinedisruption.org/endocrine-disruption/videos-and-webinars). The calls address endocrine disruption and the health impacts associated with unconventional oil and gas development.

Embracing the Future

As a testimony to how far the field has come in 25 years, it is remarkable to note that today several prestigious professional societies have called for preventive measures to avoid exposure to endocrine-disrupting chemicals. These include the Endocrine Society (Gore et al. 2015; Zoeller et al. 2012), the American College of Obstetricians and Gynecologists and the American Society for Reproductive Medicine (American College of Obstetricians and Gynecologists Committee on Health Care for Underserved Women et al. 2013), and the International Federation of Gynecology and Obstetrics (Di Renzo et al. 2015). Using their recommendations, TEDX is developing a project to provide practical advice to the general public on steps they can take to avoid exposure to endocrine-disrupting chemicals.

TEDX has recently evolved beyond the small town of Paonia in western Colorado, where it originated, and is currently developing a branch in North Carolina's Research Triangle Park (RTP), a hub of environmental health research and the home of NIEHS and a major U.S. EPA research campus. RTP represents a unique blend of academia, government, and industry. Surrounded by three major research universities: North Carolina State University, the University of North Carolina, and Duke University, it is home to roughly 100 corporations and several government and nongovernment laboratories, including many related to toxicological and biomedical sciences.

The universities provide a steady stream of well-trained students to support the research laboratories in the area. On April 29, 2016, the NIEHS and the U.S. EPA co-hosted the 19th Annual NIEHS Biomedical Career Symposium at which TEDX participated in a panel on nonprofit organizations in the biosciences. TEDX plans to make use of the human, scientific, and technological resources as it puts down new roots in the RTP area.

Conclusion

In one of her last public presentations, Colborn addressed President Barack Obama and the First Lady Michelle Obama of the United States in a direct, heartfelt, and poignant letter (https://www.youtube.com/watch?v=2r2Rx8VRq48). Identifying herself as a grandmother, she spoke of how little her generation worried about their children's development beyond obvious birth defects. She expressed her dismay at how today's parents must immediately fear the enormous odds of their children having attention deficit hyperactivity disorder, autism, asthma, diabetes, or obesity.

With her characteristic intensity and deeply knitted brow, she demanded a new program of "inner space" research, funded comparably to the country's investment in exploring outer space.

She envisioned a council of scientists, including endocrinologists, who understand the chemistry of the womb and how even small concentrations of endocrine-disrupting chemicals can cross the placenta and cause harm. Knowing she would not see such a council within her lifetime, she expressed the need for urgent action, more rapid than efforts to address climate change. Protection of the public health requires no less. Upon returning home she reflected that she had said her piece; it was up to the rest of us now.

Colborn's letter to President Obama embodies everything that she stood for. It addresses policy at the very highest level, it demands inclusion of scientists in decision-making, and it is a personal appeal to the public to demand better protection from our government. Theo Colborn was an inspiration to all. She led a full life and then dedicated herself to public service, changing environmental health research as we know it. Motivated by her words, TEDX continues to inform and inspire scientific inquiry, deliver practical information to government decision makers, and expand public understanding of endocrine disruption, and does so all in an effort to reduce the risk posed by endocrine-disrupting chemicals to the health of humans and wildlife.

References

American College of Obstetricians and Gynecologists Committee on Health Care for Underserved Women, American Society for Reproductive Medicine Practice Committee, University of California, San Francisco Program on Reproductive Health and the Environment. 2013. Exposure to toxic environmental agents. Committee Opinion No. 575. Obstet Gynecol 122(4):931–935.

Bolden AL, Kwiatkowski CF, Colborn T. 2015. New Look at BTEX: Are Ambient Levels a Problem? Environ Sci Technol 49(9):5261–5276.

Canada-United States Collaboration for Great Lakes Water Quality. 2012. Great Lakes Water Quality Agreement. Areas of Concern (Annex 1). https://binational.net/2012/09/05/2012-glwqa-aqegl/ [accessed 13 June 2016].

Carson R. 1962. *Silent Spring*. Boston, MA:Houghton Mifflin Company.

Colborn T. 1995. Pesticides—how research has succeeded and failed to translate science into policy: endocrinological effects on wildlife. Environ Health Perspect 103(suppl 6):81–85.

Colborn T, Davidson A, Green SN, Hodge RA, Jackson CI, Liroff RA. 1990. *Great Lakes Great Legacy?* Washington, DC:World Wildlife Fund.

Colborn T, Dumanoski D, Myers J. 1996. *Our Stolen Future: Are We Threatening Our Fertility, Intelligence, and Survival? A Scientific Detective Story*. New York, NY:Dutton.

Colborn T, Kwiatkowski C, Schultz K, Bachran M. 2011. Natural gas operations from a public health perspective. Hum Ecol Risk Assess 17(5):1039–1056.

Colborn T, Schultz K, Herrick L, Kwiatkowski C. 2014. An Exploratory Study of Air Quality near Natural Gas Operations. Hum and Ecol Risk Assess 20(1):86–105.

Di Renzo GC, Conry JA, Blake J, DeFrancesco MS, DeNicola N, Martin JN Jr, et al. 2015. International Federation of Gynecology and Obstetrics opinion on reproductive health impacts of exposure to toxic environmental chemicals. Int J Gynecol Obstet 131(3):219–225, doi: 10.1016/j.ijgo.2015.09.002.

Gore AC, Chappell VA, Fenton SE, Flaws JA, Nadal A, Prins GS, et al. 2015. EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals. Endocr Rev 36(6):E1–E150, doi: 10.1210/er.2015-1010.

Grossman E, Vandenberg LN, Thayer K, Birnbaum LS. 2015. Theodora (Theo) Colborn: 1927–2014. Environ Health Perspect 123(3):A54, doi: 10.1289/ehp.1509743.

Hawkins SJ, Charpentier RR, Schenk CJ, Leathers-Miller HM, Klett TR, Brownfield ME, et al. 2016. Assessment of continuous (unconventional) oil and gas resources in the Late Cretaceous Mancos Shale of the Piceance Basin, Uinta-Piceance Province, Colorado and Utah, 2016. Fact Sheet 2016-3030. Reston, VA:U.S. Geological Survey. http://dx.doi.org/10.3133/fs20163030 [accessed 13 June 2016].

Mehlman MA. 1992. Advances in Modern Environmetal Toxicology. Volume XXI. Chemically-Induced Alterations in Sexual and Functional Development: The Wildlife/Human Connection. Colborn T, Clement C, eds. Princeton, NJ:Princeton Scientific Publishing Co., Inc.

Musil RK. 2014. *Rachel Carson and Her Sisters: Extraordinary Women Who Have Shaped America's Environment.* New Brunswick, NJ:Rutgers University Press.

New York Department of Environmental Protection, Hazen and Sawyer Environmental Engineers and Scientists. 2009. Final Impact Assessment Report: Impact Assessment of Natural Gas Production in the New York City Water Supply Watershed. http://www.nyc.gov/html/dep/pdf/natural_gas_drilling/12_23_2009_final_assessment_report.pdf [accessed 13 June 2016].

NTP (National Toxicology Program). 2015. Handbook for Conducting a Literature-Based Health Assessment Using OHAT Approach for Systematic Review and Evidence Integration. https://ntp.niehs.nih.gov/ntp/ohat/pubs/handbookjan2015_508.pdf [accessed 13 June 2016].

Rochester JR. 2013. Bisphenol A and human health: a review of the literature. Reprod Toxicol 42:132–155, doi: 10.1016/j.reprotox.2013.08.008.

Rochester JR, Bolden AL. 2015. Bisphenol S and F: a systematic review and comparison of the hormonal activity of bisphenol A substitutes. Environ Health Perspect 123(7):643–650.

Schug TT, Johnson AF, Birnbaum LS, Colborn T, Guillette LJ, Crews D, et al. 2016. Minireview: endocrine disruptors: past lessons and future directions. Mol Endocrinol 30(8):833–847, doi: 10.1210/me.2016-1096.

U.S. EPA (Environmental Protection Agency). 1998. Endocrine Disruptor Screening Program (EDSP). Fed Reg 53(154):42852–42855. https://www.gpo.gov/fdsys/pkg/FR-1998-08-11/pdf/98-21522.pdf [accessed 26 August 2016].

Zoeller RT, Brown TR, Doan LL, Gore AC, Skakkebaek NE, Soto AM, et al. 2012. Endocrine-disrupting chemicals and public health protection: a statement of principles from the Endocrine Society. Endocrinology 153(9):4097–4110.

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Informing 21st-Century Risk Assessments with 21st-Century Science

Linda S. Birnbaum,[1] Thomas A. Burke,[2] and James J. Jones[3]

PDF Version (140 KB)

- Summary
- About This Article

- Understanding and preventing adverse impacts from chemicals in the environment is fundamental to protecting public health, and chemical risk assessments are used to inform public health decisions in the United States and around the world. Traditional chemical risk assessments focus on health effects of environmental contaminants on a chemical-by-chemical basis, largely based on data from animal models using exposures that are typically higher than those experienced by humans. Results from environmental epidemiology studies sometimes show effects that are not observed in animal studies at human exposure levels that are lower than those used in animal studies. In addition, new approaches such as Toxicology in the 21st Century (Tox21) and exposure forecasting (ExpoCast) are generating mechanistic data that provide broad coverage of chemical space, chemical mixtures, and potential associated health outcomes, along with improved exposure estimates. It is becoming clear that risk assessments in the future will need to use the full range of available mechanistic, animal, and human data to integrate multiple types of data and to consider nontraditional health outcomes and end points. This perspective was developed at the "Strengthening the Scientific Basis of Chemical Safety Assessments" workshop, which was cosponsored by the U.S. Environmental Protection Agency and the National Institute of Environmental Health Sciences, where gaps between the emerging science and traditional chemical risk assessments were explored, and approaches for bridging the gaps were considered.

Introduction

Understanding and preventing adverse impacts from chemicals in the environment is fundamental to protecting public health, and scientifically sound chemical risk assessments are needed to support a variety of environmental protection decisions across the United States and around the world. Risk assessments provide qualitative information about a chemical's health effects and quantitative information that helps inform the scope of national regulatory decisions, state and community decisions, and industry practices.

The 1983 four-step framework—hazard identification, dose response, exposure assessment, and risk characterization—developed by the National Research Council (NRC 1983) has shaped chemical risk assessments worldwide. However, the wide range of policy and regulatory applications within and across federal and state agencies in the United States and internationally, has led to an equally wide range of risk assessment practices. These different approaches may yield conflicting results and have contributed to concerns about the scientific credibility of risk assessments and related risk management decisions. The emergence of new methods in computational toxicology, exposure science, epidemiology, and systematic review hold great promise for advancing risk assessment. However, integration of these new approaches into established regulatory frameworks presents scientific and policy challenges.

The majority of regulatory frameworks guide risk assessment from the perspective of a single chemical or single component of a product formulation and often do not account for multiple chemical exposures and mixtures. Furthermore, most chemical risk assessments of potential human health effects rely on testing in animal models using exposures that are typically higher than those experienced by humans. This testing model requires the assessor to extrapolate to lower doses and across species, and it provides limited consideration of variability within species. All of these factors undermine confidence that current risk assessments are protective of human health, particularly for the most vulnerable individuals, communities, and life stages.

Results from environmental epidemiology studies have raised questions about whether traditional animal toxicology studies adequately predict health effects in human populations. These studies sometimes report effects that are not seen in animal studies, and hypothesis-based epidemiological studies may not yield data that can be easily incorporated into chemical risk assessments using existing frameworks and guidelines. Myriad publications in environmental and public health journals describe subtle chemical–biological interactions with population health effects that are not captured in traditional toxicity testing. The health effects observed in the epidemiological studies are typically different from end points evaluated in animal-based toxicity tests for hazard evaluation in chemical risk assessments. The real world exposure events depicted in epidemiology studies often do not correlate with exposures traditionally used in toxicity testing, which are most often much higher than exposures experienced in human populations. Furthermore, epidemiological studies incorporate background and chronic low-dose exposures that are not considered in traditional toxicity testing. Likewise, they may be able to capture population variability, which can be important for organizations charged with protecting public health.

Twenty-first century science is providing tremendous advances in systems biology, genomics and epigenetics, bioinformatics, exposure science, and environmental epidemiology, as well as innovations in chemical measurement and analytical technologies: All these advances are expanding our understanding of how chemicals can interact with biological systems. New approaches such as Toxicology in the 21st Century (Tox21; https://ncats.nih.gov/sites/default/files/factsheet-tox21.pdf) and exposure forecasting (ExpoCast; http://www.epa.gov/sites/production/files/2014-12/documents/exposure_forecasting_factsheet.pdf) are generating data that provide broad coverage of chemical space, chemical mixtures, and potential associated health outcomes, along with improved exposure estimates. Further development and use of systematic review will provide more transparency and more consistency and confidence in the integration of mechanistic, animal, and human data for use in risk assessments.

To provide a forum to discuss how science in the 21st century can bring about improvements in the risk assessment process, the U.S. Environmental Protection Agency (EPA) and the National Institute of Environmental Health Sciences (NIEHS) cosponsored the workshop "Strengthening the Scientific Basis for Chemical Safety Assessments," which took place 15–16 July 2015 in Research Triangle Park, North Carolina. Participants included individuals with the diverse expertise in toxicology, epidemiology, and risk assessment needed to move this discussion forward. At the workshop, participants discussed the gaps in understanding between the new scientific methods and conventional approaches: These discussions led to proposed activities to bridge the gaps.

Introductory talks reviewed the growing evidence that exposures to a wide variety of chemicals encountered in daily life in the United States are linked to adverse health effects, including neurological deficits in children and adults, asthma, cardiovascular disease, and cancer. Invited speakers presented case studies to illustrate and provide background information for key topic areas including accounting for exposures during critical developmental windows, capturing variability in population susceptibility, translating experimental animal findings to humans, and addressing cumulative exposures. The group also discussed the perception prevalent in the public health community that chemical risk assessments, as currently carried out by the U.S. EPA and other agencies, are not sufficiently health protective. A strong theme among the participants was that new approaches have to be developed to incorporate data beyond traditional experimental and animal studies to support chemical safety evaluations that could prevent adverse health effects in the U.S. population.

Understanding the Gaps between New and Conventional Methodologies

The Chasm between Environmental Epidemiology and Risk Assessment

It was immediately apparent that there is limited understanding or familiarity, outside of the practitioners, with how risk assessments are conducted in federal regulatory agencies. As a consequence, most research investigations are not optimally designed to provide the types of information that are needed in current assessments. This lack of appropriate design can extend through the selection of study end points and the recording and reporting of findings, to an appreciation of required study design elements to inform a risk assessment. Conversely, current chemical risk assessment practices of the U.S. EPA and other federal agencies have not evolved to optimally consider and incorporate the information emerging from observational human research. Many risk assessment professionals lack understanding of epidemiology study designs, methods, strengths, and limitations. As a result, much potentially valuable information is excluded from the regulatory risk assessment process.

Exposure, the Missing Link

Exposures, as observed, measured, and reported in environmental epidemiology studies, typically represent real-world exposures. These are often reported at levels below those used and delivered in traditional animal toxicology studies, and they are rarely confined to a single or few agents of concern, making it difficult to definitively elucidate causality in the hypothesized association with exposures. In contrast, when estimating the risks of use of a single pesticide, the assessment only considers the risk of exposure to the pesticide active ingredient, but the inert components in a pesticide formulation to which individuals are inevitably co-exposed, and which could modify the response, are usually not considered in the risk assessment. In addition, whereas exposures in observational studies encompass background exposures and chronic low-dose exposures to single or multiple chemicals, toxicological studies do not typically model or account for these.

Importance of Life-Stage Exposures and Multigenerational Effects

Many of the environmental epidemiology studies discussed at the workshop probed the importance of windows of exposures, with the focus on parent and child exposures during critical life stages, such as preconception and perinatal periods, and understanding early-life determinants of lifelong diseases. While data from epidemiological studies also point to potential amplification of the adverse effects of these early-life exposures, including multigenerational effects, it was recognized that these effects are not modeled in standard toxicological studies or evaluated in risk assessments because data on which to judge such health outcomes are largely missing and not required. It will be necessary to expand approaches used to integrate mechanistic, animal, and human data in order to bridge gaps and inform risk assessment methods. The U.S. EPA and the NIEHS are committed to helping support cross-disciplinary efforts to achieve this goal.

Understanding the Role of Nonchemical Stressors

There are many nonchemical stressors that are often overlooked in the conduct of risk assessments. Yet, current data, both from toxicological and epidemiological studies, demonstrate that physical agents such as light and noise, infectious agents, the microbiome, psychosocial factors, and nutrition can have significant impacts on health effects from chemical exposures. For example, while all the workshop participants agreed that stress is an important modifying factor for health, it is currently not considered as a risk cofactor or modeled in most studies on which risk assessments are based. However, the science that addresses biochemical markers of stress is evolving, and it was proposed that this evolution would be important to quantitatively study the interactions between stress and chemical exposures and account for both in chemical risk assessments. Stress is but one of many factors that may contribute to vulnerability within a population. Current practices that risk assessors use to account for vulnerability, such as uncertainty or safety factor adjustments, may not adequately capture true population vulnerability, such as that associated with stress or genetic variance. The extent to which this might be the case is currently unknown. There likely will be challenges in using data on nonchemical stressors in assessments that support regulatory action under various regulatory statutes in ways that promote improved public health.

Influence of Funding Priorities

It was acknowledged that research specifically aimed at addressing a data gap for the purpose of a risk assessment is not likely to be funded through the typical grants review processes of the National Institutes of Health (NIH). Perhaps because of the funding priorities, academic investigators by and large study environmental exposures in the context of understanding their contributions to a disease or related adverse mechanistic event that is often not well aligned with the typical phenotypic end points measured and relied upon in regulatory or guideline toxicology studies. At this time, these types of toxicology studies are at the foundation of most chemical risk assessments that inform chemical safety evaluations. The U.S. EPA and the NIEHS recognize the value of fostering and funding such studies and collaborations. There is concern that the funding gap is likely to grow if not addressed systematically and deliberately.

Proposed Bridging Activities

Based on discussions of immediate and longer-term activities to bridge the gaps in understanding, the workshop participants drew conclusions and recommended several activities.

Increase Communication

It is important to find mechanisms to increase communication among researchers in multiple disciplines, including toxicology, epidemiology, and risk assessment. Suggestions were made to advance this communication. For example, the U.S. EPA could sponsor hands-on risk assessment experiences for researchers through short residential courses. Scientists within the U.S. EPA and outside the agency could also form scientific teams to work together to develop ways to improve the consideration and incorporation of epidemiology data into risk assessments, including in-depth analyses of study designs, dose metrics, confounding, and sampling issues. This could be accomplished by collaborating on consensus workshops or white papers.

Enrich Funding Mechanisms

Teams of experimental and observational scientists and risk assessors could explore collaborations to design competitive grants programs that promote and fund studies to provide data of direct relevance to chemical risk assessment. This could be facilitated by the creation of dedicated grant review study sections.

Examine Methods to Make Risk Assessments More Robust and Inclusive

It was suggested that teams carry out targeted case studies to examine how well risk assessment projections for "safe exposures" relate to exposures in a human population that are being linked to adverse health effects. To help with this examination, the U.S. EPA has asked the National Academies of Sciences, Engineering, and Medicine to help develop a strategy for evaluating whether the agency's current regulatory toxicity-testing practices allow for adequate consideration of evidence of low-dose adverse human effects. A published report from this committee—Unraveling Low-Dose Toxicity: Case Studies of Systematic Review of Evidence (http://www8.nationalacademies.org/cp/projectview.aspx?key=49716)— is expected in early 2016 and could help improve understanding of cases where low-dose effects may have not been detected in current regulatory studies.

Move Away from Reliance on Apical End Points

The risk assessment community should continue to explore ways to move away from the use of traditional phenotypic effects and outcomes in regulatory guideline animal safety assessment studies. Perturbations of molecular pathways involved in adverse phenotypic end points were considered to be potentially useful and might provide a better link between molecular epidemiology findings and traditional animal toxicology studies. It was suggested that the U.S. EPA and the NIEHS convene workshops to explore the relationships between *a*) observed potentially environmentally induced diseases, *b)* the typical phenotypic responses seen in animal toxicology studies, and *c*) the adverse outcome pathways (AOPs) that might relate the two together. A logical follow-on to these activities would be to expand studies to examine chemical interactions that work through different points of an AOP, particularly with respect to dose–response relationships and considerations of chemical mixtures.

Another suggestion was to simply begin to routinely use alternative end points, such as analyzing key characteristics of biologic pathways, for risk assessments, rather than only using apical health effects. Such analyses would require significant policy and possibly legislative changes, as well as significant outreach and education, considering some of the recent judicial interpretations of regulations promulgated under existing laws.

Incorporate Interindividual Variability in Place of Default Safety Factors

One of the critical challenges in risk assessment is how interindividual variability and differential susceptibility are evaluated and incorporated. In order to address this challenge, scientific findings could be used in place of default uncertainty or safety factors to address population susceptibility. For example, one might use the profile of population variance in phase 1 or phase 2 enzyme activities for metabolism of selected chemical structures in place of default safety factors. It was pointed out, however, that variability in these enzymes in humans could be in excess of 100-fold. An alternate but related suggestion was to examine chemical structures agnostically with the intent of understanding chemical attributes that tend to produce highly variable responses across populations. This could be approached through an expansion of the Tox21–1000 Genomes Project (Abdo et al. 2015). Data from this project—with respect to 156 compounds in nearly 900 lymphoblastoid cell lines from five ethnic groups—has demonstrated that variability among individuals can be more than 200-fold. However, data from this project addresses genetic variability but does not consider other critical influences, such as life stage, diet, and the microbiome.

Characterize and Incorporate Chemical Co-exposures

Methods need to be developed to incorporate emerging data on chemical co-exposures into risk assessments. Broader applications of novel technologies to examine patterns of common chemical co-exposures in populations, as well as advances in bioinformatics and in nontargeted chemical analyses of human biospecimens, hold promise to provide this in ways that avoid the current need for large volumes of blood (Guo et al. 2015). Current chemical risk assessments do not consider every stressor, since we do not have the data or know how to do this. Instead, they most often assess cumulative risk for common modes of action as required by law and supported by science. While imperfect, this may be a useful starting point for considering improving current practices and generating missing data on co-exposures.

Study and Consider Multigenerational Effects

The potential significance of multigenerational inheritance of risks was noted, and there was recognition that this adds another vastly complicating dimension to understanding and estimating the risks of current exposures. This concept is one of the areas of scientific focus for the NIEHS 2012–2017 Strategic Goals (https://www.niehs.nih.gov/about/strategicplan/), and a systematic review of the current literature pertaining to this topic is underway. This comprehensive review will hopefully provide a basis for more definitive research in this area. Current multigenerational toxicity test methods in rats and other species have limitations, and there are opportunities to improve test guidelines and create integrated testing and assessment strategies that include mechanistic, animal, and human data.

Relevance of Emerging Science to Risk Assessments

The U.S. EPA and NIEHS, in collaboration with other agencies, have asked the National Academies of Sciences, Engineering, and Medicine to provide guidance on integrating new scientific approaches into risk-based evaluations. The report from this committee—Incorporating 21st Century Science into Risk-Based Decisions (http://www8.nationalacademies.org/cp/projectview.aspx?key=49652)—is not expected to be published until early 2016, and as such, this topic was not central to the discussions at the meeting. Nevertheless, it was broadly acknowledged that there is currently little experience or precedence for incorporating the emerging 21st-century science into risk assessments: This includes the appropriate use of Tox21 high-throughput screening (HTS) information, commensurate high-throughput exposure estimations, nontargeted metabolomics, high-throughput transcriptomic, and other forms of emerging big data. This may also require an appreciation and understanding of how to assess the validity of proposed AOPs and networks and how to use them in informing risk assessments.

Conclusions

Understanding the environmental determinants of disease and protecting susceptible and vulnerable populations are daunting scientific challenges. Addressing these challenges will require an inclusive multidisciplinary research approach and an improved recognition of the methods and informational needs of risk assessors. Progress will also require coordination across multiple federal programs and agencies—especially in resource-constrained times.

The 2015 workshop started with the recognition that there is a chasm between current risk assessment practices and evolving data from mechanistic and environmental epidemiological studies; it concluded with several concrete, practical, and achievable steps to help the U.S. EPA, the NIEHS, and the broader scientific community strengthen the scientific basis for chemical risk assessments. The resounding message of the workshop is that both federal agencies need to work with the research community to ensure that our assessments incorporate current science and consider the full range of vulnerabilities within the population. This research and assessement strategies are fundamental to our mission to ensure that our communities are safe, our air and water are clean, and our most vulnerable populations are adequately protected.

References

Abdo N, Xia M, Brown CC, Kosyk O, Huang R, Sakamuru S, et al. 2015. Population-based *in vitro* hazard and concentration–response assessment of chemicals: the 1000 Genomes high-throughput screening study. Environ Health Perspect 123(5):458–466, doi: 10.1289/ehp.1408775.

Guo L, Milburn MV, Ryals JA, Lonergan SC, Mitchell MW, Wulff JE, et al. 2015. Plasma metabolomic profiles enhance precision medicine for volunteers of normal health. Proc Natl Acad Sci USA 112(35):E4901–E4910, doi: 10.1073/pnas.1508425112.

NRC (National Research Council). 1983. Risk Assessment in the Federal Government: Managing the Process. Washington, DC:National Academy Press. Available: http://www.nap.edu/catalog/366/risk-assessment-in-the-federal-government-managing-the-process [accessed 18 February 2016].

EHN founder honored as environmental health champ

Pete Myers

Pete Myers recognized as one of 12 inaugural 'Champions of Environmental Health Research'

Oct. 10, 2016

Environmental Health News staff report

CHARLOTTESVILLE, Va. – Pete Myers, founder and chief scientist of Environmental Health Sciences, has been recognized by the National Institutes of Health for "significant contributions" to how our environment influences the health of communities, families and individuals worldwide.

Myers is one of 12 "Champions of Environmental Health Research," picked to commemorate 50 years of such work by the National Institute of Environmental Health Sciences, part of NIH. This is the first time in its history that NIH has bestowed this award.

"It's a complex research field that needs the attention of top scientists, and I congratulate these awardees for their outstanding contributions," said Dr. Francis Collins, director of the National Institutes of Health.

It's a complex research field that needs the attention of top scientists, and I congratulate these awardees for their outstanding contributions.
– Dr. Francis Collins, NIH The NIEHS is part of the National Institutes of Health and funds about 1,000 grants totaling more than $300 million a year. Overall the NIH invests $32 billion annually in medical research.

In bestowing the award, NIEHS director Linda Birnbaum cited Myers' contributions to global awareness of the health effects of endocrine-disrupting chemicals. Myers' "leadership and exceptional commitment to promote scientific excellence in environmental health science," Birnbaum wrote, has helped fuel "sound public policy decisions."

Other champions include Charles Blumberg, an architect and principal player in the sustainable buildings movement; Dr. Jeffrey Gordon, an expert on the microbiome; Dr. Philip Landrigan, a pediatrician known for decades of work protecting children against environmental threats; and Jeanne Rizzo, head of the Breast Cancer Fund.

"For someone who completed a Ph.D. in behavioral ecology almost 40 years ago and began environmental health work in earnest only in 1990, it is truly humbling to be listed alongside these giants in the field," Myers said. "I've been fortunate to have many mentors and colleagues guide me, and a terrific staff at EHS who made all this work possible."

The champions will be honored during an NIEHS 50th anniversary program on Nov. 1 in Research Triangle Park, N.C.

This is the second major public service award Myers has won this year for his work on endocrine-disrupting chemicals. In April Myers shared the Endocrine Society's ;"Laureate Award for Outstanding Public Service" with Jean Pierre Bourguignon of the University of Liege, Andrea Gore of the University of Texas and Thomas Zoeller of the University of Massachusetts. The Endocrine Society is the world's largest professional association of endocrinologists, medical doctors, scientists and educators dedicated to researching and treating conditions and diseases related to the human body's complex system of glands and hormones.

Myers is an author or co-author of numerous peer-reviewed research papers and the 1996 book, "Our Stolen Future," that explores the scientific basis for how contamination threatens fetal development.

He is chief scientist of Environmental Health Sciences, a not-for-profit organization he founded in 2002 to increase public understanding of the scientific links between environmental factors and human health. Environmental Health Sciences publishes two news websites, EHN.org and DailyClimate.org.

Myers has served as board chair of H. John Heinz III Center for Science, Economics and the Environment; the Consultative Group on Biological Diversity; and the National Environmental Trust (now part of the Pew Charitable Trusts). He is a trustee of the Jenifer Altman Foundation.

In 2013 Myers was awarded the Frank Hatch "Sparkplug" Award for enlightened public service by the John Merck Fund. And in 2014 Myers shared, with Arlene Blum and the late Theo Colborn, the Jean and Leslie Douglas "Pearl Award," bestowed by the Cornell Douglas Foundation for work providing a sustainable planet for future generations.

Learn about Pete Myers' work in this video of a talk he gave, in the round, at the Abbey Road Studios in London earlier this year.

EHN welcomes republication of our stories, but we require that publications include the author's name and Environmental Health News at the top of the piece, along with a link back to EHN's version.

For questions or feedback about this piece, contact Brian Bienkowski at bbienkowski@ehn.org.

Environmental Health **NEWS**

10 October **Environmental justice in Canada's Chemical Valley.** Home is both refuge and prison for citizens of Canada's Chemical Valley. Environmental Health News.

10 October **EHN founder honored as environmental health champ.** Pete Myers recognized as one of 12 inaugural 'Champions of Environmental Health Research'. Environmental Health News.

10 October **EHN founder honored as environmental health champ.** Pete Myers recognized by the National Institutes of Health as one of 12 inaugural 'Champions of Environmental Health Research'. Environmental Health News.

8 October **COAL: The War Years.** Where will history mark the turning points— the Gettysburgs, Antietams and Andersonvilles—of the War On Coal? Environmental Health News.

5 October **VIDEO: Calling out pollution, two dozen are arrested in Virginia.** 'Citizens' Picket' seeks more aggressive action from Gov. Terry McAuliffe on coal ash, pipelines and rising seas. Environmental Health News.

30 September **Commentary: Choose a climate savvy UN Secretary General for global stability.** The next Secretary General needs a skill set that matches 21st century challenges. Daily Climate.

29 September **One tribe's 'long walk' upstream for environmental and cultural justice.** Wisconsin's Menominee tap their forebears—and Native American cultural rebirth underway in North Dakota—on a walk to protect their river. A "Sacred Water" story. Environmental Health News.

24 September **Analysis: Environmental journalism reaches middle age, with mixed results.** There's a wariness that environmental journalists are a hybrid of activism and reporting. Can the beat ever outgrow that? Environmental Health News.

24 September **Analysis: Environmental journalism reaches middle age, with mixed results.** There's a wariness that environmental journalists are a hybrid of activism and reporting. Can the beat ever outgrow that? Environmental Health News.

21 September **Essay: Standing together.** We, Menominees, were given the responsibility to look after that river and land by the creator thousands of years ago, and that supersedes any treaty or law. This Menominee River is a part of me; its essence is within my soul. Environmental Health News.

20 September **River fight boosts a tribe's long-threatened culture.** The Menominee Tribe, fighting a losing battle with regulators over a mine near their namesake river, has emerged with a stronger, vibrant voice. Environmental Health News.

19 September **Mining in Copper Country.** While there's been a recent resurgence in mining interest in Michigan's Upper Peninsula, historically mining was to Michigan's Upper Peninsula what the auto industry is to the Lower Peninsula. Environmental Health News.

19 September **Mining leaves a Wisconsin tribe's hallowed sites at risk.** Modern boundaries complicate —and stymie—the Menominee Tribe's effort to protect burial grounds. A "Sacred Water" story. Environmental Health News.

19 September **Commentary: 25 years of endocrine disruptor research – great strides, but still a long way to go.** In celebrating 25 years of endocrine disruptor research this week we should acknowledge both the significant strides made and the need to continue this work to further protect people's health. Environmental Health News.

15 September **A call for innovation in our cities.** Rockefeller Foundation and a startup incubator offer $1m in seed money for ideas that solve pollution, inequality affecting urban poor. Environmental Health News.

Recent Environmental Health News coverage

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Environ Health Perspect; DOI:10.1289/EHP358

Project TENDR: Targeting Environmental Neuro-Developmental Risks. The TENDR Consensus Statement

PDF Version (181 KB)

- Summary
- About This Article

- **SUMMARY:** Children in America today are at an unacceptably high risk of developing neurodevelopmental disorders that affect the brain and nervous system including autism, attention deficit hyperactivity disorder, intellectual disabilities, and other learning and behavioral disabilities. These are complex disorders with multiple causes—genetic, social, and environmental. The contribution of toxic chemicals to these disorders can be prevented.

- **APPROACH**: Leading scientific and medical experts, along with children's health advocates, came together in 2015 under the auspices of Project TENDR: Targeting Environmental Neuro-Developmental Risks to issue a call to action to reduce widespread exposures to chemicals that interfere with fetal and children's brain development. Based on the available scientific evidence, the TENDR authors have identified prime examples of toxic chemicals and pollutants that increase children's risks for neurodevelopmental disorders. These include chemicals that are used extensively in consumer products and that have become widespread in the environment. Some are chemicals to which children and pregnant women are regularly exposed, and they are detected in the bodies of virtually all Americans in national surveys conducted by the U.S. Centers for Disease Control and Prevention. The vast majority of chemicals in industrial and consumer products undergo almost no testing for developmental neurotoxicity or other health effects.

- **CONCLUSION**: Based on these findings, we assert that the current system in the United States for evaluating scientific evidence and making health-based decisions about environmental chemicals is fundamentally broken. To help reduce the unacceptably high prevalence of neurodevelopmental disorders in our children, we must eliminate or significantly reduce exposures to chemicals that contribute to these conditions. We must adopt a new framework for assessing chemicals that have the potential to disrupt brain development and prevent the use of those that may pose a risk. This consensus statement

lays the foundation for developing recommendations to monitor, assess, and reduce exposures to neurotoxic chemicals. These measures are urgently needed if we are to protect healthy brain development so that current and future generations can reach their fullest potential.

A Call to Action

The TENDR Consensus Statement is a call to action to reduce exposures to toxic chemicals that can contribute to the prevalence of neurodevelopmental disabilities in America's children. The TENDR authors agree that widespread exposures to toxic chemicals in our air, water, food, soil, and consumer products can increase the risks for cognitive, behavioral, or social impairment, as well as specific neurodevelopmental disorders such as autism and attention deficit hyperactivity disorder (ADHD) (Di Renzo et al. 2015; Gore et al. 2015; Lanphear 2015; Council on Environmental Health 2011). This preventable threat results from a failure of our industrial and consumer markets and regulatory systems to protect the developing brain from toxic chemicals. To lower children's risks for developing neurodevelopmental disorders, policies and actions are urgently needed to eliminate or significantly reduce exposures to these chemicals. Further, if we are to protect children, we must overhaul how government agencies and business assess risks to human health from chemical exposures, how chemicals in commerce are regulated, and how scientific evidence informs decision making by government and the private sector.

Trends in Neurodevelopmental Disorders

We are witnessing an alarming increase in learning and behavioral problems in children. Parents report that 1 in 6 children in the United States, 17% more than a decade ago, have a developmental disability, including learning disabilities, ADHD, autism, and other developmental delays (Boyle et al. 2011). As of 2012, 1 in 10 (> 5.9 million) children in the United States are estimated to have ADHD (Bloom et al. 2013). As of 2014, 1 in 68 children in the United States has an autism spectrum disorder (based on 2010 reporting data) (CDC 2014).

The economic costs associated with neurodevelopmental disorders are staggering. On average, it costs twice as much in the United States to educate a child who has a learning or developmental disability as it costs for a child who does not (Chambers et al. 2004). A recent study in the European Union found that costs associated with lost IQ points and intellectual disability arising from two categories of chemicals—polybrominated diphenyl ether flame retardants (PBDEs) and organophosphate (OP) pesticides—are estimated at 155.44 billion euros ($169.43 billion dollars) annually (Bellanger et al. 2015). A 2009 analysis in the United States found that for every $1 spent to reduce exposures to lead, a potent neurotoxicant, society would benefit by $17–$221 (Gould 2009).

Vulnerability of the Developing Brain to Chemicals

Many toxic chemicals can interfere with healthy brain development, some at extremely low levels of exposure (Adamkiewicz et al. 2011; Bellinger 2008; Committee on Improving Analysis Approaches Used by the U.S. EPA 2009; Zoeller et al. 2012). Research in the neurosciences has identified "critical windows of vulnerability" during embryonic and fetal development, infancy, early childhood and adolescence (Lanphear 2015; Lyall et al. 2014; Rice and Barone 2000). During these windows of development, toxic chemical exposures may cause lasting harm to the brain that interferes with a child's ability to reach his or her full potential.

The developing fetus is continuously exposed to a mixture of environmental chemicals (Mitro et al. 2015). A 2011 analysis of the U.S. Centers for Disease Control and Prevention's (CDC) biomonitoring data found that 90% of pregnant women in the United States have detectable levels of 62 chemicals in their bodies, out of 163 chemicals for which the women were screened (Woodruff et al. 2011). Among the chemicals found in the vast majority of pregnant women are PBDEs, polycyclic aromatic hydrocarbons (PAHS), phthalates, perfluorinated compounds, polychlorinated biphenyls (PCBs), perchlorate, lead and mercury (Woodruff et al. 2011). Many of these chemicals can cross the placenta during pregnancy and are routinely detected in cord blood or other fetal tissues (ATSDR 2011; Brent 2010; Chen et al. 2013; Lien et al. 2011).

Prime Examples of Neurodevelopmentally Toxic Chemicals

The following list provides prime examples of toxic chemicals that can contribute to learning, behavioral, or intellectual impairment, as well as specific neurodevelopmental disorders such as ADHD or autism spectrum disorder:

- Organophosphate (OP) pesticides (Eskenazi et al. 2007; Fortenberry et al. 2014; Furlong et al. 2014; Marks et al. 2010; Rauh et al. 2006; Shelton et al. 2014).
- PBDE flame retardants (Chen et al. 2014; Cowell et al. 2015; Eskenazi et al. 2013; Herbstman et al. 2010).
- Combustion-related air pollutants, which generally include PAHs, nitrogen dioxide and particulate matter, and other air pollutants for which nitrogen dioxide and particulate matter are markers (Becerra et al. 2013; Clifford et al. 2016; Jedrychowski et al. 2015; Kalkbrenner et al. 2014; Suades-González et al. 2015; Volk et al. 2013).
- Lead (Eubig et al. 2010; Lanphear et al. 2005; Needleman et al. 1979).
- Mercury (Grandjean et al. 1997; Karagas et al. 2012; Sagiv et al. 2012).
- PCBs (Eubig et al. 2010; Jacobson and Jacobson 1996; Schantz et al. 2003).

The United States has restricted some of the production, use and environmental releases of these particular chemicals, but those measures have tended to be too little and too late. We face a crisis from both legacy and ongoing exposures to toxic chemicals. For lead, OP pesticides, PBDEs and air pollution, communities of color and socioeconomically stressed communities face disproportionately high exposures and health impacts (Adamkiewicz et al. 2011; Engel et al. 2015; Zota et al. 2010).

Policies to ban lead from gasoline, paints and other products have been successful in lowering blood lead levels in the American population (Jones et al. 2009), yet lead exposure continues to be a preventable cause of intellectual impairment, ADHD and maladaptive behaviors for millions of children (CDC 2015). Scientists agree that there is no safe level of lead exposure for fetal or early childhood development (Lanphear et al. 2005; Schnur and John 2014), and studies have documented the potential for cumulative and synergistic health effects from combined exposure to lead and social stressors (Bellinger et al. 1988; Cory-Slechta et al. 2004). Thus, taking further preventive actions is imperative.

Epidemiological, toxicological, and mechanistic studies have together provided evidence that clearly demonstrates or strongly suggests neurodevelopmental toxicity for lead, mercury, OP pesticides, air pollution, PBDEs, and PCBs. The level and type of available evidence linking exposures to toxic chemicals with neurodevelopmental disorders, including the examples in this statement, vary both within and among chemical classes. In light of this extensive evidence and continued widespread exposure, the risks for learning and developmental disorders can likely be lowered through targeted exposure reduction, starting with these example chemicals.

Majority of Chemicals Untested for Neurodevelopmental Effects

The examples of developmental neurotoxic chemicals that we list here likely represent the tip of the iceberg. Of the tens of thousands of chemicals on the U.S. Environmental Protection Agency (EPA) chemical inventory, nearly 7,700 are manufactured or imported into the United States at ≥ 25,000 pounds per year (U.S. EPA 2012). The U.S. EPA has identified nearly 3,000 chemicals that are produced or imported at > 1 million pounds per year (U.S. EPA 2006).

Only a minority of chemicals has been evaluated for neurotoxic effects in adults. Even fewer have been evaluated for potential effects on brain development in children (Grandjean and Landrigan 2006, 2014). Further, toxicological studies and regulatory evaluation seldom address combined effects of chemical mixtures, despite evidence that all people are exposed to dozens of chemicals at any given time.

Need for a New Approach to Evaluating Evidence

Our failures to protect children from harm underscore the urgent need for a better approach to developing and assessing scientific evidence and using it to make decisions. We as a society should be able to take protective action when scientific evidence indicates a chemical is of concern, and not wait for unequivocal proof that a chemical is causing harm to our children.

Evidence of neurodevelopmental toxicity of any type—epidemiological or toxicological or mechanistic—by itself should constitute a signal sufficient to trigger prioritization and some level of action. Such an approach would enable policy makers and regulators to proactively test and identify chemicals that are emerging concerns for brain development and prevent widespread human exposures.

Some chemicals, like those that disrupt the endocrine system, present a concern because they interfere with the activity of endogenous hormones that are essential for healthy brain development. Endocrine-disrupting chemicals (EDCs) include many pesticides, flame retardants, fuels, and plasticizers. One class of EDCs that is ubiquitous in consumer products are the phthalates. These are an emerging concern for interference with brain development and therefore demand attention (Boas et al. 2012; Ejaredar et al. 2015; Mathieu-Denoncourt et al. 2015; Miodovnik et al. 2014; U.S. Consumer Product Safety Commission 2014).

Regrettable Substitution

Under our current system, when a toxic chemical or category of chemicals is finally removed from the market, chemical manufacturers often substitute similar chemicals that may pose similar concerns or be virtually untested for toxicity. This practice can result in "regrettable substitution" whereby the cycle of exposures and adverse effects starts all over again. The following list provides examples of this cycle:

- When the federal government banned some uses of OP pesticides, manufacturers responded by expanding the use of neonicotinoid and pyrethroid pesticides. Evidence is emerging that these widely used classes of pesticides pose a threat to the developing brain (Kara et al. 2015; Richardson et al. 2015; Shelton et al. 2014).
- When the U.S. Government reached a voluntary agreement with flame retardant manufacturers to stop making PBDEs, the manufacturers substituted other halogenated and organophosphate flame retardant chemicals. Many of these replacement flame retardants are similar in structure to other neurotoxic chemicals but have not undergone adequate assessment of their effects on developing brains.
- When the federal government banned some phthalates in children's products, the chemical industry responded by replacing the banned chemicals with structurally similar new phthalates. These replacements are now under investigation for disrupting the endocrine system.

Looking Forward

Our system for evaluating scientific evidence and making decisions about environmental chemicals is broken. We cannot continue to gamble with our children's health. We call for action now to prevent exposures to chemicals and pollutants that can contribute to the prevalence of neurodevelopmental disabilities in America's children.

We need to overhaul our approach to developing and assessing evidence on chemicals of concern for brain development. Toward this end, we call on regulators to follow scientific guidance for assessing how chemicals affect brain development, such as taking into account the special vulnerabilities of the developing fetus and children, cumulative effects resulting from combined exposures to multiple toxic chemicals and stressors, and the lack of a safety threshold for many of these chemicals (Committee on Improving Analysis Approaches Used by the U.S. EPA 2009). We call on businesses to eliminate neurodevelopmental toxicants from their supply chains and products, and on health professionals to integrate knowledge about environmental toxicants into patient care and public health practice.

Finally, we call on policy makers to take seriously the need to reduce exposures of all children to lead—by accelerating the clean up from our past uses of lead such as in paint and water pipes, by halting the current uses of lead, and by better regulating the industrial processes that cause new lead contamination.

We are confident that reducing exposures to chemicals that can interfere with healthy brain development will help to lower the prevalence of neurodevelopmental disabilities, and thus enable many more children to reach their full potential.

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American College of Obstetricians and Gynecologists (ACOG)
ACOG supports the value of this clinical document as an educational tool (March 2016)
Child Neurology Society
Endocrine Society
International Neurotoxicology Association
International Society for Children's Health and the Environment
International Society for Environmental Epidemiology
National Council of Asian Pacific Islander Physicians
National Hispanic Medical Association
National Medical Association

References

Abt E, Rodricks JV, Levy JI, Zeise L, Burke TA. 2010. Science and decisions: advancing risk assessment. Risk Analysis 30(7):1028–1036.

Adamkiewicz G, Zota AR, Fabian MP, Chahine T, Julien R, Spengler JD, et al. 2011. Moving environmental justice indoors: Understanding structural influences on residential exposure patterns in low-income communities. Am J Public Health 101(suppl 1):S238–S245.

ATSDR (Agency for Toxic Substances and Disease Registry). 2011. Polycyclic Aromatic Hydrocarbons (PAHs): What Are the Routes of Exposure for PAHs? Available: http://www.atsdr.cdc.gov/csem/csem.asp?csem=13&po=6 [accessed 7 March 2016].

Becerra TA, Wilhelm M, Olsen J, Cockburn M, Ritz B. 2013. Ambient air pollution and autism in Los Angeles County, California. Environ Health Perspect 121(3):380–386.

Bellanger M, Demeneix B, Grandjean P, Zoeller RT, Trasande L. 2015. Neurobehavioral deficits, diseases, and associated costs of exposure to endocrine-disrupting chemicals in the European Union. J Clin Endocrinol Metab 100(4):1256–1266.

Bellinger DC. 2008. Very low lead exposures and children's neurodevelopment. Curr Opin Pediatr 20(2):172–177.

Bellinger D, Leviton A, Waternaux C, Needleman H, Rabinowitz M. 1988. Low-level lead exposure, social class, and infant development. Neurotoxicol Teratol 10(6):497–503.

Bloom B, Jones LI, Freeman G. 2013. Summary health statistics for U.S. children National Health Interview Survey, 2012. Vital Health Stat 10 (258):1–81 Available: http://www.cdc.gov/nchs/data/series/sr_10/sr10_258.pdf [accessed 24 May 2016].

Boas M, Feldt-Rasmussen U, Main KM. 2012. Thyroid effects of endocrine disrupting chemicals. Mol Cell Endocrinol 355:240–248.

Boyle CA, Boulet S, Schieve LA, Cohen RA, Blumberg SJ, Yeargin-Allsopp M, et al. 2011. Trends in the prevalence of developmental disabilities in U.S. children, 1997–2008. Pediatrics 127:1034–1042.

Brent GA. 2010. The impact of perchlorate exposure in early pregnancy: Is it safe to drink the water? J Clin Endocrinol Metab 95:3154–3157.

CDC (Centers for Disease Control and Prevention). 2014. Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2010. MMWR Surveill Summ 63(2):1–21.

CDC. 2015. Fourth National Report on Human Exposure to Environmental Chemicals, Updated Tables, February 2015. Available:

http://www.cdc.gov/biomonitoring/pdf/FourthReport_UpdatedTables_Feb2015.pdf [accessed 12 January 2016].

Chambers JG, Parris TB, Harr JJ. 2004. What Are We Spending on Special Education Services in the United States, 1999-2000? Washington, DC:American Institutes for Research. Available: http://www.csef-air.org/publications/seep/national/AdvRpt1.pdf [accessed 25 May 2016].

Chen A, Park JS, Linderholm L, Rhee A, Petreas M, DeFranco EA, et al. 2013. Hydroxylated polybrominated diphenyl ethers in paired maternal and cord sera. Environ Sci Technol 47(8):3902–3908.

Chen A, Yolton K, Rauch SA, Webster GM, Hornung R, Sjodin A, et al. 2014. Prenatal polybrominated diphenyl ether exposures and neurodevelopment in U.S. children through 5 years of age: The HOME Study. Environ Health Perspect 122(8):856–862, doi: 10.1289/ehp.1307562.

Clifford A, Lang L, Chen R, Anstey KJ, Seaton A. 2016. Exposure to air pollution and cognitive functioning across the life course—a systematic literature review. Environ Res 147(5):383–398.

Committee on Improving Risk Analysis Approaches Used by the U.S. EPA, Board on Environmental Studies and Toxicology, Division on Earth and Life Studies, National Research Council. 2009. Science and Decisions: Advancing Risk Assessment. Washington, DC:National Academies Press.

Cory-Slechta DA, Virgolini MB, Thiruchelvam M, Weston DD, Bauter MR. 2004. Maternal stress modulates the effects of developmental lead exposure. Environ Health Perspect 112(6):717–730.

Council on Environmental Health of the American Academy of Pediatrics. 2011. Chemical-management policy: prioritizing children's health. Pediatrics 127(5):983–990.

Cowell WJ, Lederman SA, Sjödin A, Jones R, Wang S, Perera FP, et al. 2015. Prenatal exposure to polybrominated diphenyl ethers and child attention problems at 3–7 years. Neurotoxicol Teratol 52(Pt B):143–150.

Di Renzo GC, Conry JA, Blake J, DeFrancesco MS, DeNicola N, Martin JN, et al. 2015. International Federation of Gynecology and Obstetrics opinion on reproductive health impacts of exposure to toxic environmental chemicals. Int J Gynecol Obstet 131(3):219–225.

Ejaredar M, Nyanza EC, Ten Eycke K, Dewey D. 2015. Phthalate exposure and childrens neurodevelopment: a systematic review. Environ Res 142(10):51–60.

Engel SM, Bradman A, Wolff MS, Rauh VA, Harley KG, Yang JH, et al. 2015. Prenatal organophosphorus pesticide exposure and child neurodevelopment at 24 months: an analysis of four birth cohorts. Environ Health Perspect 124:822–830, doi: 10.1289/ehp.1409474.

Eskenazi B, Chevrier J, Rauch SA, Kogut K, Harley KG, Johnson C, et al. 2013. *In utero* and childhood polybrominated diphenyl ether (PBDE) exposures and neurodevelopment in the CHAMACOS Study. Environ Health Perspect 121(2):257–262, doi: 10.1289/ehp.1205597.

Eskenazi B, Marks AR, Bradman A, Harley K, Barr DB, Johnson C, et al. 2007. Organophosphate pesticide exposure and neurodevelopment in young Mexican-American children. Environ Health Perspect 115(5):792–798, doi: 10.1289/ehp.9828.

Eubig PA, Aguiar A, Schantz SL. 2010. Lead and PCBs as risk factors for attention deficit/hyperactivity disorder. Environ Health Perspect 118(12):1654–1667, doi: 10.1289/ehp.0901852.

Fortenberry GZ, Meeker JD, Sánchez BN, Barr DB, Panuwet P, Bellinger D, et al. 2014. Urinary 3,5,6-trichloro-2-pyridinol (TCPY) in pregnant women from Mexico City: distribution, temporal variability, and relationship with child attention and hyperactivity. Int J Hyg Environ Health 217(2–3):405–412.

Furlong MA, Engel SM, Barr DB, Wolff MS. 2014. Prenatal exposure to organophosphate pesticides and reciprocal social behavior in childhood. Environ Int 70(9):125–131.

Gore A, Chappell V, Fenton S, Flaws J, Nadal A, Prins G, et al. 2015. Executive summary to EDC-2: The Endocrine Society's second scientific statement on endocrine-disrupting chemicals. Endocr Rev 36(6):593–602.

Gould E. 2009. Childhood lead poisoning: conservative estimates of the social and economic benefits of lead hazard control. Environ Health Perspect 117(7):1162–1167, doi: 10.1289/ehp.0800408.

Grandjean P, Landrigan PJ. 2006. Developmental neurotoxicity of industrial chemicals. Lancet 368(9553):2167–2178.

Grandjean P, Landrigan PJ. 2014. Neurobehavioural effects of developmental toxicity. Lancet Neurol 13(3):330–338.

Grandjean PW, Weihe P, White RF, Debes F, Araki S, Yokoyama K, et al. 1997. Cognitive deficit in 7-year-old children with prenatal exposure to methylmercury. Neurotoxicol Teratol 19(6):417–428.

Herbstman JB, Sjodin A, Kurzon M, Lederman SA, Jones RS, Rauh V, et al. 2010. Prenatal exposure to PBDEs and neurodevelopment. Environ Health Perspect 118(5):712–719, doi: 10.1289/ehp.0901340.

Jacobson JL, Jacobson SW. 1996. Intellectual impairment in children exposed to polychlorinated biphenyls *in utero*. N Engl J Med 335(11):783–789.

Jedrychowski WA, Perera FP, Camann D, Spengler J, Butscher M, Mroz E, et al. 2015. Prenatal exposure to polycyclic aromatic hydrocarbons and cognitive dysfunction in children. Environ Sci Pollut Res Int 22(5):3631–3639.

Jones RL, Homa DM, Meyer PA, Brody DJ, Caldwell KL, Pirkle JL, et al. 2009. Trends in blood lead levels and blood lead testing among U.S. children aged 1 to 5 years, 1988–2004. Pediatrics 123(3):e376–e385.

Kalkbrenner AE, Schmidt RJ, Penlesky AC. 2014. Environmental chemical exposures and autism spectrum disorders: a review of the epidemiological evidence. Curr Probl Pediatr Adolesc Health Care 44(10):277–318.

Kara M, Yumrutas O, Demir CF, Ozdemir HH, Bozgeyik I, Coskun S, et al. 2015. Insecticide imidacloprid influences cognitive functions and alters learning performance and related gene expression in a rat model. Int J Exp Pathol 96(5):332–337.

Karagas MR, Choi AL, Oken E, Horvat M, Schoeny R, Kamai E, et al. 2012. Evidence on the human health effects of low-level methylmercury exposure. Environ Health Perspect 120(6):799–806, doi: 10.1289/ehp.1104494.

Lanphear BP. 2015. The impact of toxins on the developing brain. Annu Rev Public Health 36:211–230.

Lanphear BP, Hornung R, Khoury J, Yolton K, Baghurst P, Bellinger DC, et al. 2005. Low-level environmental lead exposure and children's intellectual function: an international pooled analysis. Environ Health Perspect 113(7):894–899.

Lien GW, Wen TW, Hsieh WS, Wu KY, Chen CY, Chen PC. 2011. Analysis of perfluorinated chemicals in umbilical cord blood by ultra-high performance liquid chromatography/tandem mass spectrometry. J Chromatogr B Analyt Technol Biomed Life Sci 879(9–10):641–646.

Lyall K, Schmidt RJ, Hertz-Picciotto I. 2014. Maternal lifestyle and environmental risk factors for autism spectrum disorders. Int J Epidemiol 43(2):443–464.

Marks AR, Harley K, Bradman A, Kogut K, Barr DB, Johnson C, et al. 2010. Organophosphate pesticide exposure and attention in young Mexican-American children: the CHAMACOS Study. Environ Health Perspect 118(12):1768–1774.

Mathieu-Denoncourt J, Wallace SJ, de Solla SR, Langlois VS. 2015. Plasticizer endocrine disruption: highlighting developmental and reproductive effects in mammals and non-mammalian aquatic species. Gen Comp Endocrinol 219:74–88.

Miodovnik A, Edwards A, Bellinger DC, Hauser R. 2014. Developmental neurotoxicity of ortho-phthalate diesters: review of human and experimental evidence. Neurotoxicology 41:112–122, doi: 10.1016/j.neuro.2014.01.007.

Mitro SD, Johnson T, Zota AR. 2015. Cumulative chemical exposures during pregnancy and early development. Curr Environ Health Rep 2(4):367–378.

Needleman HL, Gunnoe C, Leviton A, Reed R, Peresie H, Maher C, et al. 1979. Deficits in psychologic and classroom performance of children with elevated dentine lead levels. N Engl J Med 300(13):689–695.

Rauh VA, Garfinkel R, Perera FP, Andrews HF, Hoepner L, Barr DB, et al. 2006. Impact of prenatal chlorpyrifos exposure on neurodevelopment in the first 3 years of life among inner-city children. Pediatrics 118(6):e1845–e1859.

Rice D, Barone S Jr. 2000. Critical periods of vulnerability for the developing nervous system: evidence from humans and animal models. Environ Health Perspect 108(suppl 3):511–533.

Richardson JR, Taylor MM, Shalat SL, Guillot TS III, Caudle WM, Hossain MM, et al. 2015. Developmental pesticide exposure reproduces features of attention deficit hyperactivity disorder. FASEB J 29(5):1960–1972.

Sagiv SK, Thurston SW, Bellinger DC, Amarasiriwardena C, Korrick SA. 2012. Prenatal exposure to mercury and fish consumption during pregnancy and attention-deficit/hyperactivity disorder-related behavior in children. Arch Pediatr Adolesc Med 166(12):1123–1131.

Schantz SL, Widholm JJ, Rice DC. 2003. Effects of PCB exposure on neuropsychological function in children. Environ Health Perspect 111(3):357–576.

Schnur J, John RM. 2014. Childhood lead poisoning and the new Centers for Disease Control and Prevention guidelines for lead exposure. J Am Ass Nurse Pract 26(5):238–247.

Shelton JF, Geraghty EM, Tancredi DJ, Delwiche LD, Schmidt RJ, Ritz B, et al. 2014. Neurodevelopmental disorders and prenatal residential proximity to agricultural pesticides: the CHARGE Study. Environ Health Perspect 122(10):1103–1109.

Suades-González E, Gascon M, Guxens M, Sunyer J. 2015. Air pollution and neuropsychological development: a review of the latest evidence. Endocrinology 156(10):3473–3482.

U.S. Consumer Product Safety Commission. 2014. Report to the U.S. Consumer Product Safety Commission by the Chronic Hazard Advisory Panel on Phthalates and Phthalate Alternatives. Available: https://www.cpsc.gov/PageFiles/169876/CHAP-REPORT-FINAL.pdf [accessed 24 May 2016].

U.S. EPA (U.S. Environmental Protection Agency). 2006. 2006 Inventory Update Reporting: Data Summary. Available: http://www.epa.gov/sites/production/files/documents/2006_data_summary.pdf [accessed 24 May 2016].

U.S. EPA. 2012. 2012 Chemical Data Reporting Results. Available: http://www.epa.gov/chemical-data-reporting/2012-chemical-data-reporting-results [accessed 24 May 2016].

Volk HE, Lurmann F, Penfold B, Hertz-Picciotto I, McConnell R. 2013. Traffic-related air pollution, particulate matter, and autism. JAMA Psychiatry 70(1):71–77.

Woodruff TJ, Zota AR, Schwartz JM. 2011. Environmental chemicals in pregnant women in the United States: NHANES 2003–2004. Environ Health Perspect 119(6):878–885.

Zoeller RT, Brown T, Doan L, Gore A, Skakkebaek N, Soto A, et al. 2012. Endocrine-disrupting chemicals and public health protection: A statement of principles from the endocrine society. Endocrinology 153(9):4097–4110.

Zota AR, Adamkiewicz G, Morello-Frosch RA. 2010. Are PBDEs an environmental equity concern? Exposure disparities by socioeconomic status. Environ Sci Technol 44(15):5691–5692.