Endocrine Disrupting Chemicals
A Cause For Concern?
Endocrine Disrupting Chemicals

Endocrine Disruptors

Chemicals that mimic/antagonize normal hormones and can have permanent effects in organisms as well as progeny
Types of EDCs

Natural
- Phytoestrogens
- Fungal estrogens

Synthetic
- Hormones
- Some pesticides
- Industrial by-products
- Plastic components
- Some persistent organic pollutants (POPs)
“What - me worry?”
Percentage Tested

- **Acute Toxicity**
- **Environmental Fate**
- **Ecotoxicity**
- **Mutagenicity**
- **Chronic Toxicity**
- **Reproductive Toxicity**
- **Full Set of Basic Toxicity Tests**

7% Full* Set of Basic Toxicity Tests:
* Doesn’t Include Tests of Neurodevelopmental Effects
Lead - A Cautionary Tale

6500 BC. - Lead discovered in Turkey, first mine

500 BC-300 AD.- Roman lead smelting produces dangerous emissions

100 BC. - Greek physicians give clinical description of lead poisoning
"Lead makes the mind give way."

Greek

Dioscerides - 2nd BC
Lead In Homes

LEAD
And Your Kids
Disturbing New Evidence About the Threat to Their Health
How to Protect Them
Lead in Families
EVIDENCE?
Endocrine Disrupting Chemicals

- Overview
- Mechanisms
- Windows of Susceptibility
- What To Do About EDC’s
Testicular Cancer

[Map and bar charts showing incidence rates in various countries and populations.]

- Canada: Ontario and Inuit population
- United States: Connecticut State
- United States: 9 registries

Countries: Norway, Sweden, Finland, Denmark, Estonia, Japan, Australia, New Zealand, Switzerland, East Germany.
**Testicular Dysgenesis Syndrome**

**Environmental Factors**
(including Endocrine disrupters)

- Disturbed Sertoli Cell Function
- Impaired Germ Cell Differentiation

**Testicular Dysgenesis**

- Decreased Leydig Cell Function
- Androgen Insufficiency

- Hypospadias
- Cryptorchidism
- CIS
- Testicular Cancer

- Reduced Semen Quality

**Genetic Defects**

From Skakkebæk et al.
Pubertal Development

- Unlinking Thelarche from Menarche
- Precocious Puberty?
- Increased Risk for Breast Cancer?
POLLUTION
Toxicology

- Synthesis of Disciplines
- Evolved from the Ancient Poisoners
Selective Toxicology

- Pesticides
- Herbicides
- Antibiotics
Exposure

- External Dose
- Internal dose
- Target Organ dose
PBDEs in House Dust (ppb)

External Exposure

PBDEs in Breast Milk (ppb)

Internal Exposure

A Study of Toxic Chemicals in Washingtonians

A project of the Toxic-Free Legacy Coalition:
Toxicology

*Bioaccumulation

* Biomagnification
“Almost none of the 15,000 high volume chemicals, widely used and found in the environment, have been tested during development for their endocrine-disrupting effects, either at high or background exposure doses.”

Baskin, et al
A Chemical Age

- 82,000 Chemicals Approved for Use since the 1950’s
- EPA Reviews 1,700 New Compounds Each Year
- 90% Approval Rate
- 25% Evaluated For Toxicity
Mechanisms

- Disrupt Hormone Synthesis
- Disrupt Hormone Metabolism
- Mimic/Antagonize Endogenous Hormone Effects
- Disrupt Hormone Receptor Synthesis
- Alter Target Cell Sensitivity
Toxicologic Principles

- Dose - Low dose vs. High dose
- Timing of Exposure - Sensitive Windows of Vulnerability
- Half-life - Short vs. Persistent
- Biological Availability - body storage, circulation
- Toxicity - a standard battery of animal studies
- Genetics

Risk Assessment

“Safe Dose” determined by formula that uses NOAEL (No Observed Adverse Effect Level) and multiplies by a safety factor.
Toxicology - Assessment

- Dose-Response Analysis
- LD\textsubscript{50}
- NOEL or NOAEL
Traditional: “The dose makes the poison”

New Paradigm: The dose + timing = poison
Endocrine Disrupting Chemicals

*Problematic Assessment!*
Mechanism of Action

- Hormone Mimicry
- Endogenous Hormones Blocking
- Mixture Effect
Endocrine Disrupting Chemicals

- Function at Extremely Low Concentrations
- Inverse Effects at Low and High Doses Possible

CONTROVERSIAL PHENOMENON
Hormesis

Definition: Dose Response Phenomenon Characterized by:
- Low Dose Stimulation
- High Dose Inhibition
Hormesis

* Nonlinear Dose Effect of 17-B-Trenbolone on Fathead Minnow*

* J Or U-Shaped Relationships

*Ankley, 2003*
Hormesis

The “Norm”*

*Kayajanian, 2002
Calabrese and Baldwin, 2003
Diethylstilbestrol (DES)

- 1st Gen: 40x Increased risk of breast cancer
- 2nd Gen: vaginal adenocarcinoma in females, hypospadias in male
- 3rd Gen: possible increased risk of ovarian cancer, hypospadias
- 4th Gen: ?
Figure 2
Medical journal advertisement for prenatal tablets with vitamins and diethylstilbestrol
Epigenetics

- First Defined in 1940s
- Covalent DNA Modification Proposed in 1975 as Mechanism
- Revelation That X-Inactivation and Genomic Imprinting Regulated by Epigenetic Factors
Epigenetics

- Environmental Influences Linked To Disease Phenotypes
- Epigenome Modification
- Meta-stable epialleles
Epigenome Re-Programming

- Erasure of Epigenetic Marks As Primordial Germ Cells Migrate Along Genital Ridge
- Mark Re-establishment During Gametogenesis
- 2nd Erasure During Fertilization

Am J Hum Genet 74, 2004
Epigenetic Transgenerational Actions

* Creates Opportunity for Environmental Factors To Reprogram The Germ Line

* Implications for Evolutionary Biology
Baby powder, shampoo linked to chemical risk

Researchers find phthalates

By Liz Szabo
USA TODAY

Parents who use baby powder, lotion or shampoo on their infants may unknowingly expose their children to controversial chemicals with hormone-like effects, a study shows.

Researchers found the chemicals — called phthalates — in the urine of all 163 babies tested, according to the study in today’s Pediatrics. Most of the babies, whose average age was 13 months, had seven or more types of phthalates in their urine. Concentrations of phthalates were higher in infants who were exposed to lotion, powder and shampoo than in other infants, the study shows.

Doctors are concerned about phthalates because many animal tests and a few human studies link the chemicals — a broad class of ingredients found in everything from vinyl toys and hospital tubing to cosmetics — to reproductive abnormalities, allergies and eczema, says Sheela Sathyarayana, acting assistant professor at the University of Washington.

Unborn children and infants are especially vulnerable to phthalates, Sathyarayana says. The new study suggests phthalates are absorbed through the skin, says Schettler, an expert on hormone-disrupting chemicals and science director for the advocacy group called the Environemental Healthov Head

“It’s hard to trace where these chemicals are coming from,” Sathyarayana says. “They could be coming from baby powder, lotion and shampoo.”

“Everyday” and Environmental Healthov Head

“It’s hard to trace where these chemicals are coming from,” Sathyarayana says. “They could be coming from baby powder, lotion and shampoo.”

Baby bottle danger

Chemical in plastic may be harmful

By Stacy Downs
McClatchy Newspapers

Parents, nurses and other health-care workers are circulating reports of baby bottles and sippy cups containing chemicals that may be harmful. The products are made from materials containing BPA, which can be absorbed through the skin and into the bloodstream.

Many parents are switching their babies to plastic bottles made of other materials to avoid chemical exposure, according to several reports in newspapers and online.

“BPA also is found in some plastics and food containers,” said a professor at the University of Missouri-Columbia and co-founder of the advocacy group called the Environmental Healthov Head.

Many parents are switching their babies to plastic bottles made of other materials to avoid chemical exposure, according to several reports in newspapers and online.

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Summary of Findings

- BPA is a weak estrogen and an anti-androgen, rapidly metabolized (4-6 hours)
- Upregulates estrogen alpha receptor in human body
- Binds to α-fetoprotein which normally binds to estrogen α increased estrogen circulation
- Animal studies
- Male reproductive tract
- Neurocognitive disorders
- Diminishes differences in sexually dimorphic behavior
- Early puberty
- Increased body size
- Low Doses: Breast, Uterine and Prostate Tumor Cell Proliferation
Bisphenol A and Mammary Gland

- Dosed pregnant mice at 25ng/kg from Day 9 of pregnancy through birth.
- Examined mammary glands of offspring at Day 30
  - Found increased terminal bud growth/density
  - Decreased number of apoptotic cells

Bisphenol A and Obesity

* Obesogens - Promote Adipogenesis at LOW DOSES

- DES - synthetic estrogen
  - Exposure in utero \( \rightarrow \) obese offspring that continued to be obese with restricted caloric intake/increased exercise \( \rightarrow \) 3rd generation also obese (increases in leptin, adiponectin, TG)

- Bisphenol A
Bisphenol A (BPA) Concentrations

Conditions

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Mean BPA Level, ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
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<tr>
<td>Cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td>Angina</td>
<td></td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td></td>
</tr>
<tr>
<td>Heart attack</td>
<td></td>
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<tr>
<td>Diabetes</td>
<td></td>
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<td>Liver disease</td>
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<td>Respiratory disease</td>
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<td>Asthma</td>
<td></td>
</tr>
<tr>
<td>Bronchitis or emphysema</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
</tr>
<tr>
<td>Thyroid disease</td>
<td></td>
</tr>
</tbody>
</table>

Estimates adjusted for age and sex. Error bars indicate 95% confidence intervals.

I.A. Lang, PhD; et al JAMA. 2008;300(11):1303-1310. Published online September 16, 2008
Phthalates
Phthalate Exposure in Utero

Maternal Phthalate Exposure

Testis Testosterone Production (ng/testis)

Days post conception

Gestational Days

Postnatal Days

“Phthalate syndrome”

- Malformations of Epididymis, Vas deferens, Seminal Vesicles, Prostate
- Hypospadias
- Undescended Testicles
- Nipple retention
- Reduced AGD

Gray and Foster 2003, Foster 2005
Testicular Dysgenesis Syndrome

Environmental Factors
(including Endocrine disrupters)

Testicular Dysgenesis

Disturbed Sertoli Cell Function

Impaired Germ Cell Differentiation

Decreased Leydig Cell Function

Androgen Insufficiency

Cryptorchidism

CIS

Testicular Cancer

Hypospadias

Reduced Semen Quality

Genetic Defects

From Skakkebæk et al.
Phthalates in Childhood

Hauser et al 2005 NICU Setting - found urinary levels of DEHP to be 50x higher in preterm neonates as compared to levels in children from NHANES

**FDA has released a statement saying that premature infants may be adversely affected by these chemicals**
Why are We Concerned?

Main et al – 2006

- Found a significant association between breastfeeding phthalate exposures and luteinizing hormone (positive) and free testosterone levels (negative) in newborn boys with cryptorchidism.

Swan et al – 2008

- Found a significant association between prenatal phthalate levels and decreased anogenital distance, reduced testicular descent, decreased penile width in infants.
Phthalates and Human Health

* Altered sperm quality in adult males

Duty et al. 2004, Hauser et al. 2008
Abnormalities in Response to Cumulative Phthalate Exposure

“Scientific societies such as the Endocrine Society should partner with other organizations with the scientific and medical expertise to evaluate effects of endocrine disrupting chemicals in humans”

It’s All About The Timing
Fetus - Most Sensitive Life Stage
Prenatal Exposure

www.criticalwindows.com/go_display.php
Monobutyl Phthalate in Spot Urine Samples

* A metabolite of dibutyl phthalate

Mean phthalate (MBP) metabolite levels (ppb) by AGI category

Population Health

- Effects of EDC Can be Subtle
- Increased Variance from the Mean*
- Individual Effect May Be More Difficult to Detect

*Orlando and Guillette, 2001
Sperm Density

Declines:
* United States (1938-1988)
* Western Europe (1971-1989)

No Change:
* Non-Western Countries (1978-1990)

Swan: EHP; 105: 1997
Risk Assessment

* Phase 1 - Hazard Identification
Di-ethylhexyl phthalate (DEHP)

- Phthalate Plasticizer
- 2 million tons/year
- Ubiquitous exposure
- General Uses
  - Building materials
  - Clothing
  - Packaging
  - Medical Devices

“EVERYWHERE CHEMICAL”
Prenatal Exposure

www.criticalwindows.com/go_display.php
Risk Assessment

- Phase 1 - Hazard Identification
- Phase 2 - Exposure Assessment
Toxic Chemicals Found

### Toxic Pollution Found In Washingtonians

<table>
<thead>
<tr>
<th>Toxic Chemicals</th>
<th>Pam Tazioni</th>
<th>Bill Finkbeiner</th>
<th>Karen Bowman</th>
<th>Ann Holmes Redding</th>
<th>Lisa Brown</th>
<th>Laurie Valeriano</th>
<th>Patricia Dawson</th>
<th>Denis Hayes</th>
<th>Alyson Schrier</th>
<th>Deb Abrahamson</th>
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<tbody>
<tr>
<td>PFCs (&quot;Teflon chemicals&quot;)</td>
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<td>✔</td>
<td>✔</td>
<td>✔</td>
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<td>✔</td>
<td>✔</td>
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<tr>
<td>PBDEs (toxic flame retardants)</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
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<tr>
<td>Phthalates (plasticizers and fragrance carriers)</td>
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<td>DDT (banned pesticide)</td>
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<tr>
<td>PCBs (banned industrial coolant)</td>
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<td>Arsenic</td>
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</table>
Phthalate Exposure Dose

- Neonates
- 54 Infants Classified by Exposure to DEHP Based on Medical Products
- MEHP Levels 5.1 fold in High Exposure Group

Green et al: Environment Health Perspectives, 2005
### Table C.2 Summary statistics for phthalate monoester metabolites in PPWC and NHANES

<table>
<thead>
<tr>
<th>Metabolite</th>
<th>NHANES (^2)</th>
<th>PPWC (^3)</th>
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<tr>
<td></td>
<td>50(^{th})</td>
<td>25(^{th})</td>
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<tr>
<td>MEHP</td>
<td>4.1</td>
<td>1.3</td>
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<tr>
<td>MECHP</td>
<td>13.0</td>
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<td>MEHHP</td>
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<td>MBP</td>
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<td>MBP</td>
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<tr>
<td>MMP</td>
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<tr>
<td>MBzP</td>
<td>15.4</td>
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<tr>
<td>MCPP</td>
<td>3.0</td>
<td>0.7</td>
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</table>

1. Not creatinine corrected
2. NHANES 2001-02, Female, age 6 and over
3. Maternal prenatal samples
Risk Assessment

* Phase 1 - Hazard Identification
* Phase 2 - Exposure Assessment
* Phase 3 - Dose Response Assessment
Testosterone Production

- Large Variations in Breast Milk mEHP Levels
- SHBG Levels
- LH Levels
- Free Testosterone
Prenatal Phthalate Exposure

- Anogenital Index Decreased With Increased Phthalate Exposure
- Correlated With
  - Penile Volume
  - Cryptorchidism
- Concentrations Below That Found in 25% of Female Population in the U.S.

Swan, EHP: 113(8), 2005
Anogenital Distance

- Bioassay of Fetal Androgen Activity in Animal Studies
- Sexual Dimorphism Suggested in Humans
- Prima Facie Evidence For In Utero Exposure in Humans as Well

¹Salazar-Martinez, Env Health 3:2004
AGD - Sexual Dimorphism

Beard, Sathyanaryana, Grady, 2008
Ongoing Studies at Children’s and UW

* Newborn AGD - completed in UW newborn nursery

* Case Control of AGD in cases of children with male reproductive abnormalities and controls

* PRIME - Premature Infants in the Medical Environment (NICU) @ Swedish/Prov Everett
How Do We Avoid These Chemicals?

Plastic #3 on recycling codes

* do not microwave food in plastic
* do not place hot liquids in plastic containers
* do not dish wash your plastics - leads to degradation
* use alternatives to plastic packaging when possible

Toys/Personal Care Products

* some are labeled phthalate free but difficult to know true content
* support product labeling - CA Prop 65
Precautionary Approach: Alternative Products

- Look for recycling code and avoid use of #7 (may or may not contain Bisphenol A) when possible
- Use safe alternatives such as glass or polyethylene plastic
- Choose canned foods from makers who don’t use BPA (i.e. Eden foods)
- Try to buy soups/milk/milk products in cardboard cartons
- Choose alternatives to canned foods: Fresh fruits and vegetables
- Stainless Steel Water Bottles
- Bisphenol A free bottles
How to Counsel Families

- Recognize Limited data on health impacts of modern chemicals
- Not useful to conduct body burden testing
- Work on decreasing exposures as much as possible (can never get to zero)
  - Env Working Group (pesticide in foods)
  - Env Defense Fund (safe seafood)
  - Clean Indoor Air (American Lung Association)
- Educate with appropriate resources
Policy Implications

2005 European Union, Banned use of DEHP, DBP, and BBzP in all children’s toys and childcare articles

- banned the use of DiDP, DnOP, and DINP in toys and childcare articles which can be placed in the mouth by children.

2007 Washington, Passed state law - Children’s Safe Products Act

- Restricts phthalates in children’s toys
- Also, decreases amount of lead/cadmium in toys

2008 US Federal Legislation, Toxic Toys Bill

- Restricts phthalates in children’s toys
PEHSU: Pediatric Environmental Health Specialty Unit (US EPA/ATSDR)

- Serve health care providers, public health professionals, communities, and families
- Unique interface of pediatric medicine-toxicology-teratology-epidemiology-exposure sciences
- Evidence-based Consultation and Education
- UW PEHSU: OR, ID, AK, WA
- Creates informational handouts for families
- 1-877-KID-CHEM
- [http://depts.washington.edu/pehsu/](http://depts.washington.edu/pehsu/)
A Turning Point

“Many are turning to the government for assurance that these chemicals have been assessed using the best available science. Current law doesn't allow us to give those assurances.”

Lisa Jackson, Chief, US EPA

Paradigm Shift: A chemical is harmful until proven otherwise; Precautionary Principle
As Physicians We Have a Special Knowledge and Duty to Use it to Enhance Public Health
And all that the Lorax left here in this mess was a small pile of rocks, with the one word, “UNLESS.”

UNLESS someone like you cares a whole awful lot, nothing is going to get better. It’s not.
Get Involved

- Learn More About the Topic
- Investigate
- Advocate
- Join Washington Physicians for Social Responsibility
Acknowledgements

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* Catherine Karr
* Center for Clinical and Translational Research
* Academic Enrichment Fund