Environmental Nutrition and Women’s Health - should we worry about BPA and phthalates?

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Objectives

At the end of this session, the participant will be able to:

1. Identify how the plasticizers bisphenol A (BPA) and phthalates enter the food and water supply.

2. Critically evaluate the scientific literature linking food- and water-borne BPA and phthalate exposures to health outcomes, with a focus on women’s health issues.

3. Identify three ways that dietitians can help their clients decrease their exposures to BPA and phthalates and reduce the potential health impacts of these exposures.
Environmental Nutrition

- Intersection between environmental health and nutrition

- Food and water provides needed nutrients, but are also vehicles of toxicant exposure

- Nutritional status may influence susceptibility to environmental toxicants

- Nutrients and toxicants may interact
### Nutrients may alter toxicity of environmental exposures

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Example</th>
<th>Reference (PubMed ID)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enhance absorption of the environmental chemical in the intestinal tract</td>
<td>Dietary fat increases phthalate absorption from foods stored in plastic food storage materials</td>
<td>12142236</td>
</tr>
<tr>
<td>Decrease absorption of the environmental chemical in the intestinal tract</td>
<td>Dietary fiber decreases absorption of polychlorinated biphenyls (PCBs)</td>
<td>17977574</td>
</tr>
<tr>
<td></td>
<td>Coffee and tea decreases absorption of dietary mercury</td>
<td>22014585</td>
</tr>
<tr>
<td>Increase the toxicity of the environmental exposure</td>
<td>Iron creates free radicals which can increase the toxicity of polychlorinated biphenyls (PCBs)</td>
<td>8597166</td>
</tr>
<tr>
<td>Decrease the toxicity of the environmental exposure</td>
<td>Antioxidants (vitamins A, C, E, and zinc) prevent the conversion of nitrites to adduct forming N-nitroso compounds</td>
<td>12948815</td>
</tr>
<tr>
<td>Aid in the elimination of the environmental exposure</td>
<td>Folate provides methyl-groups needed for excretion of inorganic arsenic</td>
<td>18522624</td>
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</tbody>
</table>
Endocrine disrupting chemicals

An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub) populations.

A potential endocrine disruptor is an exogenous substance or mixture that possesses properties that might be expressed to lead to endocrine disruption in an intact organism, or its progeny, or (sub) populations.

International Programme on Chemical Safety (2002)

Chemicals that may interfere with the body’s endocrine system and produce adverse developmental, reproductive, neurological, and immune effects in both humans and wildlife

National Institute for Environmental Health Sciences (NIEHS)
Bisphenol A

- First synthesized in 1891
- Evaluated as a potential synthetic estrogen in the 1930s
- Used as a plasticizer in polycarbonate plastics and epoxy resins
- Currently one of the highest volume chemicals: ~ 8 billion pounds produced annually
- Food and water thought to be the primary routes of human exposure
- 95% of Americans have detectable levels of BPA in their urine according to NHANES data
Phthalates

• Added to plastics to increase flexibility and resiliency

• Not chemically bound to the plastic polymers, and thus are able to leach or migrate out of the plastics, especially when exposed to high temperatures

• According to the EPA, more than 470 million pounds of phthalates are produced each year

• The primary route of human exposure is thought to be through food and beverages that have been in contact with plastics

• Phthalates also found in many plastics used in the medical setting, personal care products, extended release drugs and dietary supplements, PVC pipes, and even household dust

• Phthalate metabolites were detected in the urine of >75% of the 1999-2000 NHANES cohort - indicating widespread human exposure
• Both BPA and phthalates are rapidly metabolized, and excreted in the urine (24 – 48 hours).

• Unclear whether BPA and phthalates are entirely cleared from the body, or if they bioaccumulate, especially in adipose tissue.

• Humans are thought to be constantly exposed.

• Cumulative exposures are a concern, and an active area of research.
Interactions with nutrients

BPA

- BPA and genistein (a dietary phytoestrogen) may interact – findings from in vitro, animal models have been inconsistent.

Phthalates

- Most likely to leach into liquids and non-polar solvents such as fats and oils.
- Nutrients that stimulate or interact with intestinal lipases may alter phthalate absorption.

Any nutrient that up-regulates or down-regulates hepatic metabolizing enzymes (e.g. CYP450s, UGT) may alter BPA and phthalate metabolism.
Difficulties in studying health effects of BPA, phthalates in humans

- Can’t do randomized controlled trials – unethical to purposefully give someone a potentially hazardous substance
- Testing is relatively expensive
- Specimens need to be collected using specific procedures and supplies – high potential for contamination
- Exposure is repeated and varies – requires frequent testing to assess usual exposure levels
- Limitations of current technology in measuring low-dose (physiologically and environmentally relevant) exposure levels
Limitations of the currently available research

- Data primarily from cell culture and animal models
- Most human data come from NHANES – cross-sectional
- Test single compounds at a time
- Focus on acute toxicity as a result of high dose exposures
- Assume that the dose-response effect is linear
- Limited data for low-dose exposures, which are considered to be the physiologically and environmentally relevant exposure levels (similar to hormones)
## Interactions with hormones

<table>
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<tr>
<th>Hormone</th>
<th>BPA</th>
<th>Phthalates</th>
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<tr>
<td>Estrogen</td>
<td>Estrogenic activity</td>
<td>May have some (weak) estrogenic activity?</td>
</tr>
<tr>
<td>Testosterone</td>
<td></td>
<td>Blocks activity of testosterone</td>
</tr>
<tr>
<td>Thyroid</td>
<td>May alter thyroid hormone (free T3, TSH) levels</td>
<td>May alter thyroid hormone (T3, T4) levels Inhibit expression of thyroid receptor</td>
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</table>

Animal data conflicting
Low doses matter

Displayed are three different types of NMDRCs including an inverted U-shaped curve, a U-shaped curve, and a multiphasic curve. All of these are considered NMDRCs because the slope of the curve changes sign one or more times.

US Environmental Protection Agency
http://www.epa.gov/research/endocrinedisruption/non-monotonic.htm
Timing of endocrine disruptor exposure

*In utero*, early childhood thought to be critical exposure periods

- Higher rate of cellular growth
- Children tend to have less developed hepatic enzyme systems for metabolizing and eliminating EDC exposures
- Children eat and drink more per unit body weight than adults
- Normal childhood behaviors (e.g. crawling, putting objects in their mouths) puts children in closer contact with many environmental exposures

Latency = time between exposure and development of disease

- Early life exposures may manifest later in life
BPA, phthalates as environmental obesogens

- Data from **cell culture** indicates that BPA and phthalates increase adipogenesis/adipocyte differentiation and lipid accumulation in adipocytes, but also increased leptin and adiponectin expression. (PMID: 22526026)

- Data from **animal models** indicate that developmental exposure to BPA and phthalates can lead to obesity later in life.

- Cross-sectional studies of National Health and Nutrition Examination Study (NHANES) participants have reported that both urinary BPA and phthalate metabolites are positively associated with BMI and waist circumference.

- In a prospective study of 1,016 older Swedish men and women, higher serum levels of mono-isobutyl phthalate (MiBP) were statistically significantly associated with higher total fat mass, waist circumference, and trunk fat mass two years later. (PMID: 22472124)

- Another prospective study of children found that urinary monoethyl phthalate (MEP) levels were associated with BMI and WC one year later, but only among overweight children. (PMID: 22222007)
BPA and female reproductive health

Animal models indicate that BPA interferes with fertility and fecundity.

Humans:

- Higher BPA levels associated with decreased human oocyte maturation in vitro (PMID: 23904465)
- Higher urinary BPA concentrations have been associated with higher risk of implantation failure among women undergoing in vitro fertilization (PMID: 22484414)

Evidence inconsistent related to onset of puberty.

No human studies of effect of BPA exposure on pregnancy loss.
Phthalates and female reproductive health

“The epidemiological literature is sparse for most outcomes studied and plagued by small sample size, methodological weaknesses, and thus fails to support a conclusion of an adverse effect of phthalate exposure. Despite a paucity of experimental animal studies for several phthalates, we conclude that there is sufficient evidence to suggest that phthalates are reproductive toxicants.” (Kay et al. PMID: 23405971)

Stronger and more consistent evidence:

• *In utero* exposure increases risk of preterm birth
  (PMID: 14594632, 19948620, 20019910)

Evidence inconsistent related to onset of puberty, time to pregnancy, and pregnancy loss.
## BPA and breast cancer risk

Animal model and cell culture data show that BPA exposure is associated with:

- Increased risk of breast cancer (including *in utero* exposures)
- Resistance to chemotherapy (doxorubicin, cisplatin, and vinblastine)

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<tr>
<td>Lopez-Carrillo (2010) PMID: 20368132</td>
<td>case-control (n = 233/231)</td>
<td>urine</td>
<td>DEHP metabolites increased risk of breast cancer; Other phthalates decreased risk of breast cancer</td>
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Important points

• Lack of evidence does not mean “no association”

• Conflicting results between studies most likely represent issues around study design and data analysis, rather than a lack of a true biologic relationship.

• Scientists still have a number of methodologic challenges to work out before “definitive” studies can be performed.
"When an activity raises threats of harm to human health or the environment, precautionary measures should be taken even if some cause and effect relationships are not fully established scientifically. In this context the proponent of an activity, rather than the public, should bear the burden of proof. The process of applying the precautionary principle must be open, informed and democratic and must include potentially affected parties. It must also involve an examination of the full range of alternatives, including no action."

*The Wingspread Consensus Statement on the Precautionary Principle, January 1998*
Open letter to the European commission: scientifically unfounded precaution drives European commission’s recommendations on EDC regulation, while defying common sense, well-established science, and risk assessment principles

Daniel Dietrich · Sonja von Aulock · H. W. J. Marquardt · Bas J. Blaauboer · Wolfgang Dekant · James Kehrer · Jan G. Hengstler · Abby C. Collier · Gio Batia Gori · Olavi Pelkonen · Florian Lang · Frans P. Nijkamp · Kerstin Stemmer · Albert Li · Kai Savolainen · A. Wallace Hayes · Nigel Gooderham · Alan Harvey


Policy Decisions on Endocrine Disruptors Should Be Based on Science Across Disciplines: A Response to Dietrich et al.

Applications to practice

Research on human health effects is still at the very early stages – more research coming soon!

Dietetics professionals should:

• be prepared to critically evaluate the research studies as they emerge
• consider the sources of information
• synthesize the entire body of literature rather than acting on the results of any single study

Precautionary principle is warranted wherever possible.
Counseling clients/patients to limit BPA and phthalate exposures

- Prepare food from scratch whenever possible
- Store foods in glass or metal containers rather than plastic
- Never heat foods in plastic containers or dishes
- Do not place plastics in the dishwasher
- Avoid plastics with the recycling codes 3 (contains phthalates), 6 and 7 (contains BPA)
- Avoid leaving plastic water bottles in warm places (e.g. your car on a hot summer day!)

Session handout update – new link for “Check the kinds of plastics you use” patient education material
Tools and Resources

- Take Action Kit: Phase out PVC/DEHP
- Alternatives to PVC and DEHP in Health Care
- Government Science Reports on Phthalates
- Harvard Study on DEHP Exposure in NICUs
- Policies and Resolutions to Reduce PVC/DEHP
- Join the List of Hospitals Phasing Out PVC and DEHP

Take Action Kit: Phase out PVC/DEHP

HCWH has developed these tools to help health care workers take action to reduce PVC and DEHP. Get started on phasing out PVC and DEHP products in health care with help from these key tools and resources.

Fact Sheets

- The Weight of the Evidence on DEHP: Exposures Are