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Children's Health and the Environment: Opportunities for Prevention

Leonardo Trasande, MD, MPP
Associate Professor of Pediatrics,
Environmental Medicine and Health Policy
New York University

Why are children are uniquely vulnerable?

- Pound for pound, drink more water, eat more food and breathe in more air
- Less well able to detoxify or eliminate chemicals from their bodies
- Developing organ systems are more susceptible
- Greater years of life in which chronic conditions can occur as a result of early life exposures

National Academy of Sciences 1993

Evidence confirming child vulnerability

- Epidemic increases in chronic disease in US and other industrialized nations (asthma, childhood cancers, certain birth defects, learning/developmental disabilities)
 - Contemporaneous with widespread increase in use of chemicals

Trasande et al Dec 2011 Health Affairs

Evidence confirming child vulnerability

- Population studies quantify strong and consistent associations with chemical exposures
 - US National Academy of Sciences: 28% of developmental disabilities at least in part due to environment
 - Benzene and 1,3-butadiene associated with childhood cancer
 - Outdoor air pollutants are well documented to worsen and may increase risk of development of asthma

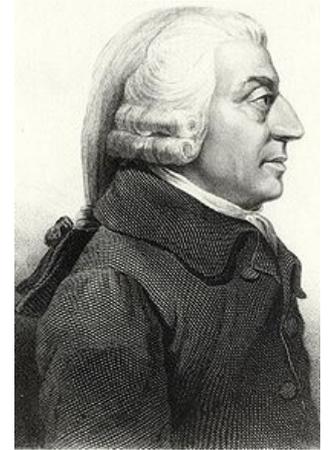
Trasande et al Dec 2011 Health Affairs

Why have we been slow to protect children?

- Regulation does not require premarket testing of chemicals
 - Fewer than 1/2 of most produced chemicals in US have any toxicity testing data; fewer than 1/5 have data with respect to impacts on development
- Epidemiologic studies post hoc take years
- Outcomes have many potential confounders
- Criteria of reproducibility, consistency
- Uncertainty about dose-response relationships (also linear pedagogy), thresholds
- Subclinical effects are not as powerful as the Minamata or Bhopal disasters

Why would Adam Smith care about environmental health?

- Environmental hazards produce market failures
 - Inefficiencies are costly to society
 - Information asymmetry
 - Externalities



Example: Air pollution

- Electricity producers emit particulate matter among other pollutants which are respiratory irritants
 - Children develop respiratory illnesses
 - Incur hospitalization, emergency room, prescription drugs and other costs (including loss of work and school)
- Costs not borne by producers
 - Overproduce electricity compared to socially optimal amount
 - More disease and disability than society willing to pay

How much do these externalities cost?

- Environmentally attributable costs of lead poisoning, methylmercury toxicity, asthma, autism, attention deficit hyperactivity disorder, childhood cancer, intellectual disability
\$76.6 billion

Trasande and Liu Health Affairs 2011

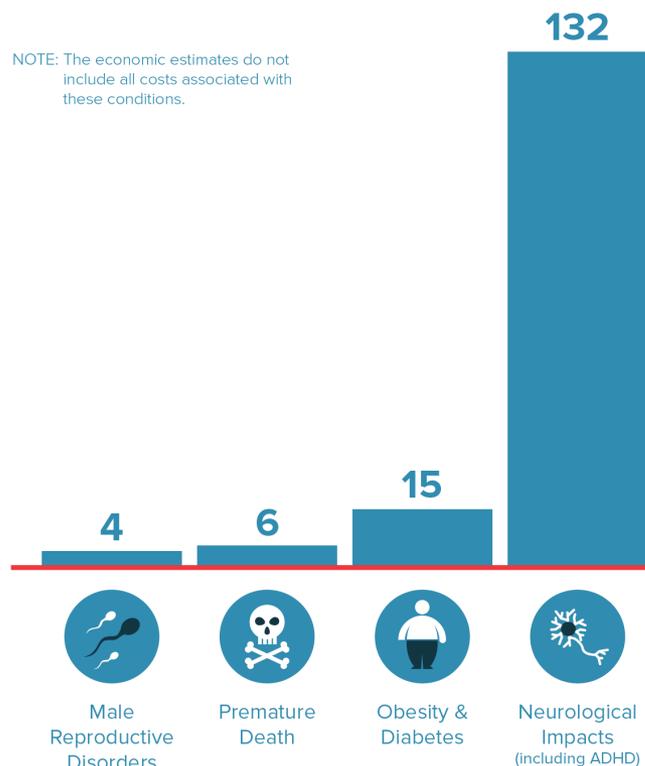
- Global costs of lead exposure in developing countries
\$992 billion (1.0% of GDP)
\$227 billion (2.0% of GDP) in China

Attina and Trasande EHP 2013

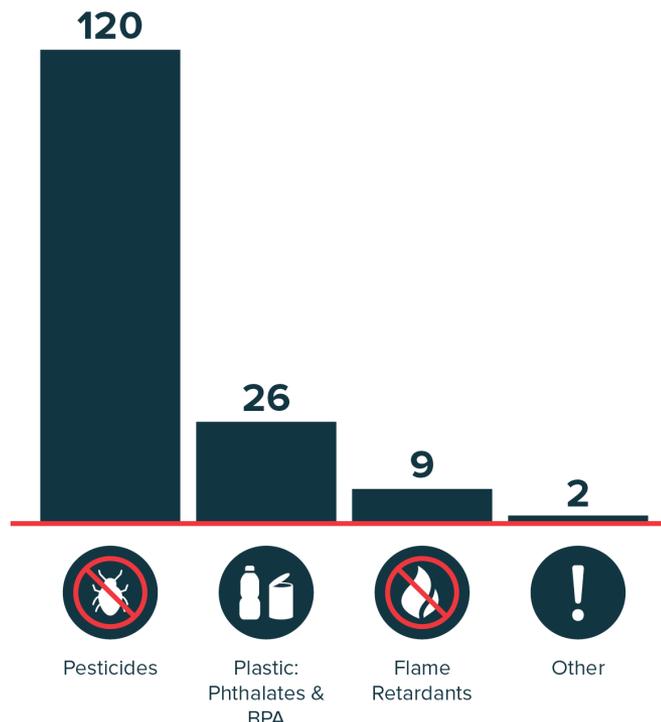
HEALTH EFFECTS FROM ENDOCRINE DISRUPTING CHEMICALS COST THE EU 157 BILLION EUROS EACH YEAR.

This is the tip of the iceberg: Costs may be as high as €270B.

€157B Cost by Health Effect



€157B Cost by EDC Type



SOME EDC-RELATED HEALTH OUTCOMES NOT INCLUDED:

- Breast Cancer
- Prostate Cancer
- Immune Disorders
- Female Reproductive Disorders
- Liver Cancer
- Parkinson's Disease
- Osteoporosis
- Endometriosis
- Thyroid Disorders

SOME EDCs NOT INCLUDED:

- Atrazine
- 2, 4-D
- Styrene
- Triclosan
- Nonylphenol
- Polycyclic Aromatic Hydrocarbons
- Bisphenol S
- Cadmium
- Arsenic
- Ethylene glycol

Endocrine Disrupting Chemicals (EDCs) interfere with hormone action to cause adverse health effects in people.

“THE TIP OF THE ICEBERG”

The data shown to the left are based on fewer than 5% of likely EDCs. Many EDC health conditions were not included in this study because key data are lacking. Other health outcomes will be the focus of future research.

Prevention stimulates the economy!

Table 2. Assumptions and results of three calculations of the economic benefit to the 2000 birth cohort resulting from reduction in lead exposure since the 1970s.

Parameter	Lower bound	Base case	Upper bound
Assumptions			
A. Reduction in BLL ($\mu\text{g}/\text{dL}$)	12.3	15.1	15.1
B. IQ–BLL slope	0.185	0.257	0.323
C. Earnings–IQ slope (%)	1.76	2.00	2.37
D. Present value of earnings of 2-year-old (in 2000 dollars)	723,300	723,300	723,300
E. Size of 2-year-old cohort	3,800,000	3,800,000	3,800,000
Results (formulas)			
Value of one IQ point (in 2000 dollars) ($C \times D$)	12,700	14,500	17,200
Gain per 1 $\mu\text{g}/\text{dL}$ (in 2000 dollars) ($B \times C \times D$)	2,350	3,720	5,550
Benefit per individual (in 2000 dollars) ($A \times B \times C \times D$)	29,000	56,100	83,800
Benefit per cohort (in 2000 dollars) ($A \times B \times C \times D \times E$)	110 billion	213 billion	318 billion

Grosse et al
Environ Health Perspect 110:563-569 (2002)

Prevention works and saves money

- Global Benefits of Phasing Out Lead From Gasoline
 - \$1-\$6 trillion/year, with a best estimate of \$2.45 trillion/year. These benefits may also be expressed as 4% of global GDP.

Tsai and Hatfield J Environ Health 2013

Solutions

- Clinical
- Research
- Policy

Clinical Solutions

- What is a Pediatric Environmental Health Specialty Unit (PEHSU)?
 - A resource for pediatricians, public health officials, school personnel, parents and others to get questions answered about children's health and the environment
- Goals of a PEHSU
 - Education of health professionals and others about children's health and the environment
 - Serve as a consultant to physicians, nurses, public health professionals, parents and others with questions about children's health and the environment



Research Solutions

- Endocrine disruptors (EDs) are chemicals that have the capacity to interfere with hormonal signaling systems
 - May mimic, block, or modulate the synthesis, release, transport, metabolism, binding, or elimination of natural hormones
 - May temporarily or permanently alter feedback loops in the brain, pituitary, gonads, thyroid, and other components of the endocrine system

Endocrine disrupting chemicals

- Highly heterogeneous group of molecules
 - industrial solvents/lubricants and their byproducts [polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), dioxins], plastics [bisphenol A (BPA)],
 - plasticizers (phthalates),
 - pesticides [methoxychlor, chlorpyrifos, dichlorodiphenyltrichloroethane (DDT)],
 - fungicides (vinclozolin), and
 - pharmaceutical agents [diethylstilbestrol (DES)].”

Chemical environmental agents and the endocrine system

- First observation by Herbst and Bern of eight cases of clear cell adenocarcinoma of the vagina Bern H 1992
- Had been exposed in utero one to two decades earlier to diethylstilbestrol (DES), a synthetic estrogen prescribed to pregnant women in the 1950s and 1960s to prevent miscarriage

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Source: J Midwifery Womens Health © 2003 Elsevier Science, Inc.

Endocrine-Disrupting Chemicals: An Endocrine Society Scientific Statement

Evanthia Diamanti-Kandarakis, Jean-Pierre Bourguignon, Linda C. Giudice, Russ Hauser, Gail S. Prins, Ana M. Soto, R. Thomas Zoeller, and Andrea C. Gore

Endocrine Section of First Department of Medicine (E.D.-K.), Laiko Hospital, Medical School University of Athens, 11527 Athens, Greece; Department of Pediatrics (J.-P.B.), Centre Hospitalier Universitaire de Liege, 4000 Liege, Belgium; Department of Obstetrics, Gynecology, and Reproductive Sciences (L.C.G.), University of California San Francisco, San Francisco, California 94131; Department of Environmental Health (R.H.), Harvard School of Public Health, Boston, Massachusetts 02115; Department of Urology (G.S.P.), University of Illinois at Chicago, Chicago, Illinois 60612; Department of Anatomy and Cell Biology (A.M.S.), Tufts University School of Medicine, Boston, Massachusetts 02111; Biology Department (R.T.Z.), University of Massachusetts, Amherst, Massachusetts 01003; and Division of Pharmacology and Toxicology (A.C.G.), The University of Texas at Austin, Austin, Texas 78712

There is growing interest in the possible health threat posed by endocrine-disrupting chemicals (EDCs), which are substances in our environment, food, and consumer products that interfere with hormone biosynthesis, metabolism, or action resulting in a deviation from normal homeostatic control or reproduction. In this first Scientific Statement of The Endocrine Society, we present the evidence that endocrine disruptors have effects on male and female reproduction, breast development and cancer, prostate cancer, neuroendocrinology, thyroid, metabolism and obesity, and cardiovascular endocrinology. Results from animal models, human clinical observations, and epidemiological studies converge to implicate EDCs as a significant concern to public health. The mechanisms of EDCs involve divergent pathways including (but not limited to) estrogenic, antiandrogenic, thyroid, peroxisome proliferator-activated receptor γ , retinoid, and actions through other nuclear receptors; steroidogenic enzymes; neurotransmitter receptors and systems; and many other pathways that are highly conserved in wildlife and humans, and which can be modeled in laboratory *in vitro* and *in vivo* models. Furthermore, EDCs represent a broad class of molecules such as organochlorinated pesticides and industrial chemicals, plastics and plasticizers, fuels, and many other chemicals that are present in the environment or are in widespread use. We make a number of recommendations to increase understanding of effects of EDCs, including enhancing increased basic and clinical research, invoking the precautionary principle, and advocating involvement of individual and scientific society stakeholders in communicating and implementing changes in public policy and awareness. (*Endocrine Reviews* 30: 293–342, 2009)



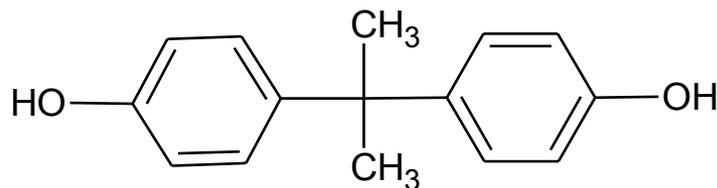
State of the Science of Endocrine Disrupting Chemicals - 2012

Edited by
Åke Bergman, Jerrold J. Heindel, Susan Jobling,
Karen A. Kidd and R. Thomas Zoeller

IOMC INTER-ORGANIZATION PROGRAMME FOR THE SOUND MANAGEMENT OF CHEMICALS
A cooperative agreement among FAO, ILO, UNDP, UNEP, UNIDO, UNITAR, WHO, World Bank and OECD



Bisphenol A (BPA)



- Used to manufacture polycarbonate resin
- Recently banned from baby bottles and sippy cups by US Food and Drug Administration
- Breakdown product of coatings intended to prevent metal corrosion in food and beverage containers
- In children, dietary sources constitute 99% of BPA exposure

Schechter et al. *Environ Sci Technol.* 2010;44(24):9425-9430
Wilson et al. *Environ Res.* Jan 2007;103(1):9-20.
Tavernise S. *New York Times*, 17 July 2012 edition.

BPA and obesity

- Laboratory studies suggest that BPA
 - Increases fat cell size
 - Disrupt adiponectin function
 - Low-grade synthetic estrogen
 - Estrogen-testosterone balance may have sex-specific differences in influence on body mass

Masuno et al. *J Lipid Res.* 2002;43(5):676-684; Sakurai K et al. *Br J Pharmacol.* 2004;141(2):209-214;

Association of urinary BPA with childhood obesity

- Nationally representative sample of 2838 US children
 - Urinary BPA measured by the Centers for Disease Control and Prevention
 - Divided population into four groups, lowest to highest
 - Children with lowest levels of BPA: 10.3% obese
 - Children with higher levels of BPA: 20.1-22.1% obese
 - Linear association of BPA with standardized measure of Body Mass Index accounting for age and gender
 - Levels of other phenols found in sunscreens and soaps not associated

Trasande et al JAMA 2012; 308(11):1113-21

Other chemicals with data suggesting role in obesity, diabetes and cardiovascular disease

- Phthalates

- Found in shampoos, soaps, lotions, flooring, food wraps

Janesick et al 2011, Trasande et al 2013

- Perfluoroalkyl chemicals

- Used in nonstick cooking, carpets and upholstery, microwave popcorn bags

Halldorsson et al 2012

- Polycyclic aromatic hydrocarbons

- Breakdown product of fuel burning, also food contaminant

Rundle et al Am J Epidem 2012

- Proximity to oil refinery in Jeddah associated with increased BP

Trasande et al Env Research 2015

- Polybrominated diphenyl ethers

- Flame retardants found in furniture, electronics

Lim et al Diabetes Care 2008

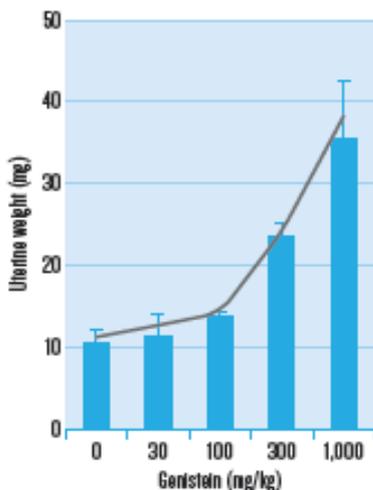
Non-linearity and non-monotonicity

CURIOUS CURVES

Researchers have found that many endocrine-disrupting chemicals do not generate the standard monotonic dose-response curves seen for other types of compound.

MONOTONIC CURVE

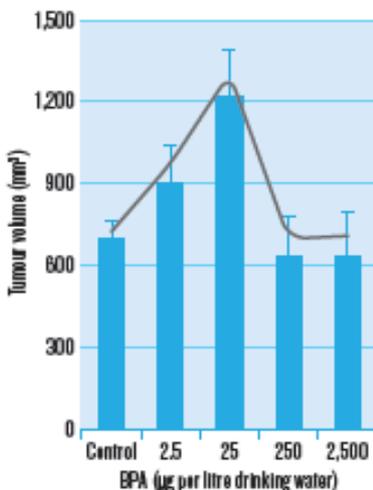
In some cases, dose and response increase together. The plant oestrogen genistein, for instance, causes the mouse uterus to increase in weight.



SOURCE: Ohta, R. et al. *J. Toxicol. Sci.* 37, 879-889 (2012)

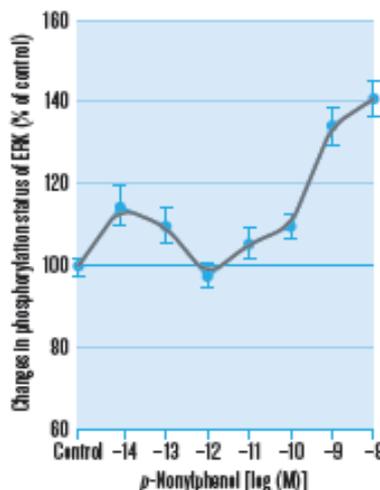
NON-MONOTONIC CURVES

Mice exposed to moderate doses of bisphenol A develop the largest tumours. Moderate and high doses are thought to induce tumour-cell proliferation, but high doses also trigger cell death.



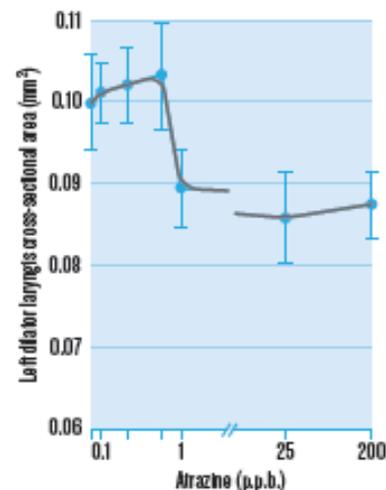
SOURCE: Jenkins, S. et al. *Environ. Health Perspect.* 119, 1604-1609 (2011)

The oestrogen mimic *p*-nonylphenol stimulates the ERK cell-signalling pathway at low and high doses. Interactions with hormone receptors and other membrane proteins explain the complex shape of the curve.



SOURCE: Bulayeva, N. N. & Watson, C. S. *Environ. Health Perspect.* 112, 1481-1487 (2004)

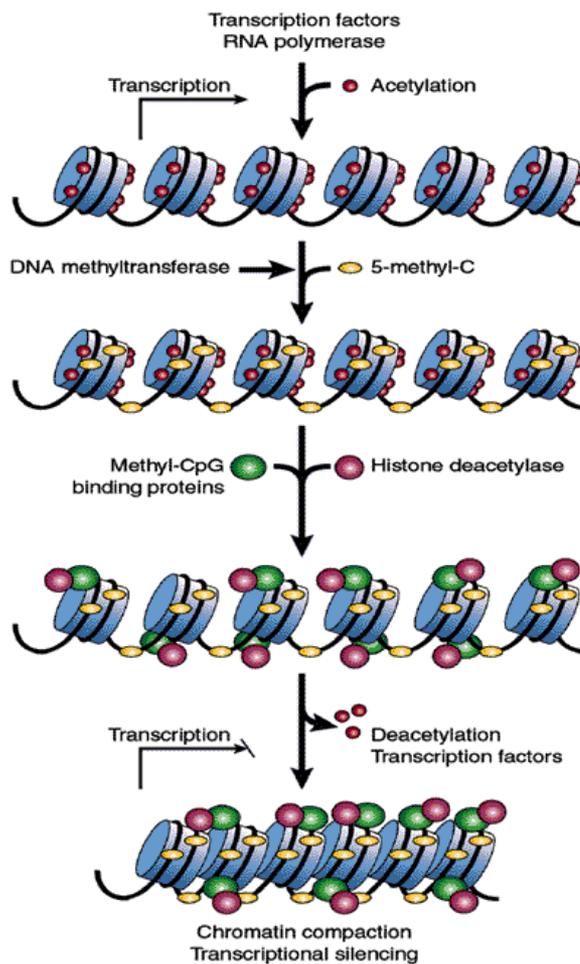
Above a certain dose, the herbicide atrazine causes the larynx muscle to shrink in male frogs. But the effect does not increase at higher doses.



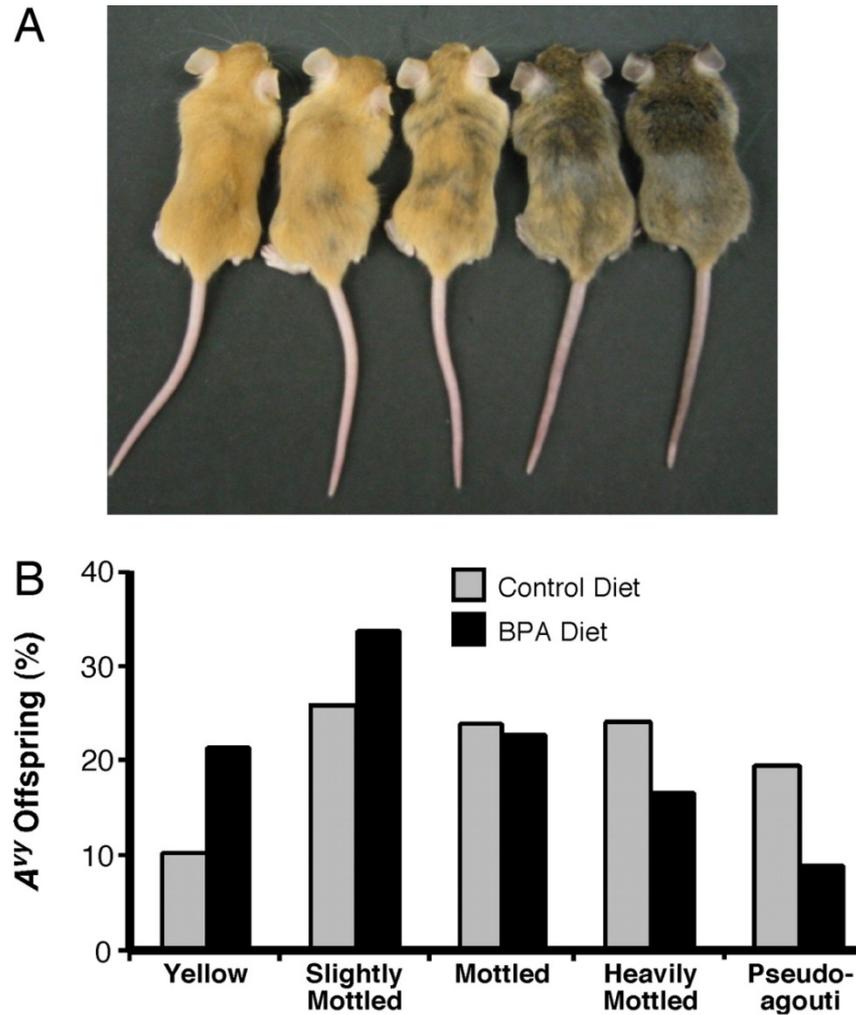
SOURCE: Hayes, T. A. et al. *Proc. Natl. Acad. Sci. USA* 99, 5476-5480 (2002).

Fagin Nature 2012

Chemical exposures and epigenetics



Maternal BPA exposure shifts offspring coat color distribution toward yellow.



Dolinoy D C et al. PNAS 2007;104:13056-13061

Policy action on BPA

- BPA banned in baby bottles and sippy cups
 - But not in other food uses



Costs of BPA exposure

- 12,404 cases of childhood obesity
- 33,863 cases of newly incident coronary heart disease
- Estimated social costs of \$2.98 billion in 2008

Trasande Health Affairs 2014

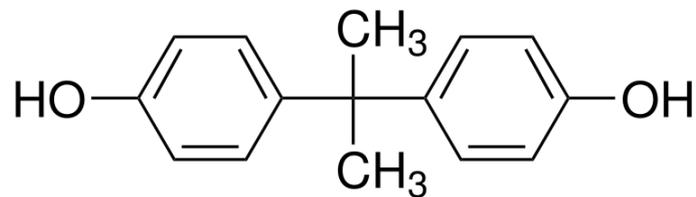
Benefits and costs of replacing BPA

- Potential cost of one BPA alternative, oleoresin = \$0.022 per can
 - 100 billion aluminum cans are produced annually
 - 100 billion x \$0.022 = **\$2.2 billion**
- Potential benefit of replacing BPA with lining free of health effects = **\$1.74 billion**
 - Does not include other effects (cognitive, asthma, breast cancer)
- Sensitivity analyses suggest as high as \$13.8 billion

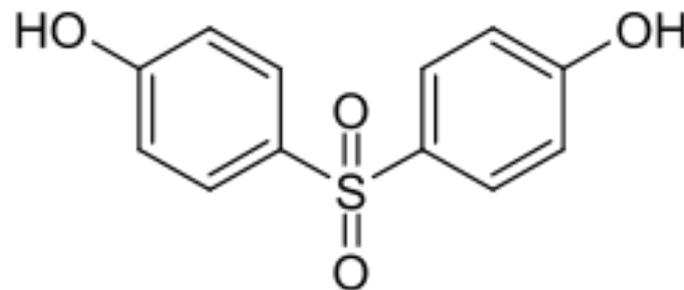
Trasande Health Affairs 2014

BPS replacing BPA?

- Emerging evidence suggests replacement of BPA and BPS
- Similar, weak estrogen like BPA
- Disrupts signaling of estrogen in animal studies
- Does not degrade as easily in seawater



Bisphenol A



Bisphenol S

Liao et al Environ Sci Technol. 2012 Jun 19;46(12):6860-6.
Liao et al Environ Sci Technol. 2012 Jun 19;46(12):6515-22.
Grignard et al Toxicol In Vitro. 2012 Aug;26(5):727-31.
Vinas and Watson EHP doi:10.1289/ehp.1205826
Danzl et al Int J Environ Res Public Health. 2009 Apr;6(4):1472-84

The increasingly global chemical picture

- OECD estimates in 2020: industrializing nations will account for 33% of global chemical demand and 31% of production
 - compared with 23 percent and 21 percent, respectively, in 1995
 - industrializing nations are expected to lead in the manufacture of high production volume chemicals
 - occurs against a backdrop of insufficient infrastructure to protect public health and the environment

Summary

- Clinical resources can be very useful to guide prevention and management of environmental exposures in children
- Substantial research is ongoing to better understand the complex relationships of environmental chemicals to disease, especially endocrine disruptors
- Regulation is needed to proactively prevent chronic childhood diseases that are increasing both in industrializing and industrialized countries
 - Benefits of improved health may be greater than costs of safer alternatives

Thanks!

- Collaborators

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