HASSENFELD CHILDREN'S HOSPITAL OF NEW YORK AT NYU LANGONE

Endocrine disrupting chemicals: a costly public health threat with opportunities for policy prevention

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Japanese Society of Public Health COI Declaration

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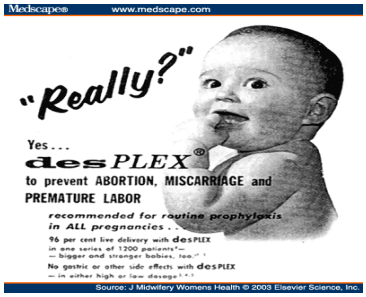
The presenter has no conflict of interest with any corporate organizations relating to this presentation

The Diethylstilbestrol Story

First observation by Herbst et al of eight cases of clear cell adenocarcinoma of the vagina
Herbst et al NEJM 1971

- 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



Chemical environmental agents and the endocrine system

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 (EDC)

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)
- pharmaceutical agents [diethylstilbestrol (DES)]

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

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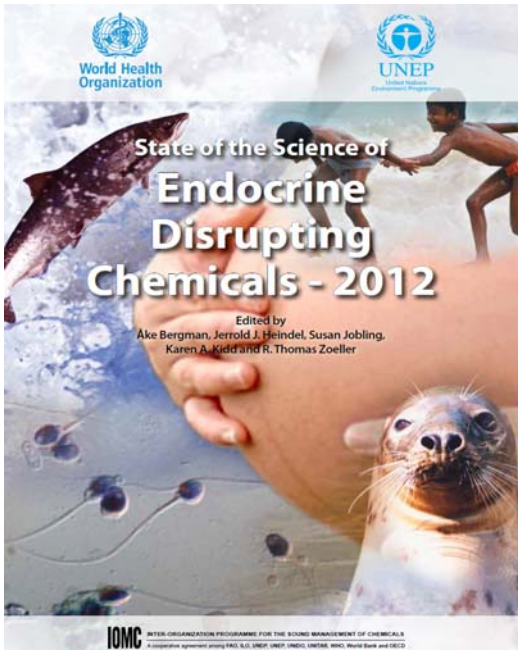
There is growing interest in the possible health threat posed by endocrine-disrupting chemicals (EDCs), which are substances in our environment, food, and consumer products that interfere with hormone biosynthesis, metabolism, or action resulting in a deviation from normal homeostatic control or reproduction. 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)**



Response to WHO/UNEP Report

WHO/UNEP report (2012) "welcomed" by all participant countries at 2015 Strategic Alliance for International Chemicals Management

- Footnote identifies only chemical and pesticide industries as having concerns about state of science
- Concerns voiced in response by Lamb et al rebutted by WHO/UNEP report authors in Reg Tox Pharm Bergman et al 2015

EDC-2: The Endocrine Society's Second Scientific Statement on Endocrine-Disrupting Chemicals

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The Endocrine Society's first Scientific Statement in 2009 provided a wake-up call to the scientific community about how environmental endocrine-disrupting chemicals (EDCs) affect health and disease. Five years later, a substantially larger body of literature has solidified our understanding of plausible mechanisms underlying EDC actions and how exposures in animals and humans—especially during development—may lay the foundations for disease later in life. At this point in history, we have much stronger knowledge about how EDCs alter gene-environment interactions via physiological, cellular, molecular, and epigenetic changes, thereby producing effects in exposed individuals as well as their descendants. Causal links between exposure and manifestation of disease are substantiated by experimental animal models and are consistent with correlative epidemiological data in humans. There are several caveats because differences in how experimental animal work is conducted can lead to difficulties in drawing broad conclusions, and we must continue to be cautious about inferring causality in humans. In this second Scientific Statement, we reviewed the literature on a subset of topics for which the translational evidence is strongest: 1) obesity and diabetes; 2) female reproduction; 3) male reproduction; 4) hormone-sensitive cancers in females; 5) prostate; 6) thyroid; and 7) neurodevelopment and neuroendocrine systems. Our inclusion criteria for studies were those conducted predominantly in the past 5 years deemed to be of high quality based on appropriate negative and positive control groups or populations, adequate sample size and experimental design, and mammalian animal studies with exposure levels in a range that was relevant to humans. We also focused on studies using the developmental origins of health and disease model. No report was excluded based on a positive or negative effect of the EDC exposure. The bulk of the results across the board strengthen the evidence for endocrine health-related actions of EDCs. Based on this much more complete understanding of the endocrine principles by which EDCs act, including nonmonotonic dose-responses, low-dose effects, and developmental vulnerability, these findings can be much better translated to human health. Armed with this information, researchers, physicians, and other healthcare providers can guide regulators and policymakers as they make responsible decisions. (*Endocrine Reviews* 36: 0000–0000, 2015)

Endocrine disruption and the developing brain

Thyroid hormone has long been known to be critical to early brain development

- Predictable outcomes of its disruption include global IQ deficits, as well as neurodevelopmental disabilities such as autism spectrum disorder (ASD), and attention-deficit hyperactivity disorder (ADHD).

Interference with sex steroid and other hormonal modes of action may also adversely impair early brain development.

Organophosphate pesticides

Principal mode of action of chlorpyrifos is through acetyl cholinesterase (AChE) inhibition, though many reports indicate neurotoxicological effects independent of AChE inhibition

- Developmental exposure of mice to levels of chlorpyrifos that had no effect on AChE activity adversely affected thyroid hormone levels
- Thyroid signalling also impaired

De Angelis et al Toxicological sciences 2009;
Jeong et al Toxicology 2006;
Levin et al Neurotoxicology and teratology 2002

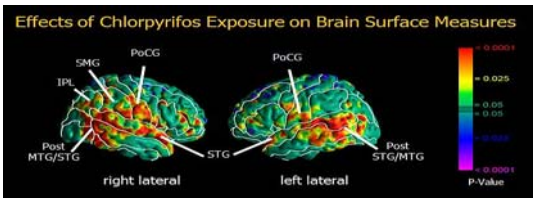
Organophosphate pesticides

Consistent dose/response relationships of organophosphate pesticide exposures in pregnancy with intellectual quotient across three carefully conducted longitudinal birth cohorts

Bouchard et al EHP 2011; Engel et al EHP 2011; Chen et al 2015

Prenatal OP exposure has been associated with magnetic resonance imaging findings in children including frontal and parietal cortical thinning

Rauh et al PNAS 2012

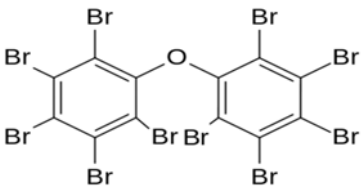


Brominated flame retardants

Large literature identifies PBDE to interfere with thyroid hormone action

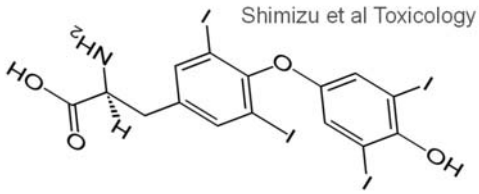
Bellanger et al JCEM 2015 (Appendix)

PBDEs may also affect the metabolism of thyroid hormone



PBDE-209 (deca)

Shimizu et al Toxicology 2013



Thyroxine (T4, thyroid hormone)

Brominated flame retardants

Four well-designed longitudinal birth cohorts have examined PBDE effects on child neurodevelopment

- Three (all US) identified consistent, exposure-response relationships with IQ, with carefully collected data on many potential confounders.

Chen et al EHP 2014; Eskenazi et al EHP 2013; Herbstman et al EHP 2010

- Fourth (from Spain), suffered from modest sample size, with few detectable PBDE levels, though this study showed substantial directionality towards cognitive and motor dysfunction at age 4.
  - IQ was not measured
  - Exposure levels in the US are much higher than in the EU.

Gascon et al Environment International 2011

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

Schecter 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

Longitudinal studies

Three studies to date with positive, although not consistent results, but all had limited frequency of measurements of BPA in pregnancy

Valvi et al Epidemiology 2013, Harley et al EHP 2013, Braun et al EHP 2014

Dutch birth cohort: higher uBPA associated with lower growth rates for fetal weight and birth weight

Snijder et al EHP 2013

- Follow-up study examining BPA at three time points in pregnancy funded by NIEHS (R01ES022972) to see if higher BPA associated with obesity, insulin resistance and blood pressure in children

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

Polybrominated diphenyl ethers

- Flame retardants found in furniture, electronics

Lim et al Diabetes Care 2008

Endocrine disruption and fertility

Fertility is a condition of a couple, where reproductive health of both sexes plays a role

Louis et al 2013

Fetal exposure to phthalates with reduced infant anogenital distance (AGD)

Swan et al EHP 2005, Bornehag et al EHP 2014

Shortened adult AGD is associated with reduced semen quality and testosterone level

Multiple studies have identified reduced male fertility and poor semen quality with multiple EDCs, including phthalates, bisphenol A, and polyfluorinated chemicals

Juul et al Nat Rev Endo 2014

What can we do limit EDC exposures?

Fortunately, there are safe and simple steps families can take at home to limit these exposures.

We can also advocate for proactive policies that limit exposures to common dietary contaminants.

Pesticide exposures are preventable

Eating organic

- Reduces urinary levels of pesticides

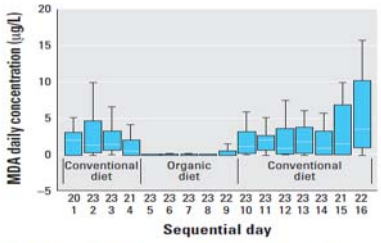


Figure 1. Box plots of DVWA of MDA concentrations in 23 children 3–11 years of age for 15 consecutive days in which conventional and organic diets were consumed. The top row of numbers on the *x*-axis represents numbers of children.

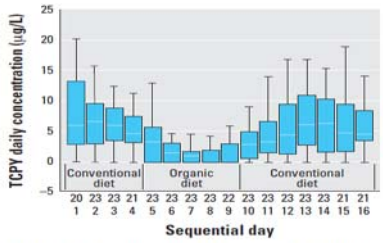


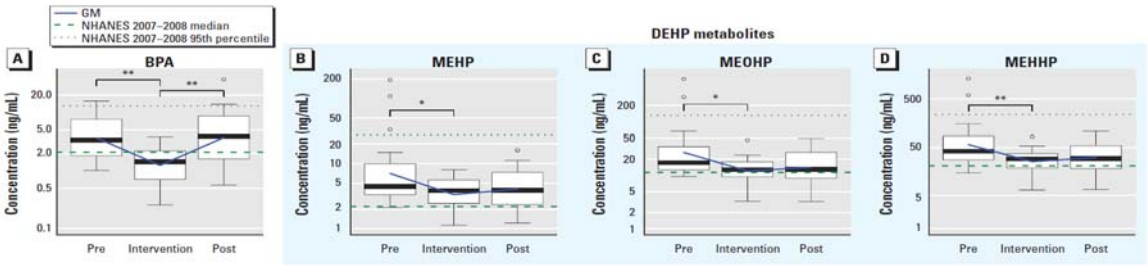
Figure 2. Box plots of DVWA of TCPY concentrations in 23 children 3–11 years of age for 15 consecutive days in which conventional and organic diets were consumed. The top row of numbers on the *x*-axis represents numbers of children.

Lu et al EHP 2006

Bisphenol and phthalate exposures are preventable

Limiting canned food consumption and avoiding processed foods

- Intervention reduced mean concentrations of BPA by 66% and DEHP metabolites by 53–56%.



Rudel et al EHP 2011

Safe and simple steps to limit bisphenols and phthalates

Avoid canned foods. Bisphenol A (BPA) doesn't discriminate by the type of can – soda, vegetables, tuna. Acidity is probably the biggest driver of absorption into food, but all types of canned food have detectable levels of BPA.

Don't microwave plastic containers or put them in the dishwasher. Heat and harsh cleaning agents are effective at getting the chemicals out of plastic.

Avoid plastic bottles with the numbers 3, 6 or 7.

If plastic bottles were meant for single use, keep them that way. Besides, reusing them raises the chance of bacterial contamination.

If plastic food containers are etched, it's time to throw them away. Etching increases the odds of leaching.

Flame retardant exposures are preventable

Replace old furniture that has exposed foam or cover it with a slipcover.

Outdoor air has lower concentrations of chemicals that accumulate from electronics, carpeting and the like, and recirculating the air a few minutes every day gets rid of other chemical residues too.

Buy products made from natural fibers (like cotton and wool), which are naturally less flammable.

Vacuum regularly with a HEPA filter and mop with a wet mop to prevent dust from accumulating.

Stop children from touching or mouthing on fire-retardant items.

Be careful when removing old carpet, which may contain PBDEs.

Make sure you get a healthy diet with enough iodine.

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

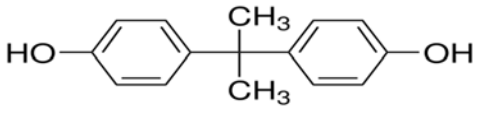
BPS replacing BPA?

Emerging evidence suggests replacement of BPA and BPS

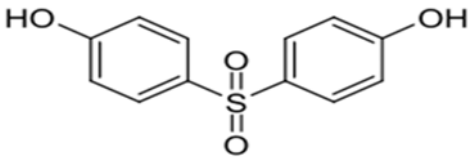
Similar, weak estrogen like BPA

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

Quantifying other EDC disease burden and costs

Development of EDC criteria in EU crucial in setting scientific and policy precedents for other national policies and for the global approach to regulation of these chemicals under agreements such as SAICM (the Strategic Approach to International Chemicals Management).

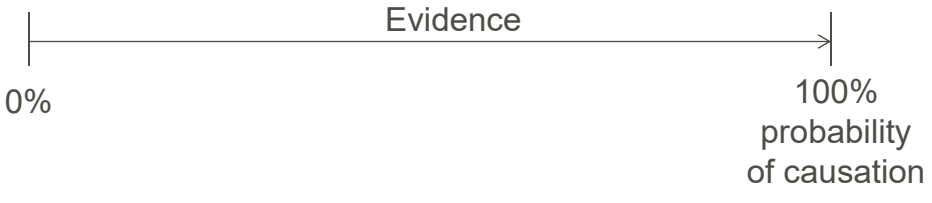
Absent estimates of the burden of disease and disability potentially produced by EDC exposures, high costs of alternatives are likely to outweigh concerns about the health consequences of using EDCs.

Causality criteria

Temporal relationship required
Others favor causality (major in bold)

- **Consistency**
- **Effect size**
- **Dose-response relationship**
- **Biological plausibility**
- Specificity
- Coherence (Coherent with existing theory/knowledge)
- Experiment (Can be prevented or ameliorated)
- Consideration of alternate explanations

Hill AB Proc Royal Soc Med 1965

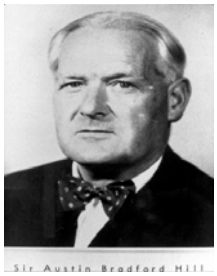


Embracing uncertainty

"What I do not believe – and this has been suggested – is that we can usefully lay down some hard-and-fast rules of evidence that must be obeyed before we accept cause and effect."

"On fair evidence we might take action on what appears to be an occupational hazard, e.g. we might change from a probably carcinogenic oil."

Uncertainty "does not confer upon us a freedom to ignore the knowledge we already have, or to postpone the action that it appears to demand at a given time."



Hill AB Proc Royal Soc Med 1965

Estimating EDC disease burden and costs in EU

Expert panels identified conditions where the evidence is strongest for causation

- Developed ranges for fractions of disease burden that can be attributed for EDCs
- Adapted GRADE Working Group and WHO criteria for evaluating epidemiologic evidence
- Adapted Danish EPA criteria for evaluating toxicology evidence
- Adapted IPCC approach to integrate epidemiology and toxicology evidence and estimate probability of causation

Monte Carlo models (1000 simulations) used to estimate realistic ranges of EDC costs across all exposure-response relationships

Trasande et al J Clin Endo Metab epub Mar 5 2015

Estimating EDC disease burden and costs in US

Leveraged NHANES 2007-8 and 2009-10

Identified cost-of-illness data from US

Generally identical approach to exposure-response relationships, reference levels

Identical probabilities of causation, Monte Carlo simulations

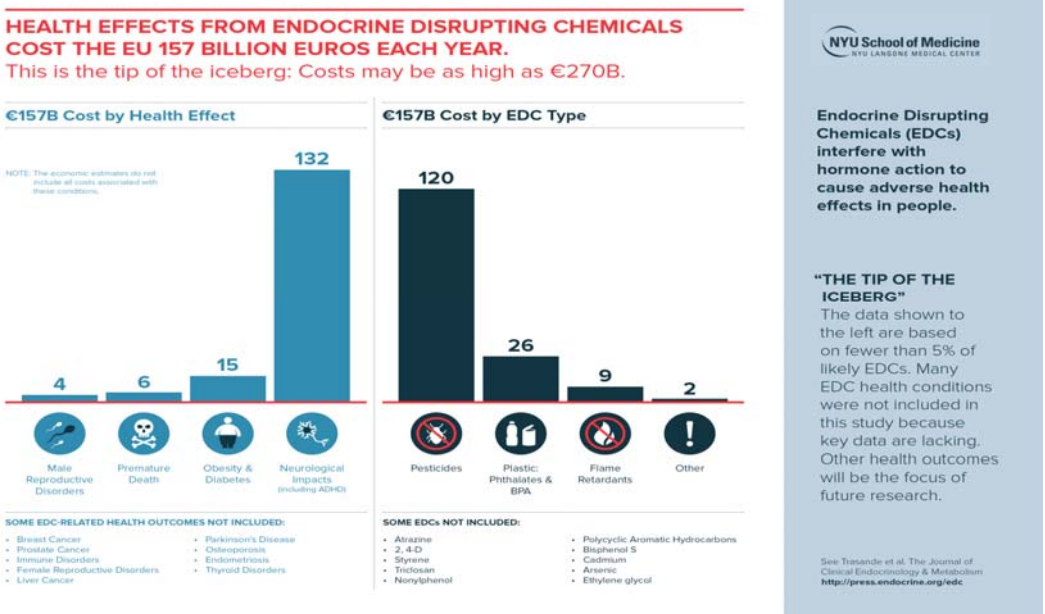
Overall Evaluations

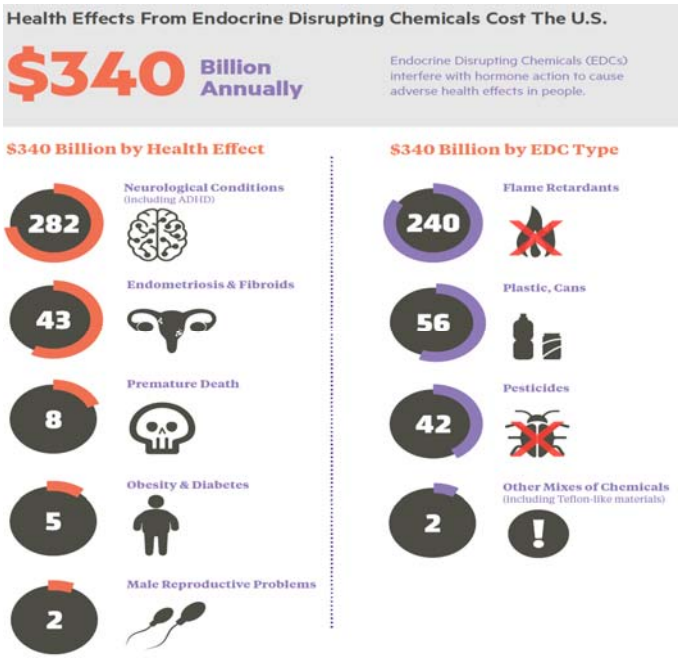
Exposure	Outcome	Strength of Human Evidence	Strength of Toxicologic Evidence	Probability of Causation
Polybrominateddiphenyl ethers (PBDE)	IQ Loss and Intellectual Disability	Moderate-to-high	Strong	70-100%
Organophosphate pesticides (OP)	IQ Loss and Intellectual Disability	Moderate-to-high	Strong	70-100%
Dichlorodiphenytrichloroethane (DDE)	Childhood obesity	Moderate	Moderate	40-69%
Dichlorodiphenytrichloroethane (DDE)	Adult diabetes	Low	Moderate	20-39%
Di-2-ethylhexylphthalate (DEHP)	Adult obesity	Low	Strong	40-69%
Di-2-ethylhexylphthalate (DEHP)	Adult diabetes	Low	Strong	40-69%
Bisphenol A (BPA)	Childhood obesity	Very low-to-low	Strong	20-69%
Polybrominateddiphenyl ethers (PBDE)	Testicular cancer	Very low-to-low	Weak	0-19%
Polybrominateddiphenyl ethers (PBDE)	Cryptorchidism	Low	Strong	40-69%
Benzyl and butylphthalates (Monobenzyl phthalate, MBzP; Monobutyl phthalate, MBP)	Male Infertility, Resulting in Increased Assisted Reproductive Technology	Low	Strong	40-69%
Monobutyl phthalate (MBP) and Di-2-ethylhexylphthalate (DEHP)	Low testosterone, Resulting in Increased Early Mortality	Low	Strong	40-69%
Multiple exposures (PBDE and OPs)	ADHD	Low-to-moderate	Strong	20-69%
Multiple exposures (phthalates)	Autism	Low	Moderate	20-39%
Dichlorodiphenyldichloroethylene (DDE)	Fibroids	Low	Moderate	20-39%
Di-2-ethylhexylphthalate (DEHP)	Endometriosis	Low	Moderate	20-39%

	USA*	European Union†	US costs (2010 US$)	EU costs[16] (US$‡)
PBDE and IQ points loss and intellectual disability	11 million IQ points lost and 43 000 cases	873 000 IQ points lost and 3290 cases	266 billion	12·6 billion
Organophosphate pesticides and IQ points loss and intellectual disability	1·8 million IQ points lost and 7500 cases	13 million IQ points lost and 59 300 cases	44·7 billion	194·0 billion
Dichlorodiphenyltrichloroethane and childhood obesity	857 cases	1555 cases	29·6 million	32·7 million
Dichlorodiphenyltrichloroethane and adult diabetes	24 900 cases	28 200 cases	1·8 billion	1·1 billion
Di-2-ethylhexylphthalate and adult obesity	5 900 cases	53 900 cases	1·7 billion	20·8 billion
Di-2-ethylhexylphthalate and adult diabetes	1300 cases	20 500 cases	91·4 million	807·2 million
Bisphenol A and childhood obesity	33 000 cases	42 400 cases	2·4 billion	2·0 billion
PBDE and testicular cancer	3600 cases	6830 cases	81·5 million	1·1 billion
PBDE and cryptorchidism	4300 cases	4615 cases	35·7 million	172·6 million
Benzylphthalates and butylphthalates and male infertility resulting in increased assisted reproductive technology	240 100 cases	618 000 cases	2·5 billion	6·3 billion
Phthalates and low testosterone resulting in increased early mortality	10 700 attributable deaths	24 800 attributable deaths	8·8 billion	10·6 billion
Multiple exposures and ADHD	4400 cases	19 400–31 200 cases	698·0 million	2·3 billion
Multiple exposures and autism	787 cases in boys, 754 cases in girls	316 cases	1·0 billion in boys, 984·0 million in girls	265·1 million
Dichlorodiphenyltrichloroethane and fibroids	37 000 cases	56 700 cases	259·0 million	216·8 million
Di-2-ethylhexylphthalate and endometriosis	86 000 cases	145 000 cases	47·0 billion	1·7 billion

The comparison uses base case estimates. Estimates are conditional on certainty of causation. EU=European Union. PBDE=polybrominated diphenyl ethers. IQ=intelligence quotient. ADHD=attention deficit hyperactivity disorder. *2010 population 310 000 000 million †2010 population 501 000 000 million. ‡Exchange rate used €1=US$1·33.

***Table 3*: Comparison of attributable disease burden and costs in the USA and European Union**





Based on current knowledge, probable costs are €163 billion in EU and $340 billion in US

- <5% of EDCs considered
- Breast cancer and many other conditions not included yet, but will be focus of future work
- Economic numbers do not consider all costs associated with these chronic conditions

Limiting our exposure to the most widely used and potentially hazardous EDCs is likely to produce substantial economic benefit.

Summary

Endocrine-related conditions are increasing

The developing endocrine system is uniquely vulnerable to disruption

Endocrine disrupting chemicals (EDC) are increasingly linked to endocrine-related conditions

EDC exposures are preventable

Preventing EDC exposures has substantial health and economic benefits

Thanks!

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- Expert panel leads: Russ Hauser, Ana Soto, Paul A. Fowler, Patricia Hunt, Juliette Legler, Ruthann Rudel, Niels Skakkebaek
- Other participants: Barbara Cohn, Frederic Bois, Sheela Sathyanarayana, Jorma Toppari, Anders Juul, Ulla Hass, Bruce Blumberg, Miquel Porta, Eva Govarts, Barbara Demeneix
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Teresa Attina

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