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

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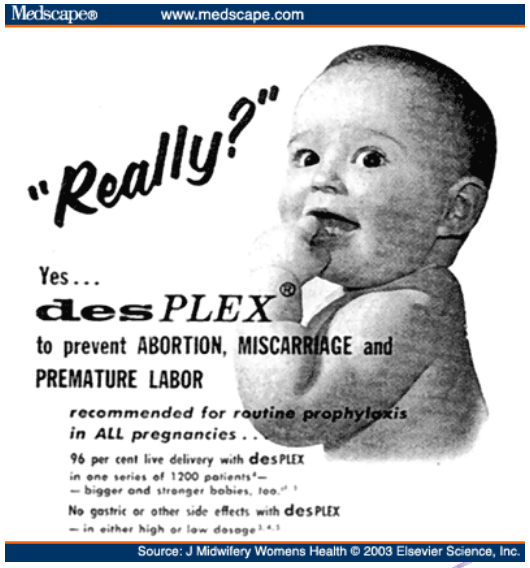
The Diethylstilbestrol Story

- 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



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)**

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Endocrine Disrupting Chemicals

- 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 by industry representatives rebutted by WHO/UNEP report authors in Reg Tox Pharm

Bergman et al 2015

  - Second Endocrine Society Scientific Statement documents strengthened evidence since initial report in 2009

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)

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Yet disease burden and cost estimates for EDCs lacking

- Institute for Health Metrics and Evaluation: 5.2% of lost DALYs
  - Occupational hazards; ambient air pollution; household air pollution (solid fuel burning); radon; childhood lead exposure

GBD Risk Factors Collaborators Lancet 2015

- WHO estimate: 24%
  - 85 diseases reasonably attributable to modifiable environmental factors

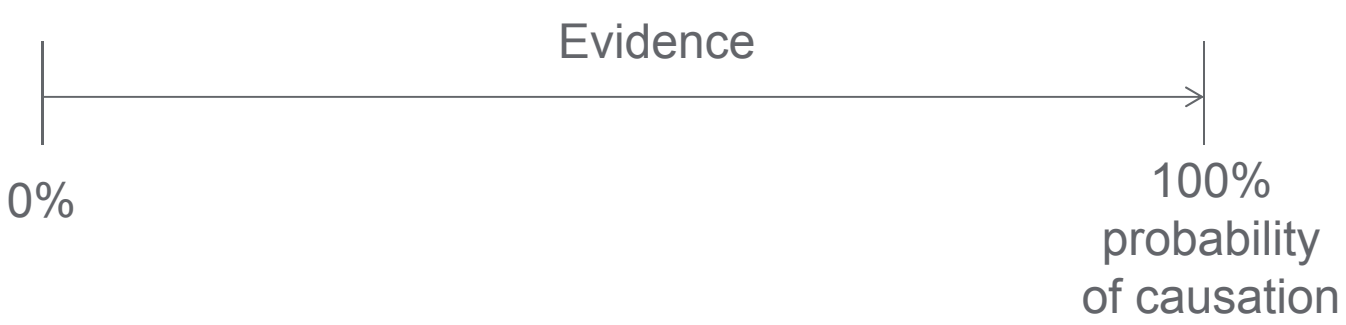
Pruss-Ustun et al Environmental Health 2008

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


Sir Austin Bradford Hill

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

Sir Austin Bradford Hill

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So how to deal with uncertainty?

- Intergovernmental Panel on Climate Change has dealt with similar issues, developing probability weighting for ranges of scenarios

Confidence level	Interpretation
Very high	90-100% probability of causation
High	70-89% probability of causation
Medium	40-69% probability of causation
Low	20-39% probability of causation
Very low	0-19% probability of causation

How to integrate epidemiologic evidence?

- The GRADE (Grading of Recommendations Assessment, Development and Evaluation) scheme is becoming increasingly popular and the preferred approach recommended for the development of WHO guidelines in the presence of uncertainty.

GRADE adapted for EDCs

Quality of evidence	Interpretation	Study design	Lower the quality in presence of	Raise the quality in presence of
High	We are very confident that the true effect lies close to that of the estimate of the effect.	Randomized trial	Study limitations: -1 Serious limitations -2 Very serious limitations -1 Important inconsistency Directness: -1 Some uncertainty -2 Major uncertainty -1 Imprecise data -1 High probability of reporting bias	Strong association: +1 Strong, no plausible confounders, consistent and direct evidence +2 Very strong, no major threats to validity and direct evidence +1 Evidence of a dose-response gradient +1 All plausible confounders would have reduced effect Additional criteria (applied across a body of evidence based on multiple study designs) : +1 Consistency across multiple studies in different settings +1 Analogy across other exposure sources
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.	Quasi-experimental (with controls) and before and after (uncontrolled) studies		
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect	Observational study		
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect	Any other evidence		

Adapted from Atkins et al BMJ 2004 and Bruce et al WHO Indoor Air Quality Guidelines 2014

Danish EPA criteria for toxicologic evidence (adapted)

Quality of evidence	Interpretation	Study design
Strong, Group 1 (Endocrine disruptor)	There is a strong presumption that the chemical has the capacity to cause the health effect through an endocrine disruptor mechanism.	The animal studies provide clear evidence of the ED effect in the absence of other toxic effects, or if occurring together with other toxic effects, the ED effects should not be a secondary non-specific consequence of other toxic effects. However, when there is e.g. mechanistic information that raises doubt about the relevance of the effect for humans or the environment, Group 2 may be more appropriate. Substances can be allocated to this group based on: •Adverse *in vivo* effects where an ED mode of action is plausible •ED mode of action *in vivo* that is clearly linked to adverse *in vivo* effects (by e.g. read-across)
Moderate, Group 2a (Suspected endocrine disruptor)	There is some evidence from experimental animals, yet the evidence is not sufficiently convincing to place the substance in Group 1.	The health effects are observed in the absence of other toxic effects, or if occurring together with other toxic effects, the ED effect should be considered not to be a secondary non-specific consequence of other toxic effects. Substances can be allocated to this group based on: •Adverse effects *in vivo* where an ED mode of action is suspected •ED mode of action *in vivo* that is suspected to be linked to adverse effects in vivo •ED mode of action *in vitro* combined with toxicokinetic in vivo data (and relevant non test information such as read across, chemical categorisation and QSAR predictions)
Weak, Group 2b (Potential endocrine disruptor)	There is some evidence indicating potential for endocrine disruption in intact organisms.	There is some in vitro/in silico evidence indicating a potential for endocrine disruption in intact organisms or effects in vivo that may, or may not, be ED-mediated.

Adapted from Hass et al http://eng.mst.dk/media/mst/67169/SIN%20report%20and%20Annex.pdf

Adapting IPCC criteria to integrate epidemiologic and toxicologic evidence

Toxicologic Evaluation / Epidemiologic Evaluation	Strong (Group 1)	Moderate (Group 2A)	Weak (Group 2B)
High	Very High (90-100%)	High (70-89%)	Medium (40-69%)
Moderate	High (70-89%)	Medium (40-69%)	Low (20-39%)
Low	Medium (40-69%)	Low (20-39%)	Very Low (0-19%)
Very Low	Low (20-39%)	Very Low (0-19%)	Very Low (0-19%)

Trasande et al JCEM 2015;
adapted from http://www.ipcc.ch/meetings/ar4-workshops-express-meetings/uncertainty-guidance-note.pdf

Application to estimate EDC disease burden and costs in EU (1)

- During a two-day workshop in the spring of 2014, five expert panels identified conditions where the evidence is strongest for causation, and developed ranges for fractions of disease burden that can be attributed for EDCs.

- Expert panel topics:
  - Neurodevelopment
  - Obesity and diabetes
  - Breast cancer
  - Male reproductive health
  - Female reproductive health

Trasande et al J Clin Endo Metab epub Mar 5 2015

Application to estimate EDC disease burden and costs in EU (2)

- When dose-response relationship identified, the affected population within the EU was divided into quartiles or other appropriate groupings that permitted quantification of a differential effect with precision.
  - Alternatively, an increment in relative risk over baseline was estimated, and a prevalence of exposure was identified in order to estimate an attributable fraction, using the Levin equation.

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

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**

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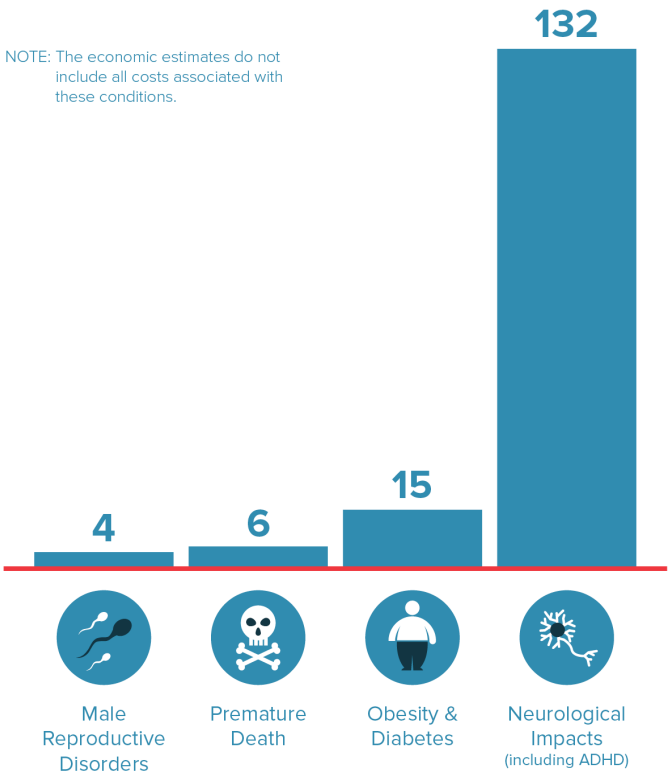
HEALTH EFFECTS FROM ENDOCRINE DISRUPTING CHEMICALS COST THE EU 157 BILLION EUROS EACH YEAR.

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

€157B Cost by Health Effect

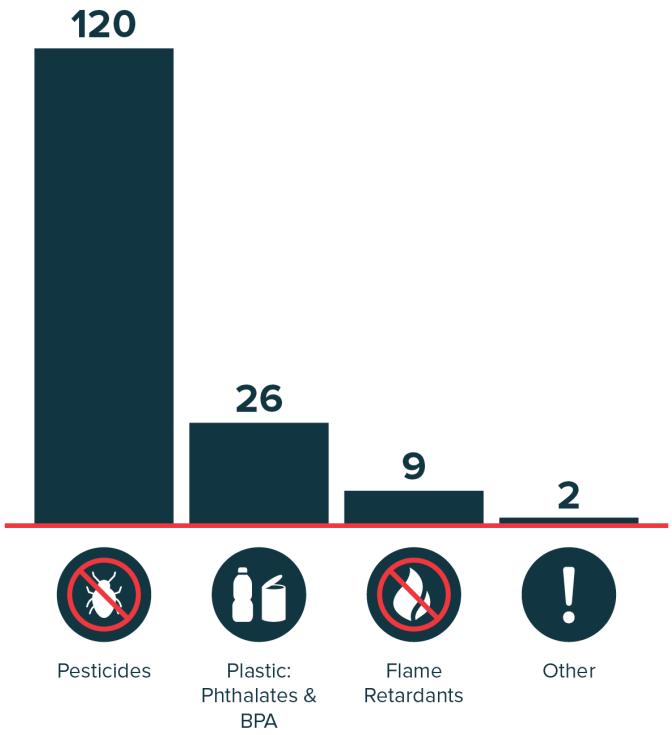
NOTE: The economic estimates do not include all costs associated with these conditions.



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

€157B Cost by EDC Type



SOME EDCs NOT INCLUDED:

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

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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.

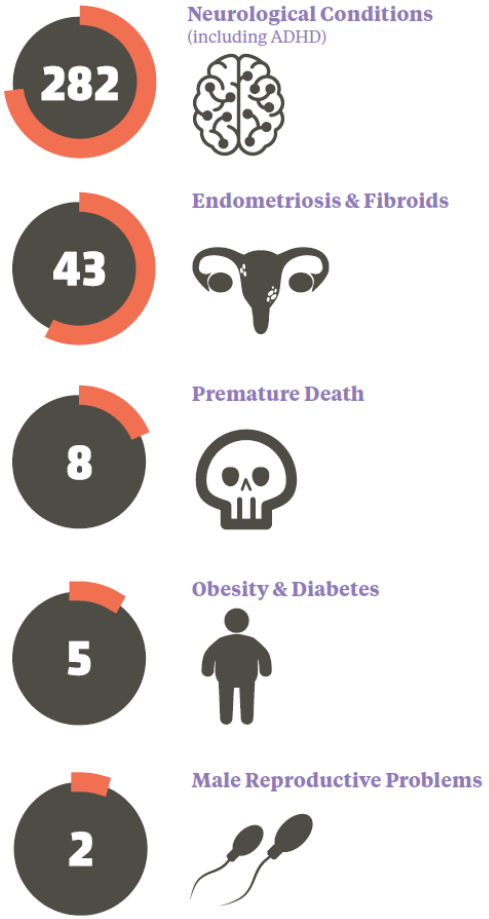
See Trasande et al. The Journal of Clinical Endocrinology & Metabolism
http://press.endocrine.org/edc

Health Effects From Endocrine Disrupting Chemicals Cost The U.S.

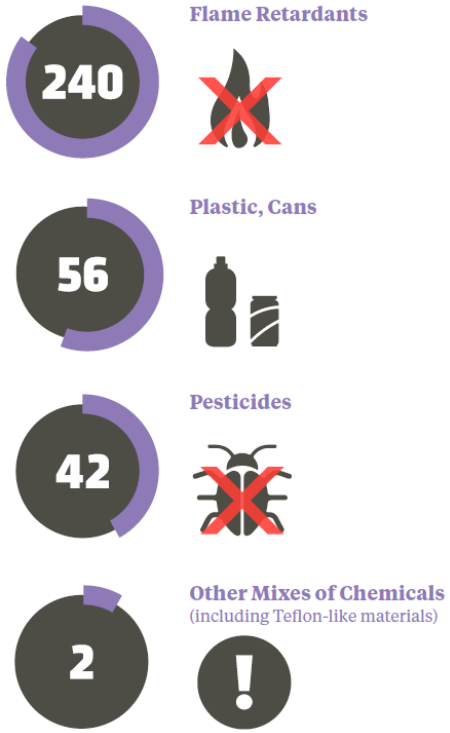
$340 Billion Annually

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

$340 Billion by Health Effect



$340 Billion by EDC Type



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Fifteen chronic conditions with strong scientific evidence for causation by endocrine disrupting chemicals (EDCs)

Based on current knowledge, probable costs are €163 billion in EU an $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.

Thanks!

- Funding
  - John Merck Fund (EU), Broad Reach (EU + US), Oak Foundation (EU)
- Steering committee: R. Thomas Zoeller, Andreas Kortenkamp, Philippe Grandjean, John Peterson Myers, Joe DiGangi, Martine Bellanger, Jerry Heindel
- 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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  - CDC: U01OH01394, U01OH01714

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