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Burden of Disease and Costs of Endocrine Disrupting Chemicals in the European Union

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Chemical environmental agents and the endocrine system

- European Union defines endocrine disrupting chemicals as "exogenous substance[s] that causes adverse health effects in an intact organism, or its progeny, secondary to changes in endocrine function"

- Highly heterogeneous group of molecules
  - industrial solvents/lubricants
  - flame retardants
  - aluminum can linings
  - plasticizers
  - pesticides
  - pharmaceutical agents

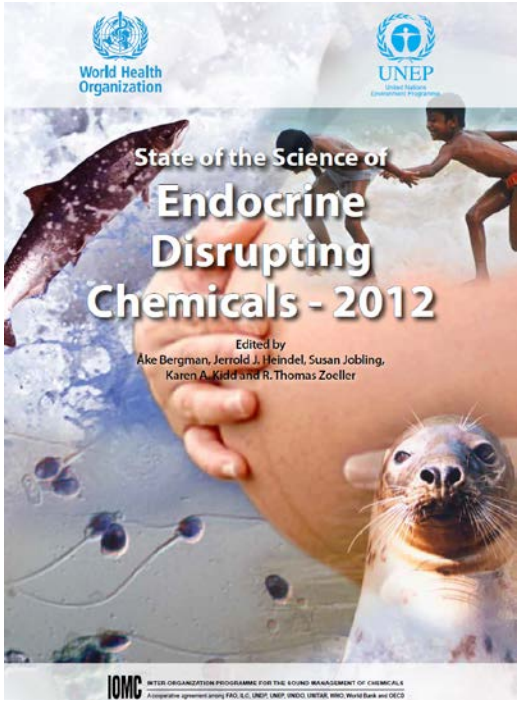
Chemical environmental agents and the endocrine system

- First observation by Herbst and Bern of cancer in young girls exposed one to two decades earlier to diethylstilbestrol (DES), a synthetic estrogen prescribed to pregnant women in the 1950s and 1960s to prevent miscarriage

- Rapidly accumulating evidence suggests that EDCs contribute to disease and disability across the lifespan
  - Neurodevelopmental deficits and disabilities
  - Infertility
  - Obesity and diabetes
  - Reproductive cancers
  - Birth defects

Strong scientific evidence

- 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

A. C. Gore, V. A. Chappell, S. E. Fenton, J. A. Flaws, A. Nadal, G. S. Prins, J. Toppari, and R. T. Zoeller

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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)

Strong evidence, but what are disease burden and costs of EDCs?

- No previous studies have estimated burden of disease and disability potentially produced by EDC exposure.

- High costs of alternatives are likely to outweigh concerns about the health consequences of using EDCs.

- To inform EU Commission ongoing decision making and impact assessment, our objective was to quantify a range of health and economic costs that can be reasonably attributed to EDC exposures in the European Union.

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

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

Epidemiologic Evaluation \ Toxicologic 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)

- To quantify attribution, prioritized dose-response relationships from the epidemiologic literature

- Also, in the presence of epidemiologic evidence for a dose-response relationship for another exposure that operates via a similar or identical mechanism, an estimate of an odds ratio or increment in disease was applied, when placed in the context of the strength of evidence assessment.

Trasande et al J Clin Endo Metab epub Mar 5 2015

Application to estimate EDC disease burden and costs in EU (3)

- 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.

- When an increment in relative risk over baseline was estimated, a prevalence of exposure was identified in order to estimate an attributable fraction, using the Levin equation:

$$AF = Prevalence_{exposure}*(RR-1)/[1+ (Prevalence_{exposure}*(RR-1))]$$

Trasande et al J Clin Endo Metab epub Mar 5 2015

Overall Evaluations

Exposure	Outcome	Strength of Human Evidence	Strength of Toxicologic Evidence	Probability of Causation
Polybrominated diphenyl ethers (PBDE)	IQ Loss and Intellectual Disability	Moderate-to-high	Strong	70-100%
Organophosphate pesticides	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	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	Male Infertility, Resulting in Increased Assisted Reproductive Technology	Low	Strong	40-69%
Phthalates	Low testosterone, Resulting in Increased Early Mortality	Low	Strong	40-69%
Multiple exposures	ADHD	Low-to-moderate	Strong	20-69%
Multiple exposures	Autism	Low	Moderate	20-39%

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Pesticides (used in agricultural production and homes)

- 13 million lost IQ points in each EU country → €124 billion lost earning potential

  →59,300 born each year with intellectual disability = additional €21.4 billion

- 1,555 obese 10 year olds = €24.6 million

- 28,200 50–64 year olds with diabetes = €835 million

Bellanger et al, Legler et al J Clin Endo Metab epub Mar 5 2015

Phthalates (used in food wraps, cosmetics, shampoos, vinyl flooring)

- 24,800 additional deaths among 55 – 64 year old men = €7.96 billion in lost economic productivity
- 618,000 additional assisted reproductive technology procedures costing €4.71 billion
- 53,900 50-64 year old women are obese = €15.6B
- 20,500 50-64 year old women are diabetic = €607M

Hauser et al, Legler et al J Clin Endo Metab epub Mar 5 2015

Flame retardants (used in electronics, furniture, mattresses)

- 873,000 lost IQ points →€8.4B lost earning potential

  →3,290 intellectually disabled children = additional €1.9 billion

- 6,830 new cases of testicular cancer = €850 million

- 4,615 children born with undescended testis = €130 million

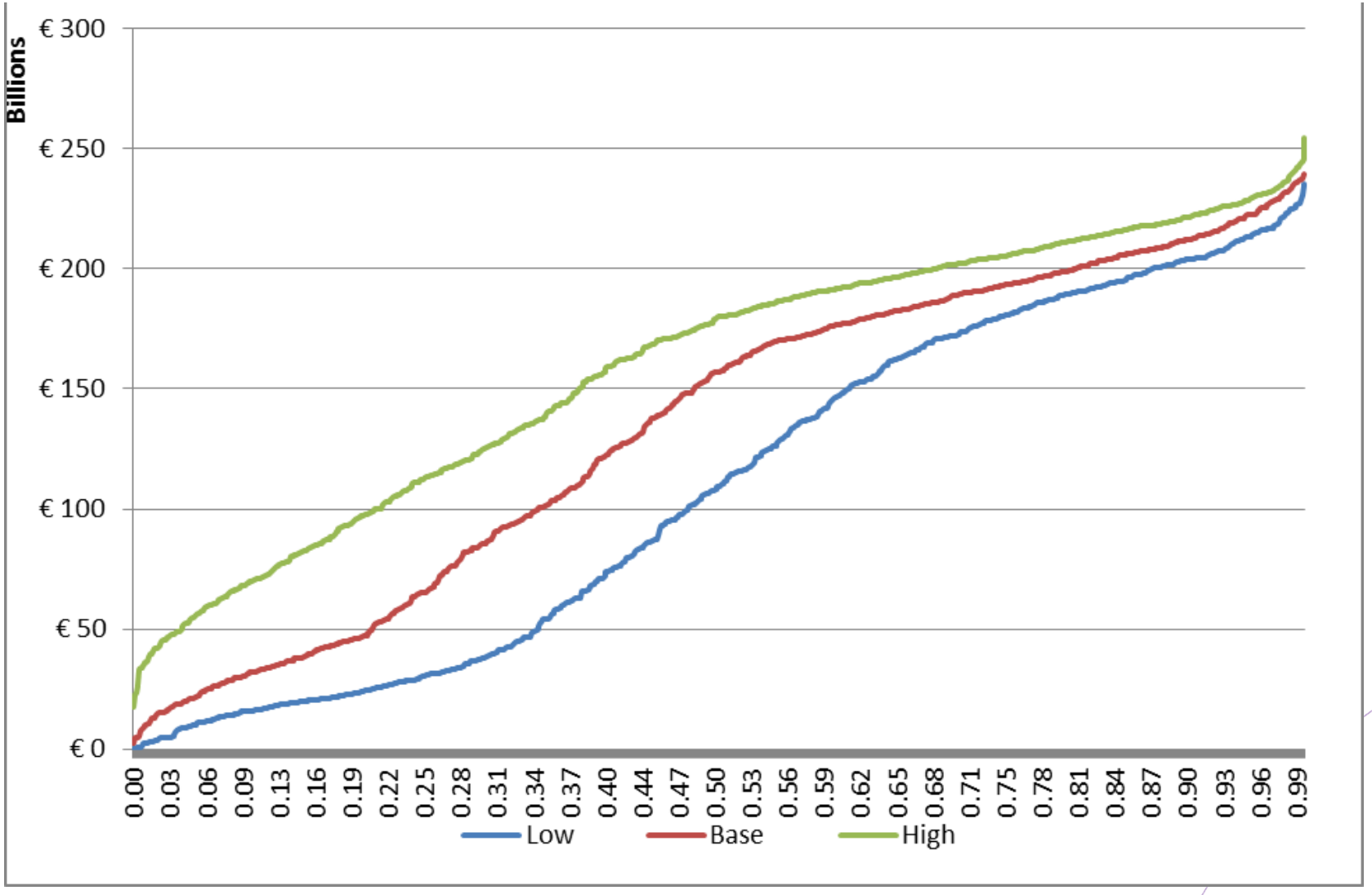
Bellanger et al, Hauser et al J Clin Endo Metab epub Mar 5 2015

Other estimates of burden and disease and costs

- 316 autistic 8 year olds each year (multiple EDCs) = €199 million
- 31,200 10 year olds with ADHD (multiple EDCs) = €1.7 billion
- Bisphenol A (used in aluminum can linings, thermal paper receipts): 42,400 obese 4 year olds each year = €1.54 billion

Bellanger et al, Legler et al J Clin Endo Metab epub Mar 5 2015

Monte Carlo Analysis



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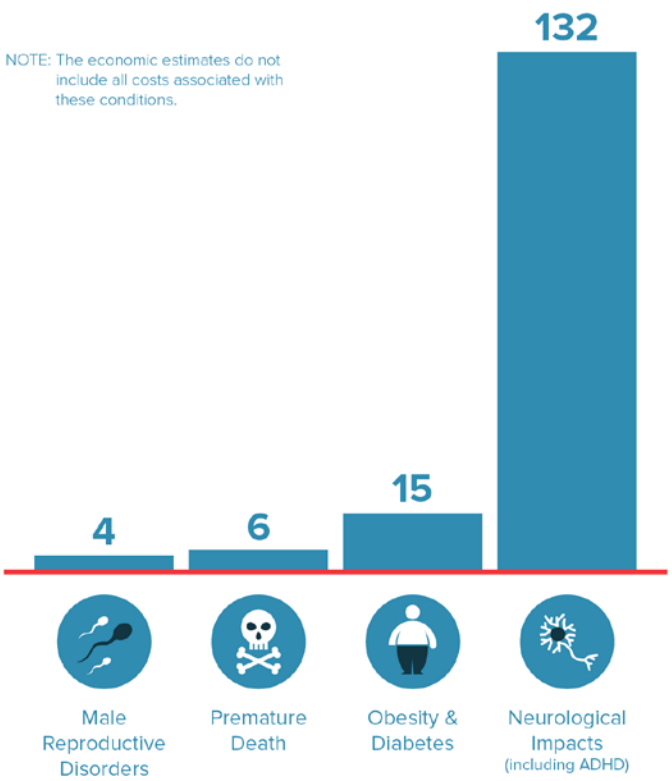
HEALTH EFFECTS FROM ENDOCRINE DISRUPTING CHEMICALS COST THE EU 157 BILLION EUROS EACH YEAR.

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

€157B Cost by Health Effect

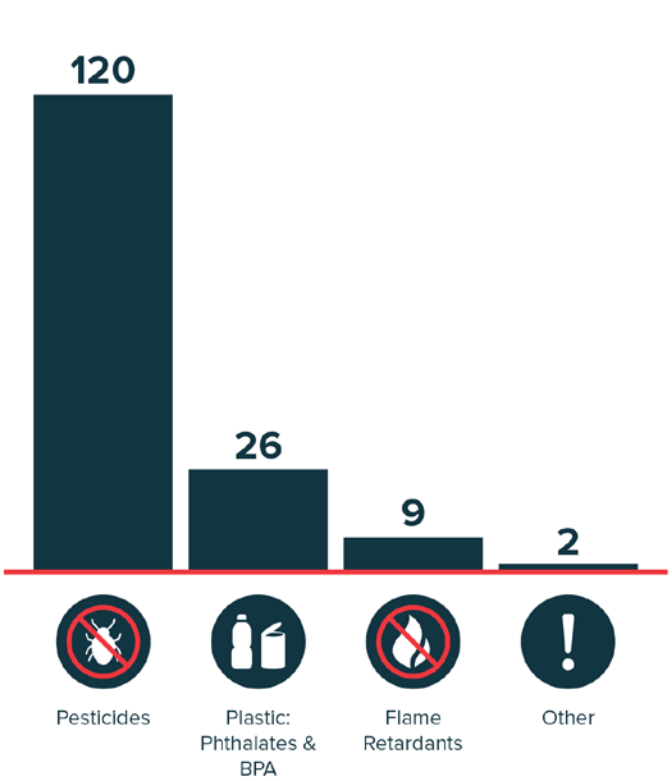
NOTE: The economic estimates do not include all costs associated with these conditions.



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

Summary

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

- Based on current knowledge, probable costs are €157 billion; could be as much as €269 billion
- <5% of EDCs considered
- Endometriosis, fibroids, 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.

Implications for US

- Findings from Europe strongly suggest that a similarly large burden of disease may be attributable to EDCs in the United States
  - Data from the Centers for Disease Control and Prevention suggest that exposures to EDCs are in many cases equal to if not higher than those in the EU.
  - More importantly, this speaks to the importance of reprising these analyses in the US context.

Importance of policy

- Cost of brominated flame retardants likely to be higher in the US, as use is more stringently limited in Europe.
- Levels of phthalates (DEHP) have decreased 17-37% in the US between 2001-10 and costs of attributable disease are likely to have decreased over that period.
- EDCs are used globally, and our findings support careful regulation as part of the Strategic Approach to International Chemicals Management.

Thanks!

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- 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
- Technical and logistical support: Charles Persoz, Robert Barouki, and Marion Le Gal of the French National Alliance for Life Sciences and Health and Lindsey Marshall, Bilal Mughal, and Bolaji Seffou of UMR7221 Paris

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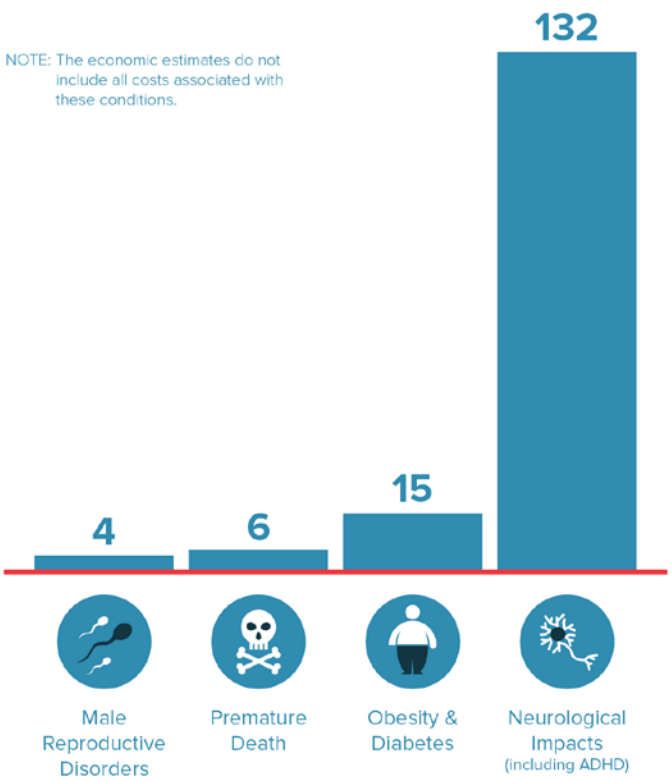

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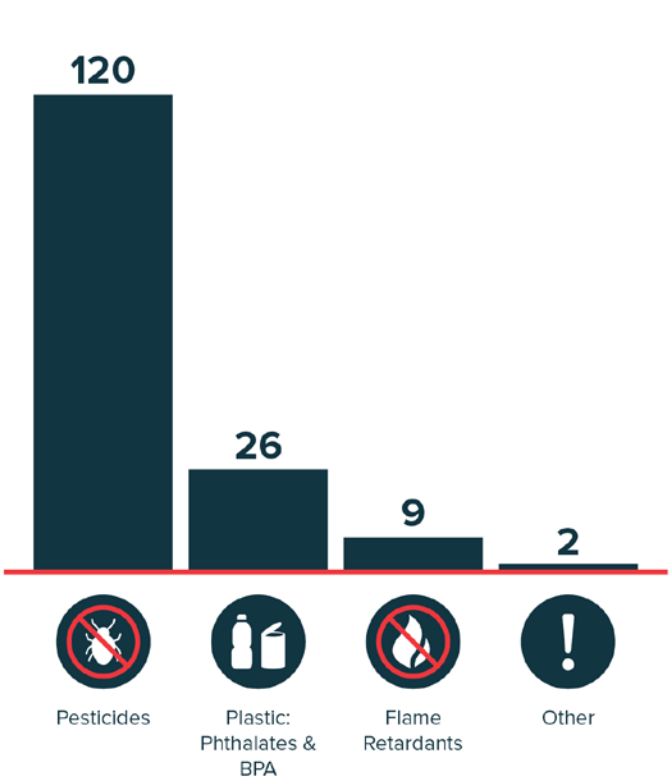

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