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)
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
Endocrine Disrupting Chemicals

  - 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
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

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

GBD Risk Factors Collaborators Lancet 2015

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

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
So how to deal with uncertainty?

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

<table>
<thead>
<tr>
<th>Confidence level</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very high</td>
<td>90-100% probability of causation</td>
</tr>
<tr>
<td>High</td>
<td>70-89% probability of causation</td>
</tr>
<tr>
<td>Medium</td>
<td>40-69% probability of causation</td>
</tr>
<tr>
<td>Low</td>
<td>20-39% probability of causation</td>
</tr>
<tr>
<td>Very low</td>
<td>0-19% probability of causation</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>Interpretation</th>
<th>Study design</th>
<th>Lower the quality in presence of</th>
<th>Raise the quality in presence of</th>
</tr>
</thead>
</table>
| 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  
- 1 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 |
| 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 | 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 |
| 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)

<table>
<thead>
<tr>
<th>Quality of evidence</th>
<th>Interpretation</th>
<th>Study design</th>
</tr>
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</table>
| Strong, Group 1     | 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  | 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      | 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.                                       |

Adapting IPCC criteria to integrate epidemiologic and toxicologic evidence

<table>
<thead>
<tr>
<th>Epidemiologic Evaluation</th>
<th>Toxicologic Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Very High (90-100%)</td>
</tr>
<tr>
<td>Moderate</td>
<td>High (70-89%)</td>
</tr>
<tr>
<td>Low</td>
<td>Medium (40-69%)</td>
</tr>
<tr>
<td>Very Low</td>
<td>Low (20-39%)</td>
</tr>
</tbody>
</table>

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
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
<table>
<thead>
<tr>
<th>Exposure</th>
<th>Outcome</th>
<th>Strength of Human Evidence</th>
<th>Strength of Toxicologic Evidence</th>
<th>Probability of Causation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polybrominated diphenyl ethers (PBDE)</td>
<td>IQ Loss and Intellectual Disability</td>
<td>Moderate-to-high</td>
<td>Strong</td>
<td>70-100%</td>
</tr>
<tr>
<td>Organophosphate pesticides (OP)</td>
<td>IQ Loss and Intellectual Disability</td>
<td>Moderate-to-high</td>
<td>Strong</td>
<td>70-100%</td>
</tr>
<tr>
<td>Dichlorodiphenyltrichloroethane (DDE)</td>
<td>Childhood obesity</td>
<td>Moderate</td>
<td>Moderate</td>
<td>40-69%</td>
</tr>
<tr>
<td>Dichlorodiphenyltrichloroethane (DDE)</td>
<td>Adult diabetes</td>
<td>Low</td>
<td>Moderate</td>
<td>20-39%</td>
</tr>
<tr>
<td>Di-2-ethylhexylphthalate (DEHP)</td>
<td>Adult obesity</td>
<td>Low</td>
<td>Strong</td>
<td>40-69%</td>
</tr>
<tr>
<td>Di-2-ethylhexylphthalate (DEHP)</td>
<td>Adult diabetes</td>
<td>Low</td>
<td>Strong</td>
<td>40-69%</td>
</tr>
<tr>
<td>Bisphenol A (BPA)</td>
<td>Childhood obesity</td>
<td>Very low-to-low</td>
<td>Strong</td>
<td>20-69%</td>
</tr>
<tr>
<td>Polybrominated diphenyl ethers (PBDE)</td>
<td>Testicular cancer</td>
<td>Very low-to-low</td>
<td>Weak</td>
<td>0-19%</td>
</tr>
<tr>
<td>Polybrominated diphenyl ethers (PBDE)</td>
<td>Cryptorchidism</td>
<td>Low</td>
<td>Strong</td>
<td>40-69%</td>
</tr>
<tr>
<td>Benzyl and butyl phthalates (Monobenzyl phthalate, MBzP; Monobutyl phthalate, MBP)</td>
<td>Male Infertility, Resulting in Increased Assisted Reproductive Technology</td>
<td>Low</td>
<td>Strong</td>
<td>40-69%</td>
</tr>
<tr>
<td>Monobutyl phthalate (MBP) and Di-2-ethylhexylphthalate (DEHP)</td>
<td>Low testosterone, Resulting in Increased Early Mortality</td>
<td>Low</td>
<td>Strong</td>
<td>40-69%</td>
</tr>
<tr>
<td>Multiple exposures (PBDE and OPs)</td>
<td>ADHD</td>
<td>Low-to-moderate</td>
<td>Strong</td>
<td>20-69%</td>
</tr>
<tr>
<td>Multiple exposures (phthalates)</td>
<td>Autism</td>
<td>Low</td>
<td>Moderate</td>
<td>20-39%</td>
</tr>
<tr>
<td>Dichlorodiphenyl dichloroethylene (DDE)</td>
<td>Fibroids</td>
<td>Low</td>
<td>Moderate</td>
<td>20-39%</td>
</tr>
<tr>
<td>Di-2-ethylhexylphthalate (DEHP)</td>
<td>Endometriosis</td>
<td>Low</td>
<td>Moderate</td>
<td>20-39%</td>
</tr>
<tr>
<td>Condition</td>
<td>USA*</td>
<td>European Union†</td>
<td>US costs (2010 US$)</td>
<td>EU costs (US$)</td>
</tr>
<tr>
<td>---------------------------------------------------------------------------</td>
<td>---------------</td>
<td>-----------------</td>
<td>---------------------</td>
<td>----------------</td>
</tr>
<tr>
<td>PBDE and IQ points loss and intellectual disability</td>
<td>11 million</td>
<td>873 000</td>
<td>266 billion</td>
<td>12.6 billion</td>
</tr>
<tr>
<td>Organophosphate pesticides and IQ points loss and intellectual disability</td>
<td>1.8 million</td>
<td>13 million</td>
<td>44.7 billion</td>
<td>194.0 billion</td>
</tr>
<tr>
<td>Dichlorodiphenyltrichloroethane and childhood obesity</td>
<td>857 cases</td>
<td>1555 cases</td>
<td>29.6 million</td>
<td>32.7 million</td>
</tr>
<tr>
<td>Dichlorodiphenyltrichloroethane and adult diabetes</td>
<td>24 900 cases</td>
<td>28 200 cases</td>
<td>1.8 billion</td>
<td>1.1 billion</td>
</tr>
<tr>
<td>Di-2-ethylhexylphthalate and adult obesity</td>
<td>5 900 cases</td>
<td>53 900 cases</td>
<td>1.7 billion</td>
<td>20.8 billion</td>
</tr>
<tr>
<td>Di-2-ethylhexylphthalate and adult diabetes</td>
<td>1 300 cases</td>
<td>20 500 cases</td>
<td>51.4 million</td>
<td>807.2 million</td>
</tr>
<tr>
<td>Bisphenol A and childhood obesity</td>
<td>33 000 cases</td>
<td>42 400 cases</td>
<td>2.4 billion</td>
<td>2.0 billion</td>
</tr>
<tr>
<td>PBDE and testicular cancer</td>
<td>3 600 cases</td>
<td>6 830 cases</td>
<td>81.5 million</td>
<td>1.1 billion</td>
</tr>
<tr>
<td>PBDE and cryptorchidism</td>
<td>4300 cases</td>
<td>4615 cases</td>
<td>35.7 million</td>
<td>172.6 million</td>
</tr>
<tr>
<td>Benzylichlorphthalates and butylphthalates and male infertility resulting in increased assisted reproductive technology</td>
<td>240 100 cases</td>
<td>628 000 cases</td>
<td>2.5 billion</td>
<td>6.3 billion</td>
</tr>
<tr>
<td>Phthalates and low testosterone resulting in increased early mortality</td>
<td>10 700 attributable deaths</td>
<td>24 800 attributable deaths</td>
<td>8.8 billion</td>
<td>10.6 billion</td>
</tr>
<tr>
<td>Multiple exposures and ADHD</td>
<td>4 400 cases</td>
<td>19 400-31 200 cases</td>
<td>698.0 million</td>
<td>2.3 billion</td>
</tr>
<tr>
<td>Multiple exposures and autism</td>
<td>787 cases in boys, 754 cases in girls</td>
<td>316 cases</td>
<td>1.0 billion in boys, 984.0 million in girls</td>
<td>265.1 million</td>
</tr>
<tr>
<td>Dichlorodiphenyltrichloroethane and fibroids</td>
<td>37 000 cases</td>
<td>56 700 cases</td>
<td>259.0 million</td>
<td>216.8 million</td>
</tr>
<tr>
<td>Di-2-ethylhexylphthalate and endometriosis</td>
<td>86 000 cases</td>
<td>145 000 cases</td>
<td>47 0 million</td>
<td>17.0 million</td>
</tr>
</tbody>
</table>

The comparison uses base case estimates. Estimates are conditional on certainty of causation. EU = European Union. PBDE = polychlorinated dibenzo-p-dioxins. 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
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

<table>
<thead>
<tr>
<th>Health Effect</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male Reproductive Disorders</td>
<td>4</td>
</tr>
<tr>
<td>Premature Death</td>
<td>6</td>
</tr>
<tr>
<td>Obesity &amp; Diabetes</td>
<td>15</td>
</tr>
<tr>
<td>Neurological Impacts (including ADHD)</td>
<td>132</td>
</tr>
</tbody>
</table>

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

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.

Some EDCs Not Included:
- Atrazine
- 2, 4-D
- Styrene
- Triclosan
- Nonylphenol
- Polycyclic Aromatic Hydrocarbons
- Bisphenol S
- Cadmium
- Arsenic
- Ethylene glycol

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

- Neurological Conditions (including ADHD): $282 billion
- Endometriosis & Fibroids: $43 billion
- Premature Death: $8 billion
- Obesity & Diabetes: $5 billion
- Male Reproductive Problems: $2 billion

$340 Billion by EDC Type

- Flame Retardants: $240 billion
- Plastic, Cans: $56 billion
- Pesticides: $42 billion
- Other Mixes of Chemicals (including Teflon-like materials): $2 billion
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!

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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

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