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Harmonizing Burden of Disease Estimation due to Environmental Chemicals

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Estimating environmental burden of disease

- Extremely informative to policy making
- 1981 US Institute of Medicine report led by Nobel Laureate Kenneth Arrow established methodology for measuring environmentally mediated burden of disease and costs
- First calculations of global burden of disease in 1993 World Development Report
  - Used disability adjusted life-years (DALYs), developed by Zeckhauser and Shepard as common metric to compare across disease and organ systems

Most recent estimates

- 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

Why the divergence?

- Causality criteria
- Subclinical effects
- Data availability

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- **Causality criteria**
- Subclinical effects
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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

GRADE Working Group Criteria

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

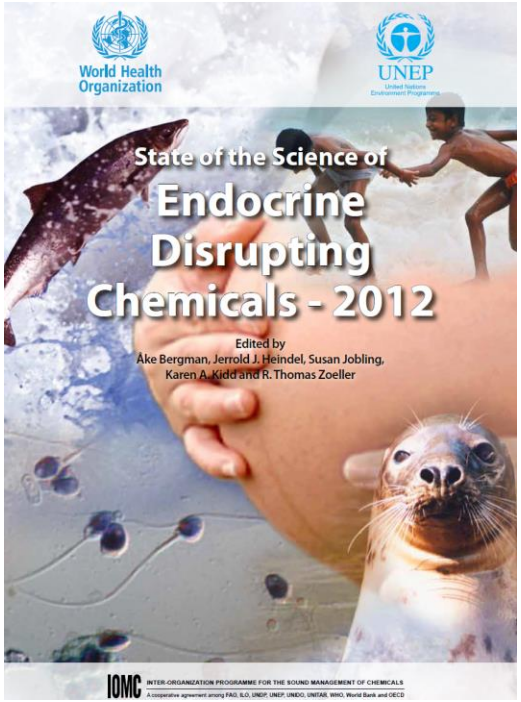
Toxicologic Evaluation / Epidemiologic Evaluation	Strong (Group 1)	Moderate (Group 2A)	Weak (Group 2B)
High	Very High (90-100%)	High (70-89%)	Medium (40-69%)
Moderate	High (70-89%)	Medium (40-69%)	Low (20-39%)
Low	Medium (40-69%)	Low (20-39%)	Very Low (0-19%)
Very Low	Low (20-39%)	Very Low (0-19%)	Very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

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

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)

Probabilities of Causation for EDCs

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%
Dichlorodiphenytrichloroethane (DDE)	Endometriosis	Low	Moderate	20-39%
Di-2-ethylhexylphthalate (DEHP)	Fibroids	Low	Moderate	20-39%

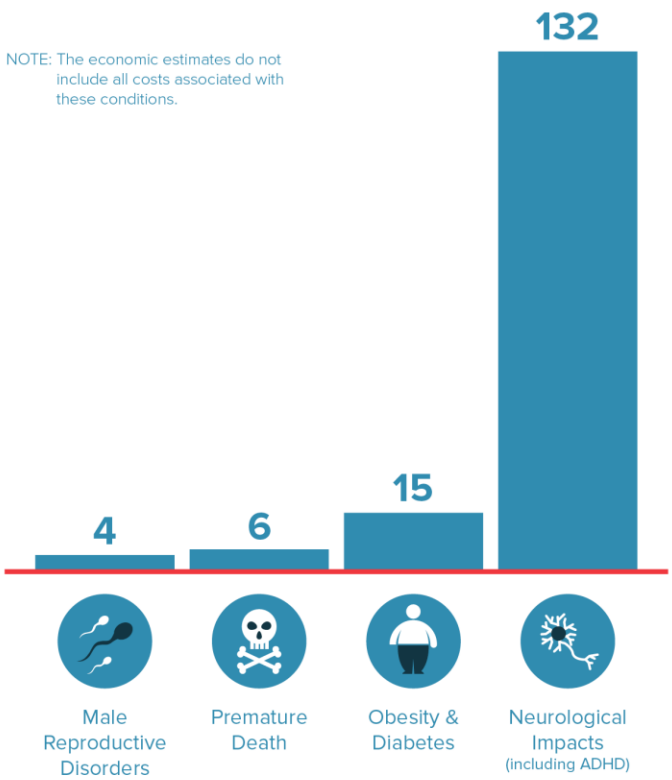
Trasande et al J Clin Endo Metab 2015; Andrology 2016

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

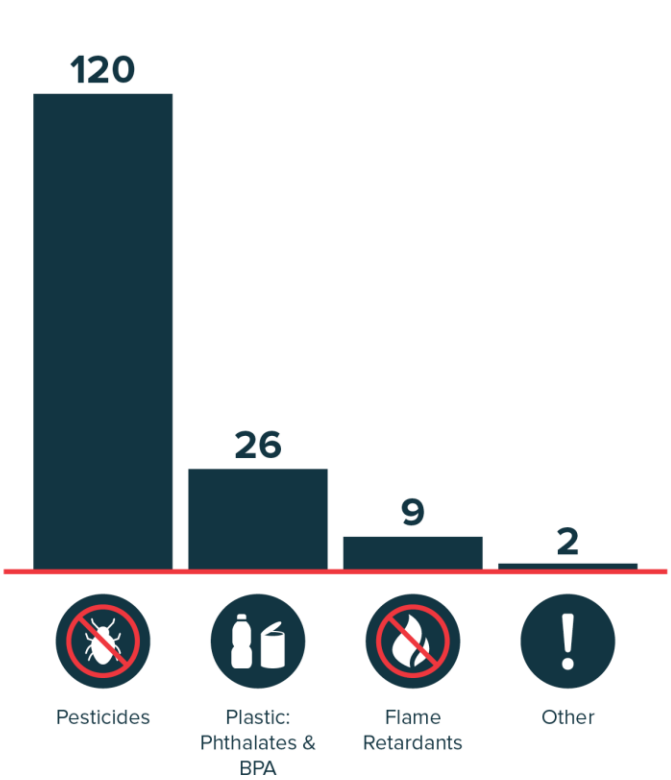
NOTE: The economic estimates do not include all costs associated with these conditions.



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 of EDC economic estimates

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

- Based on current knowledge, probable costs are €163 billion; could be as much as €270 billion
- <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.

Why the divergence?

- Causality criteria
- **Subclinical effects**
- Data availability

Childhood Lead Exposure

- GBD report estimated the global costs to 449,000 lost DALYs because of increases in mild mental retardation ($22.5 billion globally).

- Does not consider IQ losses within the normal range
  - Substantial literature documents substantial change in lifetime economic productivity for each IQ point lost

- Fails to capture the large societal losses to those children who are not shifted into the subnormal range of cognitive function.

Childhood Lead Exposure

- US: $50.9 billion lost economic productivity

  Trasande and Liu Health Affairs 2011

- EU: $57.1 billion lost economic productivity

  Trasande and Bartlett Eur J Pub Health 2014

- Global costs of lead exposure in developing countries: $977 billion (1.0% of GDP) in 2008
  - $227 billion (2.0% of GDP) in China

  Attina and Trasande EHP 2013

The importance of subclinical effects for EDCs

- Because DALY values have been estimated only for intellectual disability, approach taken in GBD would include DALY losses only from the 3,290 annual cases in the EU found to suffer intellectual disability attributable to PBDE exposure and 59,300 for organophosphates.
  - For the EU, costs from intellectual disability alone were calculated at more modest amounts of €1.2 billion and €21.4 billion, respectively.
  - The more inclusive approach yielded estimates of €9.6 billion and €146 billion, respectively.

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The importance of available biomonitoring data

- Country-specific data not available for EU at the time of our EDC analysis
- NHANES data representative of US
  - DEMOCOPHES data chiefly of convenience samples
- Capacity to model economic benefits of prevention, and state of progress

Importance of policy

- Cost of brominated flame retardants likely to be higher in the US, as use is more stringently limited in Europe.
  - Opposite likely to be true for organophosphate pesticides

	10th percentile	25th percentile	50th percentile	75th percentile	90th percentile
PBDE47 (lipid adjusted, ng/g, US NHANES, women 20-39yrs)	15.8	19.7	23.1	41.6	68.5
PBDE47, EU estimate	<LOD	<LOD	2.60	4.61	6.27
PBDE47, senstivity analysis for EU	<LOD	<LOD	1.60	2.68	3.66
Total dialkylphosphate, nmol/L, US NHANES 2007-8, women 15-49 yrs)	13.17	13.17	22.40	112.89	322.42
Total dialkylphosphate, EU estimate	79.92	175.55	280.58	741.31	1160.78
Total dialkylphosphate, EU sensitivity analysis	34.2	97.3	200	370	444.792

Industrializing country biomonitoring data

Rarely available….

- For lead in LMICs, models built to extrapolate mean and SD of lead levels based on continent distributions and year of phase out of lead in gasoline

Yet increasingly important!

- Organisation for Economic Cooperation and Development: by 2030, developing countries will comprise the leading sites for chemical manufacture and use of high production volume chemicals

OECD, UNEP Global Chemicals Outlook

- Infrastructures to protect public health and the environment may be insufficient in these countries.

- Trasande et al Health Aff 2011

Estimating EDC disease burden in Africa

- Quasi-representative biomonitoring from selected countries
  - Current estimate of childhood lead costs: 98.6 million IQ points lost, $134.7 million international dollars = 4.03% of GDP PPP

    Attina and Trasande EHP 2013
    - Based on data from five African countries (South Africa, Nigeria, Kenya, Botswana, Uganda)
  - Measurements of biomarkers in populations of concern (adult men, women of childbearing age, children)
  - Suggest not limiting to POPs (phthalate, bisphenol, organophosphates, Hg, Pb, As, Cd)

Summary

- Current environmental burden of disease approaches are disharmonized
  - Need to embrace probability of causation
  - Need to accept subclinical effects
  - Global biomonitoring program needs to be coordinated

Thanks!

- Funding (EDC work)
  - John Merck Fund, Broad Reach, Oak Foundation
- 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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