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
Why the divergence?

- Causality criteria
- Subclinical effects
- Data availability
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>
# GRADE Working Group Criteria

<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>
<tbody>
<tr>
<td>High</td>
<td>We are very confident that the true effect lies close to that of the estimate of the effect.</td>
<td>Randomized trial</td>
<td>Study limitations: -1 Serious limitations -2 Very serious limitations -1 Important inconsistency</td>
<td>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</td>
</tr>
<tr>
<td>Moderate</td>
<td>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.</td>
<td>Quasi-experimental (with controls) and before and after (uncontrolled) studies</td>
<td>Directness: -1 Some uncertainty -2 Major uncertainty -1 Imprecise data</td>
<td>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</td>
</tr>
<tr>
<td>Low</td>
<td>Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect</td>
<td>Observational study</td>
<td>-1 High probability of reporting bias</td>
<td></td>
</tr>
<tr>
<td>Very low</td>
<td>We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect</td>
<td>Any other evidence</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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>
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<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>
<th>Strong (Group 1)</th>
<th>Moderate (Group 2A)</th>
<th>Weak (Group 2B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Very High (90-100%)</td>
<td>High (70-89%)</td>
<td>Medium (40-69%)</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>High (70-89%)</td>
<td>Medium (40-69%)</td>
<td>Low (20-39%)</td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>Medium (40-69%)</td>
<td>Low (20-39%)</td>
<td>Very Low (0-19%)</td>
<td></td>
</tr>
<tr>
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<td>Low (20-39%)</td>
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<td></td>
</tr>
</tbody>
</table>

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
<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</td>
<td>IQ Loss and Intellectual Disability</td>
<td>Moderate-to-high</td>
<td>Strong</td>
<td>70-100%</td>
</tr>
<tr>
<td>Dichlorodiphenytrichloroethane (DDE)</td>
<td>Childhood obesity</td>
<td>Moderate</td>
<td>Moderate</td>
<td>40-69%</td>
</tr>
<tr>
<td>Dichlorodiphenytrichloroethane (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</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 butylphthalates</td>
<td>Male Infertility, Resulting in Increased Assisted Reproductive Technology</td>
<td>Low</td>
<td>Strong</td>
<td>40-69%</td>
</tr>
<tr>
<td>Phthalates</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</td>
<td>ADHD</td>
<td>Low-to-moderate</td>
<td>Strong</td>
<td>20-69%</td>
</tr>
<tr>
<td>Multiple exposures</td>
<td>Autism</td>
<td>Low</td>
<td>Moderate</td>
<td>20-39%</td>
</tr>
<tr>
<td>Dichlorodiphenytrichloroethane (DDE)</td>
<td>Endometriosis</td>
<td>Low</td>
<td>Moderate</td>
<td>20-39%</td>
</tr>
<tr>
<td>Di-2-ethylhexylphthalate (DEHP)</td>
<td>Fibroids</td>
<td>Low</td>
<td>Moderate</td>
<td>20-39%</td>
</tr>
</tbody>
</table>
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 (B)</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>

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

### €157B Cost by EDC Type

<table>
<thead>
<tr>
<th>EDC Type</th>
<th>Cost (B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pesticides</td>
<td>120</td>
</tr>
<tr>
<td>Plastic: Phthalates &amp; BPA</td>
<td>26</td>
</tr>
<tr>
<td>Flame Retardants</td>
<td>9</td>
</tr>
<tr>
<td>Other</td>
<td>2</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

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

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.
Why the divergence?

- Causality criteria
- Subclinical effects
- Data availability
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

<table>
<thead>
<tr>
<th></th>
<th>10th percentile</th>
<th>25th percentile</th>
<th>50th percentile</th>
<th>75th percentile</th>
<th>90th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>PBDE47 (lipid adjusted, ng/g, US NHANES, women 20-39yrs)</td>
<td>15.8</td>
<td>19.7</td>
<td>23.1</td>
<td>41.6</td>
<td>68.5</td>
</tr>
<tr>
<td>PBDE47, EU estimate</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>2.60</td>
<td>4.61</td>
<td>6.27</td>
</tr>
<tr>
<td>PBDE47, sensitivity analysis for EU</td>
<td>&lt;LOD</td>
<td>&lt;LOD</td>
<td>1.60</td>
<td>2.68</td>
<td>3.66</td>
</tr>
<tr>
<td>Total dialkylphosphate, EU estimate</td>
<td>79.92</td>
<td>175.55</td>
<td>280.58</td>
<td>741.31</td>
<td>1160.78</td>
</tr>
<tr>
<td>Total dialkylphosphate, EU sensitivity analysis</td>
<td>34.2</td>
<td>97.3</td>
<td>200</td>
<td>370</td>
<td>444.792</td>
</tr>
</tbody>
</table>
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

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

OECD, UNEP Global Chemicals Outlook

• 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

• 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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