

Human Cost Burden of Exposure to Endocrine Disrupting Chemicals: A Critical Review

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Background

Trasande et al publish seven papers in 2015 and 2016 estimating costs attributable to exposure to EDCs in U.S. and EU

€191 billion per year in EU

\$340 billion per year in U.S.

European Commission, academics, and science journalists express skepticism about validity of estimates

Major Conclusions

- Our review uncovered **substantial flaws in approach taken and conclusions drawn.**
- Trasande et al **assumed causal relationships between putative exposures to EDCs and selected diseases**, e.g., “loss of IQ” and “increased prevalence of intellectual disability,” but **did not establish them via thorough evaluation of strengths and weaknesses of underlying animal toxicology and human epidemiology evidence.**
- Consequently, assigned disease burden costs are **highly speculative and should not be considered** in weight of evidence approach underlying **any serious policy discussions** serving to protect public & regulate chemicals considered as EDCs.

Why A Critical Review Was Necessary

Economic Estimates Took On Life of Their Own

Aggressive positioning
attracted attention from
media & scientific journals
(e.g. Nature) which gave
appearance of authority

Public Health Implications

Prior to adjusting policy, cost
estimates need serious
scientific scrutiny

Timeliness of Issue on Both Sides of Atlantic

EU and U.S. pursuing two
distinct approaches to
identifying and regulating
EDCs

Our Approach

- explored how cost estimates were derived
- restated major findings as originally reported; and
- highlighted multiple shortcomings of methodology used
- **Vast majority of estimated costs** from alleged chemically-mediated **reductions in IQ and increased prevalence of intellectual disability**, so supporting evidence was more closely scrutinized

How Cost Estimates Were Derived

Reliance on heavily criticized 2012 UNEP/WHO sponsored review of the “state of the science” report

Self-appointed Steering Committee devised overall methodology; selected scientists to participate on five panels focused on purported EDC exposures and

1. neurobehavioral deficits and diseases;
2. male reproductive disorders and diseases;
3. obesity and diabetes;
4. breast cancer; or
5. female reproductive disorders and diseases

How Cost Estimates Were Derived (contd.)

Probability of causation assessed by panels using modified Delphi technique to arrive at consensus

Societal costs ascribed using human capital approach

Fraction of disease attributable to EDC exposure often estimated based on results of single epidemiology study

Limited biomonitoring data, exposure-response relationships and population size estimates combined

Trasande Original Findings

Expert panels reported consensus for “at least probable” (arbitrarily chosen as a greater than 19% probability) EDC causation for:

1. **IQ loss**, ranging from 0.52-0.84 IQ points and 0.38-5.32 IQ points **attributable to polybrominated diphenylether and organophosphates exposures**, respectively, and associated intellectual disability;
2. **Autism and Attention Deficit Disorder** attributable to alleged **multiple EDC exposures**;
3. **Childhood obesity** attributable to exposure to **DDE or BPA**;
4. **Adult obesity** attributable to exposure to **Di-2-ethylhexylphthalate**;
5. **Adult diabetes** attributable to exposure to DDE or **Di-2-ethylhexylphthalate**;

Trasande Original Findings (contd.)

6. **Cryptorchidism** attributable to exposure to **Polybrominated diphenyl ethers (PBDEs)**
7. **Male infertility** attributable to exposure to **benzyl and butyl phthalates**;
8. **Mortality associated with reduced Testosterone (T)** attributable to exposure to **phthalates**
9. **Uterine fibroids** attributable to exposure to **DDE**; and
10. **Endometriosis** attributable to exposure to **phthalates**.

Among the constellation of health outcomes that were studied, a “**very low**” (0-19%) probability of causation was determined only for **PBDE exposure as a potential cause of testicular cancer**

EU Cost Estimates

€191 billion

with sensitivity analyses suggesting costs ranging from **€81.3 billion** to **€269 billion** annually

Total cost estimate driven by reported loss of IQ and associated intellectual disability attributable to perinatal organophosphate pesticide exposure — accounting for 146B Euros (76.4%) of the 191B Euro total

Di-2-ethylhexylphthalate-attributable adult obesity second largest driver of costs at 15.6B Euro per year (8.2% of the total)

Total costs estimated in Billions of Euros annually — more than 1% of annual GDP

Authors assert actual costs are likely to be even higher given limitations to what they regarded as relatively small number of EDCs and disease conditions

U.S. Cost Estimates

\$340 billion

Attina et al (2016) applied same estimates of probability, attributable fractions of disease, and exposure-response relationships to population and biomonitoring data specific to U.S.

Largest driver of costs was loss of IQ & increased prevalence of intellectual disability, accounting for nearly 80% of total costs, this time attributable to exposures to Polybrominated diphenyl ethers (PBDEs)

Estimated \$43 billion annually (12.6% of total costs), attributed to endometriosis from phthalate exposure

Estimated Costs Due to EDC Exposures

Exposure	Outcome	Strength of Epidemiology Evidence	Strength of Toxicological Evidence	Probability of Causation, %	Base Estimates of Annual Costs	
					EU (Billion Euros)	US (Billion USD)
PBDEs	IQ loss and intellectual disability	Moderate-to-high	Strong	70–100	9.6	266
Organophosphate pesticides	IQ loss and intellectual disability	Moderate-to-high	Strong	70–100	146	44.7
DDE	Childhood obesity	Moderate	Moderate	40–69	0.02	0.03
DDE	Adult diabetes	Low	Moderate	20–39	0.83	1.8
Di-2-ethylhexylphthalate	Adult obesity	Low	Strong	40–69	15.6	1.7
Di-2-ethylhexylphthalate	Adult diabetes	Low	Strong	40–69	0.61	0.09
BPA	Childhood obesity	Very low-to-low	Strong	20–69	1.5	2.4
PBDEs	Testicular cancer	Very low-to-low	Weak	0–19	0.85	0.08
PBDEs	Cryptorchidism	Low	Strong	40–69	0.13	0.04
Benzyl and butyl phthalates	Male infertility, resulting in increased assisted reproductive technology	Low	Strong	40–69	4.7	2.5
Phthalates	Low T, resulting in increased early mortality	Low	Strong	40–69	8.0	10.6
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Multiple exposures	ADHD	Low-to-moderate	Strong	20–69	1.7	0.70
Multiple exposures	Autism	Low	Moderate	20–39	0.20	2.0

Abbreviation: ADHD, attention-deficit hyperactivity disorder.

Critical Evaluation of Methodology

Presented in detail for purposes of this presentation:

1. Role of Steering Committee
2. Literature search, selection of underlying scientific studies
3. Weight of evidence analysis
4. Evaluation of animal toxicology evidence
5. Evaluation of human epidemiology evidence
6. Framework for assessing probability of causation

Critical Evaluation of Methodology (contd.)

Not presented in detail in this presentation:

- 7. Attributable Fraction & exposure-response relationships – how they were estimated and applied*
- 8. Sources & uses of biomonitoring data*
- 9. Sources of & uses for cost data*
- 10. Cumulative effect of numerous assumptions inherent in each process step*

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Self-appointed group of eight scientists who have published research & actively engaged in advocacy on EDCs

- Designed methodology
- Selected scientist members and leaders of the five separate panels
- Trained participants
- Convened two-day meeting to arrive at consensus (deliberations ultimately extended beyond that time)

Steering Committee: Our Concerns

Steering Committee **self-appointed**, exerted influence over deliberations

Questionable selection & recruitment of associated panel members; no one to challenge or oppose hypotheses under question

Casual selection approach in stark contrast to rigorous processes employed by EU and US regulatory agencies to achieve a balance of perspectives

Clear predisposition toward those who have exhibited **strong biases on these issues**

Violated Delphi Technique best practices

1. **Role of Steering Committee**
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Systematic-review methods increasingly being applied to address environmental health questions;

When correctly conceived & executed, systematic reviews also allow others sufficient information to independently replicate work

Key initial steps include problem formulation, protocol development, & search for and selection of studies for inclusion

Abuses of systematic review method are increasing, but it remains a preferred approach

Literature Search/Underlying Studies: Our Concerns

Did not employ systematic review methodology

No description provided for methods used to search literature

No description provided for process used to select studies for evaluation

Absent adequate descriptions, authors leave themselves open to concerns of **bias and “cherry picking” literature**

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Evaluation of a body of scientific literature should employ a system of weighing individual studies (European Commission 2013; US EPA 2011):

1. according to their quality, reliability & relevance (concentrations, formulations & exposure routes chosen);
2. reproducibility of reported effects;
3. pattern of effects across and within studies;
4. number of species showing same or similar effects;
5. likelihood that species showing effect are physiologically similar to humans & not predisposed to higher susceptibility of effects due to species-specific physiology;
6. time of onset of effects; and
7. life stage affected.

WOE Analysis: Our Concerns

Although Trasande panels claimed to have employed weight of evidence approach, **no description was provided for how this was done**

No weighing of evidence was apparent

Furthermore, critical analysis of individual studies relied upon was **severely lacking**

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Steering Committee “adapted” criteria recently proposed by Danish-EPA for evaluating laboratory & animal evidence of endocrine disruption

- A. **Confirmed EDC** (assigned a score of Strong Animal Evidence by Steering Committee) when substance is known to have caused endocrine mediated adverse effects in humans or animal species living in environment
- B. When mechanistic information exists that raises doubt about relevance of effect for humans or environment, chemical classification of **Suspected EDC** (assigned a score of Moderate Animal Evidence) is more appropriate
- C. Animal evidence supported classification of chemical as **Potential Endocrine Disruptor** (assigned score of Weak Animal Evidence) when there was evidence of adverse effects in animal studies that could have either an endocrine mode of action or non-endocrine mode of action, or in vitro/in silico evidence indicating potential for endocrine disruption in intact organism

Animal Toxicology Evidence: Our Concerns

Danish-EPA criteria do not include a category for designating substance as NOT an EDC, regardless of evidence available; thus, every substance is considered, at minimum, a Potential Endocrine Disruptor and therefore Weak Animal Evidence

Danish criteria fail to consider potency

Trasande did not explicitly state how they weighted evidence derived from validated OECD Test Guideline studies versus un-replicated, non-guideline studies

Did not state how they handled issues of inconsistent findings across multiple studies, studies with small numbers of animals, studies with too few dose groups, or other concerns about study design including the statistical approach taken & execution

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Steering Committee “adapted” GRADE Working Group criteria as they were recently applied in evaluating indoor air quality criteria by World Health Organization

This revised WHO approach is referred to by the authors as “Grading of Evidence for Public Health Interventions” (GEPHI)

Human Epidemiology Evidence: Our Concerns

Trasande approach not firmly grounded in work done by others as was implied

If GRADE methodology had been used, epidemiology evidence could have, at best, been assessed as **Low or Very Low Quality**, and consequently would have relegated probability of causation estimates into **lowest tiers**

GEPHI authors modified GRADE methodology solely to incorporate “before and after” studies which are a stronger observational epidemiology design, but not relevant to the evidence Trasande relied upon

GEPHI authors had substantially more and higher quality epidemiology evidence than Trasande, but never rated quality of evidence above **Moderate**; Trasande **not justified** in rating any of the epidemiology evidence they considered above **Low or Very Low**

GEPHI authors cautioned about generalizing use of their approach (should have **disqualified** its application by Steering Committee)

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Abbreviation: ADHD, attention-deficit hyperactivity disorder.

Associations where epidemiology evidence was judged at least Moderate

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Trasande panels should **not** have judged any epidemiology evidence stronger than Low

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Trasande admit their approach is **atypical**:

“Although analyses like these are highly valuable, they have typically been limited to associations where causation is certain.”

Steering Committee repeatedly asserted they used Intergovernmental Panel on Climate Change (IPCC) Guidance for Authors document to justify approach to assigning probability of causation in face of uncertainty

Steering Committee directed panels to develop estimates of attributable fractions and societal costs even when probability of causation estimate was as low as 0-19%

Assessing Causation: Our Concerns

Admission of **atypical & speculative approach** not mentioned in abstracts or press releases, but **buried within study**

IPCC Guidance for Authors document does not offer support for Trasande approach but cautions authors to “**communicate carefully, using calibrated language**”

Based on IPCC guidance, panels **should not** have calculated any cost estimates for disorders & diseases for which they judged the probability of EDC causation to be **less than 66%**

Most definitely, panels **should not** have calculated costs where probability of causation was less than 33%

Panels deviated from their framework when they could not achieve consensus in interpreting strength of epidemiology evidence on seven of purported EDC-health outcome links

Authors did not make convincing case that current disease burden is indeed caused by exposure to alleged EDCs

Failure to acknowledge that level of uncertainty in methodology so high **that one cannot exclude possibility that costs of exposure to EDCs may be as low as zero**

Likelihood Scale (Intergovernmental Panel on Climate Change 2005)

Terminology	Likelihood of the occurrence/outcome
Virtually certain	> 99% probability of occurrence
Very likely	> 90% probability
Likely	> 66% probability
About likely as not	33 to 66% probability
Unlikely	< 33% probability
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According to IPCC terminology, these associations had **probabilities of causation so low** that estimating costs was **not** justified.

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Critical Review of Evidence for Loss of IQ and Intellectual Disability

Since neurobehavioral deficits & diseases cost estimate overwhelmingly drives total estimated cost attributable to EDCs the corresponding paper by Bellanger was examined in greater detail

Special attention paid to purported links between exposure to organophosphates (OPPs) and, separately, exposures to PBDEs and lowered IQ and increased prevalence of intellectual disability

Organophosphate Pesticides (OPPs) and IQ Loss and Intellectual Disability

At least 5 other critical reviews published that examined the link between OPPs and neurobehavioral deficits and diseases -- and reported it as essentially **non-persuasive**

- concluded that in animals, effects are seen only at doses that were high enough to produce significant brain or red blood cell acetylcholinesterase inhibition in dams or offspring
- concluded that human epidemiology evidence is weak, criticized the few studies available for problems related to their design, exposure and outcome measurements, and inadequate control of potential confounding variables (i.e., other risk factors)

Bellanger made no reference to other reviews, nor attempted to explain why conclusions differed

Original human epidemiology studies actually report relatively few statistically significant findings suggestive of adverse effects, and no consistent patterns can be found across them

Organophosphate Pesticides (OPPs) and IQ Loss and Intellectual Disability (contd.)

U.S. EPA FIFRA Science Advisory Panel (2016), “The assumption that the impaired working memory and lower IQ measures observed are caused primarily by a single insecticide (chlorpyrifos) and predicted by the blood levels at time of delivery is not supported by the scientific weight of evidence”.

Chlorpyrifos was included in U.S. EPA’s Endocrine Disruptor Screening Program Tier 1 weight-of-the-evidence evaluation of potential interaction of chlorpyrifos with estrogen, androgen, or thyroid hormone signaling pathways; EPA concluded that further testing of chlorpyrifos under EDSP Tier 2 program was unwarranted since they found no evidence of potential interaction with either of three pathways

EPA released weight of the evidence conclusions under EDSP Tier 1 for five other organophosphate pesticides for which it was similarly concluded that further testing under Tier 2 was not warranted

Polybrominated diphenyl ethers (PBDEs) and IQ Loss and Intellectual Disability

Bellanger judged animal toxicology evidence to be strong b/c of stated belief that PBDEs interfere with thyroid action and that this consequently causes IQ loss.

Ignored many lines of evidence that rodents are much more susceptible than humans to compounds interfering with thyroid action

Dose levels of PBDEs required to produce effects in rodent far exceed levels demonstrated to occur in humans.

❖ Issue highlighted for PCBs by Crofton and Zoeller 2005 (i.e. **Zoeller contradicted his own 2005 assessment** by coauthoring at least 2 cost-estimate papers by Trasande et al)

Bellanger failed to provide critical review of the three human epidemiology studies relied upon; failed to cite 2 existing critical reviews already in literature that arrived at different conclusions

Those 2 reviews cited **numerous shortcomings** in epidemiology studies as reasons why the evidence **should not be judged to be stronger**

Conclusions

Substantial shortcomings with underlying methodology render cost estimates **highly uncertain** and **immaterial** to serious policy discussions

Authors claimed to have “adapted” methods by WHO and IPCC, but instead devised their own unique approach **without a firm grounding in science or precedence**

Cost estimates derive from **assumptions of causal relationships** between putative exposures to EDCs that have not been established through any serious consideration of the strengths and weaknesses of the underlying animal toxicology and human epidemiology evidence

We did not examine in detail other 13 EDC-outcome relationships; however, recent systematic review and meta-analysis of male reproductive diseases and disorders directly challenged Trasande’s cost estimates

Conclusions (contd.)

Everyone loses when scientific method, which demands objectivity, is not met, as demonstrated by this series of economic papers

Public policy choices based on poor science or isolated findings from un-replicated studies, even while well-intentioned, will **have significant, negative consequences for individuals and society**

THANK YOU

Questions?