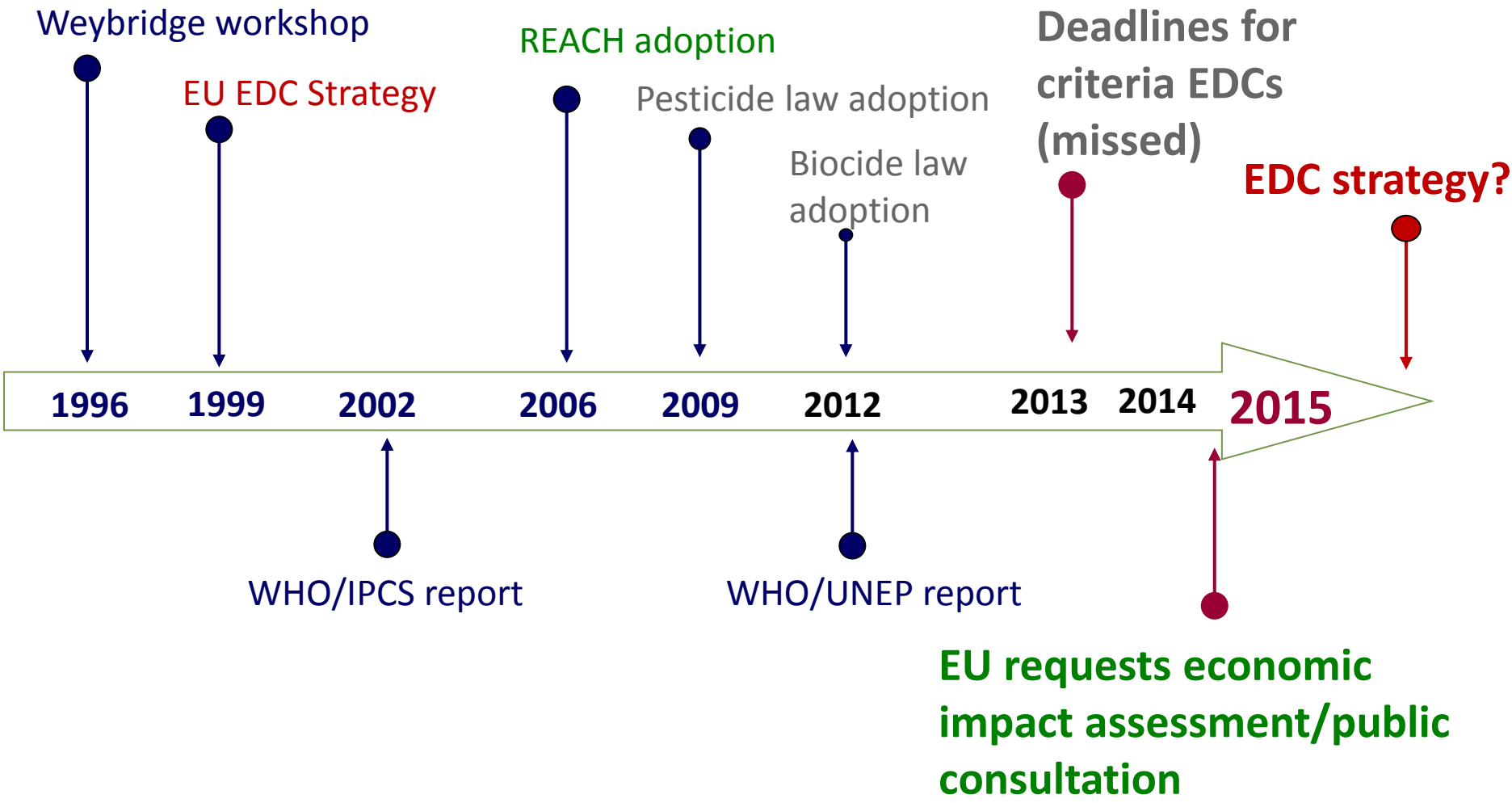
CHE call on Diabetes, Obesity and Associated Costs of EDC Exposure

April 28, 2015

Dr. Juliette Legler
Professor of Toxicology and Environmental Health
Institute for Environmental Studies
VU University Amsterdam
Juliette.legler@vu.nl

Where are we in terms of EDC regulations in Europe?



Slide courtesy of Andreas Kortenkamp, Brunel Univ. (with some adaptations)

- EU impact assessment: focused on the economic impact to industry of regulating EDCs in Europe
- In the absence of estimates of the health costs of EDC exposures, the high costs of alternatives are likely to outweigh concerns about the health consequences of using EDCs
- Objective of our work: to quantify a range of health and economic costs that can be reasonably attributed to EDC exposures in the European Union


JCEM THE JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM

ORIGINAL ARTICLE

Estimating Burden and Disease Costs of Exposure to Endocrine-Disrupting Chemicals in the European Union

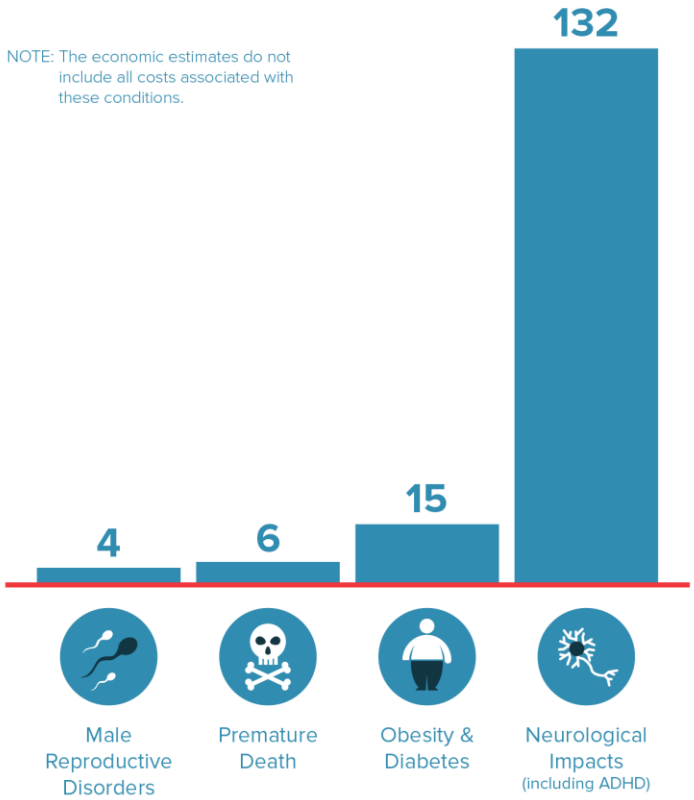
Leonardo Trasande, R. Thomas Zoeller, Ulla Hass, Andreas Kortenkamp, Philippe Grandjean, John Peterson Myers, Joseph DiGangi, Martine Bellanger, Russ Hauser, Juliette Legler, Niels E. Skakkebaek, and Jerrold J. Heindel

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

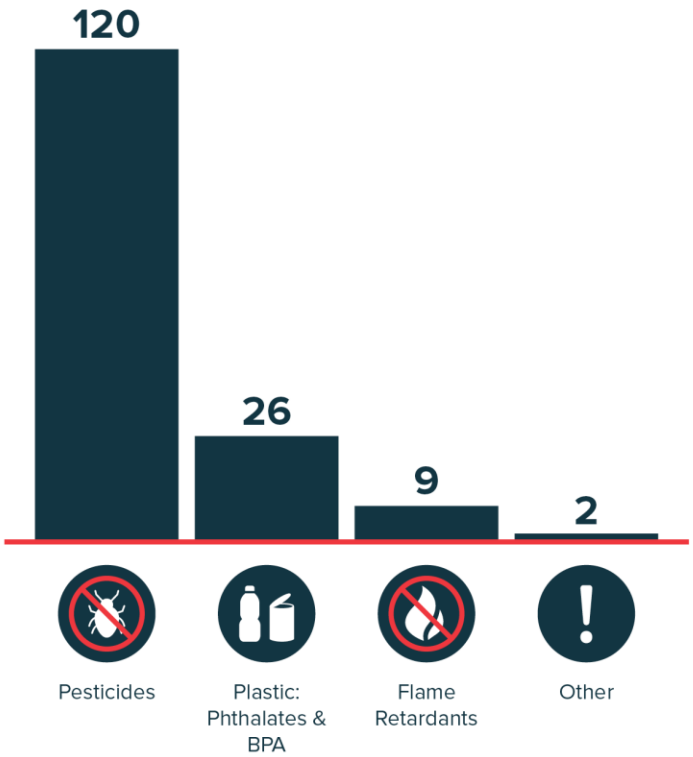
This is the tip of the iceberg: Costs may be as high as €270B.

€157B Cost by Health Effect

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



€157B Cost by EDC Type



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

NYU School of Medicine
NYU LANGONE MEDICAL CENTER

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

Slide courtesy of Leo Trasande, NYU

doi: 10.1210/jc.2014-4326 J Clin Endocrinol Metab jcem.endojournals.org

ORIGINAL ARTICLE

Obesity, Diabetes and Associated Costs of Exposure to Endocrine Disrupting Chemicals in the European Union

Juliette Legler[1], Tony Fletcher[2], Eva Govarts[3], Miquel Porta[4,5], Bruce Blumberg[6], Jerrold J. Heindel[7], Leonardo Trasande[8,9,10,11]

[1]Department of Chemistry and Biology, Institute for Environmental Studies, VU University, Amsterdam, Netherlands; [2]London School of Tropical Hygiene, London, United Kingdom; [3]Environmental Risk and Health, Flemish Institute for Technological Research (VITO), Mol, Belgium; [4]School of Medicine, Universitat Autònoma de Barcelona (UAB), Spain; [5]Hospital del Mar Institute of Medical Research (IMIM), Barcelona, and CIBERESP, Spain; [6]Department of Developmental and Cell Biology, University of California, Irvine; [7]National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA; [8]New York University (NYU) School of Medicine, NY, New York, USA; [9]NYU Wagner School of Public Service, NY, New York, USA; [10]NYU Steinhardt School of Culture, Education and Human Development, Department of Nutrition, Food & Public Health, NY, New York, USA; [11]NYU Global Institute of Public Health, NY University, NY, New York, USA

Epidemiologic and toxicological studies considered for 5 EDC-related conditions :

1. DDE-attributable Childhood Overweight
2. DDE-attributable Adult Diabetes
3. Phthalate-attributable adult overweight/obesity
4. Phthalate-attributable Adult Diabetes
5. BPA-attributable childhood obesity

Evaluating epidemiologic studies with GRADE (Grading of Recommendations Assessment, Development and Evaluation)

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

How to deal with uncertainty? Adapting IPCC criteria to integrate epidemiologic and toxicologic evidence and determine a "probability of causation"

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

Evaluation of probability of causation/strength of evidence

Exposure	Outcome	Strength of Human Evidence	Strength of Toxicologic Evidence	Probability of Causation
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%

Disease burden and exposure estimates

Dose-response relationships from the epidemiologic literature, including estimate of odds ratio or increment in disease

Exposure data from most representative European biomarker data available:

- DDE: Casas et al, 2014, Environ Int. 74c:23-31
- BPA: Covaci et a, 2014, Environ Res. S0013-9351(14)00268-0
- Phthalates: Den Hond et al, 2015, EHP, 123(3):255-63.

Legler et al J Clin Endo Metab epub Mar 5 2015

Health costs of obesity and diabetes

Peer-reviewed, published cost data were used for each condition

- Country-specific estimate of costs accounting for differences in GDP
  - main estimate of lifetime social costs for obesity at age 10 of $19,200 (Finkelstein et al, Pediatrics. 2014 133(5):854-62)
  - for adult overweight, estimated medical expenditures attributable to obesity (Cawley and Meyerhoefer 2012 J Health Econ 31:219-230)
  - loss of disability-adjusted life years (DALY) due to adult overweight or obesity (Muennig et al 2006 Am J Pub Health 96:1662)
  - Annual cost estimates for diabetes per adult (Zhang et al, 2010 Diabetes research and clinical practice 87:293-301)

Legler et al J Clin Endo Metab epub Mar 5 2015

% Childhood overweight in the European Union (EU27)
Measured heights & weights

Country	Year of Data Collection	Age Range	Boys	Girls	Cut Off Used
Austria	2003	8-12yrs	22.5	16.7	90th Centile
Belgium	2010	10-12yrs	16.9	13.5	IOTF
Bulgaria	2004	5-17yrs	22	17.9	IOTF
Cyprus	2010	10-12yrs	37.5	34.1	Cyprus specific cut off
Czech Republic	2005	6-17yrs	24.6	16.9	IOTF
England	2010	5-17yrs	21.9	23.1	IOTF
Estonia	2007/8	2-9yrs	13.6	14.9	IOTF
France	2006-7	3-17yrs	13.1	14.9	IOTF
Germany	2008	4-16yrs	22.6	17.6	IOTF
Greece	2010	10-12yrs	44.4	37.7	IOTF
Hungary	2010	10-12yrs	27.7	22.6	IOTF
Republic of Ireland	2003/4	5-12yrs	19.4	28.9	IOTF
Italy	2008	8yrs	37.2	34.7	IOTF
Latvia	2008	7yrs	15.3	15.1	IOTF
Lithuania	2008	7yrs	16.1	16.2	IOTF
Malta	2012	10-11yrs	38.9	30.1	IOTF
Netherlands	2010	10-12yrs	16.8	15.4	IOTF
Poland	2008/9	6-13yrs	28	16.1	IOTF
Portugal	2008	6-8yrs	30	26.1	IOTF
Romania	2008-12	6-10yrs	24.6	22.7	IOTF
Scotland	2010	12-15yrs	32.7	34.3	85th centile
Slovakia	2001	7-17yrs	17.5	16.2	IOTF
Slovenia	2010	10-12yrs	31.7	22.5	IOTF
Spain	2012	8-17yrs	32.3	29.5	IOTF
Sweden	2000	10yrs	17	19.5	IOTF

http://www.worldobesity.org/site_media/library/resource_images/Child_EU_March_2014_WO.pdf

Results

Table 1. DDE-Attributable Childhood Obesity, 2010

Expert Panel Evaluation of Epidemiologic Evidence	Moderate					
Expert Panel Evaluation of Toxicologic Evidence	Moderate					
Probability of Causation	40–69%					
Percentile of Exposure	**0–9**	**10–24**	**25–49**	**50–74**	**75–89**	**>90**
Percentile Assumed	0	10	25	50	75	90
Cord Serum DDE, ng/g	<LOD	10.62	22.47	50.25	112.36	211.54
Increment in Change in Weight for Age Z-score (Main Estimate) *	0.00	0.00	0.004	0.01	0.03	0.06
Relative Risk of Rapid Infant Weight Gain (Sensitivity Analysis) **	1.00	1.00	1.04	1.09	1.13	1.17
Attributable Increment in Rapid Weight Gain (Main Estimate)	0.00%	0.00%	0.12%	0.39%	0.99%	1.94%
Attributable Increment in Rapid Weight Gain (Sensitivity Analysis)	0.00%	0.00%	1.01%	2.15%	3.33%	4.30%
Attributable Fraction of Overweight at Age 10 (Main Estimate)	0.26%					
Attributable Fraction of Overweight at Age 10 (Sensitivity Analysis)	0.92%					
Attribuable Cases of Overweight (Main Estimate)	1555					
Attribuable Cases of Overweight (Sensitivity Analysis)	5463					
Costs of Attributable Overweight (Main Estimate)	24.6 million					
Costs of Attributable Overweight (Sensitivity Analysis)	86.4 million					

*Iszatt et al, 2015, EHP **Valvi et al, 2014, Obesity

Legler et al J Clin Endo Metab epub Mar 5 2015

Cost estimates (probability of causation):

1. DDE-attributable Childhood Overweight
   - 1,555 obese 10 year olds = €24.6M (40-69%)

2. DDE-attributable Adult Diabetes
   - 28,200 50–64 year olds with diabetes = €835M (20-39%)

3. Phthalate-attributable adult overweight/obesity
   - 53,900 50-64 year old women are obese = €15.6B (40-69%)

4. Phthalate-attributable Adult Diabetes
   - 20,500 50-64 year old women are diabetic = €607M (40-69%)

5. BPA-attributable childhood obesity
   - 42,400 obese 4 year olds each year = €1.54B (20-69%)

Summary

- The costs of EDC-attributable obesity and diabetes are substantial to society, in the range of €18–29 billion annually.
- This is a first assessment of metabolic disease costs associated with EDCs – intends to set the foundation upon which future analyses can be built
- Limiting our exposure to the most widely used and potentially hazardous EDCs is likely to produce substantial economic benefit.
- Our analysis shows that probability can be incorporated into burden and costs of environmentally-attributable disease.
- By making explicit the uncertainties, policy makers can weigh the tradeoffs with ongoing use of chemicals and alternatives

Many thanks to Leo Trasande, Bruce Blumberg, Tony Fletcher, Miquel Porta, Eva Govarts and Jerry Heindel

Support from the Endocrine Society, the John Merck Fund, the Broad Reach Foundation, and the Oak Foundation.

The funders and supporters had no role in the writing of the manuscript or the decision to submit it for publication