Exposure to endocrine-disrupting chemicals in the USA: a population-based disease burden and cost analysis

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Summary

Background **Endocrine-disrupting chemicals (EDCs) contribute to disease and dysfunction and incur high associated costs (>1% of the gross domestic product [GDP] in the European Union). Exposure to EDCs varies widely between the USA and Europe because of differences in regulations and, therefore, we aimed to quantify disease burdens and related economic costs to allow comparison.**

Methods **We used existing models for assessing epidemiological and toxicological studies to reach consensus on probabilities of causation for 15 exposure–response relations between substances and disorders. We used Monte Carlo methods to produce realistic probability ranges for costs across the exposure–response relation, taking into account uncertainties. Estimates were made based on population and costs in the USA in 2010. Costs for the European Union were converted to US$ (€1=$1·33).**

Findings **The disease costs of EDCs were much higher in the USA than in Europe ($340 billion [2·33% of GDP] *vs* $217 billion [1·28%]). The difference was driven mainly by intelligence quotient (IQ) points loss and intellectual disability due to polybrominated diphenyl ethers (11 million IQ points lost and 43 000 cases costing $266 billion in the USA *vs* 873 000 IQ points lost and 3290 cases costing $12·6 billion in the European Union). Accounting for probability of causation, in the European Union, organophosphate pesticides were the largest contributor to costs associated with EDC exposure ($121 billion), whereas in the USA costs due to pesticides were much lower ($42 billion).**

Interpretation **EDC exposure in the USA contributes to disease and dysfunction, with annual costs taking up more than 2% of the GDP. Differences from the European Union suggest the need for improved screening for chemical disruption to endocrine systems and proactive prevention.**

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Introduction

Since the adverse effects of endocrine-disrupting chemicals (EDCs) on human beings were first identified,[1] growing evidence has supported the hypothesis that multiple industrial chemicals are associated with adverse health effects due to endocrine dysfunction at exposure levels commonly found in the environment.[1] The Endocrine Society defines EDCs as substances that alter the hormonal and homoeostatic systems of organisms through environmental or developmental exposures, resulting in adverse health effects. EDCs include industrial solvents or lubricants and their by-products (polychlorinated biphenyls, polybrominated biphenyls, and dioxins), plastics (bisphenol A), plasticisers (phthalates), pesticides (methoxychlor, chlorpyrifos, dichlorodiphenyltrichloroethane), and pharmaceutical agents (diethylstilbestrol). Potential adverse consequences of exposure to EDCs include prostate and breast cancer, infertility, male and female reproductive dysfunction, birth defects, obesity, diabetes, cardiopulmonary disease, and neurobehavioural and learning dysfunctions.[2]

After the initial scientific statement by the Endocrine Society,[1] a group of experts, on behalf of WHO and the UN Environment Programme (UNEP), published a report documenting substantial laboratory and human evidence supporting a causative role of EDCs in disease and dysfunction across the human lifespan.[3] Initial criticisms of the WHO and UNEP report were rebutted,[4] and a second Endocrine Society scientific statement has summarised stronger evidence of disease causation.[5]

Various publications have documented substantial health and economic burdens due to EDCs in the European Union, identifying more than 99% probability of disease contribution, with the median annual associated costs estimated to be around €163 billion or 1·28% of the European Union gross domestic product.[6] Comparison of the European Union with the USA reveals that EDC exposure is much higher for organophosphate pesticides in Europe[7] and for polybrominated diphenyl ethers (PBDEs) in the USA.[8,9] These differences are driven by regulatory divergence. For pesticides and their use in food-destined crops, US regulations have been much more stringent than those in Europe. In particular, the US Food Quality Protection Act of 1996[10] requires additional safety considerations for children before pesticide use in agriculture is approved, but no such strict regulation exists in the European Union, even for pesticides that induce toxic neurodevelopmental effects.[11] For PBDEs, since 1975, California state law has required furniture with

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Research in context

Evidence before this study

Endocrine-disrupting chemicals (EDCs) have been documented to contribute substantially to disease and dysfunction in Europe, having a probability of disease contribution greater than 99%, and incurring a probable annual cost of €163 billion. Policy is, therefore, important to shape prevention of exposure. We searched PubMed for relevant studies that estimated the economic costs associated with EDC exposure in the USA, using the terms "EDCs exposure", "burden of disease", "economic costs", and "economic impacts". We placed no restrictions on the year or language of publication. The latest search was done in January, 2016. We identified no relevant estimates for EDC-attributable burden of disease or dysfunction or economic costs in the USA. Analysis of disease burden and costs attributable to EDC exposures for the USA is especially relevant because comparing Europe with the USA might reveal differences that affect the degree of EDC exposure and, thus, the probability of disease contribution.

Added value of this study

Comparisons between countries with different regulatory environments are important, and in this analysis we identified substantial differences between the European Union and the USA, including in costs (US$217 *vs* $340 billion annually), that seem to be directly linked to policy actions in the two contexts. The USA is about to implement revisions to the main regulation for synthetic chemicals (the revised Toxic Substances Control Act 1976) that will lead to greater scrutiny of the synthetic chemicals they review. Cost–benefit analyses of chemical regulation often consider costs to manufacturers but do not capture benefits of prevention. Therefore, estimates of the disease burden and economic costs of EDC exposure represent important tools for policy makers to inform decision making.

Implications of all available evidence

Regulatory action to limit the most widely prevalent and potentially hazardous EDCs could produce substantial economic benefits, and the costs of regulatory actions, for example to the producing industry, should be compared with the costs of inaction—ie, substantial disease burden and the associated economic costs. Given that some EDCs have transgenerational effects, especially through neuroendocrine disruption of reproduction, inadequate regulation of EDCs could have serious adverse consequences for future generations.

foam filling to undergo open-flame ignition testing, which has been easiest to pass by using chemical flame retardants. Owing to worries about the toxicity of chemical flame retardants and their increased use to pass this test, the law was revised in 2013 to focus on smouldering ignition tests for fabric, which can be passed without using chemical flame retardants.[12] Voluntary commitment by manufacturers to phase out the most highly brominated PBDEs, deca-PBDEs, over 3 years, with sales to cease in 2013, was encouraged but was not formally regulated. By contrast, Europe designated deca-PBDE a hazardous substance and restricted its use in 2008.[13]

In the USA, under the revised Toxic Substances Control Act 1976, chemicals need not be studied for endocrine toxic effects in laboratory studies before widespread use.[14] The US Environmental Protection Agency (EPA) has established the Endocrine Disruptor Screening Program, but has screened only 52 chemicals for endocrine activity, and testing has been based mainly on animal data. Although the EPA has developed the ToxCast and Tox 21 High Throughput Screening programmes in an effort to accelerate screening for endocrine disruption, flaws in the ability of the former to detect synthetic chemical obesogens have been exposed.[15] Furthermore, ambiguities in the system lead to broad interpretations of which chemicals fall into high priority and low priority groups. Thus, some new substances might be potentially harmful but not tested before approval, and some will be tested unnecessarily. Analyses of disease burden and costs attributable to EDC exposures in the USA are especially relevant given impending changes in regulation that will lead to greater scrutiny of synthetic chemicals for their toxicity in terms of human health, and could represent an important tool for policy makers to inform decision making. We aimed to quantify disease burdens and related economic costs due to EDC exposures in the USA to compare with the costs previously identified in Europe.

See Online for appendix

Methods

Study design

We obtained ranges for probabilities of causation which had been previously developed by expert panels assembled under the auspices of the Endocrine Society to evaluate burden of disease and costs attributable to EDCs in Europe.[16] The probabilities had been based on assessment of the toxicological and epidemiological evidence for 15 exposure–response relations between EDCs (PBDEs, organophosphate pesticides, dichlorodiphenyltrichloroethane, di-2-ethylhexylphthalate, bisphenol A, benzylphthalates and butylphthalates, and exposures to combinations of these substances; appendix) and disorders (loss of intelligence quotient [IQ] points and consequent intellectual disability, attention deficit hyperactivity disorder, autism, adult and childhood obesity, adult diabetes, cryptorchidism, testicular cancer, male factor infertility, early cardiovascular mortality due to reduced testosterone, leiomyomas, and endometriosis) with use of a modified Delphi approach to achieve consensus.[17] The Danish Environmental Protection Agency criteria were used to assess the toxicological evidence, and the GRADE

Working Group criteria to assess strength of the epidemiological evidence.[18,19] A steering committee of scientists used an adapted version of the approach first developed by the Intergovernmental Panel on Climate Change to create ranges for probability of causation based on the strength of both sets of evidence.[20]

We applied a model first used by the Institute of Medicine[21] to estimate the cost of environmentally mediated disease, described by the equations below:

attributable disease burden = increment in disease / dysfunction × attributable fraction × population size

and

attributable costs = increment in disease / dysfunction × attributable fraction × population size × cost per increment.

The attributable fraction of a risk factor can be defined as the proportional decrease in the number of cases of ill health or deaths due to reducing the risk factor,[22] and can be estimated by the following equation:

$$\text{attributable fraction} = \frac{\text{prevalence}_{\text{exposure}} \times (RR-1)}{[1 + (\text{prevalence}_{\text{exposure}} \times (RR-1))]}$$

where RR represents the relative risk of morbidity associated with the specific exposure.

Cost per case, derived from published estimates of per-case direct or indirect costs, or both, was used to calculate overall costs (adjusted with the Medical Care Consumer Price Index[23] to reflect the cost in 2010 if the estimates referred to another year), according to the incidence or prevalence of a disease and the size of the population at risk. US 2010 census estimates[24] were used to convert the prevalence or incidence values to the appropriate population size. The first equation was also used to calculate discrete increments in disease or dysfunction in the exposed group over a comparison unexposed group, as described in the European Union analysis.

To create comparable estimates for the USA, we used the exposure–response relations established for Europe and obtained nationally representative human biomonitoring data from the Centers for Disease Control and Prevention's National Health and Nutrition Examination Surveys (NHANES), which measures EDCs in nationally representative samples. NHANES is a continuous, multicomponent, nationally representative survey of the non-institutionalised US population, and is administered by the National Centers for Health Statistics of the Centers for Disease Control and Prevention. Institutional review board was not needed because of the non-human nature of this study, and LT completed an attestation form developed by the New York University School of Medicine Institutional Review Board to document this exemption.

We applied the exposure–response relations to the US population, based on biomarker data on PBDEs, dichlorodiphenyltrichloroethane, and organophosphate pesticides extracted from the 2007–08 NHANES, and on bisphenol A

	Target population	Exposure–outcome relation (base case estimates)*	Exposure–outcome relation (sensitivity analyses)
PBDE and IQ points loss and intellectual disability	All neonates	11 million IQ points lost and 43 000 cases	19 million IQ points lost and 99 000 cases
Organophosphate pesticides and IQ points loss and intellectual disability	All neonates	1·8 million IQ points lost and 7500 cases	587 000–2·0 million IQ points lost and 2000–10 000 cases
Dichlorodiphenyltrichloroethane and childhood obesity	Children aged 10 years	857 cases	NA
Dichlorodiphenyltrichloroethane and adult diabetes	Adults aged 50–64 years	243 900 cases	191 000 cases
Di-2-ethylhexylphthalate and adult obesity	Women aged 50–64 years	5900 cases	NA
Di-2-ethylhexylphthalate and adult diabetes	Women aged 50–64 years	1300 cases	NA
Bisphenol A and childhood obesity	Children aged 4 years	33 000 cases	NA
PBDE and testicular cancer	All boys and men	3600 cases	NA
PBDE and cryptorchidism	All male neonates	4300 cases	NA
Benzylphthalates and butylphthalates and male infertility resulting in increased assisted reproductive technology	Men aged 20–39 years	240 100 cases	NA
Phthalates and low testosterone resulting in increased early mortality	Men aged 55–64 years	10 700 attributable deaths	NA
Multiple exposures and ADHD	Children aged 12 years	4400 cases	79 000 cases
Multiple exposures and autism	Children aged 8 years	787 cases in boys, 754 in girls	315–1573 cases in boys, 302–1508 in girls
Dichlorodiphenyltrichloroethane and fibroids	Women aged 15–54 years	37 000 cases	NA
Di-2-ethylhexylphthalate and endometriosis	Women aged 20–44 years	86 000 cases	NA

PBDE=polybrominated diphenyl ethers. IQ=intelligence quotient. ADHD=attention deficit hyperactivity disorder. NA=alternative inputs not available to do sensitivity analyses. *Annual estimates.

Table 1: **Attributable burden of disease in the USA for 15 exposure–response relations**

	Base case estimate (US$)	Low-end estimate (US$)	High-end estimate or alternative scenario (US$)
PBDE and IQ points loss and intellectual disability	208 billion and 58·2 billion	NA	367 billion and 133 billion
Organophosphate pesticides and IQ points loss and intellectual disability	34·6 billion and 10·1 billion	11·3 billion and 3·0 billion	45·5 billion and 14·0 billion
Dichlorodiphenyltrichloroethane and childhood obesity	29·6 million	NA	57·3 million
Dichlorodiphenyltrichloroethane and adult diabetes	1·8 billion	NA	13·5 billion
Di-2-ethylhexylphthalate and adult obesity	1·7 billion	NA	NA
Di-2-ethylhexylphthalate and adult diabetes	91·4 million	NA	NA
Bisphenol A and childhood obesity	2·4 billion	NA	NA
PBDE and testicular cancer	81·5 million	24·8 million	109·3 million
PBDE and cryptorchidism	35·7 million	NA	NA
Benzylphthalates and butylphthalates and male infertility resulting in increased assisted reproductive technology	2·5 billion	NA	NA
Phthalates and low testosterone resulting in increased early mortality	8·8 billion	NA	NA
Multiple exposures and ADHD	698 million	568 million	1·95 billion
Multiple exposures and autism	1 billion for boys, 984 million for girls	410 million for boys, 393 million for girls	2·1 billion for boys, 2·0 billion for girls
Dichlorodiphenyltrichloroethane and fibroids	259 million	NA	595 million
Di-2-ethylhexylphthalate and endometriosis	47 billion	NA	NA

All estimates are for 2010. Estimates are conditional on certainty of causation. PBDE=polybrominated diphenyl ethers. IQ=intelligence quotient. NA=alternative inputs not available to do sensitivity analyses. ADHD=attention deficit hyperactivity disorder.

***Table 2*: Annual costs for disorders associated with exposure to endocrine-disrupting chemicals in the USA**

and phthalates extracted from the 2009–10 NHANES. The values were separated into quintiles (0–9th, 10th–24th, 25th–49th, 50th–74th, 75th–89th, and 90th–99th).

Economic estimates

To estimate the total costs incurred for a disorder, we used a cost-of-illness approach that encompassed direct costs (those for which payments are made, such as medical treatment) and indirect costs (those for which resources are lost, such as loss of productivity or output).[25] We followed the guidelines provided by the Panel on Cost Effectiveness and Medicine[26] and used US data sources and published US cost estimates (appendix). Additionally, we did a series of 1000 Monte Carlo simulations to generate realistic ranges of aggregate cost estimates across all the exposure–outcome relations while accounting for probability of causation.[16]

Statistical analysis

We did a descriptive analysis with Stata 12.0, following the National Center for Health Statistics guidelines. For dichlorodiphenyltrichloroethane and PBDEs, a weighted pooled-sample design was implemented in NHANES 2007–08. Sample weighting was incorporated into the pooled-sample design, and we did the descriptive analyses with the final adjusted summed sampling weights. For the other EDCs (all individual samples) the specific environmental sample weights included in each subsample were used for the descriptive analyses.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

Results

The greatest burden identified in the USA due to exposure to EDCs was neurobehavioural dysfunction resulting from in-utero exposure to PBDEs, illustrated by IQ points loss and intellectual disability (table 1). A substantial loss in IQ points and increase in the number of intellectual disability cases were also associated with exposure to organophosphate pesticides. Over 1500 cases of autism and 4400 cases of attention deficit hyperactivity disorder were also attributed to EDC exposure (table 1).

Of the phthalates, di-2-ethylhexylphthalate was estimated to be among the most substantial contributors, being associated with high numbers of cases of adult obesity and diabetes and endometriosis (table 1). Phthalates were associated with 10 700 early cardiovascular deaths due to reductions in serum testosterone. Bisphenol A exposure was associated with childhood obesity. Lower numbers of cases were associated with dichlorodiphenyltrichloroethane, exposure to which was also associated with adult diabetes and uterine fibroids requiring surgical intervention (table 1).

The estimated annual economic costs of EDC-attributable disorders were greatest for neurocognitive dysfunctions associated with PBDEs (table 2). Phthalates comprised the second-leading driver of estimated costs through the association with endometriosis, male fertility factors, adult obesity, and adult diabetes (table 2).

A comparison of costs in the USA and European Union revealed the effects of policy differences on exposure (table 3). The estimated number of PBDE-induced neurobehavioural deficits was much greater in the USA than in Europe, whereas we found the opposite for organophosphate pesticides. The estimated exposures for organophosphate pesticides and PBDE in the USA and the European Union are shown in table 4. In general, disease burdens for phthalates were larger in Europe than in the USA, where substantial decreases in these metabolites between 2001 and 2010 have been documented.[27] Detailed results are provided in the appendix.

Monte Carlo simulations yielded non-zero costs across all 1000 simulations, even under the most conservative assumptions about probability of causation, when the lowest ends of the ranges identified for each of the 15 exposure–response relations were used (figure).

We estimated that there was 5% probability that costs of EDC exposures are less than $43·3 billion annually, 90% probability that costs are at least $67·7 billion, 75% probability that costs are at least $303 billion per year, 25% probability of costs being at least $427 billion per year, and 10% probability of costs being over $512 billion per year. Notably, using the lowest end of the probability range for each relation in the Monte Carlo simulations produced a range of $259 million–608 billion (median $306 billion), which differed slightly from those obtained with the base case probability inputs (median $340 billion, range $668 million–612 billion). There was 5% probability that costs of EDC exposures are less than $11·7 billion annually, 90% probability that costs are at least $28·6 billion, a 75% probability that costs are at least $64·4 billion per year, 25% probability of costs being at least $363 billion per year, and 10% probability of costs being more than $463 billion per year. By applying the lowest end of the probability range and assuming that all relations are independent, multiplying each of the probabilities for the exposure–outcome relations suggests probability of more than 99·9% (=1−0·3×0·3×0·6×0·8×0·6×0·6×0·8×0·6×0·6×0·6×0·6×0·8×0·8×0·8×0·8) that EDCs contribute to disease. If the highly probable costs related to developmental neurotoxic effects from organophosphate pesticides and brominated flame retardants are excluded, probability remains at 99·3% that one or more of the other exposure–outcome relations are causal. Use of the highest end of the probability ranges yielded a median cost of $365 billion (range $287 billion–611 billion). Overall, of the median $340 billion cost of EDCs, $282 billion are due to neurological effects, $43 billion to endometriosis and fibroids, and $7·9 billion to early cardiovascular mortality. Also included are $5·4 billion for costs attributable to obesity and diabetes and $2·4 billion attributable to male reproductive conditions. PBDEs contribute most of the costs (around $240 billion), with phthalates and bisphenols contributing $56 billion, pesticides another $42 billion, and mixtures $2·4 billion.

	USA*	European Union†	US costs (2010 US$)	EU costs[16] (US$‡)
PBDE and IQ points loss and intellectual disability	11 million IQ points lost and 43 000 cases	873 000 IQ points lost and 3290 cases	266 billion	12·6 billion
Organophosphate pesticides and IQ points loss and intellectual disability	1·8 million IQ points lost and 7500 cases	13 million IQ points lost and 59 300 cases	44·7 billion	194·0 billion
Dichlorodiphenyltrichloroethane and childhood obesity	857 cases	1555 cases	29·6 million	32·7 million
Dichlorodiphenyltrichloroethane and adult diabetes	24 900 cases	28 200 cases	1·8 billion	1·1 billion
Di-2-ethylhexylphthalate and adult obesity	5 900 cases	53 900 cases	1·7 billion	20·8 billion
Di-2-ethylhexylphthalate and adult diabetes	1300 cases	20 500 cases	91·4 million	807·2 million
Bisphenol A and childhood obesity	33 000 cases	42 400 cases	2·4 billion	2·0 billion
PBDE and testicular cancer	3600 cases	6830 cases	81·5 million	1·1 billion
PBDE and cryptorchidism	4300 cases	4615 cases	35·7 million	172·6 million
Benzylphthalates and butylphthalates and male infertility resulting in increased assisted reproductive technology	240 100 cases	618 000 cases	2·5 billion	6·3 billion
Phthalates and low testosterone resulting in increased early mortality	10 700 attributable deaths	24 800 attributable deaths	8·8 billion	10·6 billion
Multiple exposures and ADHD	4400 cases	19 400–31 200 cases	698·0 million	2·3 billion
Multiple exposures and autism	787 cases in boys, 754 cases in girls	316 cases	1·0 billion in boys, 984·0 million in girls	265·1 million
Dichlorodiphenyltrichloroethane and fibroids	37 000 cases	56 700 cases	259·0 million	216·8 million
Di-2-ethylhexylphthalate and endometriosis	86 000 cases	145 000 cases	47·0 billion	1·7 billion

The comparison uses base case estimates. Estimates are conditional on certainty of causation. EU=European Union. PBDE=polybrominated diphenyl ethers. 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**

	10th–24th percentile of exposure (10)*	25th–49th percentile of exposure (25)*	50th–74th percentile of exposure (50)*	75th–89th percentile of exposure (75)*	90th–99th percentile of exposure (90)*
Total urinary dialkyl phosphate concentration (nmol/L)					
USA	13·17	13·17	22·40	112·89	322·42
European Union	79·92	175·55	280·58	741·31	1160·78
Total PBDE 47 concentration in serum (ng/g)					
USA	15·8	19·7	23·1	41·6	68·5
European Union	0	0	2·60	4·61	6·27

PBDE=polybrominated diphenyl ether. *Numbers in brackets show the assumed percentile.

***Table 4:* Modelled exposures to an organophosphate pesticide and a PBDE in the USA and European Union**

Discussion

Disease costs across the human lifespan associated with exposure to EDCs in the USA seem to be hundreds of billions of dollars. To place such amounts in perspective, the median annual cost of $340 billion per year that we identified represents 2·33% of the 2010 US gross domestic product ($14·582 trillion).[28] By comparison, EDC costs in the European Union were estimated to be 1·28% of the gross domestic product ($17·0 trillion).[16] Regulatory action to limit exposure to EDCs is likely to produce substantial economic benefits, which should be taken into account when considering the costs of safer alternatives. In particular, some of the main economic benefits of regulating hazardous chemicals would be related to the decreased health costs. Increased production of alternatives could ensure that substances are truly safer alternatives and not replacements with equally hazardous compounds, as was the case when bisphenol A was replaced by bisphenols S and F.[29]

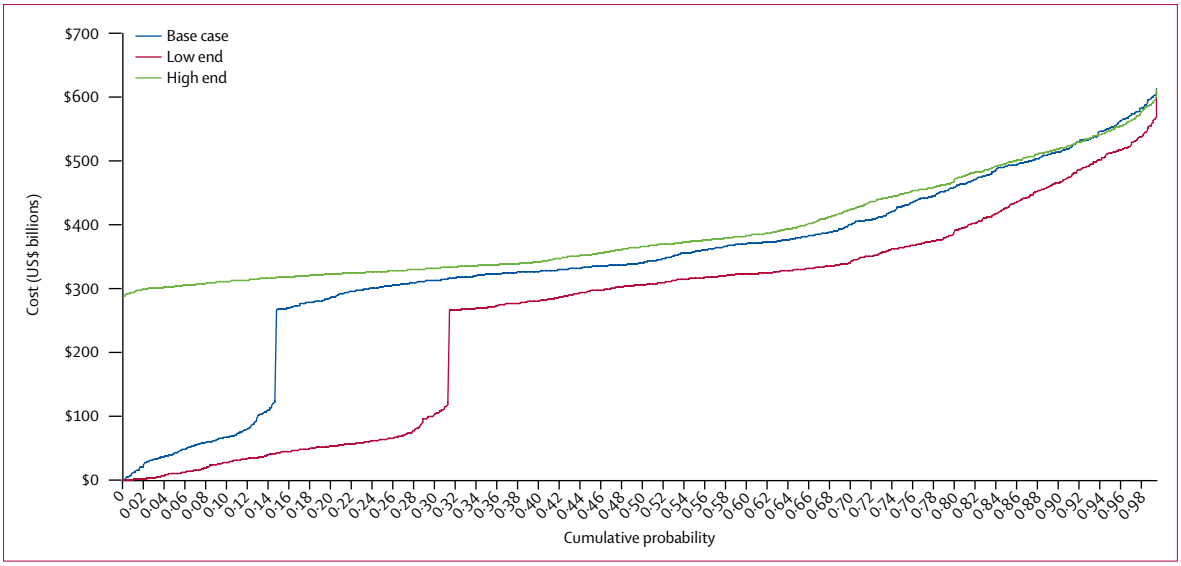

***Figure*: Results of Monte Carlo analyses**
1000 simulations done to generate realistic ranges of aggregate cost estimates across all 15 exposure–outcome relations, while taking into account probability of causation.

Calculations of the health and economic benefits associated with reducing exposure to environmental chemicals have proven extremely informative in regulatory decision making. We used rigorous approaches with proven strengths[6,16] to assess the epidemiological and toxicological literature. We acknowledge that expert opinion is, of course, not a substitute for solid epidemiological evidence about the relations between EDCs and disease or for systematic toxicological documentation on endocrine disruption and the specific mechanistic pathways. However, while the mechanisms are important, they have no bearing on the end results—disease and associated economic costs for society.

The EDCs we assessed represent an extremely small subset (<5%) of all EDCs,[30] but there is a paucity of data (exposure, toxicity, and epidemiological), especially robust data, as was required by our methods. The costs also represent a small subset of diseases that has the strongest evidence for causation for the EDCs assessed. We excluded chemicals no longer used, such as some persistent organic pollutants known to contribute to diabetes and obesity,[31] although we included some chemicals (PBDEs) that are being phased out in the USA to ensure a proper comparison with the European Union. Additionally, although use of some PBDEs is being limited, not all uses have been banned, and it remains to be seen whether remaining potential sources of contamination will need action. We also acknowledge that costs of chronic diseases can change over time, and for some disorders, such as obesity, we did aggregate lifetime cost estimates from annual data. Our approach is not unique and we are aware of this potential limitation. Finally, we only used published, peer-reviewed data on the costs of illnesses and dysfunctions; we could not account for suffering and other intangible costs that might arise from the exposure–response relations we studied. Thus, the costs and numbers of cases we calculated probably underestimate the true values associated with the use of EDCs in the USA, which will accumulate if efforts to prevent these exposures are not implemented.

Differences between the USA and European Union in the regulation of flame-retardant chemicals and the use of these chemicals in furniture and other products were drivers of the much greater exposure to PBDE in the USA than in Europe. We note that our models of disease burden extrapolate from a lesser-brominated form of PBDE, which was banned in the USA and the European Union much earlier than the more highly brominated PBDEs. However, deca-PBDEs are debrominated by ultraviolet rays and microbial and vertebrate organisms,[32] and commercial mixtures that contain only lower-brominated congeners might represent relevant sources of exposure. We anticipate that use of PBDEs in the USA will decrease after the requirement for flame-retardant chemicals in furniture is removed in California, although substantial decreases in exposure might lag due to continued use of treated furniture.

We emphasise that our estimates are based on more nationally representative data than those used to estimate burden of disease and disability in the European Union. Although we endeavoured to select the most representative exposure data for Europe, differences in data sources might have exacerbated the disparity between the USA and European Union in disease burden and costs due to EDCs (table 3). Of note, however, the differences in exposure to organophosphate pesticides and PBDEs between the USA and European Union have

been consistently documented in multiple independent samples, which supports our interpretation of our results. A quantitative comparison was not the main objective of this analysis, though, and would be better addressed in future analyses.

The 1976 Toxic Substances Control Act was updated with the Frank R Lautenberg Chemical Safety for the 21st Century Act in 2016.[33] Although praised as a bipartisan effort, the Act makes no mention of endocrine disruption. Thus, although it provides the US EPA with long overdue authority to intervene and limit production of chemical hazards and protect vulnerable populations, it makes no provision for urgently needed testing programmes. The cost of required testing is likely to be small when weighed against the $340 billion in costs we have identified as being related to exposure to EDCs.

The Act also requires review of at least ten chemicals within 1 year and 25 by the end of 3·5 years by the EPA. However, there are no new funds provided to the EPA to increase the pace of its regulatory reviews. Therefore, even assuming that there would be only 500 potentially hazardous substances among the thousands of chemicals currently in use that lack toxicity testing data, it would take 100 years to review them all. Investments are also needed to improve toxicological testing methods, which at present do not accurately detect synthetic chemical obesogens.[15]

Given the known transgenerational effects of EDCs,[34] continuing not to regulate EDCs adequately could have consequences for subsequent generations of US children. Our findings build upon those made by the Endocrine Society[5] and WHO and UNEP[3] that document the urgent public health threat posed by EDCs. The health and economic stakes involved in implementing the Frank R Lautenberg Chemical Safety for the 21st Century Act are high. For instance, various items in the Act are open to broad interpretation, such as the framework for the screening and classification of chemicals into high-priority and low-priority groups. Classification of chemicals as low priority by the EPA could preclude states from applying their own prohibitions or restrictions (eg, on production, processing, distribution, or use) owing to new pre-emption rules. The unfunded EPA mandate, therefore, raises the possibility that chemicals will not be adequately reviewed for endocrine disruption and will simply be approved for use until observational data from human beings and randomised laboratory studies accumulate.

A further concern relates to the ongoing international trade treaty negotiations between the USA and the European Union. Europe's regulatory framework, described in the Regulation, Evaluation and Authorisation of Chemical Hazards could increase protection from EDCs. How the Transatlantic Trade and Investment Partnership might handle differences in regulation of EDCs in consumer products and foods remains unclear.[35] Implementing the Lautenberg Act and navigating its interaction with this trade agreement is likely to influence future health and economic consequences of EDC exposures.

EDC exposures in the USA are likely to contribute substantially to disease and dysfunction across the human lifespan, with costs being more than 2% of the GDP. Differences in costs of EDCs between the USA and the European Union are likely to arise from regulatory action, which reinforces the need for efforts to screen chemicals for potential toxic effects to endocrine systems and to protect vulnerable populations.

Contributors

TMA and LT conceived and designed the study and did the main analysis and interpretation of the data. TMA was responsible for acquiring the data. RH, SS, PAH, J-PB, JPM, JD, and RTZ made substantial contributions to the study design and analysis of data, interpretation of data, or both, and critically reviewed the report for intellectual content. All authors approved the final version that was submitted for publication.

Declaration of interests

We declare no competing interests.

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