Please note the following before checking your manuscript

Dear Professor Kortenkamp,

Please note:

- Queries may be nested in the addresses section or in the reference list, please look out for these.
- References that could be misread — those that follow numbers, superscripted and subscripted characters, quotation marks and abbreviated units — are set in brackets, on the line (for example, we use 10 (REF. 10) instead of 10^{10}).
- Please check reference numbering carefully, as they may have been renumbered (for example, to avoid duplications).
- When marking up your corrections, please use the Commenting tools only (do not edit the text directly).
- If your article has Supplementary Information but you have not received the file(s) along with this proof, please let us know as soon as possible.
- We do not usually edit Supplementary Information in house, so should you require changes to your SI, please send a revised file and indicate what changes have been made.

ENDOCRINE DISRUPTORS

The burden of endocrine-disrupting chemicals in the USA

Andreas Kortenkamp

Endocrine-disrupting chemicals (EDCs) can contribute to the development of certain disorders and are known to have a high health-care burden in some countries. A new analysis has revealed the substantial impact of EDCs on health and associated costs in the USA.

Refers to Attina, T. M. *et al.* Exposure to endocrine-disrupting chemicals in the USA: a population-based disease burden and cost analysis. *Lancet Diabetes Endocrinol.* http://dx.doi.org/10.1016/S2213-8587(16)30275-3 (2016)

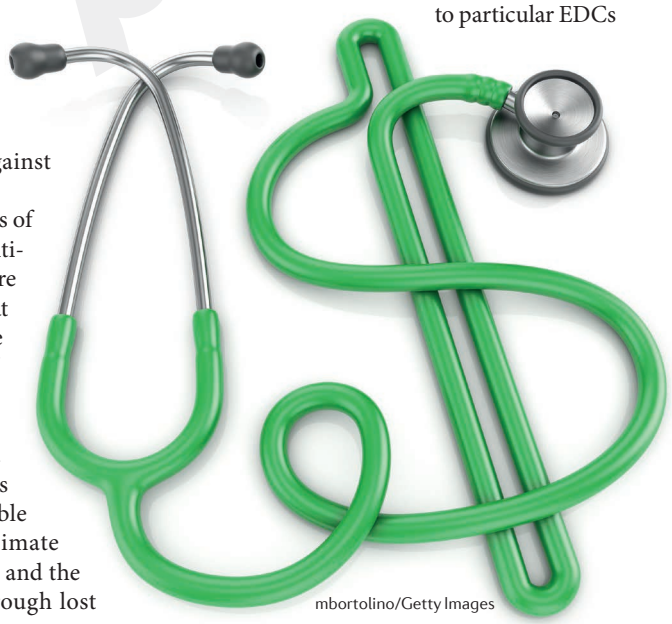
A new study by Attina and co-workers puts the annual health costs, including treatment and lost productivity, from exposure to endocrine-disrupting chemicals (EDCs) in the USA at $340 million, or 2.33% of gross domestic product (GDP)[1]. This figure is substantially higher than the equivalent estimates for the European Union (EU; $217 billion or 1.28% of GDP)[2]. Attina and colleagues attribute this difference to the diverging chemical regulatory regimes in the two regions.

Concern about EDCs derives from the fact that they produce irreversible toxicity by interfering with the programming role of hormones during development. For example, the events necessary for the initiation of male sexual differentiation in fetal life depend on the action of androgens. Androgen insufficiency during a critical time window in pregnancy (towards the end of the first trimester and the beginning of the second trimester [Au:OK?] can lead to an increased risk of non-descending testes, malformations of the penis (such as hypospadias), poor semen quality or testicular cancer[3]. EDCs that antagonise the androgen receptor or suppress fetal androgen synthesis, for example, certain fungicide pesticides or plasticisers such as phthalates, contribute to androgen insufficiency and increase the risk of developing these disorders if exposure occurs during the critical time in pregnancy[3,4]. Similar windows of susceptibility have been identified for thyroid hormone insufficiency (sufficient levels of thyroid hormone are critical for brain development) and certain hormone-related cancers such as breast cancer[4].

For these reasons, the risks from EDCs are regarded as a major global health challenge[4]. Accordingly, EU legislature has placed restrictions on pesticides with endocrine disrupting properties. To minimize exposure via food, planned regulations make provisions to refuse approval for pesticides that contain EDCs, effectively banning them[5]. These plans are vigorously opposed by the chemical industry and the UK government, on the basis of economic costs. UK government institutions have estimated the economic impact of withdrawing certain endocrine disrupting pesticides to be £160–440 million in the UK alone[6]. In the entire EU, this figure could run to several billion Euros, as a result of potential losses in crop yield. Industrial organizations have used such figures to lobby strongly against EDC regulations.

Economic impact analyses of this kind might impress politicians, but systematically ignore the savings in health costs that can arise from the avoidance of ill-health by prevention of exposure to EDCs through improved regulation. The new study by Attina and co-workers has filled this gap[1]. For illnesses attributable to EDC exposure, they estimate the direct costs of treatment and the indirect costs that arise through lost productivity. The lion share (four-fifths) of the total cost stems from the neurotoxicity attributed to polybrominated diphenyl ethers (PBDEs), which are flame retardants used in textiles and soft furnishings. These costings were derived by considering exposure–response relationships for human disorders for 15 EDCs, which provided the basis for estimates of the disease burden attributable to EDC exposure.

The critical element in this analysis is the use of a modified Delphi approach for the assessment of the strength of the exposure–response relationships. Approaches based on the Delphi system have proven strengths and have been used productively in other contexts[2], but cannot substitute for good epidemiological evidence of links between exposure to EDCs and adverse health outcomes. This weakness is a consequence of severe data constraints, as emphasized by Attina and colleagues themselves. For many EDCs, the data necessary for making robust estimates of health burdens are not available. For example, the costings for male reproductive disorders and male infertility in the article were only based on data on certain phthalates, but could not take account of new insights into the role of painkillers in disrupting male sexual differentiation[7]. A wide range of additional EDCs contribute to these disorders, but the epidemiological data needed to attribute the disorders to exposure to particular EDCs



mbortolino/Getty Images

are missing. Such studies are challenging, not least because the aetiological steps occurred during specific windows of susceptibility during fetal development. This limitation complicates the efforts of reconstructing past EDC exposures that might have led to adverse effects, and limits the ability to attribute diseases to certain exposures and to make causal inferences.

> “…these constraints will have led to underestimations of the real health costs”

As highlighted by Attina and colleagues, these constraints will have led to underestimations of the real health costs. Even so, the study gives a devastating impression of the considerable health burden and costs associated with exposure to EDCs. The article also provides a lesson on the influence of regulation on the lasting economic effects of EDCs and other chemicals. For example, restrictions on the use of flame retardant PBDEs in the EU mean generally lower exposures, with correspondingly lower health costs than in the USA, where PBDE use is higher due to fire regulations. The merit of this study is in providing a badly needed corrective to the short-term costings of the economic impact of EDC regulation. The findings give a glimpse of the considerable costs to society of inaction in this important policy area and should stimulate a substantial policy shift towards prevention of EDC exposures.

Unfortunately, prevention of exposure is no longer possible with many of the EDCs considered by Attina and co-workers. The flame retardants that contribute a substantial proportion of the health burden cannot be recovered from our tissues or from the environment through regulatory action. The only option is to deal with the pool of as yet unreleased flame retardants, such as by treating soft furnishing waste with the same caution as electronic waste.

A substantial policy change has to rely on information about the wider range of chemicals that also contribute to endocrine disruption. At present, our knowledge about the EDCs that humans are exposed to is fragmentary. As long as these data gaps persist, decision makers, regulators and public health advisers lack the orientation needed for targeting specific chemicals. At present, it is impossible to give sensible advice to pregnant women about which products to avoid. In any case, the effect of individuals avoiding certain products is rather limited, because the bulk of EDCs are present as contaminants in food, and so individuals are unable to avoid exposure. Improved regulation, not individuals attempting to avoid certain products, is urgently called for. What does it say about a society that places great emphasis on short-term economic costs, but lacks the infrastructure and the data needed for proper quantifications of the externalised costs, analysed so admirably by Attina and colleagues?

Andreas Kortenkamp is at Brunel University London, Institute of Environment, Health and Societies, Kingston Lane, Uxbridge, Middlesex UB8 3PH, UK.

Correspondence to:
andreas.kortenkamp@brunel.ac.uk

doi:10.1038/nrendo.2016.198
Published online DD Mon 2016

1. Attina, T. M. *et al.* Exposure to endocrine-disrupting chemicals in the USA: a population-based disease burden and cost analysis. *Lancet Diabetes Endocrinol.* http://dx.doi.org/10.1016/S2213-8587(16)30275-3 (2016).
2. Trasande, L. *et al.* Estimating burden and disease costs of exposure to endocrine disrupting chemicals in the European Union. *J. Clin. Endocrinol. Metab.* **100**, 1245–1255 (2015).
3. Skakkebaek, N. E. *et al.* Male reproductive disorders and fertility trends: influences of environment and genetic susceptibility. *Physiol. Rev.* **96**, 55–97 (2016).
4. Bergman, A., Heindel, J. J., Jobling, S., Kidd, K. A. & Zoeller, R. T. (eds). *State of the Science of Endocrine Disrupting Chemicals — 2012* (WHO-UNEP, 2013).
5. Slama, R. *et al.* Scientific issues relevant to setting regulatory criteria to identify endocrine-disrupting substances in the European Union. *Environ. Health Perspect.* **124**, 1497–1503 (2016).
6. Jones, G., Garthwaite, D., Wynne, S. & Twining, G. Agronomic and economic impact assessment for possible human health and ecotoxicology criteria for endocrine disrupting chemicals. Report to Chemicals Regulation Directorate. *FERA* randd.defra.gov.uk/Document.aspx?Document = 11346_PS2818finalreportfull.pdf (2013).
7. Kristensen, D. *et al.* Analgesics use — prevalence, biomonitoring and endocrine and reproductive effects. *Nat. Rev. Endocrinol.* **12**, 381–393 (2016).

Competing interests statement
The author declares no competing interests.

Author biography
Andreas Kortenkamp is Professor for human toxicology. He is actively engaged in endocrine-disrupting chemical (EDC) research, particularly of the effects of combinations of EDCs. His research interests are in establishing the mechanisms that are involved in combination effects of EDCs, and in finding ways of improving chemicals regulation to take account of mixture effects in risk assessment.

Competing interests statement
The author declares no competing interests.

Subject ontology terms
Health sciences / Risk factors
[URI /692/499]
Health sciences / Health care / Public health
[URI /692/700/478]
Health sciences / Health care / Health care economics
[URI /692/700/3934]