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Socio-economic assessment of phthalates

by Mike Holland, EMRC

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Authorised for publication by Anthony Cox, Acting Director, Environment Directorate.

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Foreword

This paper on *Socio-Economic assessment of phthalates* was prepared for the SACAME workshop in Ottawa, Canada of 30-31 August 2017, by Mike Holland, EMRC.

The workshop was organised in co-operation between the OECD Joint Meeting of the Chemicals Committee and the Working Party on Chemicals, Pesticides and Biotechnology (Joint Meeting) and Working Party on Integrating Environmental and Economic Policies (WPIEEP), and was hosted by Health Canada, with funding from the European Commission.

The paper was revised and takes into account feedback received from Delegates during and after the workshop and comments received from the Joint Meeting and WPIEEP by written procedure. The author would like to thank Nils Axel Braathen and Eeva Leinala of the OECD Secretariat for comments on previous versions of the paper. Work on this paper was conducted under the overall responsibility of Nathalie Girouard, Head of the Environmental Performance and Information Division. The indispensable support of Elvira Berrueta Imaz, Natasha Cline-Thomas and Stéphanie Simonin-Edwards in co-ordinating the editing and publication process is gratefully acknowledged.

The opinions expressed and the arguments employed are those of the author.

Abstract

This paper gives an overview of economic assessments of the benefits of the control of exposure to phthalates, a group of chemicals with numerous uses, most importantly, as a plasticiser to make rigid plastics like PVC flexible. There is significant concern that these substances can act as endocrine disrupting chemicals (EDCs), affecting both human health and ecosystems. Most of the studies considered here have taken an impact-pathway approach (IPA) to quantification of the impacts of phthalates, moving from exposure to impact assessment and then valuation. The health impacts linked to exposure to phthalates affect the reproductive system, neurodevelopment, cancer incidence, obesity, diabetes, asthma and allergy. However, the strength of association is variable, and most quantification work is focused on male reproduction.

Some similarities regarding the monetary values derived in the studies result from the use of the same source for valuation. There is also some significant variation, arising i.a. from different definitions of impacts, variation in the timeframe considered and differences in the extent to which the different elements of value are covered. However, all of the studies conclude that the costs of effects are likely to be substantial.

JEL codes: Q510, Q530, Q580

Keywords: Phthalates, health effects, valuation, chemical pollution, endocrine disrupting chemicals, socio-economic assessment

Résumé

Ce document propose un tour d'horizon des évaluations économiques des avantages procurés par la lutte contre l'exposition aux phtalates, groupe chimique faisant l'objet de nombreux usages et employé notamment comme plastifiant pour rendre souples certains plastiques rigides comme le PVC. Le fait que ces substances puissent agir comme des perturbateurs endocriniens affectant à la fois la santé humaine et les écosystèmes suscite de vives préoccupations. La plupart des études considérées ici ont choisi une approche centrée sur les chemins d'impact (IPA) pour quantifier les effets des phtalates, allant de l'évaluation de l'exposition à celle des impacts puis à une évaluation économique. Les effets sur la santé associés à l'exposition aux phtalates concernent le système reproducteur, le développement neurologique, l'incidence du cancer, l'obésité, le diabète, l'asthme et les allergies. Cependant, l'association causale est variable et la plupart des travaux de quantification se concentrent sur le système reproducteur masculin.

Certaines concordances entre les valeurs monétaires obtenues dans différentes études s'expliquent par le recours aux mêmes sources pour calculer ces valeurs. On constate aussi des divergences importantes, qui s'expliquent entre autres par les différences de définition des impacts, la variation des périodes considérées et le degré de prise en compte des différents éléments composant la valeur. Cela étant, toutes les études parviennent à la conclusion que les effets induisent vraisemblablement des coûts substantiels.

Codes JEL : Q510, Q530, Q580

Mots-clés : Phtalates, effets sur la santé, valorisation, pollution chimique, perturbateurs endocriniens, évaluation socio-économique

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Abbreviations and acronyms

ADHD	Attention Deficit Hyperactivity Disorder
AF	Attributable Fraction
AGD	Anogenital distance
ART	Assisted Reproduction Technology
BBP	Butyl benzyl phthalate
BCP	Butyl cyclohexyl phthalate
BDP	Butyl decyl phthalate
BPA	Bisphenol A
CHD	Coronary Heart Disease
DALY	Disability Adjusted Life Year
DDT	Dichlorodiphenyltrichloroethane
DAP	Diallyl phthalate
DBP	Di-n-butyl phthalate
DCP	Dicyclohexyl phthalate
DEHP	Di(2-ethylhexyl) phthalate
DEP	Diethyl phthalate
DNHP	Di-n-hexyl phthalate
DIBP	Diisobutyl phthalate
DIDP	Diisodecyl phthalate
DIHP	Diisohexyl phthalate
DIHpP	Diisoheptyl phthalate
DINP	Diisononyl phthalate
DIOP	Diisooctyl phthalate
DITP	Diisotridecyl phthalate
DIUP	Diisoundecyl phthalate
DMP	Dimethyl phthalate
DNEL	Derived no-effect level
DNOP	Di(n-octyl) phthalate
DNP	Di-n-pentyl phthalate
DPHP	Di(2-propylheptyl) phthalate
DPP	Di-n-propyl phthalate
DTDP	Ditridecyl phthalate
DUP	Diundecyl phthalate
ECHA	European Chemicals Agency
EDC	Endocrine Disrupting Chemical
EU	European Union
GRADE	Grading of Recommendations Assessment, Development and Evaluation
IPA	Impact Pathway Approach
IPCC	Intergovernmental Panel on Climate Change
N(L)OAEL	No (or Lowest) Observed Adverse Effect Level

ODP	n-Octyl n-decyl phthalate
OECD	Organisation for Economic Co-operation and Development
PBDE	Polybrominated diphenyl ether
PEC	Predicted Environmental Concentration
PNEC	Predicted No-effect Concentration
REACH	The EU Regulation on Registration, Evaluation, Authorisation and Restriction of Chemicals
RCR	Risk Characterisation Ratio
TDS	Testicular dysgenesis syndrome
US EPA	United States Environmental Protection Agency
VOLY	Value of a Life Year
VSL	Value of a Statistical Life
WHO	World Health Organization
WTP	Willingness-to-pay

Executive summary

The objective of the project overall is to support the socio-economic analysis (SEA) of chemicals by improving quantification and monetisation of morbidity and environmental impacts. The present paper reviews studies that have performed SEA on phthalates, a group of chemicals with numerous uses, most importantly, as a plasticiser to make rigid plastics like PVC flexible. There is significant concern that these widely used substances can act as endocrine disrupting chemicals (EDCs), affecting both human health and ecosystems.

Over the last five years, there has been significant growth in the estimation of the economic impacts of EDCs. The analysis that has been carried out to date demonstrates that the health costs of these chemicals in both the United States and Europe is substantial, running into the billions of euro each year. This paper has considered 12 studies, all published since 2014. Several concern the burden of exposure to EDCs generally, a few are more specific to phthalates. Limitation to the phthalate studies, in line with the original remit of the paper, would have restricted its scope and prevented consideration of several relevant reports.

Most of the studies considered here have taken an impact-pathway approach (IPA) to quantification of the impacts of phthalates, moving from exposure to impact assessment and then valuation. Most address the question of simply how large the impacts are or may be, though work by the European Chemicals Agency (ECHA) considers the case for restricting use of four common phthalates.

Many health impacts have been identified as linked to exposure to phthalates. These affect the reproductive system, neurodevelopment, cancer incidence, obesity, diabetes, asthma and allergy. However, the strength of association is variable, and most quantification work is focused on male reproduction. Several environmental impacts have also been noted, particularly for aquatic ecosystems. However, quantification of these effects, beyond assessment of the presence or absence of risk, is lacking.

It is concluded that the key uncertainties affecting the analysis lie in the impact assessment stage with respect to:

- identification of impacts relevant to specific substance under investigation
- characterisation of concentration-, exposure- or dose-response relationships
- limitation of impact assessment to sub-groups of the population, when others may also be affected
- within that, identification of any toxicological thresholds for analysis
- specification of impacts of individual phthalates.

Progress has been made on monetisation of impacts, but problems remain, particularly:

- Most studies have accounted well for health care costs and lost productivity, but not lost utility. Those that have considered lost utility tend to adopt a standard

value per QALY or DALY from the health economics literature that is not based on willingness-to pay-or to accept.

- Understanding the long-term consequences of disease, ensuring that account is taken of co-morbidities as necessary.

There is some variation in the monetary values derived in the studies that have been reviewed. Some similarities naturally come from studies using the same source for valuation. However, there is also some significant variation, arising for several reasons including different definitions of impacts, variation in the timeframe considered (annual vs. lifetime) and differences in the extent to which the different elements of value are covered. However, all of the studies conclude that the costs of effects are likely to be substantial.

It is not possible to reach a conclusion on the differences in the costs of impacts attributable to different phthalates from the results provided in the papers reviewed here, though the methods used by ECHA could be adapted for this purpose.

The use of economic assessment provides a valuable tool for assessing the desirability of further regulation of chemicals from a societal perspective, enabling the costs and benefits of action to be compared. This should lead to a more rational allocation of resource for controlling hazardous substances.

Synthèse

Ce projet a pour objectif général de faciliter l'analyse socioéconomique (ASE) des produits chimiques en améliorant la quantification et la valorisation monétaire des impacts sur la morbidité et sur l'environnement. Le présent rapport passe en revue les études qui contiennent une ASE des phtalates, un groupe de produits chimiques à usages multiples, utilisés notamment comme plastifiant pour rendre souples certains plastiques rigides comme le PVC. Le fait que ces substances, très largement utilisées, puissent agir comme des perturbateurs endocriniens (EDC) affectant à la fois la santé humaine et les écosystèmes, suscite de vives préoccupations.

Au cours des cinq dernières années, les estimations des effets économiques des EDC indiquent des valeurs en forte augmentation. Les analyses réalisées à ce jour montrent que le coût sanitaire de ces substances chimiques, tant aux États-Unis qu'en Europe, est considérable puisqu'il se chiffre en milliards d'euro chaque année. Le présent rapport a examiné 12 études, toutes publiées depuis 2014. Plusieurs concernent le coût de l'exposition aux EDC en général et quelques-unes portent plus spécifiquement sur les phtalates. Si l'on s'était limité aux travaux sur les phtalates, comme le prévoyait le projet initial, le champ d'étude aurait été limité et plusieurs autres rapports pertinents n'auraient pas pu être pris en considération.

La plupart des études considérées ici ont choisi une approche centrée sur les chemins d'impact (IPA) pour quantifier les effets des phtalates, allant de l'évaluation de l'exposition à celle des impacts puis à une évaluation économique. La plupart cherchent uniquement à déterminer si les impacts sont, ou pourraient être, importants même si des travaux menés par l'Agence européenne des produits chimiques (ECHA) étudient la possibilité de restreindre l'utilisation de quatre phtalates courants.

De nombreux effets sur la santé ont été identifiés comme étant liés à l'exposition aux phtalates. Ces effets concernent le système reproducteur, le développement neurologique, l'incidence du cancer, l'obésité, le diabète, l'asthme et les allergies. Cependant, l'association causale est variable et la plupart des travaux de quantification visent le système reproducteur masculin. Plusieurs impacts environnementaux ont également été relevés, en particulier sur les écosystèmes aquatiques. Toutefois, la quantification de ces effets, au-delà de l'évaluation de la présence ou de l'absence de risque, fait défaut.

Il apparaît que les principales incertitudes qui pèsent sur l'analyse interviennent au niveau de l'évaluation d'impact et concernent :

- L'identification des effets spécifiques de la substance étudiée
- La caractérisation des relations concentration- exposition- ou dose-effet
- Le champ couvert par l'évaluation d'impact, qui se limite à certains sous-groupes de la population alors que d'autres peuvent aussi être affectés
- Dans ce cadre, l'identification de seuils toxicologiques pour l'analyse

- La spécification des effets propres à chaque phtalate.

La valorisation monétaire des impacts a fait des progrès, mais des problèmes persistent, en particulier :

- La plupart des études ont bien pris en compte les coûts des soins de santé et la perte de productivité, mais pas la perte d'utilité. Celles qui ont considéré la perte d'utilité adoptent généralement une valeur standard par AVCQ ou AVCI, tirée des travaux d'économie de la santé, qui n'est pas basée sur le consentement à payer ou à accepter.
- Il importe de comprendre les conséquences à long terme de la maladie et d'assurer qu'il est tenu compte de la comorbidité.

Il existe des concordances et des divergences entre les valeurs monétaires obtenues dans les études considérées. Il y a naturellement concordance lorsque les évaluations utilisent les mêmes sources. On note cependant aussi des divergences importantes qui s'expliquent par diverses raisons, notamment les différentes définitions des impacts, la variation des périodes considérées (année/toute une vie) et le degré de prise en compte des différents éléments inclus dans la valeur. Cependant, toutes les études concluent que les coûts des effets risquent d'être considérables.

Il n'est pas possible de tirer de conclusion sur les différences de coûts des impacts attribuables aux différents phtalates d'après les résultats présentés dans les travaux examinés ici, mais les méthodes utilisées par l'ECHA pourraient être adaptées à cette fin.

L'évaluation économique offre un outil précieux pour déterminer s'il est souhaitable de pousser la réglementation des produits chimiques dans une perspective sociétale, en comparant les coûts et les avantages de l'action. Le recours à cet outil devrait permettre d'allouer plus rationnellement les ressources pour contrôler les substances dangereuses.

1. Introduction

The OECD is carrying out a project, SACAME,[1] funded by the European Commission, to support the socio-economic analysis of chemicals by allowing a better quantification and monetisation of morbidity and environmental impacts. The study has earlier generated a series of background papers for a workshop held in Helsinki in July 2016, based largely around the methods for quantification and monetisation of impacts.

The work is continuing with an assessment of valuations that have been carried out on the following substances:

- phthalates (the subject of this paper)
- mercury
- PFOA (perfluoro-octanic acid) and its salts
- 2-NMP (1-methyl-2-pyrroloidine)
- formaldehyde.

These were discussed at a second workshop held in Ottawa, Canada, in August 2017.

Phthalates were chosen for the assessment as they are currently the subject of regulatory activity in a number of countries, due to concerns about the volume in which they are produced and their association with a number of health and environmental impacts. This provides a growing literature on which to base the assessment of valuations performed to support risk management decision-making, including the documentation around restriction proposals and applications for authorisation made under the EU's REACH Regulation.[2]

Key questions addressed in this paper concern:

- the range of effects that have been identified for phthalates
- the extent to which these effects have been quantified
- the extent to which these effects have been monetised
- differences in approach between studies
- confidence in estimates of impact quantification and in valuation
- robustness in the conclusions of socio-economic analysis (SEA) when applied in policy assessment
- how the SEAs considered could be improved.

[1] Socio-economic Analysis of Chemicals by Allowing a better quantification and monetisation of Morbidity and Environmental impacts. http://oe.cd/sacame.

[2] Registration, Evaluation, Authorisation and restriction of Chemicals. For further information on REACH, see https://echa.europa.eu/.

2. Phthalates

2.1. Chemistry

Phthalates are esters of phthalic acid, made by reacting phthalic anhydride with alcohols from methanol and ethanol to tridecyl (C13) alcohol. This chemistry leads to a large number of different phthalates with varying properties. A list of the most common phthalates is provided in Annex 1. There is a trend in the market towards the higher molecular weight phthalates shown in the Appendix, as these are less mobile and hence less likely to disperse out of products and into the environment. In addition, they have a reduced hazard profile in comparison to medium-chain phthalates (carbon backbone length 3 to 7) which have been the focus of regulatory activities. The strongest evidence for risk is for the phthalates which have been in most common use, and which also belong to the subset of phthalates with a higher hazard profile, such as Di(2-)ethylhexyl phthalate (DEHP).

2.2. Usage

The main use of phthalates is as a plasticiser, with flexible PVC accounting for over 80% of world plasticiser consumption. Phthalates were first introduced in the 1920s. Production increased significantly with the introduction of PVC in the 1930s. Unplasticised PVC (uPVC, commonly used in buildings for windows and doors) is a rigid material: the addition of the plasticiser makes the PVC flexible and usable in many other applications including medical equipment (US EPA, 2012[1]). Phthalates can contribute as much as 50% of the weight of PVC materials. Other uses include applications as diverse as viscosity control agents, solvents, glues and personal care products.

The biggest market for phthalates globally is the People's Republic of China, accounting for around 45% of all use. Europe and the United States together account for around 25% of use, with the remainder widely spread around the world (IHS Markit, 2015[2]). The phthalate plasticiser market currently stands at around 5.5 million tonnes per year.

The widespread use of phthalates is explained both by their relatively low price and by the various properties that they confer, particularly on plastic products. The American Chemistry Council (an industry body) cites numerous technical benefits of using phthalates, including:

- They can cope with changing weather conditions, maintaining flexibility in cold conditions and resisting degradation in high temperatures, making them technically suitable for a variety of outdoor applications.
- They are durable, heat resistant and have good electrical resistivity, leading to extensive use for sheathing electrical wires and cables.
- Flexible PVC is easy to keep clean, leading to extensive use for flooring.
- Phthalates are colourless and hence do not affect the aesthetic appearance of PVC or interact with other colourants.
- Some, such as BBP, are stain resistant, making them suitable for use in flooring applications.

However, alternatives are available both to phthalates as plasticisers (Lowell Center, 2011[3]) and to the plastics themselves, though there are concerns about some of these

substances also. Concern over the effects of phthalates has led to significant growth in the non-phthalate plasticiser market in recent years. In 2005 phthalates accounted for 88% of the plasticiser market, a figure that had fallen to 70% by 2014 and is forecast to fall further in the coming years (IHS Markit, 2015[2]). FDA (2010[4]) carried out a series of surveys of phthalate use in cosmetics, finding a 'considerable' decrease in use from 2004 to 2010. To illustrate, from the 2010 survey they concluded that DEP was the only phthalate at the time still commonly used in cosmetics. Use of DBP and DMP in cosmetics has largely ceased. Differences in use between phthalates reflect variation in hazard profiles, the properties that they confer on products and the technical and economic availability of alternatives.

2.3. Health and environmental concerns

Concern over phthalates relates to their potential as endocrine disrupting chemicals (EDCs) and associated adverse effects on health and the environment. Endocrine disruption has been defined by the Endocrine Society as the capacity to affect any hormonal function. The US EPA takes a narrower definition, restricted to impacts on the oestrogen, androgen and thyroid systems.

WHO/UNEP (2012[5]) listed three main strands of evidence that had raised concern over EDCs, generally, over the last two decades:

- the high incidence and increasing trends of many endocrine-related disorders in humans
- observations of endocrine-related effects in wildlife populations
- the identification of chemicals with endocrine disrupting properties linked to disease outcomes in laboratory studies.

The WHO/UNEP (2012[5]) report concludes that endocrine-related diseases and disorders are becoming more common, or have in the past, with rates stabilising at an undesirably high level. These include:

- low semen quality
- genital malformation, particularly in baby boys
- premature birth and low birth weight
- neurobehavioural disorders such as autism and ADHD
- endocrine-related cancers (breast, endometrial, ovarian, prostate, testicular and thyroid)
- earlier onset of breast development in girls, a risk factor for breast cancer
- obesity
- Type 2 diabetes.

Several factors could be linked to these trends. However, the rate of change means that genetic factors are not a leading factor. Chemical exposures have come under particular scrutiny, drawing on laboratory and other evidence. Olsson et al. (2014[6]) notes that the evidence of a link between exposure to EDCs and effect is not equally strong in all cases. For that reason, their analysis focused on male reproductive health (cryptorchidism, hypospadias, poor semen quality and testicular germ cell cancer) alone. Other authors have also limited the scope of their analysis to the effects that they consider can be quantified with the greatest confidence.

ECHA (2016[7]) and (2017[8]) document various studies that highlight the potential for phthalates, specifically (as opposed to EDCs more generally) to impact human health.

2.4. Linking impacts to specific substances

Evidence of impact is provided by several types of information:

- toxicological research identifying plausible mechanisms for impact
- animal studies that show impacts of various substances (typically on rodents) of a similar nature to impacts that are increasing in prevalence in the human population
- epidemiological studies that show elevated prevalence of symptoms that have been linked to EDC substances
- observations suggesting that the same effects that are of concern for the human population are also present in wildlife.

There are several mechanisms through which chemicals may affect the endocrine system,[3] for example through

- binding to endocrine receptors and adding to the normal hormonal signal
- binding to the receptor and blocking the normal hormonal signal
- affecting hormone synthesis and hence increasing or decreasing the amount of natural hormone that is available for signalling
- altering hormone metabolism or hormone transport and storage within bodily tissue (again, increasing or decreasing hormone amount)
- affecting the levels of mature hormone receptors.

Regulatory impact assessments tend to be carried out on a substance by substance basis.[4] The substance by substance approach should be recognised as a simplification, as one mechanism may be affected by more than one substance, and a substance may operate through a number of mechanisms. Therefore, levels of other substances following the same pathway or targeting the same receptor may also be relevant to the impact assessment. Relationships between these different substances may be complex, rather than simply additive, leading to non-linearities in response. These factors create uncertainty in the attributable fraction of impact to a particular substance and hence to the outcome of assessment.

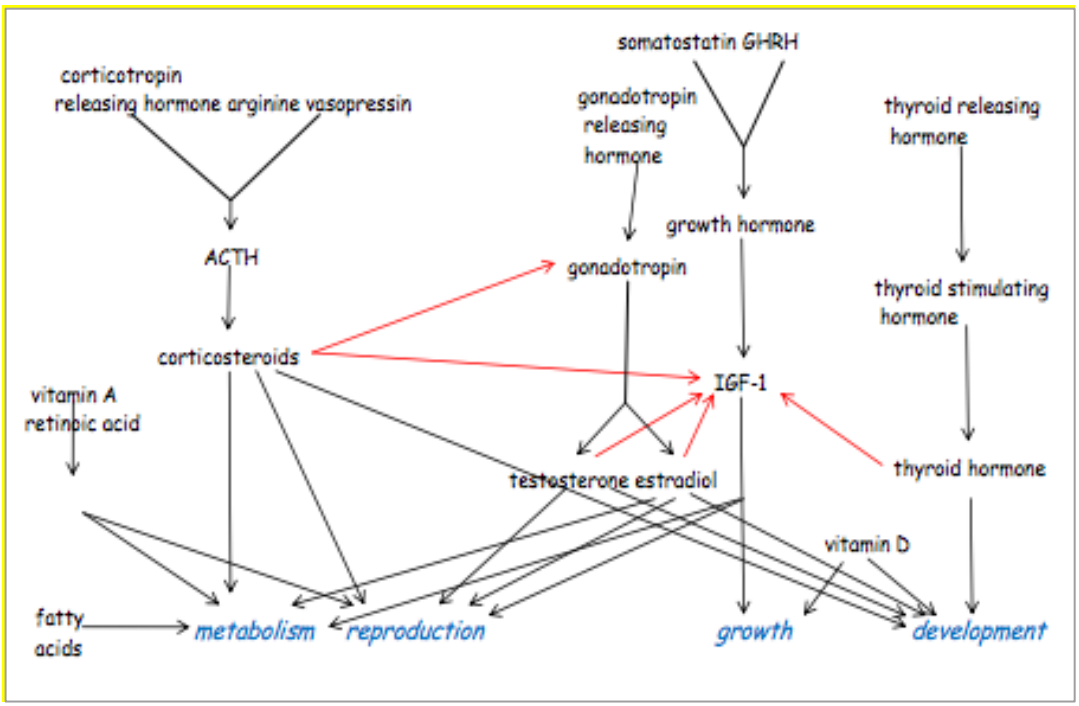
Yang et al. (2015[9]) consider the molecular pathways involved. For the phthalate DEHP they found evidence of 21 molecular pathways that change significantly due to exposure in the testis. For the purposes of illustration, Figure 2.1, from OECD (2012[10]), provides examples of various pathways that can be affected by EDCs, illustrating the complexity of the mechanisms by which EDCs operate.

[3] www.tipedinfo.com/tiped_tier/what-is-endocrine-disruption/.

[4] ECHA (2016[7]) provides an exception, in considering the effects of four phthalates in a single restriction dossier.

Figure 2.1. Examples of hormonal pathways that can be affected by endocrine disruption

Hormonal pathways that can be affected by endocrine disruption, resulting in symptoms of metabolic syndrome and disruptions in reproduction, growth and development.



Source: OECD (2012[10]).

Despite a substantial amount of further knowledge, characterisation of EDC impacts is not straightforward as there are several factors that complicate the identification and assessment of human health impacts relating to (for the purposes of this paper) phthalate exposure:

- Many substances in widespread use have been identified as proven or potential endocrine disruptors. The population is exposed to many of these at the same time.
- EDCs are not the only risk factor associated with the effects that have been linked to EDCs. Other factors identified by Olsson et al. (2014[6]) include:
  - diet
  - body mass index and waist circumference
  - obesity
  - smoking
  - sedentary life styles
  - alcohol consumption
- Experimental work on animals (typically rats and mice) needs to be extrapolated to human subjects.
- Some effects, such as on male fertility, take many years after exposure starts to become evident.

- There is a tendency for the literature to focus on specific substances. ECHA (2017[8]), for example, notes that the literature on DIBP is sparse compared to that for DEHP and DBP.[5]
- There is a failure in some experimental work to consider relevant exposure levels (e.g. for DIBP).
- For some observed effects, such as decreased anogenital distance or nipple retention in boys, consequences are unknown. It is possible that there is no significance in the impact. However, evolutionary theory suggests an underlying logic for the norm.
- Exposure to phthalates is almost universal in the population, given their widespread use and so there is no unexposed control population available for study.

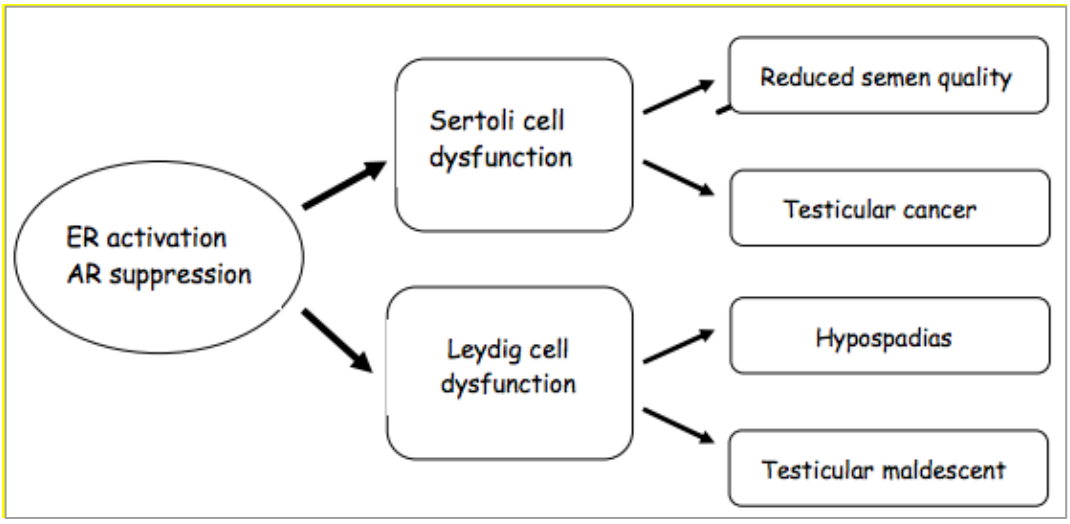
As will become clear, there is thus a tendency in the literature to focus on a sub-set of substances and impacts, for which it is considered that evidence is most robust and hence that estimates of impact will be most reliable.

2.5. Effects linked to phthalates, specifically

The best characterised impacts of phthalates are those that affect male development. Figure 2.2 illustrates the "'cascade" of events leading to testicular dysgenesis syndrome (taken from OECD (2012[10])).

Figure 2.2. Proposed cascade of events leading to testicular dysgenesis syndrome

ER – oestrogen receptor; AR – androgen receptor



Source: Source: OECD (2012[10]).

ECHA (2016[7]) produced a dossier proposing a restriction under the EU's REACH Regulation on four phthalates with anti-androgenic properties as these were considered

[5] The same can be said of impact work on other substance groups. For example, in the field of air pollution there has been a disproportionate amount of effort devoted to epidemiological studies of fine particles relative to other common air pollutants.

the effects for which the most robust data were available for risk assessment. The dossier also briefly discusses evidence on other effects:

- Immunotoxicity: Some phthalates have been found to have adjutant properties in studies on rodents, not causing sensitisation but increasing the allergic response.
- Obesity: Obesogenic effects of phthalates have been considered, leading to mechanistic understanding, with exposure during the foetal period considered critical. However, the role of prenatal exposure to phthalates on obesity in the population remains unclear (Kim and Park, 2014[11]).
- Neurodevelopment: Reviews by Braun et al. (2013[12]) and Miodovnik et al. (2014[13]) highlight impacts on neurodevelopment and behavioural disorders including autism, ADHD, learning disabilities and altered play behaviour. Animal studies are suggestive that some, though not all, behavioural effects may be linked to sex differentiation.
- Carcinogenicity: The conclusions of animal studies on links between phthalates and cancer are variable. IARC (the International Agency for Research on Cancer) has classified DEHP in Category 2B (possibly carcinogenic to humans). Of the four phthalates considered by ECHA, no carcinogenicity studies were found for DBP and DIBP.
- Repeated dose toxicity, the potential for impacts from lower doses repeated regularly, than those required to induce “acute” toxicity from a single dose: There is some evidence for repeated dose toxicity in experimental animals for reproductive organs, the liver and kidneys. However, findings are variable both between phthalates, and between studies.

3. Review of the principal valuation studies

This chapter describes the principal valuation studies identified in this review. The studies are all recent, the oldest dating from 2014. This reflects the emerging nature of the science of the impacts that are relevant to phthalates, and a growing appreciation of the usefulness of valuing impacts for setting policy priorities for chemicals and making a well-structured case for further action if appropriate. Papers are described in date order, dealing with the oldest first, in order that trends in the science, should they be present, might be identified.

Several papers considered here do not deal with phthalates specifically. An example is the first paper by Trasande (2014[14]) which investigates impacts associated with exposure to bisphenol A (BPA). Whilst BPA is not a phthalate (and hence not truly within the scope of this paper), the Trasande paper is notable as a fore-runner of several of the papers that follow (particularly those described in Sections 3.2 and 3.4). Limitation to work specific to phthalates would have had two disadvantages:

1. It would have restricted the scope of the literature reviewed.
2. It may have obscured the inter-relationships between the impacts of substances.

The following issues are important here for those studies that are not directly related to phthalates:

- the methods used for assessment of impacts of a similar nature to those of concern from phthalate exposure
- the unit values adopted for quantification of specific types of impact
- the approaches taken to dealing with the uncertainties that affect the analysis.

3.1. Trasande, 2014

Trasande (2014[14]) describes the "potential" social costs of childhood obesity and adult coronary heart disease (CHD) attributable to exposure to BPA in the United States in 2008, and the benefits of withdrawing it from food use. The cautious use of language is notable, with a common theme in the studies considered here being recognition of the uncertainties involved in assessment.

Trasande describes the research that has linked BPA with a variety of conditions:

- adverse neurobehavioral development
- cancer
- asthma
- reduced fertility outcomes
- obesity
- cardiovascular disease.

In doing so, the paper recognises that these effects are multifactorial, and not solely, or necessarily mainly, a function of BPA exposure. Trasande refers to methods

recommended by the Institute of Medicine (1981[15]) for quantifying environmentally attributable costs for multifactorial conditions, and follows this guidance in determination of the attributable fraction (AF) of disease linked to BPA. Details of the analysis are provided in the online appendix to the paper. Analysis was restricted to assessment of childhood obesity (and its consequences for the adult population), and to CHD in those aged 40-74, as these were the effects of BPA for which evidence was considered most robust. The author notes that newly incident CHD develops across a broad range of ages in adulthood, but restricted the analysis to the age group considered in the large prospective study by Melzer et al. (2012[16]) that was used to estimate the disease burden. For childhood obesity, the author selected the cohort of 12-year-old children as the population at risk "because by that age, obesity is a condition that is difficult to reverse, with resultant cardiovascular and other consequences in adulthood independent of later life BPA and other environmental exposures."

Exposure assessment drew on the results of NHANES (2003-08 National Health and Nutrition Survey) for which data on urinary BPA levels, used as the measure of exposure, were available for both adults and children. A function derived from the Melzer et al. study was then used to quantify the incidence of CHD linked to BPA (odds ratio of 1.11 per 4.56 ng per mL). Obesity was modelled using the increment in body mass index (BMI) Z-score per unit change in urinary BPA, which was combined with data on the population BMI. Consideration was then given to persistence of obesity from 12-year-old children into adulthood.

The cost analysis for CHD used lifetime cost estimates from the American Heart Association cardiovascular disease forecast of 2008 of USD 44 177 per case (2008 price). For costs of obesity (but it appears, not CHD), account is taken of impacts on health utility through quantifying QALY losses, and valuing each QALY at USD 50 000. For future costs, a discount rate of 3% is applied.[6] The source papers indicate a detailed breakdown of medical costs, but this is not taken through to the Trasande paper in full, though aggregate unit values can be calculated as follows (2008 prices):

- healthcare cost per case of coronary heart disease: USD 44 200
- healthcare cost per case of child obesity: USD 2 200
- healthcare cost of adult obesity: USD 51 900
- QALY cost linked to: USD 50 000 per QALY (average USD 17 800 after discounting at 3%).

Several conservative assumptions were made in the analysis, including:

- restriction of analysis to a limited set of possible health impacts
- restriction of analysis to age groups to those for which results were available in the epidemiological literature
- assumption of no effect in the groups exposed to lower levels of BPA.

The origin of the QALY valuation of USD 50 000 is not well-defined in the literature, though it appears to have originated from consideration of end-stage renal dialysis in the late 1980s and early 1990s. Grosse (2008[17]) regards it as an arbitrary threshold used in health decision-making and calls for estimates of WTP and the opportunity costs of healthcare resources to be developed instead. As such, it factors in disutility, but it is

[6] There is further sensitivity analysis around the QALY value (USD 20 000 to 200 000) and discount rate (0-5%).

questionable whether the values underestimate or overestimate these costs in the absence of valuations specifically of obesity: they are set at a level that is considered appropriate to the distribution of healthcare budget, rather than to a level commensurate with public preferences. The QALY valuation is not applied to CHD, for which only healthcare costs are considered.

The results are summarised in Table 3.1.

Table 3.1. Estimated annual impacts of BPA exposure in the United States in 2008

2008 USD

Burden of disease calculation	
Cases of childhood obesity	12 404
Associated healthcare costs	USD 28 million
Cases of adult obesity	9 427
Associated healthcare costs	USD 489 million
Associated loss of QALYs	54 677
Costs of lost QALYs	USD 972 million
Total costs of obesity linked to BPA	USD 1.49 billion
Cases of newly incident adult coronary heart disease	33 863
Associated costs	USD 1.50 billion
Costs associated with CHD and obesity combined	USD 2.98 billion
Range	USD 889 million to USD 14.6 billion
Calculation of benefit of removing BPA from food use	
Reduced cases of childhood obesity (including subsequent increase in adult obesity	6 236
Associated benefits	USD 748 million
Reduced cases of adult coronary heart disease	22 350
Associated benefits	USD 987 million
Total benefits	USD 1.74 billion per year
Range	USD 889 million to USD 13.8 billion

Source: Trasande (2014[14]).

Whilst not addressing phthalates, Trasande (2014[14]) demonstrates the potential for quantifying impacts of an EDC on obesity and coronary heart disease, and of valuing healthcare costs and QALYs. Uncertainties in the methods for determination of the attributable fraction of disease must be recognised.

Given the lack of information available on the derivation of the QALY value of USD 50 000, it is unknown whether it implicitly seeks to account for impacts on both productivity and utility. The figure of USD 50 000 is not greatly different to some estimates of the value of a life year (e.g. the EUR 40 000 estimated for the European Union by Desaigues et al. (2011[18])). Given differences in approach, this agreement should be considered coincidental: had the original analysis of the QALY value selected a different health endpoint than end-stage renal dialysis, the value adopted may have been very different as it is evaluated against health care cost rather than willingness-to-pay.

3.2. HEAL, 2014

The HEAL (2014[19]) report was funded by the Health and Environmental Alliance, an NGO based in Brussels. The report consists of a technical report by the academics who

undertook the research,[7] and a front-end written by HEAL, summarising the findings of the study. The analysis provides a cost calculation for a list of diseases linked to the human endocrine system, including reproductive and fertility problems, genital development in boys, cancer of the breast, prostate and testes, obesity, diabetes and childhood behavioural disorders. The analysis considered a range of EDCs, and so again, was not restricted to phthalates.

The cost analysis focused on healthcare (direct) costs and in some cases also lost productivity (indirect costs) (see Table 3.2). Costs associated with lost health utility (referred to elsewhere as "intangible costs") were not accounted for. The total (direct + indirect) cost associated with the conditions considered (rather than the contribution of EDCs) was EUR 636 billion per year in the EU28, broken down to the different effects listed in Table 3.3.

Table 3.2. Cost elements covered for each type of impact in the HEAL study

Effect	Direct cost	Indirect cost
Human fertility ART treatment	✓	
Cryptorchidism and hypospadias	✓	
Breast cancer	✓	✓
Prostate cancer	✓	✓
Autism	✓	✓
ADHD	✓	
Obesity	✓	
Diabetes	✓	✓

[7] Alistair Hunt of the University of Bath and Julia Ferguson of Cranfield School of Management.

Table 3.3. Costs by impact, summarising the results of the HEAL report

Effect	Cost per case (2010)	Total EU28 burden, EUR billion per year	Source of cost data
Human fertility – ART treatment	Denmark: EUR 11 319 Netherlands: EUR 51 822	2.4 - 3.1	Denmark: Christiansen et al. (2014[20]) Netherlands: citation no longer available
Cryptorchidism and hypospadias	EUR 5 715 to 8 415	0.9 - 1.3	Hsieh et al. (2009[21])
Breast cancer	Unit cost unspecified	16	Luengo-Fernandez et al. (2013[22])
Endometrial cancer	No cost data available	Not quantified	
Thyroid cancer	No cost data available	Not quantified	
Prostate cancer	Unit cost unspecified	9	Luengo-Fernandez et al. (2013[22])
Testicular cancer	No cost data available	Not quantified	
Autism	EUR 12 445	226	Lavelle et al. (2014[23])
ADHD	EUR 10 650	0.7	Pelham et al. (2007[24])
Obesity	Unit cost unspecified	81	Derived using European Commission (2006[25])
Diabetes	Unit cost unspecified	300	Kanavos et al. (2012[26])
Total		EUR 636 billion per year	

The question then arose of how much of this total estimate should be attributed to EDC exposure. An indicative range of 2-5% was adopted, providing a range for the quantified elements of the analysis of EUR 12-31 billion per year. It is understood[8] that this was derived drawing on the research by Trasande (2014[14]) discussed above, from which an estimate of 1.8% of attributable disease was linked to a single substance (BPA).

Given the nature of the analysis, based around total cost estimates for various conditions, unit cost estimates are not available from the report for many of the effects listed. Those that are available are illustrative, providing some insight to the size of particular elements of cost. However, these costs vary significantly between countries, as the following examples show:

- ART treatment Netherlands: EUR 51 822 per live birth
- ART treatment Denmark: EUR 11 310 per live birth
- Estimated average calculated here as total cost of ART treatments divided by number of treatment cycles: EUR 5 000 per treatment cycle. Multiple treatments are often necessary per live birth.

Neither the authors nor HEAL make any pretence to great accuracy in these estimates, recognising the limitations in the availability of response functions. Instead, the results are used to indicate that the scale of impact associated with EDC exposure in the EU28 may be significant in terms of both the size of impacts and their economic equivalent, particularly given the limitations in the valuation (omitting any account of "intangible" costs). It is noted that the attributable fraction adopted in the work (2-5%) is lower than in some of the other studies considered here (for example, it is very much at the lower end of the range of 2-40%, best estimate 20%, adopted by Olsson et al. (2014[6])).

[8] The HEAL report does not cite Trasande (2014[14]), but it is clearly the source of the results on which HEAL's analysis is based.

For the purpose of guidance for socio-economic assessment of phthalates, specifically, the identification of data describing direct and indirect costs for a range of endpoints is useful, though of course incomplete as it lacks utility costs. The impact assessment in terms of the attributable fraction is speculative, extrapolating from Trasande (2014[14]), and does not provide a basis for assessment of phthalates, generally, nor (in consequence) of individual phthalates. It is recognised that this was not the objective of the HEAL work, which is focused on a simpler question of whether the economic damage associated with EDCs is likely significant or not.

3.3. Olsson et al., 2014

The Olsson et al. (2014[6]) report was produced with funding from the Nordic Council of Ministers, and focuses on the societal costs of impacts on male reproductive health, specifically cryptorchidism[9], hypospadias[10], poor semen quality and testicular germ cell cancer. It was considered that the casual link between impact and EDCs is relatively well established for these impacts.

Olsson et al. (2014[6]) cites the following evidence for young Danish men as the basis for concerns about possible impacts of EDCs in the Nordic countries: "Semen quality in 40% of young Danish men is so low, they are expected either to have longer waiting time to pregnancy, or in the worst cases (6%) not to be able to have children without clinical help, (Andersson et al., 2008[27]). Up to 8% of Danish children are now conceived through assisted fertilisation. Furthermore, in Denmark absence of one or both testes from the scrotum in baby boys at birth has increased from 2% to 9% over the last 50 years (Boisen et al. (2004[28]) and (2005[29])), girls develop breasts one year earlier than they did 15 years ago (Aksglaede et al., 2009[30]) and testicular cancer rates are among the highest in Europe – 1% of all Danish men develop testicular cancer (Andersson et al., (2008[27]), Jacobsen et al. (2006[31])).” Olsson et al. does not comment on the prevalence of these effects in the other Nordic countries, for example to indicate whether they are more prevalent amongst the Danish population than others in the region, and then within the EU to which the analysis of impacts in the Nordic countries is extrapolated in the paper.

In this study, as elsewhere, recognition is given to the need to consider a range of literature when considering causality:

> "The strength of the evidence between exposure to endocrine disruptors and the effects on male reproductive health seems convincing when the biological plausibility is combined with human epidemiological and case studies, effects observed in wildlife and effects observed in laboratory animals exposed to endocrine disruptors."

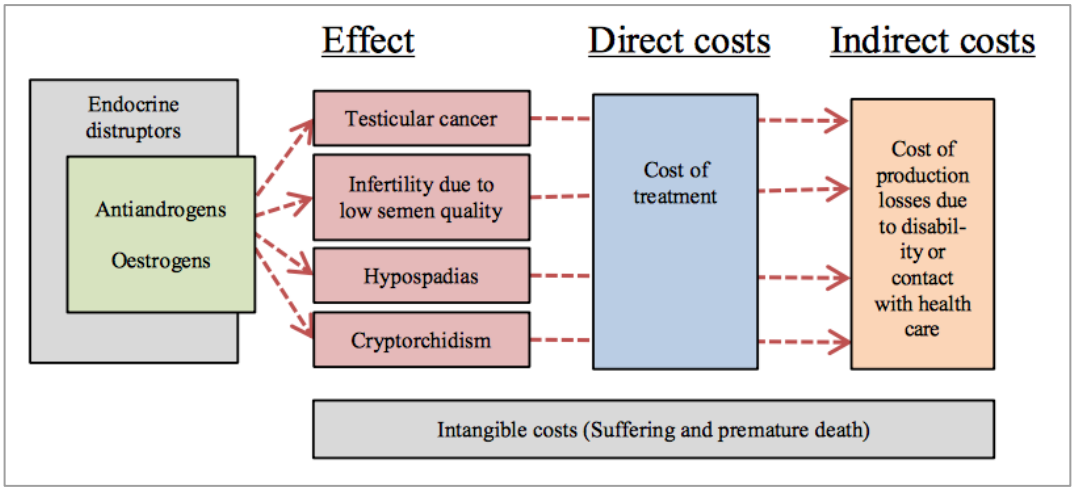
Following review of the evidence, the paper adopts the following impact pathway for analysis, cf. Figure 3.1. Impact-pathway for assessment of associated costs of EDC action on male fertility:

[9] Cryptorchidism: failure of one or both testes to descend to the scrotum.

[10] Hypospadias: a condition in males where the opening of the urethra is on the underside of the penis, rather than at the tip.

Figure 3.1. Impact-pathway for assessment of associated costs of EDC action on male fertility

As adopted by Olsson et al. (2014).



Source: Olsson et al. (2014[6]).

Despite the link between substance and effect being considered as well elaborated in the literature, a lack of information permitting definition of a response function to quantify the attributable fraction of disease was noted. The best estimate of impact was taken as 20%, in a range from 2% to 40%, derived following consultation with experts. As noted above, a complication arises because other environmental factors have also been linked to the effects of interest here, including diet, lack of exercise, smoking and alcohol consumption, so the adoption of a broad range seems reasonable. More problematic is the adoption of any point within the 2-40% range as a guide for policy making.

The cost analysis accounts for:

- Direct tangible costs (costs of treatment in the health care system)
- Indirect tangible costs (e.g. from sickness leave from work) and
- Intangible costs (loss of life years and loss of quality of life).

Incidence data and unit cost estimates used by Olsson et al. (2014[6]) are shown in Table 3.4. Incidence data are taken from European statistics and hence should be robust for the region considered in the paper. The direct cost estimates are taken from assessment of treatment costs, an issue that the paper addresses in detail, and so should again be robust (accepting that there will be variation around the EU, and that costs developed in the Nordic countries may not reflect well those in the less affluent EU Member States). Indirect costs per case are, again, based around reasonably detailed assessment of the consequences of illness and seem likely to be robust (in any case, they are small compared to direct and intangible costs, so error in these figures is unlikely to be significant for the results overall). The so-called intangible costs addressing WTP not to experience disease and premature death are more problematic. They are calculated by combining an estimate of the QALY (quality-adjusted life-year) loss per case and a value of EUR 70 200 (2013 price) per QALY (drawing on information from ECHA). The issues identified here are as follows:

1. There is little information available describing the QALY loss for the conditions considered – an issue that the authors are quite open about. The authors

themselves raise concern that the QALY loss estimate for hypospadias seems high, given that surgery is generally successful and that there is little or no evidence of psychosexual impairment of boys with hypospadias.

2. There is extensive variation in QALYs even amongst this limited literature: for testicular cancer there is a factor 2 variation in estimates from the only relevant paper identified, depending on the method adopted for elicitation of the QALY (time trade-off vs. standard gamble).
3. There is only a limited literature on which to base the value of a QALY, based around valuation of a life year (VOLY). The linkage of the QALY to VOLY is questionable in itself.
4. Valuation of mortality using the VOLY concept has drawn criticism, not least from OECD, and is not practised widely.

Table 3.4. Incidence data for the EU28, and unit costs as adopted by Olsson et al. (2014)

2013 EUR, values have been discounted to account for the time delay between exposure and effect.

	Testicular cancer	Male infertility	Hypospadias	Cryptorchidism
Expected yearly incidence (total)	15 390	103 935	11 222	26 171
Assumed 20% attribution to EDCs	3 078	20 787	2 444	5 234
Direct costs per case	EUR 2 340	EUR 2 720	EUR 10 297	EUR 4 429
Indirect costs per case	EUR 1 900	EUR 760	EUR 1 243	EUR 1 045
QALY loss per case	1.09		0.4	0.42
Value of QALY loss ("intangible" cost per case)	EUR 76 740		EUR 28 077	EUR 29 200
Total cost	EUR 80 980	EUR 3 480	EUR 39 617	EUR 34 674

Source: Olsson et al. (2014[6]).

In the cost estimates for infertility due to reduced semen quality, intangible costs are not included, due to difficulties in finding reliable sources that quantify these aspects.

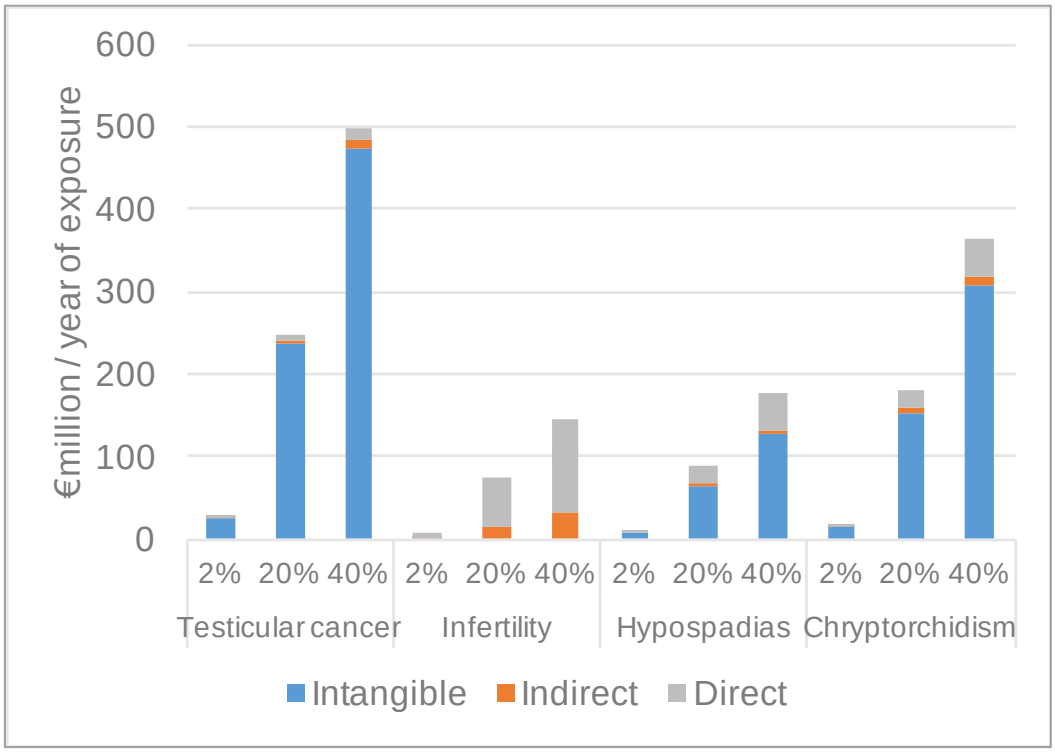
The direct and indirect costs have been discounted by a rate of 4% per year, while the intangible costs are discounted by a pure time preference rate of 1.5% per year. The different treatment for the intangible costs is justified in the paper by assuming either that willingness-to-pay for improved quality-of-life will grow in line with economic output, counteracting the discount rate, or that human suffering due to illness is unaffected by economic growth.

The paper provides results for both the Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) and the EU28, results for which are shown in the following figure[11] and in Table 3.5:

[11] The EU28 results were calculated by extrapolation from those for the Nordic countries, with a factor 17 difference between the two.

Figure 3.2. Costs on human male reproduction in the EU28 due to endocrine disruption

For four effects with varying assumptions on attributable fraction. "Intangible" costs were not quantified for infertility.



Source: Olsson et al. (2014[6]).

Table 3.5. Total cost estimates for impacts of EDCs on human male fertility

Assuming an attributable fraction of 20%.

Region	Discounting	Total per year of exposure
Nordic countries	Discounted	EUR 36 million
Nordic countries	Undiscounted	EUR 77 million
EU28	Discounted	EUR 592 million
EU28	Undiscounted	EUR 1 267 million

Source: Olsson et al. (2014[6]).

Whilst these results consider only some of the effects that have been linked to EDCs, they do address the effects for which the science seems most robust. In the context of this paper, it is also important to note that they are for aggregate exposure to EDCs, rather than to phthalates specifically.

The question again arises of what use regulators can make of these results when considering not EDCs in general, but phthalates specifically. The difficulty of determination of the attributable fraction is again highlighted, and illustrated by the factor 20 variation in the range adopted, even though the paper does not seek to attribute impacts to specific EDCs. However, the paper contains useful data on the incidence of illness.

Accepting that the QALY valuation approach leads to a reasonable estimate of utility losses, the study also demonstrates the importance of accounting for utility losses, as these dominate costs for the impacts for which they are included. This seems likely to be the case for most medical conditions that are commonplace and for which treatment is routinely given, which should include any that can be linked with confidence to specific EDCs based on information at the population level.

3.4. Studies of the costs of exposure to endocrine disrupting chemicals in the EU

This section discusses a series of papers published in 2015 and 2016 seeking to describe the burden of disease attributable to EDCs in the EU. Four papers are considered:

- an overview of the methods and results by Trasande et al. (2015[32])
- analysis of diabetes and obesity by Legler et al. (2015[33])
- analysis of cognitive deficit and neurodevelopmental disabilities by Bellanger et al. (2015[34])
- analysis of impacts on male fertility and genital development by Hauser et al. (2015[35]).

This is then followed by two further papers published in 2016 updating and extending the results of the original series of papers:

- an updated overview of the methods and results by Trasande et al. (2016[36])
- analysis of female reproductive disorders by Hunt et al. (2016[37]).

A further paper by Attina et al. (2016[38]) is considered below, which applied a very similar approach to quantify impacts in the United States (Section 3.5).

3.4.1. Trasande et al., 2015

Trasande et al. (2015[32]) addresses the burden and disease costs of exposure to EDCs in the EU. As such, the study is again not specific to phthalates, but is intended to cover their effects as well as those of other EDCs. The paper provides details of the general methodology and results of the work, with other papers, some of which are discussed here, providing greater detail on certain aspects of the work.

The study is notable for developing a functional approach for quantification of overall burden that does not obscure the science that underpins the method. The main problem faced is that there are many substances to be addressed, and a shortage of concentration-, exposure- or dose-response relationships with which to work.

Key to the analysis is the determination of the attributable fraction (AF) that combines the prevalence of illness with the risk of developing that disease from some risk factor. A first part of this concerns assessment of causality between a risk factor and a disease. This was carried out taking account of both toxicological and epidemiological information, using a probability framework based on that used by the IPCC. Epidemiological evidence was assessed using the GRADE framework of WHO, and toxicological evidence using criteria developed by the Danish EPA for assessing laboratory and animal evidence of endocrine disruption.

Assessment was not carried out for substances already banned in the EU.

The Steering Committee for the study noted three general approaches on which to base attribution to EDCs which they describe as follows:

1. trends in incidence/prevalence over and above a baseline that would be difficult to attribute to genetics accompanied by information on likely causal mechanisms by EDCs and/or increasing exposure;
2. data from genetic studies that permit quantification of the remaining environmental contribution (within which one might posit EDC to contribute a portion); and
3. dose-response relationships from the epidemiological literature.

In general, the Steering Committee prioritised the third approach. In the absence of epidemiological evidence for a dose-response relationship, they considered that the presence of toxicological data documenting effect and mechanism might suggest a strong basis from which to reason an incremental effect in humans.

The complexity of the task is illustrated by reference to the factors that the authors had to deal with, notably:

- simultaneous exposure to large number of substances of concern
- a variety of impacts, varying significantly in nature
- the dependence of impact on the time of exposure
- variable sensitivity across the population
- limited human data.

Dose-response functions were derived using a Delphic approach drawing on the evidence available from the literature, involving discussion between experts, and designed to elicit high and low bounds. Potential non-linearity and non-monotonicity were considered. The use and further development of existing protocols for assessing information reduced the subjectivity of the process.

It is necessary to ask to what extent the use of a Delphic approach deviates from standard practice in the development of response functions for health and environmental impact assessment more widely. In truth, any approach that brings together a number of experts in the field of health impact assessment linked to chemical and pollutant exposures will be at least partly Delphic in nature, especially when dealing with simultaneous exposures to multiple agents and a variety of impacts. The paper notes that the Global Burden of Disease project similarly relies on expert opinion, but focuses on relationships where there is strongest evidence, and this currently does not include the impacts addressed here.

A human capital approach was used for valuation, accounting for:

- direct costs linked to health care
- indirect costs in terms of the value of lost output of workers and retirees suffering disability or premature death.

Where necessary, values were extrapolated from the United States, adjusting for variation in the ratio of each European country in terms of PPP adjusted per capita GDP. No account was taken of reduced utility. Referring to the work of Olsson et al. (2014[6]) above and other papers where utility has been factored into the assessment, it is likely that this provides a significant bias to underestimation in the economic estimates of damage.

Uncertainty analysis was carried out with an emphasis on the use of Monte Carlo techniques. A limitation of the method in this case is clearly the subjectivity in definition of best estimates, of the ranges around those best estimates and of the shape of the probability distribution. However, given the use of Delphic methods with a number of

experts being involved in the appraisal, the authors have addressed this issue of subjectivity in a proactive and pragmatic way.

Results for effects relevant here for phthalates (including "multiple exposures" where it is considered here that phthalates are part of the mix) are shown in Table 3.6 and Table 3.7.

Table 3.6. Estimated annual impacts of phthalates and exposure to multiple EDCs in the EU

2010

Substance	Effect	Strength of human evidence	Strength of toxicological evidence	Probability of causation	Base estimate
DEHP	Adult obesity	Low	Strong	40-69%	53 900 cases in older women
DEHP	Adult diabetes	Low	Strong	40-69%	20 500 cases in older women
Benzyl and butyl phthalates	Male infertility requiring assistance for reproduction	Low	Strong	40-69%	618 000 additional assisted reproductive technology procedures
Phthalates	Low testosterone in men aged 55 to 64, leading to early mortality	Low	Strong	40-69%	24 800 deaths annually
Multiple exposures	ADHD	Low to moderate	Strong	20-69%	19 400 to 31 200 new cases
Multiple exposures	Autism	Low	Strong	20-39%	316 cases of autism

Source: Trasande et al. (2015[32]).

Table 3.7. Annual costs associated with exposure to phthalates and multiple EDCs

For the EU in 2010, 2010 EUR

Substance	Effect	Base estimate	Low	High
DEHP	Adult obesity	EUR 15 billion	=	=
DEHP	Adult diabetes	EUR 0.6 billion	=	=
Benzyl and butyl phthalates	Male infertility requiring assistance for reproduction	EUR 4.7 billion	=	=
Phthalates	Low testosterone leading to early mortality	EUR 8.0 billion	=	=
Multiple exposures	ADHD	EUR 1.7 billion	EUR 1.2 billion	EUR 2.8 billion
Multiple exposures	Autism	EUR 0.2 billion	EUR 0.08 billion	EUR 0.4 billion
Total		EUR 30 billion		

Note: "=" denotes effects for which low and high estimates matched the best estimate.
Source: Trasande et al. (2015[32]).

The valuation of deaths linked to low testoterone concentrations relied on assessment of lost productivity, averaging out at EUR 320 000 per case. Applying a full VSL in the region of EUR 3 million per death (OECD, 2012[39]) would clearly have increased the estimated costs markedly from EUR 8 billion to a maximum of around EUR 75 billion per year (the precise figure depending on the time profile of impacts and thus how these results should be discounted, if at all).

The analysis of uncertainty presented in the paper highlights the potentially broad ranges that may apply: the broadest range derived from the Monte Carlo simulation was EUR 44 million to 235 billion, with a median of EUR 109 billion (noting that this included several effects, including impacts on IQ that were highly valued, that were not linked to phthalate exposure). Narrower ranges were derived taking account of the very high confidence of effect for some of the substance-effect combinations. From the results

presented in the paper, an 80% confidence interval of EUR 32 billion to EUR 212 billion annually for the full set of substances considered was derived.

3.4.2. Legler et al., 2015

The Legler et al. (2015[33]) study is one of the components of the Trasande et al. (2015[32]) study, results for which were given above, dealing specifically with obesity and diabetes. Given that both diseases are at epidemic levels in Europe, the link to exposure to substances such as DEHP is certainly worthy of consideration.

From both a health and economic perspective, it is wrong to limit attention to "diabetes" and "obesity" specifically, as both are linked to a range of co-morbidities. Diabetes-attributable expenditures in the EU are estimated to reach around EUR 100 billion annually by 2030.

The analysis limited the studied populations. For obesity, the population at risk was limited to women aged 50 to 64 and for diabetes to adults, but again in the 50 to 64 year age band. The authors state that the costs that they quantify are likely to be significant underestimates, bearing in mind that they are limited to direct costs for diabetes and obesity, and indirect costs for obesity only, hence leaving out the costs of co-morbidities which are common with both conditions, and loss of utility.

3.4.3. Bellanger et al., 2015

Bellanger et al. (2015[34]) addresses the impacts of EDCs on cognitive deficit and neurodevelopmental disabilities. It addresses PBDE (polybrominated diphenyl ether) and organophosphates as well as phthalates. Cost estimates were based on lifetime economic productivity, lifetime costs for autism spectrum disorder and annual cost for ADHD, like other papers in the series addressing healthcare costs and productivity loss, but not disutility impacts through reduced wellbeing.

Bellanger et al. (2015[34]) comment on the paucity of information for development of response functions for phthalates and autism, with concerns over the use of the Social Responsiveness Score used by the study from which the response function was taken. Given these concerns, the authors cite quantified impacts as a function of EDC exposure more generally, rather than phthalate exposure specifically.

Overall cost estimates relevant to phthalate exposure were provided above in Table 3.7, with unit cost estimates described in Table 3.10 below, which summarises unit cost estimates from all of the studies considered. Bellanger et al. reduced the overall estimates for autism and ADHD by around 45% to account for the potential for double counting with intellectual disability.

3.4.4. Hauser et al., 2015

Hauser et al. (2015[35]) considered the following effects:

- male infertility attributed to phthalate exposure
- reduced testosterone concentrations in 55 to 64 year old men due to phthalate exposure, leading to premature death in this age group
- cryptorchidism linked to prenatal PBDE (polybrominated diphenyl ether) exposure
- testicular cancer linked to prenatal PBDE exposure.

The approach follows that defined in the Trasande et al. (2015[32]) paper. Unit cost estimates are taken from other sources (see Table 3.10). Like other papers in this series, it is understood that these costs account for healthcare and lost productivity, but not reduced utility.

For mortality specifically, impacts were modelled in terms of lost productivity, valued at, on average, EUR 320 000 per case, or roughly one tenth of the value of the VSL recommended by OECD (2012[39]) for the EU28.

3.4.5. Hunt et al., 2016

Hunt et al. (2016[37]) considered impacts of EDCs on two of the most common reproductive disorders affecting women, endometriosis and fibroids. Analysis was limited to the EDCs for which there were sufficient epidemiological studies and where the probability of causation was estimated to be high, drawing on the Delphic elicitation approach that underpins the series of papers. The conceptual framework followed addresses "ovarian dysgenesis syndrome" (ODS), akin to the testicular dysgenesis syndrome seen in males and covered repeatedly already in this report. Support for ODS comes from the experiences of medical use of diethylstilbestrol (DES), a synthetic oestrogen that was prescribed to women from the 1940s to the 1970s to prevent miscarriage. Regrettably, experience has shown that use of the drug increased a variety of reproductive conditions in women. Hunt et al. (2016[37]) note that associations have also been reported with several conditions in males who were exposed in utero. Further support for the hypothesis comes from studies on rodents further investigating the issue. The paper notes that observations on females to assess ODS are more difficult than on males, as they require invasive procedures.

The problems are less difficult for assessment of conditions such as endometriosis and fibroids, common conditions with an estimated incidence of up to 70% of women in total. These are leading causes of female infertility and have significant impacts on quality of life, for example through pain. Hunt et al. (2016[37]) proceeded to quantify effects of EDCs on these impacts in terms of the effects of DDE (diphenyldichloroethene) on fibroids and phthalates on endometriosis, deriving response functions from Trabert et al. (2014[40]) and Buck Louis et al. (2013[41]) respectively. The valuation of the costs of treating fibroids used a study of national databases for England, Germany and France (Farrugia et al., 2009[42]). For endometriosis, cost per patient were adapted from 2009 estimates for Belgium, and accounted for both healthcare, lost economic productivity and other indirect costs (Klein et al., 2014[43]). Results are shown below in Table 3.8 and Table 3.9 in the context of other results from the series of studies, as reported by Trasande et al. (2016[36]).

3.4.6. Trasande et al., 2016

The third Trasande paper, (2016[36]), is similar to the Trasande et al. (2015[32]), but is updated by adding in the results of Hunt et al. (2016[37]) for endometriosis and fibroids. Results are shown below.

Table 3.8. Estimated annual impacts of phthalates and exposure to multiple EDCs in the EU

2010

Substance	Effect	Strength of human evidence	Strength of toxicological evidence	Probability of causation	Base estimate
DEHP	Adult obesity	Low	Strong	40-69%	53 900 cases in older women
DEHP	Adult diabetes	Low	Strong	40-69%	20 500 cases in older women
Benzyl and butyl phthalates	Male infertility requiring assistance for reproduction	Low	Strong	40-69%	618 000 additional assisted reproductive technology procedures
Phthalates	Low testosterone in men aged 55 to 64, leading to early mortality	Low	Strong	40-69%	24 800 deaths annually
Multiple exposures	ADHD	Low to moderate	Strong	20-69%	19 400 to 31 200 new cases
Multiple exposures	Autism	Low	Strong	20-39%	316 cases of autism
DDE	Fibroids	Low	Moderate	20-39%	
Phthalates	Endometriosis	Low	Moderate	20-39%	

Source: Trasande et al. (2016[36]).

Table 3.9. Annual costs associated with exposure to phthalates and multiple EDCs

For the EU, in 2010.

Substance	Effect	Base estimate	Low	High
DEHP	Adult obesity	EUR 15 billion	=	=
DEHP	Adult diabetes	EUR 0.6 billion	=	=
Benzyl and butyl phthalates	Male infertility requiring assistance for reproduction	EUR 4.7 billion	=	=
Phthalates	Low testosterone leading to early mortality	EUR 8.0 billion	=	=
Multiple exposures	ADHD	EUR 1.7 billion	EUR 1.2 billion	EUR 2.8 billion
Multiple exposures	Autism	EUR 0.2 billion	EUR 0.08 billion	EUR 0.4 billion
Phthalates	Endometriosis	EUR 1.3 billion	=	=
Total		EUR 30 billion		

Note: "=" denotes effects for which low and high estimates matched the best estimate.
Source: Trasande et al. (2016[36]).

Table 3.10. Unit cost data

Used in the papers linked to Trasande et al. (2015, 2016) and associated papers.

Effect	Unit cost (2010 EUR)	Discount rate	Source
Direct cost per obese adult	EUR 21 500 per case	3%	Legler et al. (2015[33]) (adapted from Cawley and Meyerhofer, (2012[44]))
Indirect cost per obese adult	EUR 268 000 per case	3%	Legler et al
Direct cost for attributable cases of diabetes	EUR 27 700 to 29 600 per case	3%	Legler et al. (2015[33]) (adapted from Zhang et al. (2010[45]))
Lost economic activity from deaths linked to low T	EUR 320 000 per case	Unspecified	Hauser et al. (2015[35]) (adapted from Max (2013[46])
Cryptorchidism	EUR 28 000 per case	Unspecified	Hauser et al. (2015[35]) (from Olsson et al. (2014[6]))
Male infertility	EUR 7 600 per case	Unspecified	Hauser et al. (2015[35]) (adapted from Christiansen et al. (2014[20]))
Testicular cancer	EUR 124 000 per case	Unspecified	Hauser et al. (2015[35]) (from Olsson et al. (2014[6]))
IQ loss	EUR 9 600 per IQ point	3%	Bellanger et al. (2015[34]) (from Gould (2009[47]))
Autism	EUR 630 000 per case	3%	Bellanger et al. (2015[34]) (from Buescher et al., (2014[48]))
Intellectual disability	EUR 360 000 per case	3%	Bellanger et al. (2015[34]) (adapted from Olesen et al. (2012[49]); Gustavsson et al. (2011[50]))
ADHD	EUR 77 000 per case	3%	Bellanger et al. (2015[34]) (adapted from Le et al. (2014[51]))
Direct cost for treatment of endometriosis	EUR 2 000 per case per year	Costs increased by 4% per year from 2009 to 2010	Hunt et al. (2016[37]) (adapted from Klein et al. (2014[43]))
Indirect cost (productivity loss) for endometriosis	EUR 6 600 per case per year	Costs increased by 4% per year from 2009 to 2010	Hunt et al. (2016[37]) (adapted from Klein et al. (2014[43]))
Direct cost for fibroid treatment	EUR 2 900 per case per year	Costs increased by 4% per year from 2009 to 2010	Hunt et al. (2016[37]) (adapted from Farrugia et al. (2009[42]))

3.5. Attina et al., 2016

Attina et al. (2016[38]) provide a US perspective to the work of Trasande et al. (2015[32]) and (2016[36]). The overall approach is almost identical to that used by Trasande et al. (2015[32]) and (2016[36]) [12] in that expert panels were brought together to consider the weight of evidence of causality for a range of response function/substance combinations using a modified Delphic approach. The response functions were those established for Europe, with exposure assessed using representative human biomonitoring data from the NHANES surveys of 2007-8 and 2009-10, depending on substance (detailed information on these is provided in the online appendix to the paper). Attina et al. acknowledge that expert opinion is 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, they also note that whilst an understanding of mechanism is important, that understanding has no impact on the final results, provided of course that there is some underlying causal mechanism (hence the focus on assessing the weight of causality).

The study provides analysis using 15 exposure-response functions between substances and disorders. The work considers EDCs generally and, for some functions, phthalates

[12] The list of authors includes Trasande, and several others linked to his (2015[32]) and (2016[36]) papers described here.

specifically. The paper starts by noting the work described above to quantify the impacts of EDCs in the EU, and key differences in exposure between the EU and the United States, in particular that EDC exposure for organophosphate pesticides is greater in Europe, whilst exposure to PBDE is higher in the United States. These initial observations feed through to the results. A literature search performed in January 2016 found no relevant estimates for EDC-attributable burden of disease or dysfunction or economic costs in the United States (reflecting the emerging European bias in the present paper).

Results are shown in Table 3.11, including data for the EU as well as the United States (the EU results are mostly as above, but converted to US dollars).

Table 3.11. Attributable burden of disease and associated costs for impacts of EDCs

In the United States and Europe

Substance / Effect	Population	US cases / IQ points / deaths	EU cases	US cost (2010 USD)	EU cost (2010 USD)
PBDE / IQ loss, intellectual disability	All neonates	11 million IQ points 43 000 cases	873 000 IQ points 3 290 cases	USD 266 billion total USD 208 billion USD 58 billion	USD 13 billion total
Organophosphate pesticides / IQ loss, intellectual disability	All neonates	1.8 million IQ points 7 500 cases	13 million IQ points 59 300 cases	USD 45 billion total USD 35 billion USD 10 billion	USD 194 billion total
DDE / childhood obesity	Children aged 10 years	857 cases	1 555 cases	USD 30 million	USD 33 million
DDE / adult diabetes	Adults aged 50 64 years	24 900 cases	28 200 cases	USD 1.8 billion	USD 1.1 billion
DEHP / adult obesity	Women aged 50 64 years	5 900 cases	53 900 cases	USD 1.7 billion	USD 21 billion
DEHP / adult diabetes	Women aged 50 64 years	1 300 cases	20 500 cases	USD 91 million	USD 810 million
BPA / childhood obesity	Children aged 4 years	33 000 cases	42 400 cases	USD 2.4 billion	USD 2.0 billion
PBDE / testicular cancer	All boys and men	3 600 cases	6 830 cases	USD 82 million	USD 1.1 billion
PBDE / cryptorchidism	All male neonates	4 300 cases	4 615 cases	USD 36 million	USD 170 million
Benzyl-, butyl-phthalates / male infertility	Men aged 20 39 years	240 100 cases of ART use	618 000 cases of ART use	USD 2.5 billion	USD 6.3 billion
Phthalates and low testosterone	Men aged 55 64 years	10 700 attributable deaths	24 800 attributable deaths	USD 8.8 billion	USD 11 billion
Multiple EDCs / ADHD	Children aged 12 years	4 400 cases	19 400-31 200 cases	USD 700 million	USD 2.3 billion
Multiple EDCs / autism	Children aged 8 years	787 boys754 girls	316 cases	USD 1.0 billion USD 980 million	USD 270 million (total)
DDE / fibroids	Women aged 15 54 years	37 000 cases	57 000 cases	USD 259 million	USD 220 million
DEHP / endometriosis	Women aged 20 44 years	86 000 cases	145 000 cases	USD 47 billion	USD 1.7 billion

Note: Brown-shaded boxes highlight the 5 effects with greatest damage in the United States and EU.
Source: Attina et al. (2016[38]).

Unit values for each impact are not presented in the paper, but have been calculated from the results given in the Appendix to it (Table 3.12). It is noted that some of the results in the Appendix did not match those cited in the main paper. Results have been converted to 2010 EUR using the exchange rate of USD 1.33 per EUR cited in the paper.

Table 3.12. Unit values calculated from Attina et al. (2016)

2010 USD

Effect	Substance	Impact	Cost (USD million)	Unit cost, USD	Unit cost, EUR	Units c)
IQ points loss	PBDE	10 772 495	208 000	19 308	14 518	Cost per IQ point
Intellectual disability	PBDE	43 238	58 200	1 346 038	1 012 059	Cost per case
IQ points loss	Organophosphate	1 793 428	34 600	19 293	14 506	Cost per IQ point
Intellectual disability	Organophosphate	7 533	10 100	1 340 767	1 008 096	Cost per case
Autism	Phthalate	1 540	2 010	1 305 195	981 349	Cost per case
ADHD	Organophosphate	4 411	698	158 241	118 978	Cost per case
ADHD	PBDE	10 408	1 650	158 532	119 197	Cost per case
Overweight children	DDE	857	30	34 539	25 969	Cost per case
Adult diabetes	DDE	24 937	1 800	72 182	54 272	Cost per case
Adult obesity	Phthalate	5 909	1 690	286 004	215 041	Total cost per case
Adult obesity	Phthalate	5 909	106	17 939	13 488	Direct cost per case
Adult obesity	Phthalate	5 909	1 580	267 389	201 044	Indirect cost per case
Adult diabetes	Phthalate	1 292	91	70 743	53 190	Total cost per case
Childhood obesity	BPA	33 312	2 400	72 046	54 170	Total cost per case
Childhood obesity	BPA	33 312	714	21 434	16 116	Indirect cost per case
Childhood obesity	BPA	33 312	1 700	51 033	38 370	Cost per case
Cryptorchidism	PBDE	4 267	36	8 367	6 291	Cost per case
Male infertility, ART a)	Phthalate	171 259	2 500	14 598	10 976	Cost per case
Male infertility, ART b)	Phthalate	240 000	2 500	10 417	7 832	Cost per case
Testicular cancer	PBDE	3 578	82	22 778	17 126	Cost per case
Low T deaths a)	Phthalate	19 796	8 810	445 044	334 619	Lost productivity per case
Low T deaths b)	Phthalate	10 700	8 810	823 364	619 071	Lost productivity per case
Fibroids	DDE	37 173	259	6 967	5 239	Cost per case
Endometriosis a)	Phthalate	82 883	47 000	567 064	426 364	Cost per case
Endometriosis b)	Phthalate	86 000	47 000	546 512	410 911	Cost per case

Note: a) Number of cases taken from Appendix. b) Number of cases taken from the tables in the main paper, where the two differ. c) Costs cover healthcare and productivity, but not utility losses.

Like many of the studies considered here, Attina et al. (2016[38]) limit the assessment of the cost of illness to "direct" (healthcare) costs, and "indirect" costs of lost productivity. No account was taken of lost health utility through pain, emotional distress, dysfunction, etc., for most effects, apart from adult obesity (including adult obesity arising from childhood obesity) and endometriosis. The approach used in these cases was to convert the quantified impacts to disability adjusted life years (DALYs) and then to value these at the USD 50 000 figure applied in health economics work in the United States. Where appropriate, a discount rate of 3% was used (DDE attributable diabetes, phthalate attributable adult obesity and diabetes, BPA attributable childhood obesity accounting for lifetime impacts).

La Merill (2016[52]) provides comment on the Attina paper, starting by highlighting the differences between the United States and Europe:

- US impacts are estimated to be higher than those in the EU despite the higher population of the latter.

- The greatest costs in the United States are associated with PBDE flame retardants, followed by phthalates, whilst in Europe the largest contribution is from pesticides.

However, in both regions the highest costs are linked to loss of IQ points and intellectual disability.

La Merill (2016[52]) notes that phthalates are still widely used in the United States and ubiquitous in human samples despite not being persistent pollutants. She notes that amongst the EDCs assessed by Attina et al. (2016[38]), DEHP had the highest costs through links to diabetes and obesity. These effects are not included in the US EPA's definition of EDC properties, which are restricted to impacts on the oestrogen, androgen and thyroid systems, unlike the definitions used by the EU and the US-based Endocrine Society that address the entire endocrine system. La Merrill calls for a harmonisation of definitions towards those that are more encompassing, in order to better target policy in this area.

In order to gain a better understanding of regulatory priorities, further data is needed, though in the short term, studies like Attina et al.'s provide a useful indication of the scale of the benefits of action. The need to gather more data prior to taking regulatory action of course needs to be carefully assessed, given costs of inaction.

3.6. ECHA 2016 and 2017: Proposed restriction on four phthalates

The ECHA (2016[7]) restriction dossier, submitted in 2016, focused on the use of bis(2-ethylhexyl) phthalate (DEHP), benzyl butyl phthalate (BBP), dibutyl phthalate (DBP) and diisobutyl phthalate (DIBP) in articles. The four phthalates were also included in Annex XIV of REACH, which lists substances and their uses requiring Authorisation. Applications for authorisation were received only for certain uses of DEHP and DBP. The 2016 proposal from ECHA and Denmark built on the previous restriction proposal prepared by Denmark in 2011 and took account of the applications for authorisation that had been submitted and granted. The proposal presents additional information on hazard, exposure, costs and benefits compared to the earlier submission, to better target the restriction. For the present paper, only the 2016 submission has been considered.

The proposal seeks to restrict the placing on the market of the following articles containing the four phthalates in a concentration, individually or in combination, above of 0.1% of the plasticised material by weight:

1. any (indoor or outdoor) articles whose phthalate-containing material may be mouthed or is in prolonged contact with human skin or any contact with mucous membranes, and
2. any phthalate-containing articles that are used (including stored) in an indoor environment where people are present under normal and reasonably foreseeable conditions and potentially exposed via inhalation. This does not apply to articles that are used only in industrial or agricultural workplaces by workers.

The proposal aims to restrict the sale of articles containing the four phthalates because of their impacts on human health. These articles are mainly:

- flooring
- coated fabrics and paper
- recreational gear and equipment
- mattresses

- footwear
- office supplies and equipment
- wires and cables
- other articles moulded from or coated with plastic.

The proposal was unusual under REACH in that it deals with several substances simultaneously. This decision was taken after consideration of:

- the structural and metabolic similarities of the substances
- the anti-androgenic properties exhibited by each substance, and demonstration of these properties in animal studies
- ability to induce changes in germ-cell differentiation (DBP, DIBP, DEHP)
- similarities in use and exposure patterns.

The restriction proposal (ECHA, 2016[7]) discusses the dose addition process used in the evaluation (Annex B.1.5). Other details of the methods relevant to the present paper are mainly described in Annex D.[13]

All four substances are classified under the EU's CLP (Classification, Labelling and Packaging) regulation as reprotoxic, Category 1B (presumed to have reprotoxic potential for humans based on results of animal studies). BBP and DBP are also categorised as Aquatic Acute 1, and BBP as Aquatic Chronic 1, reflecting impacts on the aquatic environment. ECHA's Member State Committee also agreed that the four phthalates are endocrine disruptors for human health, and that DEHP is an endocrine disruptor in the environment. Assessment of environmental effects was not, however, pursued beyond the risk assessment stage, though this identified some cases where PEC/PNEC ratios (Predicted Environmental Concentration / Predicted No-effect Concentration) exceeded 1 around some production or manufacturing sites.

Analysis focused principally on reproductive toxicity as this formed the basis of the N(L)OAELs (No [or Lowest] Observed Adverse Effect Levels) and DNELs (Derived No-Effect Levels) used in the combined risk assessment. Developmental effects considered in the risk assessment were on male reproduction, in relation to:

- testicular development (germ cell depletion,[14] reduced testicular weight)
- delayed onset of puberty
- increased incidence of hypospadias (a condition where the opening of the urethra is on the underside of the penis)
- increased incidence of cryptorchidism (the failure of one or both testes to descend to the scrotum)

Consideration of the potential for other impacts, on immunotoxicity, metabolism, neurodevelopment, carcinogenicity and repeated dose toxicity found some evidence for additional effects, though conclusions of different studies were variable, and for some of the phthalates there was a lack of information in the literature (e.g. regarding carcinogenicity in relation to DBP and DIBP). It was concluded that by not considering

[13] The Annex to the Background Document (ECHA, (2017[8])) to the development of the opinion of the ECHA Committees is confidential, but the parts relevant to this paper are the same as in the Annexes to ECHA (2016[7])

[14] Here, referring to the cells that generate sperm.

these effects further, there was potential that the focus on reproductive toxicity "might" lead to underestimation of risk.

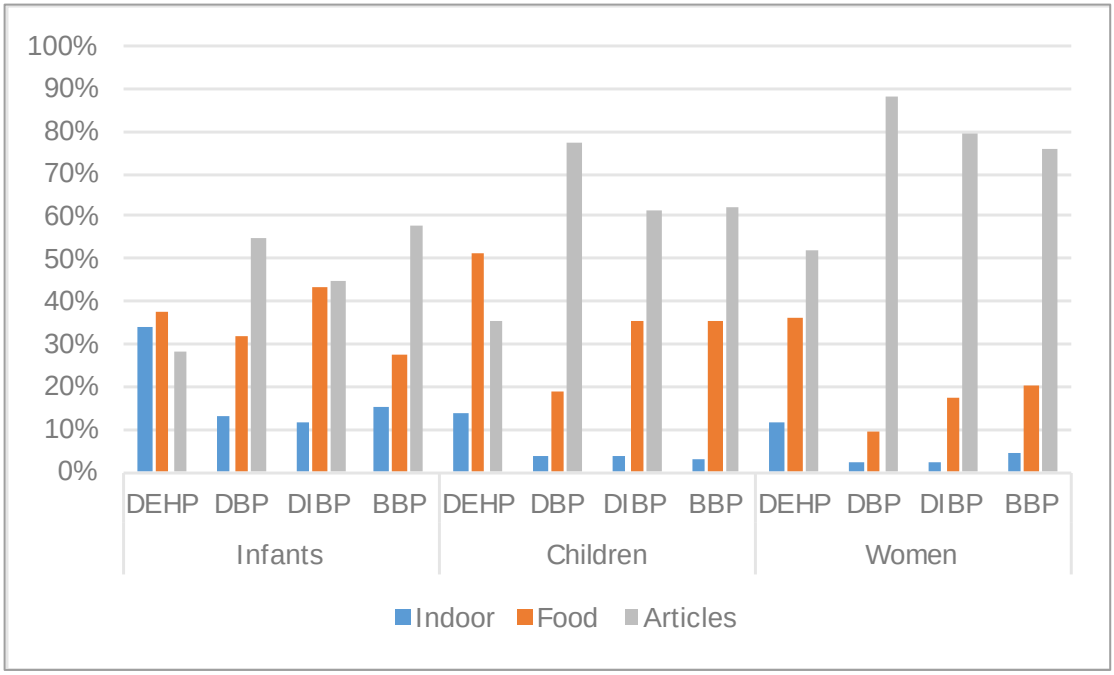
The risk assessment reviewed the literature to develop NOAEL and LOAEL values. These were adjusted, using ECHA guidance, by uncertainty factors to account for inter- and intra-species differences, allometric differences (concerning the relationship between the size of organisms and their physiology) and extrapolation from LOAEL to NAEL where no estimate of NOAEL was available. Comparison of these levels with exposure estimates provides a means of assessing whether risk is present and adverse effects are to be observed.

Distributional issues were discussed in relation to the exposure assessment, higher exposures found in some studies in those of lower socio-economic status, possibly linked to dietary differences. This was not taken through to the analysis.

The exposure assessment found the importance of exposure through articles to increase with age (Figure 3.3 and Figure 3.4). Exposure via the indoor environment was prominent for DEHP for infants, but in all other cases low relative to exposure through food and articles.

Figure 3.3. % "typical" exposure attributable to four phthalates from the indoor environment, food and articles

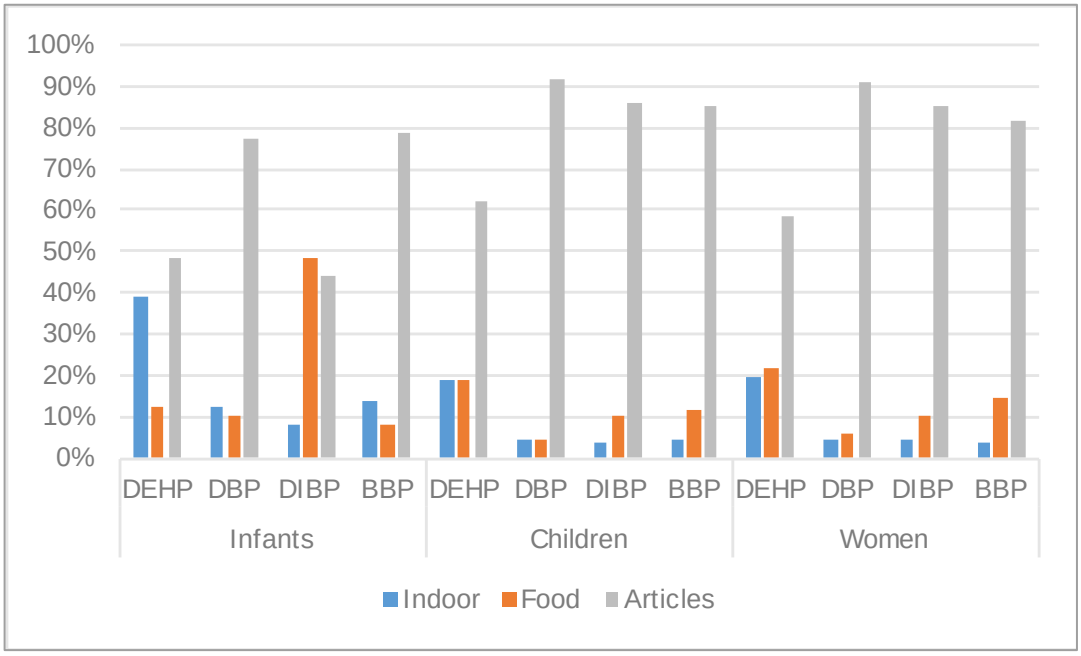
Modelled estimates for infants, children and women



Source: ECHA (2016[7]).

Figure 3.4. % "reasonable worst case" exposure attributable to four phthalates from the indoor environment, food and articles

Modelled estimates for infants, children and women



Source: ECHA (2016[7]).

In general, the risk assessment found that RCRs[15] for individual phthalates estimated using biomonitoring data did not exceed the DNELs previously derived, though there were some exceptions for DBP. Combining the RCRs for the four phthalates, however, generated an aggregate RCR above 1 for most (16 out of 18) EU countries considered for child exposure, and one third of those considered for exposure of mothers (6 out of 18). Approximately 5% of new-born boys (130 000) were at risk from in-utero exposure in 2014 and 16% (400 000) from direct exposure, indicating potential even at this early stage of analysis for a significant socio-economic impact. Modelled data indicated that the combined RCRs for infants under typical conditions were close to 1, but below 1 for both children and mothers. "Reasonable worst case" estimates were significantly higher than one for infants (2.63), above 1 for children (1.34) and just below 1 for mothers (0.9).

Consideration of the likelihood of impacts relevant for human health concluded that:

- There is strong evidence for effects equivalent in humans to those of "rat phthalate syndrome" considered under the heading of testicular dysgenesis syndrome (TDS): reduced semen quality, testicular injury, decreased anogenital distance (AGD), increased nipple retention, increased incidence of hypospadias and cryptorchidism, delayed puberty onset and changes in germ cell differentiation. It was noted that cryptorchidism, hypospadias and poor semen quality, and possibly reduced AGD, are risk factors for one another, and for testicular germ cell cancers. It was stated that there was epidemiological evidence

[15] Risk Characterisation Ratios, expressed as exposure divided by the derived no-effect level (DNEL).

to support the relevance of effects observed in laboratory rats also been observed in humans. It was also noted that many men have sperm levels below WHO reference values for fertility.

- There is moderately strong evidence for risks of immunological effects in children and from reduction in semen quality for exposure of adult men.
- There is weak evidence that the four phthalates cause delayed onset of puberty in boys and girls, delayed mammary gland development in women from foetal exposure, for effects on female reproductive development, neurodevelopment and metabolism from exposure to the four phthalates during gestation, and for liver carcinogenesis from exposure during adulthood.

Environmental impacts were addressed only qualitatively in the assessment. Particular concern was raised over DEHP and its impacts on the development of wildlife, particularly fish and top predators (ECHA, 2014[53]).

The main assessment of health and economic benefits of the proposed restriction concerned outcomes for male fertility, summarised in Table 3.13. The results are based around a mid-point estimate of 0.08% of males suffering infertility because of diminished androgen activity during stages of critical foetal development or early childhood due to exposure to phthalates from articles covered by the proposed restriction. Analysis considers impacts from 2050 onward, reflecting the time at which many of those born in the period affected by the restriction would expect to become parents.

The derivation of the figure of 0.08% was based on combining the following information:

- the fraction of couples who do not achieve pregnancy within 1 year and seek medical treatment (15%)
- the fraction with abnormal semen parameters (50%)
- the fraction whose diagnosis may be associated with exposure to chemicals with an anti-androgenic mode of action and other unknown causes (54%)
- the fraction that can be associated with exposure to chemicals only (50%, in a range of 25% to 75%)
- the fraction that can be associated with exposure to the four phthalates in articles (4%).

The attribution of the final 4% fraction associated with exposure to the four phthalates was in turn based on:

- an estimate of the share of cases due to phthalates (13%, drawing on Kortenkamp et al. (2011[54]))
- the fraction of these cases attributable to the four phthalates (90%, based on world tonnages for all phthalates and hazard reflected by differences in oral DNELs)
- the fraction of these cases attributable specifically to exposure to the four phthalates in articles (40%, drawing on use data and exposure modelling).
- For male infertility there is a reasonably rich literature enabling a number of other (non-phthalate) causes to be factored out of the analysis. However, uncertainty in the exposure-response assessment must be recognised. It is not clear what the +/- 50% range around the mid estimate of attributable fraction represents, whether plausible extremes, or simply an indicative range.
- Results (Table 3.13) show an undiscounted estimate of benefits of EUR 40 million per year linked to the proposed restriction. Discounting at 4% reduces this to EUR 9.76 million, though this does not account for an increase in willingness-to-pay in future years as incomes rise. Factoring this into the analysis

at an assumed 2% per year (reflecting long-term growth rates) raises the value to EUR 19.6 million per year.

It is then concluded by ECHA that these costs may be an underestimate of the damage to society of male infertility for the following reasons:

- Impacts on the male reproductive system lead to several conditions (as discussed above) that could entail additional treatment costs and years of anguish, additional to the estimate provided above.
- There is a bias to underestimation in the incidence rate for male infertility.
- The analysis does not account for the direct, indirect and intangible costs associated with the need for repeat cycles of treatment prior to fertilisation, or cases where couples wish for more than one child.

Table 3.13. Summary of estimated social damage related to male infertility

Infertility due to exposure to DEHP, DBP, DIBP and BBP in articles covered by the proposed restriction

Steps in analysis	Mid-point
Average annual male births (Eurostat, 2020-2050)	2 600 000
Fraction of cases of infertility attributable to DEHP, DBP, DIBP and BBP in articles	0.08%
Annual number of cases of infertility due to DEHP, DBP, DIBP and BBP in articles	2110
Unit costs per case	
Direct costs	EUR 5 479
Indirect costs	EUR 1 918
Intangible (WTP)	EUR 11 586
Total costs	
Direct costs	EUR 11 560 000
Indirect costs	EUR 4 046 000
Intangible (WTP)	EUR 24 447 000
Total annual social costs of male infertility (from 2050 onward)	EUR 40 053 000
weighted average per case	EUR 18 980
Total annual social costs of male infertility (discounted to 2014 with 4% social time preference rate)	EUR 9 760 000
weighted average per case	EUR 4 630
Total annual social costs of male infertility (discounted to 2014 with 2% effective social time preference rate)	EUR 19 635 000
Weighted average per case	EUR 9 310

Note: 2014 values, average, representative year analysis.
Source: Adapted from ECHA, (2017[8]).

Further costs are then added in, relating to the reduced incidence of cryptorchidism (EUR 13.9 million per year) and hypospadias (EUR 9.1 million per year), generating a total quantified benefit of EUR 32.8 million per year with figures discounted at 4% from 2050, and not accounting for growth of incomes over this period. The quantification of these benefits is reliant on a simplified approach to attribution of observed incidence to exposures, though the ranges adopted for the analysis are broader than those for male infertility. At the same time, it is worth noting that the midpoint estimate for both, at 20% of observed cases, is lower than the 27% used for male infertility, which may be suggestive of conservatism.

Several additional effects linked to phthalate exposure are listed in the restriction proposal (Table 3.14). The high figures shown indicate that even a small number of additional cases of many of the effects would significantly increase the estimated benefits

described above. However, these figures need in some cases to be treated with caution. Taking the figures given for obesity (EUR 290 000 per case), autism (EUR 630 000 per case) and low testosterone levels in men (EUR 320 700 per case), a question arises of the severity of cases possibly induced by phthalate exposure relative to the severity considered in the original studies. It would be unwise to assume that these figures represent an average case unless this is absolutely clear from the analysis.

Benefits of the proposed restriction are offset against the impacts that would be associated with substitutes. The authors factor in use of what they consider to be the most hazardous alternative, DINP, providing a conservative perspective.

The value for a statistical case of cancer (VSCC) cited by ECHA (2017[8]) was EUR 350 000, derived by ECHA using information from ECHA (2014[55]), later published as Alberini and Ščasný (2017[56]), as a starting point. However, Alberini and Ščasný (2017[56]) provide a different estimate of EUR 578 000. There is a debate as to how the morbidity contribution to a VSCC can be best modelled, leading to the derivation of the different values.

The comparison of costs and benefits carried out by ECHA starts with what is stated to be an overestimate of costs to industry of EUR 16.9 million per year, higher than the EUR 9.1 million per year associated with reduced male fertility, but less than EUR 32.8 million per year benefit accounting for other plausible and quantifiable benefits (linked to cryptorchidism and hypospadias). On the basis then that benefits exceed costs, the restriction is justifiable. Alternative perspectives are considered to back up this decision, based on break-even analysis.

In a final stage, consideration is given to the effect of uncertainties on the benefit-cost ratio, both on the direction of likely bias and (in crude terms) the magnitude of bias. For only 2 of the 17 uncertainties listed is it considered likely that they bias in favour of demonstrating a net benefit (in both cases by underestimating costs), and then only to what is identified as to a minor degree. Thirteen of the uncertainties are reported as biasing against deriving net benefit, including one to a major degree (exclusion of other health impacts) and one to a moderate degree (lack of account given to economic growth out to 2050). The “moderate” rating for this second uncertainty appears conservative given that benefits would double were it taken into account (and then the benefits for increasing male fertility alone would exceed the costs of the restriction).

Table 3.14. Costs per case for effects that have not been quantified

Cited by ECHA (2017[8])

	Weight of evidence	EUR per case	Comments	Price year
		Male reproductive effects		
Reduced semen quality	Strong		Effect estimated	
Cryptorchidism	Moderate		Effect estimated	
Hyospadias	Moderate		Effect estimated	
Testicular changes	Strong		Effect estimated	
Decreased foetal testosterone	Strong		Effect has several health outcomes, some of which have been assessed	
Decreased AGD	Strong		Predictive of other effects, some of which are quantified. Impact of decreased AGD per se is unclear.	
Germ cell changes	Strong	EUR 81 000	Indirect and intangible costs per case of testicular cancer (Olsson, 2014[6])	?
Increased risk of testicular cancer	Weak	EUR 3.5 million	VSL (ECHA, 2014[55])	2012
		EUR 350 000	Value of a statistical case of cancer (ECHA, 2014[55])	2012
		EUR 410 000	Value of cancer morbidity (ECHA, 2014[55])	2012
		Developmental effects on males and females		
Delayed age of puberty onset	Weak		Hormone therapy may be required, more severe cases may have additional social and behavioural impacts	
Persistent mammary gland changes	Weak		May be predictive of other effects, some of which are monetised	
Delayed mammary gland development	Weak		Hormone therapy may be required, more severe cases may have additional social and behavioural impacts	
Effects on female reproduction	Weak	EUR 29 700	Infertility (Ščasný and Zvěřinová, 2014[57])	2012
		EUR 126 200	Preterm birth leading to very low birth weight (Ščasný and Zvěřinová, 2014[57])	2012
		EUR 8 620		2010
		EUR 3 000	Endometriosis (Hunt et al., 2016[37])	2010
			Fibroid treatment (Hunt et al., 2016[37])	
Neurodevelopmental effects	Weak	EUR 630 000	Autism (Bellanger et al., 2015[34])	2010
		EUR 90 000	ADHD (Bellanger et al., 2015[34])	2010
Effects on metabolism	Weak	EUR 29 600	Diabetes (Legler et al., 2015[33])	2010
		EUR 290 000	Obesity (Legler et al., 2015[33])	2010
		Other effects		
Immunological impacts	Moderate/ strong			
Liver carcinogenesis	Weak	EUR 3.5 million	VSL (ECHA, 2014[55])	2012
		EUR 350 000	Value of a statistical case of cancer (ECHA, 2014[55])	2012
		EUR 410 000	Value of cancer morbidity (ECHA, 2014[55])	2012
		Effects from exposure in adulthood		
Reduced semen quality	Moderate	EUR 7 630	ART costs (Hauser et al., 2015[35])	2010
Low testosterone levels in men	Weak	EUR 320 700	Loss of economic productivity (Hauser et al., 2015[35])	2010

The principal uncertainty in the benefit estimation is identified as determination of the aetiological fraction, the share of total cases across the population that can be attributed to exposure to the four phthalates considered. As noted, for cryptorchidism and hypospadias the fraction is estimated using very broad ranges (2% to 50%, with a mid-point of 20%), though for male infertility the range is smaller (+/- 50% of the mid estimate of 27%). This

narrowing of the range was possible given the depth of statistics on factors leading to infertility.

4. Discussion

4.1. Generic impact assessment framework

Most of the studies considered here have taken an impact-pathway approach (IPA) to quantification of the impacts of phthalates, moving from exposure to impact assessment and then valuation.

HEAL (2014[19]) takes a top-down approach, first quantifying the value of health impacts that have been linked to EDC exposure, and then allocating a share of those impacts (2 to 5%) to EDCs. This share is based on review of the earlier study by Trasande (2014[14]) considering effects of BPA on obesity and CHD. The impact-pathway approach is preferable in any policy assessment where there is sufficient data for its implementation, because it makes best use of available science. The nature of the analysis also leads to an understanding of the benefits of specific actions to control the use of a substance. Further to that, the IPA naturally leads to consideration of the likely impacts of available alternatives, which may be quite different to the original substance (the potential for "regrettable substitution"). However, the use of top-down methods can aid understanding of the potential magnitude of effects overall and hence the potential for underestimation of impacts: reliance solely on studies following the IPA may never open out the question of the extent to which analysis fully describes the problems faced.

The Trasande et al. (2015[32]) and (2016[36]) studies create a systematic approach to the evaluation of evidence on EDC substances, drawing together experts from several disciplines. The approach is valuable in several ways, for example:

1. It has succeeded in generating damage estimates for a variety of substances and effects.
2. It summarises confidence in estimates in detail, for example, seeking to account for variability in the proof of causation from toxicological and epidemiological evidence.

The ECHA (2016[7]) proposal for restricting use of 4 phthalates provides a case where the objective concerned the impact assessment of a proposal for legislation, in contrast to the other studies considered that were more research oriented (though certainly policy relevant). The study limited quantification to those impacts that were considered quantifiable with the greatest confidence (those linked to male reproduction). However, it built on this a framework for dealing with uncertainty, accounting for unquantified biases by defining the direction of bias on the benefit-cost ratio and distinguishing between those biases likely to be important from those that were not.[16]

[16] See Table 34, page 92, of the ECHA (2017[8]) report.

4.2. Implementation of the impact-pathway approach

Table 4.1 reviews the strength of analysis at each stage of the impact pathway:

Table 4.1. Comments on the strength of assessment at different stages of the impact pathway.

Stage of assessment	Comments
Release of phthalates	Good information on phthalate production and use is available.
Exposure assessment	Data on exposure to phthalates is available from biomonitoring studies including the COPHES / DEMOCOPHES project in Europe (Schindler et al., 2014[58]) and NHANES in the USA. The extent to which this provides information on a range of different phthalates, rather than a limited number considered as key indicators, is questionable.
Impact identification	Many health impacts have been identified as linked to exposure to phthalates. These affect the reproductive system, neurodevelopment, cancer incidence, obesity, diabetes, asthma and allergy. However, the strength of association is variable. Several environmental impacts have also been noted, particularly for aquatic ecosystems. However, quantification of these effects beyond assessment of the presence or absence of risk is lacking.
Impact assessment	Information on the population at risk, incidence of disease, etc., is readily available in Europe and the US. The key difficulty for the impact assessment lies in determination of the attributable fraction of disease for any specific substance. From the toxicological research there will typically be a need to extrapolate information across concentration ranges and often between species.
Valuation of impacts	In most cases, health impacts are valued using at least the direct costs associated with medical care. In some, productivity losses are also added in. However, in rather few cases is account taken of disutility, even though this accounts for the largest share of impacts when included (see, e.g. Olsson et al. (2014[6])). Amongst the US studies there is a tendency to value disutility by reference to QALY or DALY loss, applying a value of USD 50 000 per QALY or DALY. This value was derived from the health economics literature some years ago and its continued use must be questioned.
Benefits transfer	Processes for benefits transfer (to different countries and over different time periods) seem robustly applied across the studies considered. Inflation of direct healthcare costs has considered rates specific to the health sector. Discount rates of 3% or 4% are used as appropriate in all studies where relevant.
Uncertainty assessment	Several studies provide ranges for effects and their values. However, the actual meaning and validity of these ranges may not be apparent. The ECHA (2017[8]) background document on the proposed restriction of four phthalates provides a good example of uncertainty assessment in the context of CBA.
Stage of assessment	The ECHA (2017[8]) background document on the proposed restriction of four phthalates provides a good example of uncertainty assessment

From this, it is concluded that the key uncertainties affecting the analysis lie in the impact assessment stage with respect to:

- identification of impacts relevant to specific substance under investigation
- characterisation of concentration/exposure/dose response relationships
- limitation of impact assessment to sub-groups of the population, when others may also be affected
- within that, identification of any toxicological thresholds for analysis.

Whilst an understanding of the mechanism of action of a substance (alone or in combination with others that have similar effects) can be useful in answering these questions, it is not essential for impact quantification.

Given a lack of quantitative exposure-response data on human response to specific phthalates, it is necessary to work with other information, for example from animal studies and from human epidemiology where co-exposure to risk cannot be directly controlled. The problems in extrapolating information from other situations are demonstrated by ECHA (2017[8]) in its Table 7, showing the derivation of the DNEL, and

involving assessment factors to adjust for interspecies differences, allometric differences and intra-species variability. The same report also demonstrates the limited availability of response functions for specific substances, when it lists unit costs (EUR per case, EUR per episode, EUR per death, etc.) for a variety of impacts that are considered relevant but which were not quantifiable.[17] The limited availability of information for the four phthalates is perhaps surprising (and certainly indicative of a broader problem) given the concern that has been expressed about them for many years.

Thresholds become especially problematic when dealing with impacts whose cause is multi-factorial: toxicologically based thresholds may not be exceeded by a substance considered in isolation, but may be exceeded by the collective action of a group of substances (or other risk factors) that target the same health condition, particularly if they follow the same mechanism of effect. The approach of ECHA (2016[7]) and (2017[8]) in considering four phthalates collectively, rather than individually is notable, given that almost all previous restriction proposals under REACH have dealt with single substances only.

Specific consideration needs to be given to the robustness of the monetisation step, given the focus here on valuation. The key difficulties here lie in the following:

- The availability of information on the costs of lost utility. In many cases, this is not considered at all, with quantification based solely on healthcare costs or healthcare plus lost productivity. Several studies have valued utility for at least some elements by applying a standard value of USD 50 000 per QALY or DALY, based on US practice in health economics. The question for which this value was developed concerns the efficient allocation of resources available for public healthcare: a critical question when considering how society can best benefit from the money available to healthcare providers. However, this is a different perspective to the question faced here, where analysis seeks to assess whether the benefits of continued use of a substance outweigh its costs to society. One might argue that the two should be linked, but there is no evidence that this is the case, and significant evidence that it is not from the valuation literature.
- Understanding the long-term consequences of disease, ensuring that account is taken of co-morbidities as necessary. There is limited evidence that this is done comprehensively. Partial account may be made when costing out impacts on productivity where data permit. However, impacts on healthcare costs are unlikely to be factored in unless they are accounted for specifically in the impact assessment.

All authors have followed appropriate procedures for benefits transfer. There is little variability in the discount rates used (3 or 4% in all studies).

A further problem concerns valuation of impacts that may be a consequence of several factors. How, for example, should one interpret a death linked to EDC exposure, when the timing of the death of any individual will be a complex function of (taking an example of relevance here):

- exposure to phthalate leading to low testosterone levels, increasing the risk of premature death

[17] The reason for listing the unit cost data in the paper is to demonstrate that a few additional cases of various effects would add substantially to the benefit-cost ratio, reinforcing the robustness of the conclusions reached on the validity of the proposed restriction.

- poor diet
- smoking
- lack of exercise
- alcohol consumption
- exposure to other environmental and genetic stresses.

This issue is important in other fields of environmental pollution also, notably in relation to assessment of air pollution impacts. COMEAP (2010[59]) considers that the number of deaths quantified in assessment of exposure to fine particles does not represent the number of people whose death is influenced to any degree by exposure to pollution, but the number of "equivalent attributable deaths" linked to the added burden on health arising from exposure. The reasoning is that the individuals affected by air pollution will also be affected by other stresses (as above) and each of these will contribute in some way to the timing of death. COMEAP concluded that the estimated number of deaths that could be associated at least partially to PM exposure was likely higher or much higher than the estimated number of deaths. Expressed as "equivalent attributable deaths" strengthens the logic of valuing mortality using the value of statistical life rather than a life years lost approach using either an estimate of VOLY or the value of a QALY or DALY, as has been applied in several of the studies above.

4.3. Summary of unit values

Table 4.2 summarises the unit values used in the various studies described in Section 3. Cases where costs have included healthcare (direct) costs, productivity (indirect) losses and disutility ("intangible" costs) are shown in green text. Cases where only 2 of these elements are shown in blue font and those where only 1 element was considered in brown font. Estimates focused on phthalates specifically are identified with the grey shading. Some of the studies considered here did not consider phthalates specifically, but rather exposure to multiple EDCs (e.g. HEAL (2014[19]); Olsson et al. (2014[6]); some parts of the Trasande studies).

There is a mix of agreement and disagreement in values between studies. Some of the agreement naturally comes from studies using the same source for valuation (e.g. ECHA (2017[8]) refers to Olsson et al. (2014[6]) for testicular cancer costs). However, there is also some significant disagreement in the table. As an example, Trasande (2014[14]) values child obesity at EUR 1 650 whilst Attina et al. (2016[38]) apply EUR 54 000 per case. Reasons for variation are that the valuations are not always directly comparable, with the lower value perhaps addressing impacts on an annual basis, or the upper value adding in co-morbidity, or estimates accounting for different parts of the mix of direct, indirect and disutility costs.

The language used to describe the different elements of cost requires comment. The terms "direct cost", "indirect cost" and "intangible cost" (=disutility) are used on a common basis in most of the papers considered. Use of the word "intangible" is inappropriate as it downplays the importance of the loss of health utility. As results from the papers demonstrate, these costs, when accounted for, outweigh the others considered in the analysis.

Several factors make the cost estimates incomplete:

1. the limited account taken of disutility
2. limits in the range of effects for which assessment has been carried out

3. the failure to provide monetised estimates of harm to ecosystems.

Each of these factors has potential to add significantly to the damage estimates identified here.

Table 4.2. Summary of unit values used in the studies reviewed above

All figures in EUR, price years in second row of table

	Trasande (2014[14])	HEAL (2014[19])	Olsson et al. (2014[6])	Trasande et al. (2015[32]) and (2016[36])	Attina et al. (2016[38])	ECHA (2017[8])
Price year	**2008**	**2010**	**2013**	**2010**	**2010**	**2010/12/14**
			Obesity, diabetes			
Childhood obesity	1 650				54 000	
Overweight children					26 000	
Adult obesity	39 000			290 000	215 000	[290 000]
Diabetes		Unspecified		28 000	54 000	[29 600]
			Neurodevelopment			
Autism		12 445		630 000	981 000	[630 000]
ADHD		10 650		77 000	119 000	[90 000]
IQ point loss				9 600	14 500	
Intellectual disability				360 000	1.0 million	
			Reproductive system			
Female infertility						[29 700]
Preterm birth with VLBW infant						[126 000]
Fibroids				2 900	5 200	[3 000]
Endometriosis				8 600	415 000	[8 620]
Male infertility			3 480	7 600	7 800 - 11 000	18 980
Cryptorchidism		5 715 - 8 415	34 674	28 000	6 291	28 000
Hypospadias		Unspecified	39 617			16 900
Human fertility. treatment		4 500 - 51 822				
Reduced semen quality						[7 630]
Low-T deaths				320 000	0.33 to 0.62 million	[320 000]
			Cancers			
VSL						[3.5 million]
Statistical case of cancer						[350 000]
Value of cancer morbidity						[410 000]
Breast cancer		Unspecified				
Endometrial cancers		Not quantified				
Thyroid cancer		Not quantified				
Prostate cancer		Unspecified				
Testicular cancer			80 980	124 000	17 000	[81 000]
			Other conditions			
Coronary heart disease	33 000					
Allergy episode						[18]
Asthma episode						[50]

Note: Cells shaded brown include effects linked to phthalates. Figures in square brackets for ECHA 2017 were not used in the report. Brown font: One of direct, indirect and disutility costs accounted for. Blue font: Two of direct, indirect and disutility costs accounted for. Green font: Direct, indirect and disutility costs accounted for. Red font: No quantification of costs.

4.4. Relative values attached to different phthalates

It is not possible to reach a conclusion on the differences in the costs of impacts attributable to different phthalates from the results provided in the papers reviewed here. In the studies reviewed here, several types of impacts are considered against an aggregate of phthalate or multiple EDC exposure. Adult obesity and diabetes is considered specifically against DEHP exposure and generates substantial costs in the work of both Trasande et al. (2015[32]) and (2016[36]) for Europe and Attina et al. (2016[38]) for the United States. Given that DEHP is the phthalate produced in greatest volume, and there is toxicological and other evidence that demonstrates its impacts on health, it is not surprising that it generates significant costs. However, to take this as evidence that it is more harmful than other phthalates per unit mass would be wrong: the literature may be biased towards DEHP simply because it is produced in greater volume than other phthalates and has been monitored more extensively as a result.

The methods used by ECHA (2016[7]) and (2017[8]) account for the relative hazard of the four phthalates considered in the restriction proposal, based on oral DNELs. This approach provides a mechanism for quantifying differences in impact between phthalates, though disaggregated results are not provided.

4.5. Closing remarks

Over the last 5 years there has been significant growth in the estimation of the economic impacts of endocrine disrupting chemicals. The analysis that has been carried out to date demonstrates that the health costs of these chemicals in both the United States and Europe is substantial, running into the billions of euros each year. It is notable that different legislative priorities in Europe and the United States have led to sizeable differences in the magnitude of damage estimates of substances for those effects for which quantification has proved possible (noting the importance of PBDE in the United States and of organophosphate pesticides in Europe).

For the purpose of developing targeted control strategies, the development of estimates against a basket of EDCs ("multiple exposures", "phthalates", etc.) is problematic as it does not indicate precisely where resources should best be employed to reduce risk. This requires systematic assessment of anthropogenic EDCs to improve understanding of hazard profiles of substances individually and collectively, and to enable identification of which substances have the highest risk potential when exposure is accounted for. Reference to the toxicological properties of substances is important: too much reliance on epidemiological data may create an incomplete picture and one that takes many years to develop. In the meantime, of course, society will be incurring the costs of inaction.

The use of economic assessment provides a valuable tool for assessing the desirability of further regulation of chemicals from a societal perspective, enabling the costs and benefits of action to be compared. This should lead to a more rational allocation of resource. However, it is important to retain an understanding of the biological and physical impacts that underpin the economic outputs of analysis, especially when, as in the case of phthalates, there are long-term consequences of action or inaction.

Annex 1: Table of the most common phthalates[18]

Name	Structural formula	Mol weight, g/mol	CAS No.
Dimethyl phthalate, DMP	$C_6H_4(COOCH_3)_2$	194.18	131-11-3
Diethyl phthalate, DEP	$C_6H_4(COOC_2H5)_2$	222.24	84-66-2
Diallyl phthalate, DAP	$C_6H_4(COOCH_2CH{=}CH_2)_2$	246.26	131-17-9
Di-n-propyl phthalate, DPP	$C_6H_4[COO(CH_2)_2CH_3]_2$	250.29	131-16-8
Di-n-butyl phthalate, DBP	$C_6H_4[COO(CH_2)_3CH_3]_2$	278.34	84-74-2
Diisobutyl phthalate, DIBP	$C_6H_4[COOCH_2CH(CH_3)_2]_2$	278.34	84-69-5
Butyl cyclohexyl phthalate, BCP	$CH_3(CH_2)_3OOCC_6H_4COOC_6H_{11}$	304.38	84-64-0
Di-n-pentyl phthalate DNPP	$C_6H_4[COO(CH_2)_4CH_3]_2$	306.40	131-18-0
Dicyclohexyl phthalate DCP	$C_6H_4[COOC_6H_{11}]_2$	330.42	84-61-7
Butyl benzyl phthalate, BBP	$CH_3(CH_2)_3OOCC_6H_4COOCH_2C_6H_5$	312.36	85-68-7
Di-n-hexyl phthalate, DNHP	$C_6H_4[COO(CH_2)_5CH_3]_2$	334.45	84-75-3
Diisohexyl phthalate, DIHP	$C_6H_4[COO(CH_2)_3CH(CH_3)_2]_2$	334.45	146-50-9
Diisoheptyl phthalate, DIHpP	$C_6H_4[COO(CH_2)_4CH(CH_3)_2]_2$	362.50	41451-28-9
Butyl decyl phthalate, DBP	$CH_3(CH_2)_3OOCC_6H_4COO(CH_2)_9CH_3$	362.50	89-19-0
Di(2-ethylhexyl) phthalate, DEHP, DOP	$C_6H_4[COOCH_2CH(C_2H_5)(CH_2)_3CH_3]_2$	390.56	117-81-7
Di(n-octyl) phthalate, DNOP	$C_6H_4[COO(CH_2)_7CH_3]_2$	390.56	117-84-0
Diisooctyl phthalate, DIOP	$C_6H_4[COO(CH_2)_5CH(CH_3)_2]_2$	390.56	27554-26-3
n-Octyl n-decyl phthalate, ODP	$CH_3(CH_2)_7OOCC_6H_4COO(CH_2)_9CH_3$	418.61	119-07-3
Diisononyl phthalate, DINP	$C_6H_4[COO(CH_2)_6CH(CH_3)_2]_2$	418.61	28553-12-0
Di(2-propylheptyl) phthalate, DPHP	$C_6H_4[COOCH_2CH(CH_2CH_2CH_3)(CH_2)_4CH_3]_2$	446.66	53306-54-0
Diisodecyl phthalate, DIDP	$C_6H_4[COO(CH_2)_7CH(CH_3)_2]_2$	446.66	26761-40-0
Diundecyl phthalate, DUP	$C_6H_4[COO(CH_2)_{10}CH_3]_2$	474.72	3648-20-2
Diisoundecyl phthalate, DIUP	$C_6H_4[COO(CH_2)_8CH(CH_3)_2]_2$	474.72	85507-79-5
Ditridecyl phthalate, DTDP	$C_6H_4[COO(CH_2)_{12}CH_3]_2$	530.82	119-06-2
Diisotridecyl phthalate, DITP	$C_6H_4[COO(CH_2)_{10}CH(CH_3)_2]_2$	530.82	68515-47-9

[18] https://en.wikipedia.org/wiki/Phthalate#Table_of_the_most_common_phthalates

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