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Male Reproductive Disorders, Diseases, and Costs of Exposure to Endocrine-Disrupting Chemicals in the European Union

Russ Hauser, Niels E. Skakkebaek, Ulla Hass, Jorma Toppari, Anders Juul, Anna Maria Andersson, Andreas Kortenkamp, Jerrold J. Heindel, and Leonardo Trasande*

Introduction: Increasing evidence suggests that endocrine-disrupting chemicals (EDCs) contribute to male reproductive diseases and disorders.

Purpose: To estimate the incidence/prevalence of selected male reproductive disorders/diseases and associated economic costs that can be reasonably attributed to specific EDC exposures in the European Union (EU).

Methods: An expert panel evaluated evidence for probability of causation using the Intergovernmental Panel on Climate Change weight-of-evidence characterization. Exposure-response relationships and reference levels were evaluated, and biomarker data were organized from carefully identified studies from the peer-reviewed literature to represent European exposure and approximate burden of disease as it occurred in 2010. The cost-of-illness estimation utilized multiple peer-reviewed sources.

Results: The expert panel identified low epidemiological and strong toxicological evidence for male infertility attributable to phthalate exposure, with a 40–69% probability of causing 618 000 additional assisted reproductive technology procedures, costing €4.71 billion annually. Low epidemiological and strong toxicological evidence was also identified for cryptorchidism due to prenatal polybrominated diphenyl ether exposure, resulting in a 40–69% probability that 4615 cases result, at a cost of €130 million (sensitivity analysis, €117–130 million). A much more modest (0–19%) probability of causation in testicular cancer by polybrominated diphenyl ethers was identified due to very low epidemiological and weak toxicological evidence, with 6830 potential cases annually and costs of €848 million annually (sensitivity analysis, €313–848 million). The panel assigned 40–69% probability of lower T concentrations in 55- to 64-year-old men due to phthalate exposure, with 24 800 associated deaths annually and lost economic productivity of €7.96 billion.

Conclusions: EDCs may contribute substantially to male reproductive disorders and diseases, with nearly €15 billion annual associated costs in the EU. These estimates represent only a few EDCs for which there were sufficient epidemiological studies and those with the highest probability of causation. These public health costs should be considered as the EU contemplates regulatory action on EDCs. **(*J Clin Endocrinol Metab* 100: 1267–1277, 2015)**

During the past few decades, rates of testicular germ cell cancer (TGCC) have increased among young men all over the world, particularly among Caucasians. The highest incidences of TGCC have been found among Caucasians in Europe, the United States, Chile, Australia, and New Zealand, indicating a genetic component to testicular cancer. In the United States, Caucasians are significantly more prone to develop TGCC, although the disparity is decreasing (1). Denmark and Norway have witnessed quite dramatic increases over only two gener-

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* Author affiliations are shown at the bottom of the next page.

Abbreviations: AGD, anogenital distance; ART, assisted reproductive technology; CI, confidence interval; DBP, dibutyl phthalate; DEHP, diethylhexyl phthalate; EDC, endocrine-disrupting chemical; ERR, exposure-response relationship; EU, European Union; MBP, monobutyl phthalate; MBzP, monobenzyl phthalate; OR, odds ratio; PBDE, polybrominated diphenyl ether; TGCC, testicular germ cell cancer; TTP, time to pregnancy.

ations (2, 3), and previous "low-incidence" countries like Finland, Italy, Spain, and Holland are now catching up with rather substantial increases (4). In addition, on average a 25% increase in Europe can be expected by 2025, according to the International Agency for Research in Cancer.

Genome-wide association studies show that genetics can only explain 20–25% of TGCC (5), suggesting a role for environmental factors such as endocrine-disrupting chemicals (EDCs). Studies on immigrants to Sweden from Denmark and Finland have shown that the first generation of children carry the risk of TGCC from their home country, whereas the next generation growing up in Sweden obtains the Swedish risk of TGCC (6), also suggesting a role for environmental factors. Numerous biological studies are in line with the fetal hypothesis for testicular cancer (7, 8). The precursor cell for TGCC, the carcinoma in situ cell, expresses embryonic markers similar to primordial germ cells (9). Furthermore, given that the epidemic of TGCC has occurred over a relatively short period of time (ie, decades), it is likely that only environmental factors can explain the trends.

There are also data to suggest that the incidence of cryptorchidism, a strong risk factor for TGCC, is increasing (10, 11), although the incidences vary (12). Phthalates, pesticides, brominated flame retardants, diethylstilbestrol, and dioxins are among the synthetic chemicals that have been identified as plausible contributors (13). Male infertility is also common, although exact numbers are difficult to ascertain because it must be considered a condition of a couple, where the reproductive health of both sexes plays a role (14). In Denmark, where reliable registration of all types of assisted reproduction takes place, 8% of all children are now born after assisted reproduction (http://www.fertilitetsselskab.dk). Although genetic forms of male infertility exist, including chromosome disorders, eg, Klinefelter syndrome (15) and Y microdeletions (16), in most cases no known etiology exists. Epidemiological studies have explored associations of reduced male fertility and poor semen quality with multiple EDCs, including phthalates, bisphenol A, and polyfluorinated chemicals (17).

Infertility due to poor semen quality, as in cryptorchidism and hypospadias, is also a risk factor for decreased Leydig cell function with a decreased T/LH ratio (18). There are now three large studies from the United States, Denmark, and Finland showing serum T levels falling among otherwise healthy men in the general population, with some, but not all, of the results explained by increasing rates of obesity (18–20). Because T has a fundamental role for normal male physiology and health (21), these trends raise concerns about a role for environmental endocrine disruptors in reduced sex steroids.

This epidemic of male reproductive problems, which cannot be explained by genetic changes, has occurred contemporaneously with increasing exposures to various environmental factors through modern lifestyle. Increasing evidence shows that such exposures include multiple EDCs that can induce male reproductive disorders and diseases in experimental animals similar to what we are witnessing in humans. The EDCs causing such effects in experimental animals include chemicals such as phthalates, including dibutyl phthalate (DBP) and diethylhexyl phthalate (DEHP); pesticides, including procymidone, vinclozolin, linuron, and prochloraz; bisphenol A; the dichlorodiphenyltrichloroethane metabolite p,p'-Dichlorodiphenyldichloroethane; and UV filters, such as octyl methoxycinnamate and 4-methylbenzylidene camphor (22, 23). Concurrent with the accumulating evidence in animal studies, there are an increasing number of human studies suggesting that EDCs may contribute to male reproductive disorders and diseases (24).

The burden of male reproductive health problems is significant, both at the individual and population level. They are also costly. Prevention of EDC exposures has the potential to reduce the incidence of many male reproductive disorders and diseases and their associated health care and other social costs in the European Union (EU) (24). In the context of the ongoing regulatory process, we therefore examined probability of causation for EDCs in male reproductive disorders and quantified the potential burden of disease and costs.

Materials and Methods

Overall approach

The expert panel focused on four exposure-outcome relationships: 1) phthalates and infertility; 2) polybrominated diphenyl ethers (PBDEs) and testicular cancer; 3) PBDEs and cryptorchidism; and 4) phthalates and reduced serum T. The panel selected these exposure-outcome relationships from many others because of the presence of well-conducted human and animal studies to assess reproductive effects of these EDCs. We adhered to the

Department of Environmental Health (R.H.), Harvard T.H. Chan School of Public Health, Boston, Massachusetts 02115; Department of Growth and Reproduction (N.E.S., A.J., A.M.A.), Rigshospitalet, EDMaRC and University of Copenhagen, DK-2100 Copenhagen, Denmark; National Food Institute (U.H.), Technical University of Denmark, 2800 Kgs Søborg, Denmark; Departments of Physiology and Pediatrics (J.T.), University of Turku, 20014 Turku, Finland; Brunel University (A.K.), London UB8 3PH, United Kingdom; National Institute of Environmental Health Sciences (J.J.H.), Division of Extramural Research and Training, Research Triangle Park, North Carolina 27709; New York University (NYU) School of Medicine (L.T.), New York, New York 10016; NYU Wagner School of Public Service (L.T.), New York, New York 10012; NYU Steinhardt School of Culture, Education, and Human Development (L.T.), Department of Nutrition, Food, and Public Health, New York, New York 10003; and NYU Global Institute of Public Health (L.T.), New York, New York 10003

approach described in the accompanying overarching manuscript (92) in evaluating the strength of the epidemiological (25, 26) and toxicological literature (27) and assigning probability of causation (28). The Supplemental Data describes exposure biomarker inputs used to model exposure in the EU and approaches to valuing costs of testicular cancer, cryptorchidism, infertility and the subsequent need for assisted reproductive technology (ART), and mortality due to reductions in T, whereas subsequent sections of this article describe the estimation of affected populations and attributable prevalence/incidence.

Modeling PBDE-attributable cryptorchidism

The expert panel selected a case-control study of breast milk PBDE in relationship to cryptorchidism to extrapolate attributable burden and costs (29). The population distribution of PBDE in breast milk in the EU (10th, 25th, 50th, 75th, and 90th percentiles) was extrapolated from levels in serum using data from a systematic review that identified a serum/milk ratio averaging 0.8, with a range of 0.54–0.9 (93). The mean ratio was used in main estimates, whereas the entire range was incorporated in sensitivity analyses. Following a request from the panel, the first author of this case-control study calculated odds ratios (ORs) for cryptorchidism per natural log unit (30). We then exponentiated them by the ratio of the estimated PBDE levels in breast milk, assuming a reference level corresponding to the 50th percentile in the EU. This exponentiation generated OR values in each of the highest quantiles in the EU, which were multiplied by incidence of congenital cryptorchidism to generate exposed incidence of cryptorchidism. Although past estimates have identified prevalence of cryptorchidism ranging from 0.9–1.8% (31), the panel used a 1% baseline in this analysis. The attributable incidence was then applied against the number of births for each country in 2010, which was obtained from Eurostat (32).

Modeling phthalate-attributable infertility

The panel selected a longitudinal study (the Longitudinal Investigation of Fertility and the Environment [LIFE] Study) examining relationships of paternal urinary phthalate metabolites with time to pregnancy (TTP) as a basis for quantifying couples seeking ART due to decreased male fertility (33). ART was defined as medically indicated for TTP $>$ 12 months, and 56% of couples with TTP $>$ 12 months proceeded to ART in our modeling, based upon data from Boivin et al (34). The population of women in a consensual union between the ages of 20 and 44 years in Europe were assumed to have male partners with urinary phthalate concentrations corresponding to the 10th, 25th, 50th, 75th, and 90th percentiles of adults in the DEMOCOPHES project. Data on women in a consensual union were available from the United Nations Department of Economics and Social Affairs (35) in 25 of the EU countries (except Croatia, Cyprus, and Luxembourg), and the exposed population in each of the 25 countries was reduced by the percentage of the population using any contraceptive method. The population of 20- to 44-year-old men was divided into exposure percentile ranges (0-ninth, 10–24th, 25–49th, 50–74th, 75–89th, and 90–99th). The lowest exposure grouping was estimated to have no exposure, whereas the other groups were assumed to have exposure corresponding to the lower bound of the range (eg, 10th percentile for all women in the 10–24th percentile grouping). To calculate the OR for fecundity in each exposure group, the fecundity OR from the LIFE Study for monobenzyl phthalate (MBzP) or monobutyl phthalate (MBP) was exponentiated by the ratio of the estimated concentration in each exposure group to a reference level of 0.2 ng/mL (the limit of detection typically identified in most studies). For example, the 10th percentile was divided by 0.2 and exponentiated by the OR for the LIFE Study to estimate OR of fecundity for the 10–24th exposure percentile of the EU population. Recognizing that infertility is not rare and that application of the OR could lead to overestimation, we estimated relative risk from OR using the formula of Zhang and Yu (36).

To translate reduced fecundity into increases in TTP $>$ 12 month, data on TTP from a German study of 346 natural family planning couples (mean age of female partner, 29 $\pm$ 3.7 y) were obtained (37). This study measured TTP over a 12-month period. We modeled shifts from the TTP in the EU by multiplying months to conception for each exposure group of the population by the inverse of the relative risk of infecundity corresponding to the appropriate level of exposure. The percentage of the population shift in TTP due to phthalate exposure above 12 months was quantified as the incremental prevalence of infertility attributable to MBzP or MBP. This incremental prevalence was only applied to 92% of the population, corresponding to the percentage who conceived in $<$ 12 months in the German study. The panel determined there to be substantial laboratory evidence for dose-additive effects of the parent compounds of MBzP and MBP and agreed upon addition of the attributable infertility for MBzP to the attributable infertility for MBP after subtracting the product of the two percentages to avoid double counting.

Modeling PBDE-attributable testicular cancer

The expert panel used a case-control study of testis cancer in relation to the sum of maternal PBDE-47, PBDE-99, and PBDE-153 in serum (above the median in the controls, 3.66 ng/g lipid). Using the PBDE-47 biomarker estimated mean and SD in the EU, the percentages above 3.66 ng/g were estimated using the NORMDIST function in Microsoft Excel for base case estimates and sensitivity analyses. The panel recognized that this approach would underestimate the attributable cases because the researchers in the primary study did not have individual-level data on each congener. The exposure prevalence above 3.66 ng/g of PBDE-47 was input into the Levin equation along with the OR for testicular cancer to calculate the PBDE-attributable fraction. Sensitivity analyses recalculated the attributable fraction based upon alternate estimates of biomarkers of the EU, yielding a different percentage of exposure above 3.66 ng/g. The resultant attributable fractions were applied against the testis cancer incidence in the EU (38) and population estimates from the World Bank (39) to calculate annual PBDE-attributable cases of testicular cancer in the EU.

Modeling phthalate-attributable decreases in T

The panel used a cross-sectional study of a nationally representative US sample in 2011–2012 (40) to quantify decrements in T in the European population attributable to phthalate exposure among 55- to 64-year-old men. Meeker and Ferguson (40) identified exposure-response relationships (ERRs) of urinary total DEHP metabolites and urinary MBP with serum T levels among 40 to 60 year olds, expressed as a percentage decrement per unit increase in phthalate metabolite on the basis of the interquartile range in the US sample. Given that estimated EU levels of MBP are much higher than that identified in the US sample, the ERR for MBP may not apply in the highest ranges of exposure.

The ERR was therefore only applied until the 75th percentile (11.2 μg/dL) in the Meeker and Ferguson (40) study. ERRs for total DEHP metabolites were applied over the entire range of biomarkers in the EU as estimated from DEMOCOPHES. For MBP and DEHP metabolites, the 10th percentile was applied as a reference level. For populations in the 25–49th, 50–74th, 75–89th, and 90–99th percentiles, decrements in T attributable to DBP (the MBP parent compound) and DEHP were quantified and added together to generate decrements in T attributable to phthalates.

Modeling public health consequences of decreased T

The panel used a meta-analysis of 11 longitudinal studies (mean age, 61 y; average follow-up, 10 y) that identified increased all-cause mortality (RR 1.35, 95% confidence interval [CI], 1.13–1.62) in associations with lower T levels, expressed on the basis of a difference between the lowest and highest tertiles (41). Data from a large, representative European sample (42) were used to identify an increment in T between the lowest and highest tertiles (5.10 nmol/L) on which to apply the RR of 1.35 from the meta-analysis. After generating an increase in risk of mortality per nmol/L decrease in serum T, this was applied against the decrement in T due to phthalates in each exposed quantile to generate relative risk of death due to phthalate-attributable decreases in T. Baseline age-standardized mortality rates were obtained by Organisation for Economic Co-operation and Development from each country (43). Applying these rates to the estimated relative risk in the presence of reduced T generated the phthalate-exposed mortality rate, from which the baseline rate was subtracted to generate the attributable increment in death rate. This increment in death rate was applied against population data from the United Nations from each country (44) to generate the attributable number of annual deaths among 55 to 64 year olds.

Results

PBDE-attributable cryptorchidism

The panel identified a high-quality case-control study exploring the association between cryptorchidism and PBDE concentrations in breast milk (62 cryptorchid males and 68 controls) and placenta (95 cryptorchid males and 185 controls) (29). Breast milk and placenta concentrations were considered proxies for fetal exposure. Positive associations were found between breast milk concentration of PBDEs and cryptorchidism in the Danish and combined Danish-Finnish mother-child pairs, but not in the Finnish mother-child pairs alone. The overall OR per log unit increase in PBDE-47 was 5.6 (95% CI, 1.7–18.6) (45). The Finnish data demonstrated a directionality of associations similar to the Danish data, but it was not statistically significant ($P \geq .06$). There were no associations of placental PBDEs with cryptorchidism in either cohort. Breast milk contains more fat than placental tissue, and therefore the PBDE concentrations in the placental tissue were lower, and measurements were less certain. Because this was only a single small case-control study, the panel's confidence in the effect estimate is limited, and thus the panel evaluated the strength of evidence to be low.

There are no developmental animal toxicity studies investigating whether PBDEs induce cryptorchidism. However, exposure in adult male rats has shown clear adverse effects and antiandrogenicity in a Hershberger assay (46). Also, developmental exposure has been shown to affect anogenital distance (AGD) and preputial separation in male pups (47). There are several in vitro studies showing an antiandrogen mechanism of action (46, 48). Cryptorchidism is considered as one of the classical effects of exposure to antiandrogenic substances during male sexual development (49). The panel therefore identified strong toxicological evidence for PBDEs as an antiandrogen causing cryptorchidism in experimental animals. Using the Intergovernmental Panel on Climate Change (IPCC) criteria, the sum of the toxicological and epidemiological evidence suggests 40–69% probability of causation.

Using the range of scenarios for serum PBDE based upon available data as well as a range of breast milk/serum ratios, the upper median of EU newborns was exposed to levels ranging from 3.25–7.83 ng/g, with lower (1.78–4.07 ng/g) and higher (6.02–14.51 ng/g) bound scenarios

Table 1. PBDE-Attributable Cryptorchidism in Europe, 2010

Expert panel evaluation of epidemiological evidence	Low					
Expert panel evaluation of toxicological evidence	Strong					
Probability of causation, %	40–69					
Percentile of exposure	0–9	10–24	25–49	50–74	75–89	>90
Percentile assumed	0	10	25	50	75	90
Estimated breast milk PBDE-47 (base case)	<LOD	<LOD	<LOD	3.25	5.76	7.83
Estimated breast milk PBDE-47 (lower bound)	<LOD	<LOD	<LOD	1.78	2.98	4.07
Estimated breast milk PBDE-47 (higher bound)	<LOD	<LOD	<LOD	6.02	10.66	14.51
Odds of cryptorchidism (base case)	1.00	1.00	1.00	1.00	1.53	1.93
Odds of cryptorchidism (lower bound)	1.00	1.00	1.00	1.00	1.47	1.86
Attributable increment in cryptorchidism	4615 (4155–4615)					
Attributable costs of cryptorchidism	€130 million (€117–130 million)					

Abbreviation: LOD, limit of detection.

(Table 1). Using the 50th percentile as the reference level, main estimates identified ORs of 1.53 and 1.93 in the two most highly exposed groups, comprising one-fourth of the population, while lower bound estimates identified ORs of 1.47 and 1.86, respectively. Using these inputs, the panel estimated 4615 attributable cases (sensitivity analysis, 4155–4615) with associated costs of €130 million (sensitivity analysis, €117–130 million).

Phthalate-attributable ART

The panel identified several epidemiological studies exploring the associations between urinary concentrations of phthalate metabolites and poorer semen quality, a predictor of fertility (50). Several publications on men from infertility clinics found decreased semen quality in relation to higher urinary concentrations of phthalate metabolites (51–53). However, studies among young men from the general population did not find associations of urinary concentrations of phthalate metabolites with poorer semen quality (54, 55). Differences in the study population may account for differences in sensitivity to phthalates, with couples presenting to infertility clinics at increased risk of poorer semen quality in relation to phthalate exposure. The lack of consistent findings across the studies dampened confidence of the panel for the presence of dose-response relationships in the positive studies. Overall, the panel identified low strength of the epidemiological evidence for phthalate exposure causing reduced semen quality, thereby contributing to the increased need for ART.

The panel recognized, based on toxicological studies, that the period of fetal development is more vulnerable to phthalate and other antiandrogen exposures than adult exposures. Additional and supportive human data associate fetal exposure to phthalates with reduced infant AGD (56, 57), and shortened adult AGD is associated with reduced semen quality (58) and T level (59). Tracking of AGD from infancy to adulthood has not been studied, however, and so this evidence did not increase confidence in the degree of causation by the panel.

Lower semen quality has an impact on the TTP and the ability to have a child (60, 61). In addition to the publications on phthalates and semen quality, there is recent additional evidence supporting the association of phthalates with reduced male fertility. Buck Louis et al (33) studied 505 couples planning a pregnancy and found an association between higher paternal urinary concentrations of MBP and MBzP and increased TTP, most likely mediated through altered semen quality. The panel agreed that this prospective study, well controlled for confounders with an ERR, provided further support for causation, but the panel also agreed that the study did not have data on semen quality to suggest a mediation path leading to increased TTP. The panel therefore assessed low epidemiological evidence supporting causation of adult phthalate exposure with increased TTP.

In reviewing the toxicological data on phthalate exposure and fertility outcomes, the panel identified extensive and strong evidence that developmental exposure to several antiandrogenic phthalates affected male reproductive development, leading to a long list of adverse effects including reduced AGD, increased prevalence of hypospadias and cryptorchidism, reduced T, and low sperm counts in adulthood (22, 62, 63). Although the adult male reproductive system is less sensitive to phthalate exposure, insofar as higher doses are required to affect fertility outcomes (64, 65), the panel agreed that the toxicological evidence for phthalate-induced infertility is strong.

The LIFE study found associations of MBzP and MBP with increased TTP quantified by fecundity ORs (0.82 and 0.77, respectively, in full multivariable models) using Cox proportional hazard models (33). The panel suggested using a reference level of 0.2 ng/mL, the typical level of detection for urinary phthalates in most laboratories.

In each of the exposed groups anticipated to have urinary phthalate concentrations corresponding to the 10th, 25th, 50th, 75th, and 90th percentiles in DEMOCOPHES, fecundity ORs of 0.68–0.85 were identified for MBzP, whereas ORs of 0.52–0.65 were identified for MBP (Table 2). Attributable increments in infertility over and above the baseline of 8% ranged from 2–6% for MBzP and 6–11% for MBP. Attributable increments in infertility rates across the entire EU population were 3.30 and 7.15%, respectively. After accounting for double counting, the attributable increment in infertility was 9.38%. In the EU, excluding Croatia, Cyprus, and Luxembourg (for which no data were available), 59.5 million women 15–49 years of age were identified to be in a consensual union, of whom 11.8 million were ages 20–44 and not using contraception. Applying the attributable increment of 9.38% and accounting for only 56% of couples seeking medical care, 618 000 infertility treatments were identified, at a cost of €4.71 billion. Overall, using the IPCC criteria, the probability of causation of male infertility by phthalate exposure was identified to be 40–69%.

PBDE-attributable testis cancer

The panel identified case-control studies in which EDC levels were measured, three of which measured EDCs in men with testis cancer compared to control men (66, 67). However, in some studies the exposure was measured outside the relevant perinatal window (7, 8), ie, exposure after birth, and therefore only the study by Hardell et al (67) was considered further.

Table 2. Phthalate-Attributable Male Infertility and Resulting ART, 2010

Expert panel evaluation of epidemiological evidence	Low					
Expert panel evaluation of toxicological evidence	Strong					
Probability of causation, %	40–69					
Percentile of exposure	0–9	10–24	25–49	50–74	75–89	>90
Percentile assumed	0	10	25	50	75	90
Urinary MBzP, ng/mL	0	1.4	2.5	4.5	8.7	18
MBzP-exposed fecundity OR	1.00	0.85	0.80	0.76	0.72	0.68
Urinary MBP, ng/mL	0	8.9	14.9	24.5	41.4	68
MBP-exposed fecundity OR	1.00	0.65	0.61	0.58	0.55	0.52
Rate of infertility across entire population of couples attributable to MBzP, %	3.30					
Rate of infertility across entire population of couples attributable to MBP, %	7.15					
Total rate of infertility across entire population attributable to MBP +/or MBzP (accounting for double counting), %	9.38					
Women ages 15–49 in consensual union, n	59 527 000					
Women ages 20–44 in consenual union not using contraception, n	11 765 294					
Attributable infertility cases seeking medical care, n	618 000					
Cost of ART attributable to phthalate exposure	€4.71 billion					

The panel focused on one case-control study associating maternal levels of PBDEs with testis cancer in their sons (67). This study assumed that current maternal levels are a proxy for fetal exposure decades in the past. There was a statistically significant increased OR of 2.5 (95% CI, 1.02 to 6.0) of testis cancer in relation to higher maternal levels of the sum of PBDE-47, -99, and -153 measured at the time of diagnosis of testis cancer in cases. One of the limitations was that maternal exposure was measured decades after pregnancy with the index son (case or control). The study sample size was small (44 cases and 45 controls). Based on these limitations, our confidence in a single study was reduced below the usual low confidence provided by an observational study, and the panel determined the level of evidence to be very low.

Although there is no animal model of testis cancer, as previously described in the context of cryptorchidism, PBDEs are antiandrogenic (46). Chemicals that disturb androgen signaling may adversely effect testis development (46, 68), which in turn may increase the risk of testis cancer. Despite substantial plausibility, due to the absence of an animal model for testis cancer, the panel found weak experimental evidence for causation by PBDEs.

Using the IPCC criteria, the panel agreed on a probability of causation between 0 and 19%. Attributable fractions were estimated to range from 13.0–35.3%, with a base estimate of 35.3% (Table 3). In total, 19 350 annual cases of testicular cancer were identified, of which 6830 were attributable (range, 2520–6830), with associated costs of €848 million (range €313 million to 848 million).

Phthalate-attributable reductions in T and resultant increased mortality (Table 4)

The panel identified 11 manuscripts on the association of the levels of urinary phthalate metabolites and serum T in adult men (40, 51, 54, 55, 69–75). Studies on men from infertility clinics were eliminated because T levels may be lower than in men of the general population of the same age, limiting their appropriateness for modeling the association of phthalates with T. Because the focus of the panel was on the potential association of EDCs with lower T mediating increased risk of all-cause mortality, the review

Table 3. PBDE-Attributable Testicular Cancer in Europe, 2010

Expert panel evaluation of epidemiological evidence	Very low
Expert panel evaluation of toxicological evidence	Weak
Probability of causation, %	0–19
Exposure prevalence (sensitivity analysis), %	36.4 (10.0, 36.4)
OR	2.5
Attributable fraction (sensitivity analysis), %	35.3 (13.0, 35.3)
Annual incidence	0.0000764
Annual newly incident cases, n	19 349
Attributable cases (sensitivity analysis), n	6830 (2520–6830)
Attributable costs (sensitivity analysis)	€848 million (€313–848 million)

Table 4. Phthalate-Attributable Decreases in T in Europe, 2010

Expert panel evaluation of epidemiological evidence	Low					
Expert panel evaluation of toxicological evidence	Strong					
Probability of causation, %	40–69					
Percentile of exposure	0–9	10–24	25–49	50–74	75–89	>90
Percentile assumed	0	10	25	50	75	90
Urinary MBP, micromolar	<LOD	0.040	0.067	0.110	0.186	0.306
Urinary DEHP metabolites, micromolar	<LOD	0.025	0.042	0.076	0.136	0.238
MBP-related change in T (assuming 10th percentile reference level), %	0.00	0.00	−4.07	−4.07	−4.07	−4.07
DEHP related changes in T (assuming 10th percentile reference level), %	0.00	0.00	−2.04	−6.22	−13.46	−25.77
Change in mean T, nmol/L	0.00	0.00	−1.01	−1.70	−2.89	−4.92
Mortality RR (assuming 1.35 RR per 5.10 nmol/L increment in T)	1	1	1.06	1.10	1.19	1.34
Deaths of 55− to 64-y-old men (baseline), n	241 187					
Incremental deaths resulting from phthalate-attributable T, n	24 820					
Lost economic productivity	€7.96 billion					

Abbreviation: LOD, limit of detection.

was further limited to studies on men from the general population by excluding one study on selected fertile men and two studies in an occupational setting, resulting in four studies on urinary phthalate metabolites and serum T levels in adult men from the general population. The panel therefore focused on four studies on urinary phthalate metabolites and serum T levels in adult men from the general population (40, 54, 55, 73).

Three of the studies were of young men (ages 18–40 y) and did not show inverse association of phthalate exposure with T (54, 55, 73). The only study of older, middle-aged men from the general population (40–60 y old) showed negative associations between levels of urinary phthalates and serum T levels (40). In the Meeker et al study (40), among the strata of middle-age men (age, 40–60 y) there were negative associations of urinary levels of MBP and sum of DEHP metabolites with lower T. There were significant 12.9% (95% CI, −20.3, −4.87) and borderline significant decreases of 7.84% (−15.8, 0.85) in serum T with an interquartile range increase in MBP and DEHP metabolites, respectively.

As described in the discussion of phthalates and male infertility, the period of fetal development is more vulnerable to phthalate and other antiandrogen exposures than adult exposures. Additional and supportive human data associate fetal exposure to phthalates with reduced infant AGD (56, 57), and adult AGD is associated with reduced semen quality (58) and T level (59). Yet, the absence of data about tracking of AGD from infancy to adulthood limited the strength of epidemiological evidence beyond the low level.

As described in the context of infertility, the toxicological data identifying phthalate inhibition of T synthesis is extensive and strong for developmental exposure in animal studies (76, 77). Although the adult male reproductive system is less sensitive to phthalate exposure (77) and interspecies differences in the impact of DBP on T have been suggested (77), the panel agreed that the toxicological evidence for phthalate-induced inhibition of T synthesis is strong for DEHP (78), diisononyl phthalate, butylbenzyl phthalate, and DBP (79). Using the IPCC criteria, the toxicological and epidemiological evidence support a 40–69% probability of causation.

Exposures to DBP and DEHP were identified to be essentially ubiquitous in the EU population, although as a conservative measure, we used the 10th percentile (0.040 μM for DBP, 0.025 μM for DEHP) as a reference level, with levels as high as 0.306 and 0.238 μM, respectively, in the 10% most highly exposed portion of adult men. Three-fourths of the population were estimated to have a 4.07% reduction in T due to DBP exposure, whereas DEHP-attributable decrements in T were more varied (2.04 to 25.77% decreases). Overall, 1.01 to 4.92 nmol/L decrements in mean T were estimated, with associated relative risks of mortality ranging from 1.06 to 1.34. In total, 24 820 deaths were attributable to phthalate-attributable reductions in T, with €7.96 billion in associated lost economic productivity.

Discussion

The major finding of the present study is that exposures to specific EDCs across the life span are likely to substantially contribute to male reproductive disorders and diseases in the EU, with economic costs of approximately €15 billion annually. Prevention of exposure to PBDEs, and phthalates in particular, is likely to reduce disease, disability, and even death among European citizens while reducing health care expenditures and other social costs.

The present analysis was limited to chemical exposures for which the most substantial epidemiological and toxicological evidence has accumulated to support causation. There is documented widespread exposure to many other EDCs, such as bisphenol A, parabens, polyfluorinated

chemicals, and newer flame retardants (eg, Firemaster 550) (40, 80–83). However, due to the lack of sufficient epidemiological studies at this time, the panel was unable to consider these in its deliberations. The panel was limited by the absence of epidemiological studies linking fetal exposures with later life conditions such as infertility that arise 30 or more years later. Absent such data, the panel was unable to assert with certainty estimates of disease burden due to earliest life exposure, and instead focused on quantifying attributable disease to adult exposure. Furthermore, the panel did not consider cumulative exposure to multiple EDCs that may act additively to adversely impact androgenic signaling that disrupts human male reproductive tract development and adversely affects male reproductive health (84).

The panel acknowledged the possibility of reverse causation between low T and cardiovascular disease and recognized the presence of two studies suggesting adverse cardiovascular effects of T replacement therapy in older men (85, 86), which might argue against the implication of mortality and lost economic productivity due to phthalate-attributable reductions in T. The panel noted that the Vigen et al study (85) was retrospective, based on registry data, and lacked information about cumulative dose. The Basaria et al study (86) administered rather high doses of T, for which the platelet aggregation effects and smooth muscle proliferation could have outweighed the benefits of compensating for lower endogenous production. Multiple observational studies have suggested that reduced endogenous production of T is associated with increased risk of mortality, chiefly due to cardiovascular events (41). We also note the potential overlap of phthalates-attributable mortality in men with phthalate-attributable obesity and diabetes, despite control in studies of T and mortality for body mass index. The obesity and diabetes panel (87) did not attribute obesity and diabetes to phthalate exposures in men due to lack of epidemiological studies in that subpopulation, and so double counting is not a concern.

The panel could have also included cost estimates of osteoporotic fractures as downstream effects of phthalate-attributable lower T, although the association between T and osteoporosis is influenced by aromatase activity (88) and thereby estradiol levels. T is a precursor to estradiol, which is more predominant in its effects on bone, although T may also have direct effects (89). Given the uncertainty of the influence of phthalates on the T-estrogen axis, the panel decided not to model osteoporotic fractures as costs of phthalate-induced effects.

Most studies of phthalate exposures have examined T, whereas emerging research suggests that the ratio of T to LH, dihydrotestosterone, and other biomarkers may be more reflective of androgen disruption and more directly in the causal pathway of male reproductive conditions due to EDCs. As this domain of research evolves, the estimation of EDC-attributable male reproductive morbidities may evolve to account for these biomarkers.

Major strengths of our approach include the transparent use of available data to define exposure-related outcomes and the distribution of exposures in EU countries, and such estimates will become more precise as better evidence becomes available. The causal attribution is supported by experimental data, and judgment in regard to reference levels, impact of covariates, and steepness of the dose-dependence of the outcomes was based on consensus among the authors. Likewise, biomarker data were not available for all EU countries, and judgment was used in extrapolating to the EU as a whole. By this approach, the authors attempted to avoid underestimating the burden of disease simply because of insufficient or lacking data (90). On the other hand, the calculations could not take into account potential differences between exposure levels in the member states.

Having raised appropriate caveats, the present study suggests substantial economic benefits to prevention of EDC exposure, which should be placed alongside the costs of developing safer alternatives. The burden of male reproductive morbidity attributable to PBDE is likely to be even more substantial in the United States, where exposures remain substantially higher. In contrast, the burden attributable to phthalates may be more modest in the United States (where data from national surveys suggest lower levels of MBP and DEHP metabolites) (91) compared to the EU. This speaks to the substantial influence of regulatory policy on human health and disease and should inform thoughtful and proactive prevention of environmental hazards.

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Address all correspondence and requests for reprints to: Leonardo Trasande, MD, MPP, Associate Professor, Department of Pediatrics, NYU School of Medicine, 227 East 30th Street, Room 109, New York, NY 10016. E-mail: leonardo.trasande@nyumc.org.

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