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

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Context: A growing body of evidence suggests that endocrine-disrupting chemicals (EDCs) contribute to female reproductive disorders.

Objective: To calculate the associated combined health care and economic costs attributable to specific EDC exposures within the European Union (EU).

Design: 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. Cost-of-illness estimation used multiple peer-reviewed sources.

Setting, Patients and Participants and Intervention: Cost estimation was carried out from a societal perspective, ie, including direct costs (eg, treatment costs) and indirect costs such as productivity loss.

Results: The most robust EDC-related data for female reproductive disorders exist for 1) diphenyldichloroethene-attributable fibroids and 2) phthalate-attributable endometriosis in Europe. In both cases, the strength of epidemiological evidence was rated as low and the toxicological evidence as moderate, with an assigned probability of causation of 20%–39%. Across the EU, attributable cases were estimated to be 56 700 and 145 000 women, respectively, with total combined economic and health care costs potentially reaching €163 million and €1.25 billion.

Conclusions: EDCs (diphenyldichloroethene and phthalates) may contribute substantially to the most common reproductive disorders in women, endometriosis and fibroids, costing nearly €1.5 billion annually. These estimates represent only EDCs for which there were sufficient epidemiologic 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*** **101: 1562–1570, 2016)**

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in USA

Received July 14, 2015. Accepted January 6, 2016.

Abbreviations: DDE, diphenyldichloroethene; DEHP, di-(2-ethylhexyl) phthalate; DEMOCOPHES, Demonstration of a Study to Coordinate and Perform Human Biomonitoring on a European Scale; DES, diethylstilbestrol; EDC, endocrine-disrupting chemical; EU, European Union; ODS, ovarian dysgenesis syndrome; OR, odds ratio; PCBs, polychlorinated biphenyls; PCOS, polycystic ovarian syndrome; POP, persistent organic pollutant; TCDD, tetrachlorodibenzo-p-dioxin.

In 2007, Buck Louis and Cooney postulated that environmental factors can impact the developing ovary and female reproductive tract, inducing structural and functional changes that may manifest as reproductive disorders later in life and predispose women to complex diseases such as cancer. This conceptual framework was termed the ovarian dysgenesis syndrome (ODS) (1, 2), paralleling the testicular dysgenesis syndrome, which links similar interrelated health endpoints across the lifespan in males after periconceptional or in utero exposures (3).

The most compelling support for ODS comes from the human diethylstilbestrol (DES) exposure paradigm. DES is a synthetic estrogen prescribed from the 1940s to 1970s to pregnant women with "high-risk" pregnancies in an attempt to prevent miscarriage. The reproductive repercussions of fetal DES exposure became evident when cases of a rare vaginal clear cell adenocarcinoma were observed in young DES daughters (4, 5). Subsequent data from nearly 50 years of DES cohort studies provides clear evidence that in utero, DES exposure increased the incidence of a host of reproductive abnormalities in women, including vaginal adenosis, cervical and vaginal hypoplasia, uterine and tubal abnormalities, infertility, early menopause, and breast cancer (6, 7). Some associations are reported for in utero DES exposure and the presence of male urogenital abnormalities and complex medical diseases later in adulthood (8, 9), although the mechanisms of action are unclear (10).

Importantly, support for the ODS hypothesis also comes from the results of subsequent experimental studies in rodents that recapitulated and extended the human findings. For example, exposure during pre-/perinatal development is associated with an increased risk of leiomyoma in the adult in both DES exposed women (11–13) and mice (14), and with changes in the expression of estrogen-responsive genes in adult uterine tissue (15).

Although the effects of DES exposure on fertility likely result from changes to both the ovary and reproductive tract, ovarian effects are difficult to characterize. This is not surprising, because subtle changes to the developing ovary with or without changes in hormonal signaling can manifest as a wide range of phenotypes. These include diminished fecundity (longer time-to-pregnancy), reproductive impairment (eg, conception delay or pregnancy loss), infertility, or gynecological disorders such as endometriosis, fibroids, premature ovarian insufficiency/failure, or polycystic ovarian syndrome (PCOS). Biological plausibility that relatively minor changes in the developing ovary has lifelong consequences is demonstrated by the link between maternal smoking and reduced fecundity in daughters although effects on the fetal ovary are subtle (16). Of added concern are the increasingly reported associations between infertility or gynecological disorders and gravid diseases such as type 2 diabetes (17), not to mention later onset adulthood diseases. Such examples include a higher risk of autoimmune disorders and cancer for women with endometriosis and PCOS, a higher risk of gestational diabetes and metabolic or cardiovascular disease among women with PCOS, and a greater risk of cancer among infertile women in comparison with unaffected women (18–25).

Although a growing body of evidence supports the ODS conceptual paradigm and the vulnerability of the developing ovary to the actions of endocrine-disrupting chemicals (EDCs) (26), characterizing the effects of exposures on the developing ovary remains a formidable research challenge. In part, this can be attributed to the "hidden" data problem, the inability to observe early reproductive endpoints in females relative to males without invasive procedures. Such hidden endpoints include some of the earliest gene- and sperm-related contributions to the developing embryo, all of which occur before implantation. These early endpoints are well suited to investigation in population subgroups, such as couples undergoing assisted reproductive technologies and such initiatives are underway for select EDCs and oocyte maturation or blastocyst formation (27). However, the ability to link exposures during development to ovarian function in adult women remains a critical data gap.

In contrast to the complex ovarian phenotype, effects of environmental exposures on the female reproductive tract can manifest as gross structural changes (such as endometriosis and fibroids) that are easier to characterize. Together, endometriosis and fibroids represent the most common female reproductive disorders with an estimated combined incidence of up to 70% of women overall (28–31). Given their cryptic nature, many women with either endometriosis or fibroids remain asymptomatic or undiagnosed and gynecological comorbidity may exist. As such, estimating incidences at the population level relies on prevalence estimates largely from women seeking clinical care. Nevertheless, an estimated 176 million women worldwide have been diagnosed with endometriosis (32, 33). Among women undergoing surgeries that allow for visual diagnosis, endometriosis has been reported in 30%–50% of pelvic surgery patients and 4%–43% of tubal sterilization patients, irrespective of presenting signs and symptoms (34–38). Estimating the incidence of uterine fibroids poses similar problems. Although some 20%–40% of women of childbearing age are affected, disease incidence is strongly influenced by both age and race and, in some populations the lifetime risk may be as high as 60% (39, 40).

Because they are leading causes of female infertility and a range of other conditions affecting quality of life such as pain (41), these reproductive disorders impose a high personal burden. In addition, they also represent a major societal burden, representing a substantial portion of the health care costs for women and a leading cause of work disturbances and lost productivity. In terms of estimated annual costs per woman in the European Union (EU), health and lost productivity together cost around €8000, whereas hospital costs alone for fibroid treatment average over €3000 (42–45). Furthermore, the rising incidences of endometriosis and fibroids with age (46) increases the risk of comorbidity, which will multiply the cost burdens of the diseases.

The Endocrine Society recently released its second Scientific Statement on EDCs (47). This document reviews the mechanistic, experimental, and epidemiological evidence for the role of EDCs in the genesis and progression of obesity and diabetes, female and male reproductive disorders, hormone-sensitive cancers in females, prostate cancer, and developmental and functional disorders of the thyroid and neuroendocrine systems. Importantly, the mode of action of EDCs in the body is varied, complex, and dependent upon both the tissue and developmental stage of exposure (eg, see table 2 in Ref. 47). Nevertheless, as summarized in the Endocrine Society statement, evidence for effects of a host of EDCs, including bisphenol A, phthalates, pesticides, and persistent organic pollutants (POPs) on the developing ovary and reproductive tract is growing into a compelling body of evidence.

The prevention of EDC exposures has the potential to minimize the onset and progression of female reproductive diseases in the EU, and the resultant reduction in associated health care and other social costs could have major economic implications. Thus, cost information is essential in the context of regulatory decisions. We therefore extended previous estimates of societal cost (48–51), examining the probability of causation of female reproductive conditions for EDCs, and quantifying the potential associated costs and burden of disease.

Materials and Methods

The expert panel focused on 2 exposure-outcome relationships: adult diphenyldichloroethene (DDE) exposure with fibroids and adult phthalate exposure with endometriosis. The expert panel considered dioxins, polychlorinated biphenyls (PCBs) and other persistent pollutants, but following the approach of other manuscripts in this series (48–51), the panel chose not to examine these chemicals, because they are already regulated under the Stockholm Convention. The panel selected these exposure-outcome relationships because of the availability of well-conducted observational human studies to assess effects of these EDCs on female reproductive disorders. The panel recognized that substantial laboratory studies suggest effects of earlier female reproductive tract perturbations as a result of developmental exposures in animal (52) but noted an absence of longitudinal studies to assess such effects in humans. We adhered to the approach described in the accompanying overarching manuscript in evaluating strength of the epidemiological (using the World Health Organization GRADE Working Group criteria) (53, 54) and toxicological literature (using criteria consistent with that proposed in the EU roadmap for evaluating endocrine disruptors) (55, 56), and to assigning probability of causation (adapting the Intergovernmental Panel on Climate Change criteria) (57).

Modeling DDE exposures among adult females in the EU

We used data pooled from twelve European birth cohorts by Govarts et al, in which measured maternal and cord blood levels of DDE as ng/g (58). 10th, 25th, 50th, 75th, and 90th percentiles in cord serum were converted to maternal serum levels using a conversion factor of 0.2:1, as described by the authors. For the purpose of this analysis, the distribution of DDE metabolites in nonpregnant women in the EU was assumed to match the distributions obtained for pregnant women from the pooled European birth cohort data.

Modeling phthalate exposures among adult females in the EU

10th, 25th, 50th, 75th, and 90th percentiles for mothers were obtained from the Demonstration of a Study to Coordinate and Perform Human Biomonitoring on a European Scale (DEMOCOPHES) for the sum of di-(2-ethylhexyl) phthalate (DEHP) metabolites, monoethylphthalate, monoisobutylphthalate, monobutylphthalate, and monobenzylphthalate in urine from general population samples (59). Molar concentrations were estimated by dividing concentrations in ng/mL by the appropriate molecular weight, multiplying by 1000. For the purpose of this analysis, the distribution of phthalate metabolites in women in the EU was assumed to be identical to the distributions obtained for mothers from DEMOCOPHES data.

Modeling DDE-attributable fibroids

Women in the EU between the ages of 15 and 54 years in the year 2010 were assumed to have a distribution of DDE levels corresponding to those identified by Govarts et al (58) and divided into percentile ranges on the basis of their DDE measurements (0th–9th, 10th–24th, 25th–49th, 50th–74th, 75th–89th, and 90th–99th percentiles). The lowest grouping was treated as a reference category, whereas the other groups were assumed to have levels corresponding to the lower value of the interval (eg, 10th percentile for all women in the 10th–24th percentile grouping). The panel took the exposure-response relationship from a study of DDE and fibroids in a large cohort of women undergoing laparoscopy or laparotomy for gynecological complaints (n = 473) (60). The published odds ratio (OR) was applied to the exposure distribution of the population subdivided into 0th–9th, 10th–24th, 25th–49th, 50th–74th, 75th–89th, and 90th–99th percentiles. Having calculated the appropriate OR for each exposed group, the OR was multiplied against the incidence rate surgical/radiological interventions for myomas. For incidence

data inputs, we used incidence rates from an analysis of large national databases from England, Germany, and France (42). A population-weighted average of incidence rates from the 3 countries was applied to the other European countries in our study. These rates were applied against population estimates of 15- to 54-year-old women in 2010 from Eurostat to estimate the number of DDE-attributable incident interventions for myomas (61).

Modeling phthalate-attributable endometriosis

The expert panel selected a study of phthalates and endometriosis in population and operative cohorts that identified significant associations of DEHP metabolites with endometriosis (62). For the purpose of analysis, women between the ages of 20–44 years in Europe were assumed to have urinary phthalate concentrations corresponding to the 10th, 25th, 50th, 75th, and 90th percentile of adults in the DEMOCOPHES project. The population of 20- to 44-year-old women was divided into percentile ranges (0th–9th, 10th–24th, 25th–49th, 50th–74th, 75th–89th, and 90th–99th percentiles). The lowest grouping was the reference category, whereas the other groups were assumed to have levels corresponding to the lowest extreme (eg, 10th percentile for all women in the 10th–24th percentile grouping). ORs were calculated by exponentiating the endometriosis OR identified for DEHP metabolites to the ratio of the estimated concentration to 0.2 ng/mL. The baseline incidence of endometriosis was obtained from a German national analysis (63) and multiplied by the appropriate OR to identify the exposed rate of endometriosis. After subtracting the unexposed rate of endometriosis, the incremental rate of endometriosis within each group was multiplied by country-level population estimates obtained from Eurostat for 20- to 44-year-old women in 2010 (61), and the appropriate percentage of the country population corresponding to the percentile range, to estimate attributable cases.

Economic cost estimates for fibroids

Costs per case for surgical/radiologic interventions for myomas were identified from an analysis of large national databases from England, Germany, and France (42). A population-weighted average of costs per case from the 3 countries was applied to the other European countries in our study, after further adjustment by the ratio of each country's per capita gross domestic product to that of Germany, to account for differences in purchasing power across the EU (64). To update the cost estimates from 2005 to 2010, 4% annual increases in costs per case were applied, accounting for well-documented trends across Europe in medical costs (65).

Economic cost estimates for endometriosis

Costs per patient were adapted from 2009 estimates in Belgium, accounting for direct medical costs, as well as lost economic productivity and other indirect costs (66). Further adjustment was made by multiplying the ratio of each country's per capita gross domestic product to that of Belgium, to account for differences in purchasing power across the EU (64). To update the cost estimates from 2009 to 2010, 4% annual increases in costs per case were applied, accounting for well-documented trends across Europe in medical costs (65).

Results

DDE-attributable fibroids

The panel considered the evidence supporting a role for both a predisposing effect of developmental exposures as well as an effect of adult exposures on the development of fibroids. In rodents, DES exposure during fetal development induces alterations to the developing reproductive tract that are remarkably similar to those reported in DES daughters (67). Importantly, rodent models also provide evidence that developmental exposures to other EDCs induce similar effects (68–70). Thus, it is important to note that other EDCs, including methoxychlor and the POPs, PCBs, and dichlorodiphenyltrichloroethane (DDT), have been implicated in the development of uterine fibroid disease (71–73). These toxicological studies support an endocrine disruptor mode of action for adverse health impacts due to chemical exposures. Based on these data, the expert panel evaluated the animal/experimental toxicological data supporting POP causation of fibroids to be moderate, based upon the limited literature.

In addition to studies of the effects of developmental exposures, we found 11 studies of fibroids in adult women that examined a variety of environmental exposures, including phthalates, POPs, phenols, trace elements, and dietary/lifestyle (Supplemental Table 1) (60, 75–80). The body of evidence is observational in nature largely stemming from available groups of women for study. As such, authors used various designs (many cross-sectional), defined exposures and outcomes differently, and either did or did not consider other covariates. The panel chose the Trabert et al (60) study for calculations based on: the large sample size (n = 473) recruited from 14 clinical centers, diagnosis by ultrasonography or at laparoscopy and the use appropriate methods for exposure characterization in serum and omental fat for lipophilic chemicals. None of the other studies were able to incorporate all of these factors into their study design. When excluding women diagnosed with endometriosis, the authors reported several PCBs that were significantly associated with an increased risk of fibroids. The ability to quantify lipophilic chemicals in omental fat is a strength, as serum concentrations are only proxy of internal dose. To our knowledge, no study has been conducted to follow the offspring of women whose exposures have been quantified during sensitive windows of development (from preconception through adulthood) and in various biologic media that would allow for the estimation of the onset and progression of gynecologic disorders including fibroids. Such work will be possible in the near future in light of several birth cohort studies with children approaching adolescence or young adulthood. In considering the entire evi-

dence base, the expert panel rated the epidemiologic evidence for causation of fibroids by DDE exposure to be low. Together, the epidemiological and toxicological evaluations resulted in the expert panel endorsing a 20%–39% probability of causation of fibroids by DDE.

Applying the OR from the Trabert et al (60) study to DDE biomarker data from twelve countries in the EU and using the 10th percentile as a reference level, results in OR estimates for fibroids of 1.11–1.51. Applying this to a 2.227/1000 annual incidence rate, incremental prevalence in the EU attributable to DDE ranges between 2.45/10 000 and 1.15/1000 for the most highly exposed quantiles of the population (Table 1). Thus, in 2010, an estimated 56 700 women underwent interventions for myoma requiring surgical attention attributable to adult DDE exposures. These cases cost €163 million.

Phthalate-attributable endometriosis

The panel identified evidence to support the hypothesis that exposures quantified shortly before the disease diagnosis are associated with incident disease in women. Experimental evidence suggests that after the implantation of human endometrial tissue into the mesentery of rats and mice, 12 weeks of tetrachlorodibenzo-p-dioxin (TCDD) treatment resulted in a significant induction of endometriosis in both rodent species (81). Important primate data also suggest a dose-dependent association in both the incidence and severity of endometriosis in a cohort of rhesus monkeys exposed chronically to TCDD (82). Subsequently, specific PCB congeners (numbers 77 and 126) also were associated with endometriosis in this same colony of rhesus monkeys (83). Collectively these emerging studies suggest an endocrine disruptor mode of action for TCDD and PCB-specific congeners leading to the development of endometriosis. Of note, the rhesus monkey experiments were longitudinal in nature and conducted in a primate model that is physiologically similar to humans. Therefore, the expert panel felt that these were very high quality experiments supporting adverse effects resulting from an endocrine disruptor mode of action from TCDD and PCB studies. On the basis of these limited data, the expert panel extrapolated a potential endocrine mode of action in animal/experimental toxicological supporting phthalate causation of endometriosis to be moderate.

Evidence linking classes of environmental chemicals to endometriosis in humans is rapidly emerging, with approximately 34 publications examining a variety of chemicals including heavy metals, POPs, phthalates, and bisphenol A (Supplemental Table 2). Significant methodological limitations (eg, varying methods of recruitment, disease criteria, methods for detection and quantification of analytes, and inadequate statistical power) preclude the use of most these studies in evaluating the role of EDCs in the development of endometriosis. Eight of the 34 publications focused on phthalates as the primary exposure (62, 84–86, 88–90). The panel evaluated all 8 studies; several were rejected due to small sample size, and several others were judged to have important methodological limitations, including reliance on self-reported endometriosis rather than the gold standard of surgically visualized disease, inappropriate comparison groups, or assessment of phthalate exposure occurring after diagnosis. The expert panel found the Buck Louis et al (62,84-86,88-90) study to be the most responsive to data gaps and other methodological considerations including modern exposure assessment, recruitment technique using age and residence matching, direct surgical visualization of outcome in operative cohort, and large sample size. In this study, a population based sample of 495 women undergoing operative evaluation for endometriosis was compared with an age and residence matched population sample of 131 women, and 6 different phthalate metabolites were significantly associated with a 2-fold increase in the odds of endometriosis diagnosis in the population cohort. Among women undergoing surgery, mono-octyl phthalate was associated with significantly increased ORs of 1.38 (95% confidence interval 1.10, 1.72) based on direct surgical visualization and mono-2-ethylhexyl phthalate 1.35 (95% confidence interval 1.03, 1.78) when restricting comparison with women with a normal pelvis. Based on the quality of the adult epidemiologic data, the panel assigned the quality of

Table 1. Fibroids Attributable to DDE in Europe, 2010

Expert Panel Evaluation of Epidemiologic Evidence	Moderate	Low				
Probability of causation	20%–39%					
Percentile of exposure	0–9	10–24	25–49	50–74	75–89	>90
Percentile assumed	0	10	25	50	75	90
Serum DDE, ng/g	0	473	1000	2236	5000	9414
OR	1.00	1.00	1.11	1.24	1.38	1.51
Unexposed incidence	0.00227					
Incremental incidence	0	0	0.000245	0.000537	0.000864	0.00115
Attributable cases	56 700					
Attributable costs	€163 million					

epidemiologic evidence as low based on the limited literature and methodological considerations in light of the emerging research in the field. These evaluations resulted in the expert panel endorsing a 20%–39% probability of causation of endometriosis by phthalates.

To estimate attributable disease burden, the panel used a large cohort study (n = 495) that identified a dose-response relationship between urinary phthalate measurements obtained contemporaneously with the diagnosis of endometriosis (62). Applying an OR of 1.35 per log unit increase in total phthalates to European urinary total phthalate measurements from DEMOCOPHES (Table 2), the incremental incidence attributable to phthalates ranged from 1.21/1000 to 2.82/1000. In total, this analysis suggests that 145 000 cases of endometriosis among 20- to 44-year-old women, with associated costs of €1.25 billion in 2010, were attributable to phthalates.

Discussion

The main finding of our study is that EDC exposure may contribute to causation of fibroids and endometriosis, with associated costs in the EU of approximately €1.41 billion annually. This suggests that prevention of exposures to DDE and phthalates alone would substantially reduce disease and disability among European women while decreasing health care expenditures and other social costs.

We applied a conservative approach to the difficult task of attributing disease burden and costs of EDC exposure in the female, focusing on 2 of the most common female conditions that are also among the most straightforward in terms of assessing the role of EDCs in etiology. It is important to note that our approach has several limitations that almost certainly result in a substantial underestimation of attributing disease burden. First, our analysis focused only on adult exposures. Despite the growing body of experimental data linking EDC exposure during fetal development with reproductive aberrations in the adult (74), and aside from the iatrogenic effects on offspring of prescribing DES to pregnant women, there are no epidemiological data known to us linking fetal exposure to reproductive abnormalities in adult women. Furthermore, reliance upon animal model studies is complicated by species-specific differences in biology and sensitivity to and/or clearance of EDCs, necessitating careful assessment of animal model findings for human relevance. Fetal exposure, however, has the potential to affect reproduction by multiple routes (eg, by interfering with the development of the brain, reproductive tract, and ovary), and likely poses the greatest risk to female reproductive health. Although the 20- to 30-year gap between exposure and the recognition of reproductive impairment (or even longer in terms of diagnoses such as premature menopause) presents challenges in establishing etiologic links, ongoing birth cohort studies around the globe provide hope for updating the burden of disease and cost estimates presented here in the near future. Nevertheless, the absence of existing studies of fetal and periconceptional exposures which are important windows of exposure prevented inclusion of attribution for these exposures, and represents a major limitation of this analysis presented here, one that likely underestimates attributable disease burden.

Second, our analysis only focused on specific reproductive tract disorders. Because characterizing the effects of exposures on the developing ovary remains a formidable research challenge, the panel elected to focus on 2 major reproductive tract abnormalities, fibroids and endometriosis. Although it is highly appropriate to focus on these extremely important uterine tract health deficits, PCOS, infertility and pregnancy complications also affect a considerable number of women, have major cost implications and are increasingly linked to EDC exposures. Thus, it is important to recognize that the cost burdens calculated in this analysis do not represent all, or even most, of the reproductive costs associated with human female exposure. Exposure of the mother during gestation can lead to poorer health and function of the offspring, and also will have considerable cost implications in terms of maternal stress-induced illness and lost productivity due to childcare burdens. Indeed, given the importance of the uterine environment and of postnatal maternal care, using disease

Table 2. Endometriosis Attributable to Phthalates in Europe, 2010

Expert panel evaluation of epidemiologic evidence	Moderate	Low				
Probability of causation	20%–39%					
Percentile of exposure	0–9	10–24	25–49	50–74	75–89	>90
Percentile assumed	0	10	25	50	75	90
Urinary total DEHP metabolites, ng/mL	0	9.70	16.30	29.80	53.20	93.00
Unexposed incidence	0.0035					
Incremental incidence	0	0.00121	0.00154	0.00195	0.00238	0.00282
Attributable cases	145 000					
Attributable costs	€1.25 billion					

management costs alone provides an incomplete assessment of cost burden. Further, the cost analysis of the 2 gynecological disorders was limited to health care costs and lost work time directly associated with disease treatment, and did not take into account the increasingly reported associations between infertility, gynecological disorders, gravid diseases, or other later onset adulthood diseases. Important examples include a higher risk of autoimmune disorders and cancer for women with endometriosis, a higher risk of gestational diabetes and metabolic or cardiovascular disease among women with PCOS, and a greater risk of cancer among infertile women in comparison with unaffected women (18–25). Thus, even this attempt to restrict the analysis of cost burden to 2 specific reproductive tract disorders must be considered an underestimate of the exposure-associated cost burden from an overall health perspective.

Finally, this analysis does not represent the cost to female reproductive health of exposure to all EDCs. For reasons of extensive data gaps already outlined, we only quantified attributable burden for 2 classes of EDCs, DDEs and phthalates. Many other EDCs with similar modes of action likely adversely affect female health and function. The polycyclic aromatic hydrocarbons represent a large and ubiquitous class of chemicals with extensive exposure profiles. These compounds act via an extensive range of mechanisms and receptors, including the aryl hydrocarbon and estrogen receptors and have been associated with adverse outcomes in offspring (85) and have known effects on reproductive organs (87). Thus, analysis of the burden imposed by exposure only to DDEs and phthalates is a further source of potential underestimation of the health burden and cost implications of EDC exposure.

Despite the complexities of the field and the numerous caveats outlined above, the present analysis provides some evidence of the health care burden imposed by the 2 most common female reproductive tract disorders, endometriosis and fibroids. If, as we suggest, our analysis provides a conservative estimate that represents the "tip of the iceberg," the greater than €1.41 billion per annum cost estimated for the clinical management of 2 reproductive tract diseases associated with exposure to 2 EDCs suggests that new measures to prevent EDC exposure might have considerable personal and economic benefits.

Acknowledgments

We thank the many helpful discussions with Germaine Buck Louis and her valuable comments on the manuscript. We also thank Charles Persoz, Robert Barouki, and Marion Le Gal of the French National Alliance for Life Sciences and Health and Barbara Demeneix, Lindsey Marshall, Bilal Mughal, and Bolaji Seffou of the UMR 7221 Paris for providing technical and logistical support throughout the project.

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This work was supported by The Endocrine Society, the John Merck Fund, the Broad Reach Foundation, and the Oak Foundation.

Disclosure Summary: The authors have nothing to disclose.

References

1. **Buck Louis G, Cooney M.** Effects of environmental contaminants on ovarian function and fertility. In: Gonzalez-Bulnes A, ed. *Novel Concepts in Ovarian Endocrinology*. Kerala, India: Transworld Research Network; 2007.
2. **Buck Louis G, Cooney MA, Peterson CM.** Ovarian dysgenesis syndrome. *J Dev Orig Health Dis*. 2011;2:25–35.
3. **Skakkebaek NE, Rajpert-De Meyts E, Main KM.** Testicular dysgenesis syndrome: an increasingly common developmental disorder with environmental aspects. *Hum Reprod*. 2001;16:972–978.
4. **Herbst AL, Green TH Jr, Ulfelder H.** Primary carcinoma of the vagina. An analysis of 68 cases. *Am J Obstet Gynecol*. 1970;106:210–218.
5. **Herbst AL, Scully RE.** Adenocarcinoma of the vagina in adolescence. A report of 7 cases including 6 clear-cell carcinomas (so-called mesonephromas). *Cancer*. 1970;25:745–757.
6. **Hatch EE, Troisi R, Wise LA, Titus-Ernstoff L, et al.** Preterm birth, fetal growth, and age at menarche among women exposed prenatally to diethylstilbestrol (DES). *Reprod Toxicol*. 2011;31:151–157.
7. **Hoover RN, Hyer M, Pfeiffer RM, et al.** Adverse health outcomes in women exposed in utero to diethylstilbestrol. *N Engl J Med*. 2011;365:1304–1314.
8. **Palmer JR, Herbst AL, Noller KL, et al.** Urogenital abnormalities in men exposed to diethylstilbestrol in utero: a cohort study. *Environ Health*. 2009;8:37.
9. **Troisi R, Hyer M, Hatch EE, et al.** Medical conditions among adult offspring prenatally exposed to diethylstilbestrol. *Epidemiology*. 2013;24:430–438.
10. **Mitchell RT, Sharpe RM, Anderson RA, et al.** Diethylstilboestrol exposure does not reduce testosterone production in human fetal testis xenografts. *PLoS One*. 2013;8:e61726.
11. **D'Aloisio AA, Baird DD, DeRoo LA, Sandler DP.** Early-life exposures and early-onset uterine leiomyomata in black women in the Sister Study. *Environ Health Perspect*. 2012;120:406–412.
12. **Mahalingaiah S, Hart JE, Wise LA, Terry KL, Boynton-Jarrett R, Missmer SA.** Prenatal diethylstilbestrol exposure and risk of uterine leiomyomata in the Nurses' Health Study II. *Am J Epidemiol*. 2014;179:186–191.
13. **Baird DD, Newbold R.** Prenatal diethylstilbestrol (DES) exposure is associated with uterine leiomyoma development. *Reprod Toxicol*. 2005;20:81–84.
14. **Newbold RR, Moore AB, Dixon D.** Characterization of uterine leiomyomas in CD-1 mice following developmental exposure to diethylstilbestrol (DES). *Toxicol Pathol*. 2002;30:611–616.
15. **Greathouse KL, Cook JD, Lin K, et al.** Identification of uterine leiomyoma genes developmentally reprogrammed by neonatal exposure to diethylstilbestrol. *Reprod Sci*. 2008;15:765–778.
16. **Fowler PA, Childs AJ, Courant F, et al.** In utero exposure to cigarette

smoke dysregulates human fetal ovarian developmental signalling. *Hum Reprod*. 2014;29:1471–1489.
17. **Tobias DK, Gaskins AJ, Missmer SA, et al.** History of infertility and risk of type 2 diabetes mellitus: a prospective cohort study. *Diabetologia*. 2015;58:707–715.
18. **Barry JA, Azizia MM, Hardiman PJ.** Risk of endometrial, ovarian and breast cancer in women with polycystic ovary syndrome: a systematic review and meta-analysis. *Hum Reprod Update*. 2014;20:748–758.
19. **de Wilde MA, Veltman-Verhulst SM, Goverde AJ, et al.** Preconception predictors of gestational diabetes: a multicentre prospective cohort study on the predominant complication of pregnancy in polycystic ovary syndrome. *Hum Reprod*. 2014;29:1327–1336.
20. **Fauser BC, Tarlatzis BC, Rebar RW, et al.** Consensus on women's health aspects of polycystic ovary syndrome (PCOS): the Amsterdam ESHRE/ASRM-Sponsored 3rd PCOS Consensus Workshop Group. *Fertil Steril*. 2012;97:28–38.e25.
21. **Joham AE, Boyle JA, Zoungas S, Teede HJ.** Hypertension in reproductive-aged women with polycystic ovary syndrome and association with obesity. *Am J Hypertens*. 2015;28:847–851.
22. **Kim JJ, Hwang KR, Choi YM, et al.** Complete phenotypic and metabolic profiles of a large consecutive cohort of untreated Korean women with polycystic ovary syndrome. *Fertil Steril*. 2014;101:1424–1430.
23. **Verit FF, Yucel O.** Endometriosis, leiomyoma and adenomyosis: the risk of gynecologic malignancy. *Asian Pac J Cancer Prev*. 2013;14:5589–5597.
24. **Sinaii N, Cleary SD, Ballweg ML, Nieman LK, Stratton P.** High rates of autoimmune and endocrine disorders, fibromyalgia, chronic fatigue syndrome and atopic diseases among women with endometriosis: a survey analysis. *Hum Reprod*. 2002;17:2715–2724.
25. **Jensen A, Sharif H, Kjaer SK.** Use of fertility drugs and risk of uterine cancer: results from a large Danish population-based cohort study. *Am J Epidemiol*. 2009;170:1408–1414.
26. **Peretz J, Vrooman L, Ricke WA, et al.** Bisphenol a and reproductive health: update of experimental and human evidence, 2007–2013. *Environ Health Perspect*. 2014;122:775–786.
27. **Ehrlich S, Williams PL, Hauser R, et al.** Urinary bisphenol A concentrations and cytochrome P450 19 A1 (Cyp19) gene expression in ovarian granulosa cells: an in vivo human study. *Reprod Toxicol*. 2013;42:18–23.
28. **Marino JL, Eskenazi B, Warner M, et al.** Uterine leiomyoma and menstrual cycle characteristics in a population-based cohort study. *Hum Reprod*. 2004;19:2350–2355.
29. **Downes E, Sikirica V, Gilabert-Estelles J, et al.** The burden of uterine fibroids in five European countries. *Eur J Obstet Gynecol Reprod Biol*. 2010;152:96–102.
30. **Eskenazi B, Warner ML.** Epidemiology of endometriosis. *Obstet Gynecol Clin North Am*. 1997;24:235–258.
31. **Viganò P, Parazzini F, Somigliana E, Vercellini P.** Endometriosis: epidemiology and aetiological factors. *Best Pract Res Clin Obstet Gynaecol*. 2004;18:177–200.
32. **Rogers PA, D'Hooghe TM, Fazleabas A, et al.** Priorities for endometriosis research: recommendations from an international consensus workshop. *Reprod Sci*. 2009;16:335–346.
33. **Adamson DG, Kennedy S, Hummelshoj L.** Creating solutions in endometriosis: global collaboration through the World Endometriosis Research Foundation. *J Endometr*. 2010;2:3–6.
34. **Matorras R, Rodríguez F, Pijoan JI, et al.** Women who are not exposed to spermatozoa and infertile women have similar rates of stage I endometriosis. *Fertil Steril*. 2001;76:923–928.
35. **Balasch J, Creus M, Fábregues F, et al.** Visible and non-visible endometriosis at laparoscopy in fertile and infertile women and in patients with chronic pelvic pain: a prospective study. *Hum Reprod*. 1996;11:387–391.
36. **Rawson JM.** Prevalence of endometriosis in asymptomatic women. *J Reprod Med*. 1991;36:513–515.
37. **Williams TJ, Pratt JH.** Endometriosis in 1,000 consecutive celiotomies: incidence and management. *Am J Obstet Gynecol*. 1977;129:245–250.
38. **Sangi-Haghpeykar H, Poindexter AN 3rd.** Epidemiology of endometriosis among parous women. *Obstet Gynecol*. 1995;85:983–992.
39. **Zimmermann A, Bernuit D, Gerlinger C, Schaefers M, Geppert K.** Prevalence, symptoms and management of uterine fibroids: an international internet-based survey of 21,746 women. *BMC Womens Health*. 2012;12:6.
40. **Khan AT, Shehmar M, Gupta JK.** Uterine fibroids: current perspectives. *Int J Womens Health*. 2014;6:95–114.
41. **Gao X, Yeh YC, Outley J, Simon J, Botteman M, Spalding J.** Health-related quality of life burden of women with endometriosis: a literature review. *Curr Med Res Opin*. 2006;22:1787–1797.
42. **Fernandez H, Farrugia M, Jones SE, Mauskopf JA, Oppelt P, Subramanian D.** Rate, type, and cost of invasive interventions for uterine myomas in Germany, France, and England. *J Minim Invasive Gynecol*. 2009;16:40–46.
43. **Prast J, Oppelt P, Shamiyeh A, Shebl O, Brandes I, Haas D.** Costs of endometriosis in Austria: a survey of direct and indirect costs. *Arch Gynecol Obstet*. 2013;288:569–576.
44. **Simoens S, Dunselman G, Dirksen C, et al.** The burden of endometriosis: costs and quality of life of women with endometriosis and treated in referral centres. *Hum Reprod*. 2012;27:1292–1299.
45. **Hansen KE, Kesmodel US, Baldursson EB, Schultz R, Forman A.** The influence of endometriosis-related symptoms on work life and work ability: a study of Danish endometriosis patients in employment. *Eur J Obstet Gynecol Reprod Biol*. 2013;169:331–339.
46. **Haas D, Chvatal R, Reichert B, et al.** Endometriosis: a premenopausal disease? Age pattern in 42,079 patients with endometriosis. *Arch Gynecol Obstet*. 2012;286:667–670.
47. **Gore AC, Chappell VA, Fenton SE, et al.** EDC-2: The Endocrine Society's second scientific statement on endocrine-disrupting chemicals. *Endocr Rev*. 2015;36:E1–E150.
48. **Bellanger M, Demeneix B, Grandjean P, Zoeller RT, Trasande L.** Neurobehavioral deficits, diseases, and associated costs of exposure to endocrine-disrupting chemicals in the European union. *J Clin Endocrinol Metab*. 2015;100:1256–1266.
49. **Hauser R, Skakkebaek NE, Hass U, et al.** Male reproductive disorders, diseases, and costs of exposure to endocrine-disrupting chemicals in the European union. *J Clin Endocrinol Metab*. 2015;100:1267–1277.
50. **Legler J, Fletcher T, Govarts E, et al.** Obesity, diabetes, and associated costs of exposure to endocrine-disrupting chemicals in the European union. *J Clin Endocrinol Metab*. 2015;100:1278–1288.
51. **Trasande L, Zoeller RT, Hass U, et al.** Estimating burden and disease costs of exposure to endocrine-disrupting chemicals in the European union. *J Clin Endocrinol Metab*. 2015;100:1245–1255.
52. **Alwis ID, Maroni DM, Hendry IR, et al.** Neonatal diethylstilbestrol exposure disrupts female reproductive tract structure/function via both direct and indirect mechanisms in the hamster. *Reprod Toxicol*. 2011;32:472–483.
53. **Atkins D, Eccles M, Flottorp S, et al.** Systems for grading the quality of evidence and the strength of recommendations I: critical appraisal of existing approaches The GRADE Working Group. *BMC Health Serv Res*. 2004;4:38.
54. **Schünemann HJ, Schünemann AH, Oxman AD, et al.** Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ*. 2008;336:1106–1110.
55. **European Union.** Roadmap for evaluation of endocrine disruptor chemicals. 2014. Available at http://ec.europa.eu/smart-regulation/impact/planned_ia/docs/2014_env_009_endocrine_disruptors_en.pdf. Accessed October 15, 2014.
56. **Hass U, Christiansen S, Axelstad M, et al.** Evaluation of 22 SIN List 2.0 substances according to the Danish proposal on criteria for endocrine disrupters. 2012. Available at http://eng.mst.dk/media/mst/67169/SIN%20report%20and%20Annex.pdf. Accessed May 12, 2014.

57. **Intergovernmental Panel on Climate Change.** Guidance notes for lead authors of the IPCC Fourth Assessment Report on addressing uncertainties. 2005. Available at http://www.ipcc.ch/meetings/ar4-workshops-express-meetings/uncertainty-guidance-note.pdf. Accessed May 12, 2014.
58. **Govarts E, Nieuwenhuijsen M, Schoeters G, et al.** Birth weight and prenatal exposure to polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroethylene (DDE): a meta-analysis within 12 European Birth Cohorts. *Environ Health Perspect*. 2012;120:162–170.
59. **Den Hond E, Govarts E, Willems H, et al.** First steps toward harmonized human biomonitoring in Europe: demonstration project to perform human biomonitoring on a European scale. *Env Health Perspect*. 2015;123:255–263.
60. **Trabert B, Chen Z, Kannan K, et al.** Persistent organic pollutants (POPs) and fibroids: results from the ENDO study. *J Expo Sci Environ Epidemiol*. 2015;25:278–285.
61. **United Nations Economic Commission for Europe.** Population, 5-year age groups, by sex. 2014. Available at http://w3.unece.org/PXWeb2015/pxweb/en/STAT/STAT_30-GE_01-Pop. Accessed August 26, 2014.
62. **Buck Louis GM, Peterson CM, Chen Z, et al.** Bisphenol A and phthalates and endometriosis: the Endometriosis: Natural History, Diagnosis and Outcomes Study. *Fertil Steril*. 2013;100:162–169.e161–e162.
63. **Abbas S, Ihle P, Köster I, Schubert I.** Prevalence and incidence of diagnosed endometriosis and risk of endometriosis in patients with endometriosis-related symptoms: findings from a statutory health insurance-based cohort in Germany. *Eur J Obstet Gynecol Reprod Biol*. 2012;160:79–83.
64. **World Bank .** GDP per capita, PPP (current international $). 2014. Available at http://data.worldbank.org/indicator/NY.GDP.PCAP.PP.CD. Accessed May 22, 2014.
65. **Erixon F, van der Mare E.** What is driving the rise in health care expenditures? An inquiry into the nature and causes of the cost disease. ECIPE working paper number 05/2011. 2011. Available at http://www.ecipe.org/media/publication_pdfs/what-is-driving-the-rise-in-health-care-expenditures-an-inquiry-into-the-nature-and-causes-of-the-cost-disease_1.pdf. Accessed September 3, 2014.
66. **Klein S, D'Hooghe T, Meuleman C, Dirksen C, Dunselman G, Simoens S.** What is the societal burden of endometriosis-associated symptoms? A prospective Belgian study. *Reprod Biomed Online*. 2014;28:116–124.
67. **McLachlan JA, Newbold RR, Bullock BC.** Long-term effects on the female mouse genital tract associated with prenatal exposure to diethylstilbestrol. *Cancer Res*. 1980;40:3988–3999.
68. **Suzuki A, Sugihara A, Uchida K, et al.** Developmental effects of perinatal exposure to bisphenol-A and diethylstilbestrol on reproductive organs in female mice. *Reprod Toxicol*. 2002;16:107–116.
69. **Newbold RR, Jefferson WN, Padilla-Banks E.** Long-term adverse effects of neonatal exposure to bisphenol A on the murine female reproductive tract. *Reprod Toxicol*. 2007;24:253–258.
70. **Newbold RR, Jefferson WN, Padilla-Banks E.** Prenatal exposure to bisphenol a at environmentally relevant doses adversely affects the murine female reproductive tract later in life. *Environ Health Perspect*. 2009;117:879–885.
71. **Fei X, Chung H, Taylor HS.** Methoxychlor disrupts uterine Hoxa10 gene expression. *Endocrinology*. 2005;146:3445–3451.
72. **Takayama S, Sieber SM, Dalgard DW, Thorgeirsson UP, Adamson RH.** Effects of long-term oral administration of DDT on nonhuman primates. *J Cancer Res Clin Oncol*. 1999;125:219–225.
73. **Bredhult C, Bäcklin BM, Bignert A, Olovsson M.** Study of the relation between the incidence of uterine leiomyomas and the concentrations of PCB and DDT in Baltic gray seals. *Reprod Toxicol*. 2008;25:247–255.
74. **Fowler PA, Bellingham M, Sinclair KD, et al.** Impact of endocrine-disrupting compounds (EDCs) on female reproductive health. *Mol Cell Endocrinol*. 2012;355:231–239.
75. **Pollack AZ, Buck Louis GM, Chen Z, et al.** Bisphenol A, benzophenone-type ultraviolet filters, and phthalates in relation to uterine leiomyoma. *Environ Res*. 2015;137:101–107.
76. **Lambertino A, Turyk M, Anderson H, Freels S, Persky V.** Uterine leiomyomata in a cohort of Great Lakes sport fish consumers. *Environ Res*. 2011;111:565–572.
77. **Eskenazi B, Warner M, Samuels S, et al.** Serum dioxin concentrations and risk of uterine leiomyoma in the Seveso Women's Health Study. *Am J Epidemiol*. 2007;166:79–87.
78. **Luisi S, Latini G, de Felice C, et al.** Low serum concentrations of di-(2-ethylhexyl)phthalate in women with uterine fibromatosis. *Gynecol Endocrinol*. 2006;22:92–95.
79. **Weuve J, Hauser R, Calafat AM, Missmer SA, Wise LA.** Association of exposure to phthalates with endometriosis and uterine leiomyomata: findings from NHANES, 1999–2004. *Environ Health Perspect*. 2010;118:825–832.
80. **Wise LA, Palmer JR, Reich D, Cozier YC, Rosenberg L.** Hair relaxer use and risk of uterine leiomyomata in African-American women. *Am J Epidemiol*. 2012;175:432–440.
81. **Cummings AM, Metcalf JL, Birnbaum L.** Promotion of endometriosis by 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats and mice: time-dose dependence and species comparison. *Toxicol Appl Pharmacol*. 1996;138:131–139.
82. **Rier SE, Martin DC, Bowman RE, Dmowski WP, Becker JL.** Endometriosis in rhesus monkeys (*Macaca mulatta*) following chronic exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin. *Fundam Appl Toxicol*. 1993;21:433–441.
83. **Rier SE, Turner WE, Martin DC, Morris R, Lucier GW, Clark GC.** Serum levels of TCDD and dioxin-like chemicals in rhesus monkeys chronically exposed to dioxin: correlation of increased serum PCB levels with endometriosis. *Toxicol Sci*. 2001;59:147–159.
84. **Upson K, Sathyanarayana S, De Roos AJ, et al.** Phthalates and risk of endometriosis. *Environ Res*. 2013;126:91–97.
85. **Rundle A, Hoepner L, Hassoun A, et al.** Association of childhood obesity with maternal exposure to ambient air polycyclic aromatic hydrocarbons during pregnancy. *Am J Epidemiol*. 2012;175:1163–1172.
86. **Huang PC, Tsai EM, Li WF, et al.** Association between phthalate exposure and glutathione S-transferase M1 polymorphism in adenomyosis, leiomyoma and endometriosis. *Hum Reprod*. 2010;25:986–994.
87. **Sadeu JC, Foster WG.** The cigarette smoke constituent benzo-[a]pyrene disrupts metabolic enzyme, and apoptosis pathway member gene expression in ovarian follicles. *Reprod Toxicol*. 2013;40:52–59.
88. **Itoh H, Iwasaki M, Hanaoka T, Sasaki H, Tanaka T, Tsugane S.** Urinary phthalate monoesters and endometriosis in infertile Japanese women. *Sci Total Environ*. 2009;408:37–42.
89. **Reddy BS, Rozati R, Reddy BV, Raman NV.** Association of phthalate esters with endometriosis in Indian women. *BJOG*. 2006;113:515–520.
90. **Cobellis L, Latini G, De Felice C, et al.** High plasma concentrations of di-(2-ethylhexyl)-phthalate in women with endometriosis. *Hum Reprod*. 2003;18:1512–1515.