The Journal of Clinical Endocrinology & Metabolism

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

--Manuscript Draft--

Manuscript Number:	JC-15-2873R1
Article Type:	Original Article
Full Title:	Female Reproductive Disorders, Diseases & Costs of Exposure to Endocrine Disrupting Chemicals in the European Union
Short Title:	Female Reproductive Disorders & EDCs
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Section/Category:	Sexual and Gender-Dependent Endocrinology
Manuscript Classifications:	Sexual and Gender-Dependent Endocrinology; Endometriosis; Fibroids
Keywords:	Endocrine Disrupting Chemicals; economic costs; Endometriosis; fibroids; leiomyoma
Abstract:	Context: A growing body of evidence suggests that endocrine disrupting compounds (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 was 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 utilized multiple peer-reviewed sources. Setting, Patients and Participants and Intervention: Cost estimation was carried out from a societal perspective, i.e. including direct costs (e.g. treatment costs) and indirect costs such as productivity loss. Results: The most robust EDC-related data for female reproductive disorders exists for (a) DDE-attributable fibroids and (b) 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 (DDE 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.
Secondary Abstract:	We calculated combined health care and economic costs of female reproductive conditions due to specific endocrine disrupting chemicals within the European Union. We found that EDCs contribute substantially to the most common reproductive disorders in women, endometriosis and fibroids, costing nearly €1.5 billion annually.
Funding Information:	John Merck Fund, the Broad Reach — Not applicable

	Foundation and the Oak Foundation
Author Comments:	DISCLOSURE STATEMENT: The authors have nothing to disclose.
Additional Information:	
Question	**Response**
STEROID HORMONE ASSAYS: Does your submission include steroid hormone assays? (If you have questions, please contact the editorial staff at jcem@endocrine.org)	No
CELL LINES: Does your submission include cell lines? (If you have questions, please contact the editorial staff at jcem@endocrine.org)	No

R. Paul Robertson, MD
Editor-in-Chief
The Journal of Clinical Endocrinology & Metabolism

Dr. Robertson,

We are delighted to have received such positive reviews for our manuscript, # JC-15-2873; "Female Reproductive Disorders, Diseases & Costs of Exposure to Endocrine Disrupting Chemicals in the European Union." In an accompanying document, you will find responses in italics to each point raised. Together these modifications have served to greatly improve the manuscript.

We look forward to further communication and final acceptance for publication.

Sincerely,

Leonardo Trasande, MD, MPP on behalf of the coauthors

Reviewer #1: Hunt et al, Female Reproductive Disorders, Diseases & Costs of Exposure to Endocrine Disrupting Chemicals in the European Union
This MS is part of a series on EDS, disease and costs of exposure (4 articles in the April 2014 issue of this journal). Like the already published articles, it contains very valuable information about the economic burden of disease attributable to ADULT exposure to EDS.
This is a clearly written article. Although the readership of this journal presumably is mainly clinical endocrinologists, this reviewer suggests giving a brief description of the known modes of action of DDE and phthalates (the first time the word mechanism appears is on page 18 and is unreferenced).

Additionally or alternatively, given that binding to receptors is just one of the modes of action, it would be good to add one or two paragraphs on animal toxicology on the evidence that these chemicals produce comparable results in rodents and humans. The authors have indicated that the effects of DES in humans and animals are highly similar. Could this be stated about DDE and phthalates with regard to the end points covered by this MS?

This reviewer is correct - an important chunk was missing from the originally submitted version. However, because it is an extremely sizeable chunk, we chose to address it by inserting a brief summary of and reference to the Endocrine Society's most recent review of EDCs. This provides – in a single place – the best summary of the available evidence of the reproductive hazards posed by EDCs. The mode of action of these chemicals is complex and, for many reported effects, remains incompletely understood. Thus, we found this difficult to summarize briefly and addressed this concern by including a statement regarding mechanism of action in the paragraph summarizing the Endocrine Society statement and referring the reader to a relevant table in this document.

We thank this reviewer for suggesting the inclusion of a bigger picture view at the outset, it strengthens the paper.

This reviewer's comments are given as a suggestion to improve the manuscript. It is entirely up to the authors to decide whether or not to follow this advice.

Reviewer #2:
This manuscript describes the review of numerous papers demonstrating links between endocrine disruptor exposure and latent female reproductive disease and has linked this potential causality

to the cost burden of the chosen disease end points in the EU. This approach was interesting and eye-opening. Although I had few disagreements with the choice of papers, the reason for focusing on the chosen studies, or the resources that were used to assess the cost of disease burden, the paper suffered in the clarity in Methods and Results sections. It is not clear if the authors just needed to go over the paper once more or if apples and oranges were being compared.

Suggested changes:
Introduction –
You may want to consider changing the phrase "DES experience". Something like "human prenatal DES exposure paradigm" might be a little more descriptive?

We have revised as suggested.

It seems that some important description of DES effects are missing… animals and humans share similar malformations of the female repro tract following prenatal DES exposures and the DES-derived clear cell tumors in women were not mentioned as affecting the female repro tract.

We find this comment puzzling because clear cell adenocarcinoma is mentioned at the onset of the DES section.

Methods –
In organizing this section, is it possible to talk about one disease outcome and then the other? I understand why you did it the way it is in the present manuscript, but it really bounced around and it moving realted sections together would help focus on the outcome.

We followed the structure of previous papers. We do sympathize with the reviewer's concern but have not made further changes.

In the data that was used from the DEMOCOPHES study, I feel the need to know if this was data from urine (more appropriate than blood) and was there anything unusual about the women in this study (infertile, etc)??

DEMOCOPHES measurements were in urine and in a general population (now explicated).

I would like to know more about how sure we should be in the choice of data without having to go read the entire paper. We do not have information on other papers that were considered in these circumstances, so should have some detail on the "best" paper.

Supplemental tables providing brief information on all papers providing information on exposure associations for leiomyoma and endometriosis are included in this revision.

In the modeling DDE-fibroids section, "Women in the EU…. "is too vague. Which women? Where is this information coming from? There is no reference.

This is clarified as follows: "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.[57] and divided into percentile ranges on the basis of their DDE measurements (0-9th, 10-24th, 25-49th, 50-74th, 75-89th, 90-99th)."

In the same paragraph, for reference 59, give the number of women in the cohort (vs "large cohort").

This has been added – thank you.

Same paragraph, more detail is needed for how incidence rates were "obtained". This sentence is not clear.

We have clarified further.

Additionally, when you talk about applying these rates to the number of women, it is not clear that you have 5 year groupings from the database referenced (#60).

The reference cited has 5-year population data across the lifespan. These were summed as appropriate to generate the relevant population data.

Results –
The results section seems to need another going over. At the end of the first paragraph on pg 14, the conclusions sentence is misplaced. The header of the next paragraph is wrong, I believe, and the conclusion statement of the first paragraph on page 15 should say POPS maybe, but instead says phthalates – the paragraph was all about TCDD and PCBs – and this is confusing as I thought it would be about phthalates. This is the only major issue – it was hard to follow all the different chemicals discussed when I thought this would be about DDE and fibroids only and phthalates and endometriosis. Your tables very clearly state DDE and fibroids and Phthalates and endometriosis – results section does NOT match this.

We regret the error, which is now corrected.

In the first paragraph of the results, please indicate how many studies were considered.

*The revision addresses this issue through citation.*In the second paragraph, first sentence, please be clear on which end point these studies were chosen.*We have clarified as requested.*

In the bottom paragraph on pg 15, the seven references should be provided in the text - it helps to provide those authors with information on whether or not their papers thought to be some of the best, as you then clarify why you chose the one paper in the end. It should help them design better studies in the future… This long paragraph, which extends to most of page 16, contains no references and should have several. Please add in the needed references.

In response to these comments we have created two supplemental tables that summarize the human studies considered in this analysis. Because the experimental evidence is extensive, a similar summary is not possible and we have simply referenced the most relevant references in the text.

The second paragraph on page 16 is not clear enough. Where did the values listed come from?

We have identified the sample size, and clarified data source for phthalate values.

There is not enough explanation. What is the age group of the women, again?

We have clarified the age range as requested.

Discussion –
You say the "…..exclusion of fetal and peri-conceptional exposures…" in the first paragraph on pg 18, when in fact you didn't exclude the data, there just isn't any. This needs to be clear.

Thank you -- revised as requested.

In the second paragraph on pg 19, you again refer to only DDE and phthalate as the focus of this assessment. Very confusing based on the comments I provided above – results section does not agree with this.
Also, Table 1 and 2 clearly talk about DDE and Phthalates…..

We have revised as follows: "For reasons of extensive data gaps already outlined, we only quantified attributable burden for two classes of EDCs - DDEs and phthalates."

This manuscript is important and I think the comments here will improve future versions of your message.

Thanks – these were indeed very helpful.

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

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Keywords: endocrine disrupting chemicals, economic costs, endometriosis, fibroids, leiomyoma, women's health

Abbreviations: diethylstilbestrol (DES); diphenyldichloroethene (DDE); di-(2-ethylhexyl) phthalate (DEHP); diethylstilbestrol (DES); Endocrine disrupting chemicals (EDC); exposure-response relationship (ERR); European Union (EU); Intergovernmental Panel on Climate Change (IPCC); odds ratio (OR); Ovarian Dysgenesis Syndrome (ODS); polycystic ovarian syndrome (PCOS)

Acknowledgements**:** We gratefully acknowledge the many helpful discussions with Germaine Buck Louis and her valuable comments on the manuscript. Research reported in this publication was supported by the Endocrine Society, the John Merck Fund, the Broad Reach Foundation and the Oak Foundation. The funders and supporters had no role in the writing of the manuscript or the decision to submit it for publication. We 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.

Abstract

Context: A growing body of evidence suggests that endocrine disrupting compounds (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 was 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 utilized multiple peer-reviewed sources.

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

Results: The most robust EDC-related data for female reproductive disorders exists for (a) DDE-attributable fibroids and (b) 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 (DDE 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.

Introduction

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 (TDS) which links similar interrelated health endpoints across the lifespan in males following peri-conceptional or *in utero* exposures.(3)

The most compelling support for ODS comes from the human diethylstilbestrol (DES) ~~experience~~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/peri-natal 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 since 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 (e.g. 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 to unaffected women.(18-25)

Although a growing body of evidence ~~exists supporting~~ supports the ODS conceptual paradigm and the vulnerability of the developing ovary to the actions of endocrine disrupting chemicals (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 prior to 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 endocrine disrupting chemicals (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 ~~are estimated as~~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 EU, health and lost productivity together cost around €8,000 while hospital costs alone for fibroid treatment average over €3,000.(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 endocrine disrupting chemicals or EDCs.(47) This document reviews the mechanistic, experimental, and epidemiological evidence for the role of endocrine disrupting chemicals 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 (e.g., see Table 2; ref (47)). Nevertheless, as summarized in the Endocrine Society statement, evidence for effects of a host of EDCs, including bisphenol A (BPA), 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 endocrine disrupting chemicals, and quantifying the potential associated costs and burden of disease.

~~Prevention of EDC exposures minimize the onset of female reproductive diseases in the EU, reducing associated health care and other social costs. In the context of the ongoing regulatory process in the EU, we therefore examined the probability of causation of female reproductive conditions for endocrine disrupting chemicals, and quantified the potential burden of disease and associated costs.~~

Methods

The expert panel focused on two exposure-outcome relationships: adult diphenyldichloroethene (DDE) exposure with fibroids and adult phthalate exposure with endometriosis. The expert panel considered dioxins, polychlorinated biphenyls and other persistent pollutants, but following the approach of other manuscripts in this series, (48-55) 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(56), 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 WHO GRADE Working Group criteria)(57, 58) and toxicological literature (using criteria consistent with that proposed in the European Union roadmap for evaluating endocrine disruptors)(59, 60), and to assigning probability of causation (adapting the Intergovernmental Panel on Climate Change criteria).(61)

Modeling DDE Exposures among Adult Females in the EU

We utilized data pooled from twelve European birth cohorts by Govarts et al, in which measured maternal and cord blood levels of DDE as ng/g.(62) 10^{th}, 25^{th}, 50^{th}, 75^{th} and 90^{th} 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 non-pregnant 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-ethylhexylphthalate metabolites, monoethylphthalate, monoisobutylphthalate, monobutylphthalate and monobenzylphthalate in urine from general population samples.(63) 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.[57] and divided into percentile ranges on the basis of their DDE measurements (0-9th, 10-24th, 25-49th, 50-74th, 75-89th, 90-99th). The lowest grouping was treated as a reference category, while the other groups were assumed to have levels corresponding to the lower value of the interval (e.g., 10th percentile for all women in the 10-24th percentile grouping). The panel took the exposure-response relationship (ERR) from a study of DDE and fibroids in a large cohort of women undergoing laparoscopy or laparotomy for gynecological complaints (n=473) (64). The published odds ratio (OR) was applied to the exposure distribution of the population subdivided into 0-9th, 10-24th, 25-49th, 50-74th, 75-89th, and 90-99th percentiles. Having calculated the appropriate OR for each exposed group, the odds ratio was multiplied against the incidence rate surgical/radiological interventions for myomas. , ~~w~~For incidence data inputs, we used ~~hich was obtained~~

~~identified~~incidence rates from an analysis of large national databases from England, Germany and France. (42) A population-weighted average of incidence rates from the three countries was applied to the other European countries in our study. These rates were applied against population estimates of 15-54 year old women in 2010 from Eurostat to estimate the number of DDE-attributable incident interventions for myomas.(65)

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.(66) 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 10^{th}, 25^{th}, 50^{th}, 75^{th} and 90^{th} percentile of adults in the DEMOCOPHES project. The population of 20-44 year old women was divided into percentile ranges (0-9^{th}, 10-24^{th}, 25-49^{th}, 50-74^{th}, 75-89^{th}, 90-99^{th}). The lowest grouping was the reference category, while the other groups were assumed to have levels corresponding to the lowest extreme (e.g., 10^{th} percentile for all women in the 10-24^{th} 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(67) 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 20-44 year old women in 2010(65), 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 three 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 European Union.(68) 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.(69)

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.(70) 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 European Union.(68) 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.(69)

Results

Persistent Organic Pollutant-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.(71) Importantly, rodent models also provide evidence that developmental exposures to other EDCs induce similar effects.(72-74) Thus, it is important to note that other EDCs, including methoxychlor and the persistent organic pollutants (POPs), PCBs and DDT have been implicated in the development of uterine fibroid disease.(75-77) 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 (Supplementary Table 1). ~~We found 11 studies of adult women that examined a variety of environmental exposures. Of these, 3 focused on phthalates, 2 focused on POPs, 1 focused on phenols, and 3 focused on dietary/lifestyle factors.(78-84)~~ 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 2014 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 evidence 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 ~~endometriosis~~ fibroids by ~~phthalates~~DDE.

Applying the odds ratio (OR) from the Trabert et al 2014 study to DDE biomarker data from twelve countries in the EU and using the 10^{th} percentile as a reference level, results in OR estimates for fibroids of 1.11-1.51. Applying this to a 2.227/1,000 annual incidence rate, incremental prevalence in the EU attributable to DDE ranges between 2.45/10,000 to 1.15/1,000 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.

Persistent Organic Pollutant-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 ~~reflects~~ suggests that following the implantation of human endometrial tissue into the mesentery of rats and mice, 12 weeks of TCDD treatment resulted in a significant induction of endometriosis in both rodent species.(85) Important primate data also suggest~~s~~ a dose-dependent association in both the incidence and severity of endometriosis in a cohort of Rhesus monkeys exposed chronically to TCDD.(86) Subsequently, specific PCB congeners (#77 and #126) also were associated with endometriosis in this same colony of Rhesus monkeys.(87) 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~~3~~** publications examining a variety of chemicals including heavy metals, POPs, phthalates, and BPA (Supplementary Table 2). Significant methodological limitations (e.g., varying methods of recruitment, disease criteria, methods for detection and quantification of analytes, and inadequate statistical power) preclude the use of the majority of 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 (66, 88-94). The panel evaluated all eight 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. ~~Seven of the 33 publications focused on phthalates as the primary exposure and, of these, 3 reported positive results. The other four studies 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, and assessment of phthalate exposure occurring after diagnosis.~~ The expert panel found the Buck Louis et al. 2013 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 six different phthalate metabolites were significantly associated with a twofold increase in the odds of endometriosis diagnosis in the population cohort. Among women undergoing surgery, mono-octyl phthalate

was associated with significantly increased odds ratios of 1.38 (95% CI 1.10, 1.72) based on direct surgical visualization and mono 2-ethyl hexyl phthalate 1.35 (95% CI 1.03, 1.78) when restricting comparison to women with a normal pelvis. Based on the quality of the adult epidemiologic data, the panel assigned the quality of 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 utilized a large cohort study (n=495) that identified a dose-response relationship between urinary phthalate measurements obtained contemporaneously with the diagnosis of endometriosis.(66) Applying an odds ratio 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 1.21/1,000 to 2.82/1,000. In total, this analysis suggests that 145,000 cases of endometriosis among 20-44 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 two of the most common female conditions that are also amongst 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(95), 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 (e.g., by interfering with the development of the brain, reproductive tract, and ovary), and likely poses the greatest risk to female reproductive health. Although the 20-30 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 ~~exclusion~~ absence of existing studies of fetal and peri-conceptional exposures ~~as~~ 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 two major reproductive tract abnormalities, fibroids and endometriosis. While 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 child-care burdens. Indeed, given the importance of the uterine environment and of postnatal maternal care, utilizing disease management costs alone provides an incomplete assessment of cost burden. Further, the cost analysis of the two 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 to unaffected women.(18-25) Thus, even this attempt to restrict the analysis of cost burden to two 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, ~~this assessment focused on~~we only quantified attributable burden for ~~only~~ two 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(96) and have known effects on reproductive organs.(97) 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 two 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 two reproductive tract diseases associated with exposure to two EDCs suggests that new measures to prevent EDC exposure might have considerable personal and economic benefits.

Table 1. DDE-Attributable Fibroids, Europe, 2010.

Expert Panel Evaluation of Epidemiologic Evidence	Low					
Expert Panel Evaluation of Toxicologic Evidence	Moderate					
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
Odds Ratio	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					

Table 2. Endometriosis Attributable to Phthalates in Europe, 2010.

Expert Panel Evaluation of Epidemiologic Evidence	Low					
Expert Panel Evaluation of Toxicologic Evidence	Moderate					
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					

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Supp Table 1

Supp Table 2

Supplemental Table 1
Human uterine leiomyoma: Summary of adult association studies

Reference	Exposure	Comments
Trabert et al, 2015[1]	POPs	N= 473 surgical patients Association w/ serum levels of several PCBs
Pollack et al, 2015[2]	BPA Phthalates UV filters	N= 495 surgical patients No significant OR w/ adjustment for relevant covariants
Johnstone et al, 2014[3]	Cobalt Cadmium	N= 473 surgical patients Odds of fibroid dx higher w/ increased serum cadmium and lead levels
Shen et al, 2013[4]	Plastics Cosmetics Food additives	Han women in Nanjing, China N= 600 with leiomyoma; 600 without
He et al, 2013[5]	Diet Physical activity Stress	N= 73 with leiomyoma; 210 without
Wise et al, 2012[6]	Hair relaxer	Women from Black Women's Health Study
Lambertino et al, 2011 (7)	POPs	Self reported uternine leiomyoma in women from Great Lakes Fish Consumption Study
Huang et al, 2010[8]	Phthalates	N= 35 with leiomyoma; 29 controls Significantly higher urinary MEHP levels than controls
Weuve et al, 2010[9]	Phthalates	N= 151 self-reported leiomyoma in 1999-2004 NHANES; positive association for MBP, inverse association for MEHP
Eskenazi et al, 2007[10]	POPs	History of leiomyoma in women from Seveso, Italy 20 years after chemical explosion and TCDD exposure
Luisi et al, 2006[11]	Phthalates	N= 15 with leiomyoma; 20 healthy controls Lower serum DEHP, MEHP in women w/ fibroids

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Supplemental Table 2
Human endometriosis: Summary of adult association studies

Reference	Exposure	Comments
Pollack et al, 2015[1]	BPA Phthalates UV filters	N= 495 surgical patients No significant OR w/ adjustment for relevant covariants
Pollack et al, 2013[2]	Trace elements	Matched cohort design No significant associations
Buck Louis et al, 2013[3]	BPA Phthalates	Population and operative cohorts. Select phthalates associated w/ higher odds of endometriosis
Upson et al, 2013[4]	Pesticides	Case-control study using WREN data N=248 endometriosis, 538 controls Association with serum βHCH concentrations
Upson et al, 2013[5]	Phthalates	Population-based case-control study Inverse association between urinary MEHP and endometriosis
Vichi et al, 2012[6]	PCBs	Case-control study with laprascopic diagnosis N=181 endometriosis, 162 controls Increased blood levels associated with disease
Trabert et al, 2010[7]	PCBs	Case-control study N= 251 surgically confirmed endometriosis, 538 age matched controls (not confirmed) No consistent patterns of risk
Huang et al, 2010[8]	Phthalates	Case control study N=28 endometriosis, 29 controls (surgically confirmed) Elevated but nonsignificant OR
Weuve et al, 2010[9]	Phthalates	Cross-sectional study using 1999-2004 NHANES Sef-reported diagnosis Positive associations for MBP, inverse for MEHP
Cooney et al, 2010[10]	Pesticides	N=100 patients undergoing laparoscopy Increased OR for highest compared to lowest tertile for several organochlorine pesticides

Simsa et al, 2010[11]	Dioxin-like compounds	Surgical patients; N= 96 endometriosis, 106 control Significant odds ratio for women with highest plasma concentrations
Porpora et al, 2009[12]	Dioxin-like compounds	Case-control study of laparoscopy patients N=80 cases, 78 controls Association between increased PCB and p,p'-DDE serum concentrations
Itoh et al, 2009[13]	Phthalates	Japanese infertility patients N=57 endometriosis, 80 controls (laparoscopic dx) No significant associations
Niskar et al, 2009[14]	PCBs DDE	Case-control study of laparoscopy patients N=90 endometriosis, 34 controls No associations
Jackson et al, 2008[15]	Lead Cadmium Mercury	Cross sectional study using 1999-2004 NHANES data and self-reported endometriosis Dose-response association with cadmium
Itoh et al, 2008[16]	Cadmium	Infertile Japanese women; 54 cases, 74 controls No association with urinary cadmium levels
Hoffman et al, 2007[17]	PBBs PCBs	Study of women inadvertantly exposed to PBBs in 1973. Self-reported endometriosis. No association between PBB exposure and disease.
Porpora et al, 2006[18]	PCBs	Case-control study of nulliparous Italian women N=40 cases, 40 w/ benign gynecological conditions Association between blood levels and disease
Quaranta et al, 2006[19]	PCBs DDE	Laparoscopy patients N=10 endometriosis, 8 controls Significantly higher serum PCB and DDE levels with endometriosis
Heilier et al, 2006[20]	Cadmium Lead	N= 119 cases, 25 controls Lower lead levels in cases
Reddy et al, 2006[21]	Phthalates	Laparoscopy patients N=49 endometriosis, 59 controls Significantly higher concentrations of phthalate esters with endometriosis and correlations with

		disease severity
Louis et al, 2005[22]	PCBs	Laparoscopy patients N=32 endometriosis, 50 controls Significantly elevated OR for 3rd tertile PCBs
Heilier et al, 2005[23]	Dioxins PCBs	Case-control study; N=25 cases, 21 controls Increased risk association for dioxin and total dioxin-like PCB serum concentrations
Tsukino et al, 2005[24]	Dioxins PCBs	Infertile Japanese women; N= 58 cases, 81 controls No significant associations
Heilier et al, 2004[25]	Cadmium	Case-control study; N= 29 No difference in serum cadmium concentration
De Felip et al, 2004[26]	Dioxins PCBs	Case-control study of 22 Italian, 18 Belgian women No significant difference between cases and controls
Corbellis et al, 2003[27]	Phthalates	Laparoscopy patients N=59 endometriosis, 24 age-matched controls Significantly higher plasma DEHP with disease
Fierens et al, 2003[28]	Dioxins PCBs	Population-based studies of exposed Belgian women No significant associations
Eskenazi et al, 2002[29]	TCDD	Population-based historical cohort study; 19 endometriosis, 277 nondiseased No significant association
Pauwels et al, 2001[30]	Dioxins PCBs	Infertile women N= 34 cases, 29 controls No significant associations
Taskinen et al, 1999[31]	Formaldehyde Organic solvents	Occupationally exposed women Suggestion of association
Lebel et al, 1998[32]	PCBs Chlorinated pesticides	Case-control study of laparoscopy patients N=86 endometriosis, 70 controls No significant differences

Mayani et al, 1997[33]	TCDD	Infertile women undergoing larparoscopy; N=44 endometriosis, 35 age-matched controls
Gerhard and Runnebaum, 1992[34]	PCBs	Women with hormonal irregularities PCB values significantly higher in women with endometriosis

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