Obesity, Diabetes and Associated Costs of Exposure to Endocrine Disrupting Chemicals in the European Union

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Context: Obesity and diabetes are epidemic in the European Union. Exposure to endocrine disrupting chemicals (EDC) is increasingly recognized as a contributor, independent of diet and physical activity.

Objective: To estimate obesity, diabetes and associated costs that can be reasonably attributed to EDC exposures in the European Union.

Design: An expert panel evaluated evidence for probability of causation using weight-of-evidence characterization adapted from that applied by the Intergovernmental Panel on Climate Change. Exposure-response relationships and reference levels were evaluated for relevant EDCs, and biomarker data were organized from peer-reviewed studies to represent European exposure and burden of disease. Cost estimation as of 2010 utilized published cost estimates for childhood obesity, adult obesity and adult diabetes.

Setting, Patients and Participants and Intervention: Cost estimation was performed from the societal perspective.

Results: The panel identified a 40–69% probability of dichlorodiphenyldichloroethylene (DDE) causing 1,555 cases of overweight at age 10 (sensitivity analysis: 1,555–5,463) in 2010 with associated costs of €24.6 million (sensitivity analysis: €24.6–86.4 million). A 20–39% probability was identified for DDE causing 28,200 cases of adult diabetes (sensitivity analysis: 28,200–56,400) with associated costs of €835 million (sensitivity analysis: €835 million-16.6 billion). The panel also identified a 40–69% probability of phthalate exposure causing 53,900 cases of obesity in older women and €15.6 billion in associated costs. Phthalate exposure was also found to have a 40–69% probability of causing 20,500 new-onset cases of diabetes in older women with €607 million in associated costs. Prenatal BPA exposure was identified to have a 20–69% probability of causing 42,400 cases of childhood obesity, with associated lifetime costs of €1.54 billion.

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Obesity and diabetes are epidemic, affecting a substantial and increasing number of children and adults globally, including in the EU. More than half of European adults are overweight or obese (1). The impact of the childhood obesity epidemic among children is concentrated in southern European countries, with 15% overweight or obese in Greece, Italy, Portugal and Spain (2). Projections by the International Diabetes Foundation suggest that 10% of adults will have diabetes or impaired glucose tolerance by 2030 (3).

Obesity is well documented to contribute to a broad array of comorbidities in addition to diabetes, including gallbladder disease, hypertension, coronary heart disease (CHD) and certain cancers (4). In the United States, the first projected decrease in life expectancy since the Great Depression is expected due to the twin epidemics of obesity and diabetes (5, 6). Obesity and diabetes are also costly to society; even in childhood, obesity is associated with increases in health care expenditures (7–9). Children who are obese are more likely to remain so as adults, with attributable and ongoing impacts on quality of life (QOL) and costs throughout the lifespan (10). In the European Union, annual diabetes-attributable expenditures have been estimated to exceed $100 billion, and expected to approach $125 billion by 2030 (11).

The epidemics of obesity and diabetes have occurred contemporaneously with increasing use of and exposure to environmental chemicals, including chemicals that disrupt hormonal function (4, 12, 13). Further, epidemiologic and/or toxicologic studies also suggest that environmental chemicals contribute to cause obesity and diabetes, independent of poor diet and physical inactivity; such chemicals include (but are not limited to) tributyltin (14), organophosphate pesticide, fungicides, phthalates, (15–17) environmental phenols, (18, 19) heavy metals, cigarette smoke, outdoor air pollutants and persistent organic pollutants (20). Toxicologic studies identify multiple endocrine mechanisms by which environmental chemicals may induce obesity and diabetes; (21–24) for example, phthalates are selective agonists of peroxisome proliferator associated receptors that are critical to lipid and carbohydrate metabolism; (15) bisphenol A (BPA) is a synthetic estrogen (25) and has been documented to convert preadipocytes into adipocytes (26). Early life represents the greatest window of vulnerability to developmental perturbations in physiology with long-term and potentially lifelong consequences, (27) though exposures across the lifespan are well-documented to contribute to obesity and diabetes (23, 28).

Environmental contributors to obesity and diabetes can be prevented through proactive regulation. In the United States, the costs of BPA-attributable childhood obesity were estimated at $1.74 billion in 2008, with $748 million in annual benefits achievable through substitution of BPA in the lining of aluminum cans with an alternative free of health effects (29). Yet, this cost estimate does not account for emerging evidence that other endocrine disrupting chemicals (EDC) contribute to obesity and diabetes. If decreasing human exposure to EDCs has the potential to curb the twin epidemics of obesity and diabetes in the EU, then policies and regulatory action could be executed more quickly than behavioral interventions, which can be difficult to implement or maintain.

In the context of emerging evidence regarding EDC contribution to obesity and diabetes, and well developed methods for calculating economic impacts of environmentally mediated diseases, (30, 31) the present paper attempts to utilize current epidemiological and mechanistic data linking EDC exposure to obesity and diabetes to estimate the attributable disease burden and costs to society. As environmental contributions to the burden of disease may be easily underestimated due to uncertainties in the evidence, (32) the authors attempted to generate realistic estimates based on the strength of evidence using a framework first developed in regard to climate change (33). We focused on costs attributable to exposures in Europe in the context of active regulatory decision-making on EDCs.

Materials and Methods

The expert panel focused on five exposure-outcome relationships: prenatal DDE exposure with obesity, adult DDE exposure with diabetes, adult phthalate exposure and obesity, adult phthalate exposure and diabetes, prenatal BPA exposure and obesity. The panel selected these exposure-outcome relationships because of the presence of well-conducted longitudinal human and animal studies to assess developmental effects of these EDCs. The panel chose not to estimate the burden of obesity and diabetes for polychlorinated biphenyls and hexachlorobenzene with obesity and diabetes because these chemicals are already regulated under the Stockholm Convention (34). We adhered to the approach described in the accompanying overarching manuscript (35) in evaluating strength of the epidemiologic (using the WHO GRADE Working Group criteria) (36, 37) and toxicologic literature (using criteria consistent with that proposed in the European Union roadmap for evaluating endocrine disruptors).
(38, 39), and to assigning probability of causation (adapting the Intergovernmental Panel on Climate Change criteria) (33). An Appendix describes exposure biomarker inputs used to model exposure in the EU and approaches to valuing costs of obesity and diabetes, while subsequent sections describe estimation of affected populations and attributable prevalence/incidence.

**Modeling DDE-attributable Childhood Overweight**

For purposes of modeling disease burden, births in the EU in the year 2010 were divided into percentile ranges (0-ninth, 10–24th, 25–49th, 50–74th, 75–89th, 90–99th). The lowest grouping was treated as a reference category with no exposure, while the other groups were assumed to have levels corresponding to the lower value of the interval (eg, 10th percentile for all births in the 10–24th percentile grouping). The panel took the exposure-response relationship (ERR) from a European combined analysis of longitudinal studies associating prenatal and postnatal DDE levels with early infant growth (40). Growth was quantified as the change in weight-for-age z-score between birth and 24 months; the pooled estimate for prenatal exposure was a change of 0.12 across the interquartile range (p,p'-DDE: 60–448 ng/g lipid). The mean change in z-score was then converted into a change in proportion of people with early infant weight gain (using the 0.67 cut-point for rapid growth proposed by Monteiro and Victora (41)), assuming change in weight-for-age z score is normally distributed with mean 0 and SD 1 and using the NORMDIST function in Excel 2010 (Microsoft; Redmond, WA). Thus for each percentile range group relative to the 0-ninth percentile a prevalence of rapid early infant weight gain was computed.

As a sensitivity analysis, the panel took the ERR from a longitudinal study (42) associating prenatal DDE levels with early infant weight gain, presented as relative risk (RR) per log unit of DDE level, to estimate the RR for each percentile range group relative to the 0-ninth percentile. Using these RRs for each group, exposed prevalences of early infant weight gain were computed.

The association for overweight at age 10 with rapid infant weight gain has been estimated from relevant studies in a meta-analysis by Ong and Loos (43). Using their figure (OR 1.84, and the Levin formula (44)), the expected prevalence of overweight (aged 10) in the presence of DDE exposure was computed for each group. For each exposure group above the referent, an attributable fraction (AF) was computed in the exposed scenario. A similar calculation was performed to compute an AF in the unexposed scenario. Subtracting the AF in the unexposed scenario from the AF in the exposed scenario yielded the increment in AF attributable to DDE exposure. The number of overweight children in each country was then calculated by multiplying the AF by the overweight prevalence for each of the EU countries (2) by population estimates of ten-year old children in each country, using 2010 population data from the United Nations (45).

**Modeling DDE-attributable Adult Diabetes**

The population of 50–64 year olds was divided into 0-ninth, 10–24th, 25–49th, 50–74th, 75–89th and 90–99th percentiles. The lowest grouping was assumed to have no exposure, while the other groups were assumed to have levels corresponding to the lowest extreme.

To extrapolate burden of diabetes attributable to DDE, the OR from a meta-analysis for newly incident diabetes in the highest quartile of exposure (1.25) (46) was applied against 3.1/1000, a large, recent and long-term longitudinal study of newly incident diabetes (EPIC) (47). The resultant increment in newly incident diabetes was applied to the 75–89th and 90–99th percentile groups in the EU. As an alternative data input, results were obtained from a longitudinal cohort examining DDE and newly incident diabetes (48). Estimated DDE levels were compared to ranges (<2.2 ng/g, 2.2–3 ng/g, and >3 ng/g) studied in relationship to annual increments in diabetes and the appropriate increment was assigned (0.0075 or 0.0155 cases/person year, in EU populations with estimated DDE levels in either of the two respective higher ranges) (48).

In the main and alternative estimates of attributable diabetes, the appropriate increment was assigned and multiplied against population estimates for 50–64 year olds for each of the EU countries from Eurostat to estimate the attributable annual increment in newly incident persons with diabetes (45). Recognizing that some 50–64 year olds in the exposed populations already were diabetic, to avoid overestimation, we reduced our estimate by the EU diabetes prevalence, using data from OECD (49).

**Modeling phthalate-attributable adult overweight/obesity**

The expert panel selected a longitudinal study of phthalate exposure and obesity (16) to extrapolate attributable weight gain and obesity in the European Union. The population of 50–64 year old women in Europe was divided into identical percentile ranges, with the lowest grouping assumed to have no exposure. As with phthalate-attributable diabetes, the effect measure was derived from a study population subdivided into percentile exposure groups which did not match directly onto the exposure groups available for the European population. Incremental weight gains from the higher quartiles in the study were linearly interpolated to estimate annual weight gain, and each quantile in the longitudinal study of phthalate exposure and obesity (16) was assigned an exposure value as the median value in that group. The no effect level was taken to be midpoint for the highest group with a nonsignificant association (P < .05). Taking that point as a baseline, a simple linear fit of weight gain vs exposure value for subsequent groups was used to predict weight gain for each midpoint (in this case, the mean) in the population exposure categories.

The appropriate weight gain in kg/y was then applied as a shift in BMI across the population of women (who comprised the study population from which the extrapolation was made), assuming a normal distribution. Mean Body Mass Index (BMI) in each of the 28 EU countries in 2008 was identified from a previous publication, and assumed to have a standard deviation (SD) of 6 (50). A height of 1.6 m was used to estimate mean weight from the country mean BMI and SD, and after adding the corresponding weight gain, a new mean BMI was calculated corresponding to the appropriate increase in weight. Increments in obesity (BMI > 30) for each country were calculated using the NORMDIST function in Excel and subtracting the preshift obesity prevalence from the obesity prevalence in the exposed scenario. Population data for 50–64 year olds in 2010 were obtained for each of the 28 EU countries from Eurostat, and multiplied by increments in obesity to calculate incremental cases of obesity (45).
Modeling Phthalate-attributable Adult Diabetes

The panel identified a longitudinal study of phthalate exposure and diabetes as the basis of extrapolation for health impact assessment (51). 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. Given that the effect measure was derived from a study population subdivided into percentile exposure groups which did not match directly onto the exposure groups available for the European population, the risks were linearly interpolated as follows. For published epidemiologic results divided into quintiles, each was assigned an exposure value as the midpoint or median value in that group. The no effect level was taken to be midpoint for the highest group with a nonsignificant association ($P < .05$). Taking that point as a baseline (OR = 1.0), a simple linear fit of OR vs exposure value for subsequent groups was used to predict risk for each midpoint in the population exposure categories.

Having calculated the appropriate OR for each exposed group, the OR was multiplied against the annual incidence of diabetes identified in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohorts between 1991 and 2007 from eight of the ten EPIC countries to calculate an incident rate in the presence of phthalate exposure (47). After subtracting the baseline rate of diabetes, the incremental rate of diabetes was applied against the population estimate of 50–64 year olds (45).

Modeling BPA-attributable childhood obesity

The population of 4 year olds was divided into percentile ranges (0–9th, 10–24th, 25–49th, 50–74th, 75–89th, 90–99th). The lowest grouping was assumed to have no exposure, while the other groups were assumed to have levels corresponding to the lowest extreme (eg, 10th percentile for all children in the 10–24th percentile grouping). Increments in BMI Z-score at age 4 were identified from a longitudinal study of prenatal BPA exposure, as linear increments per log$_{10}$ unit increase in urinary BPA (52). The 25th percentile in DEMOCOPHES (1 µg/L) was used as a reference level for estimating disease burden. Increments in BMI Z-score calculated from the linear dose-response relationship for each quantile of the population, and shifts in BMI Z-score were then modeled across the population to calculate attributable cases of obesity in 4-year olds.

Results

DDE-Attributable Childhood Obesity

The panel identified thirteen longitudinal observational studies of developmental DDE exposure and weight-related outcomes in childhood. A number of the studies showed results in the same cohorts: two studies were from the US Collaborative Perinatal Project (CPP) from the early 1960s, (53, 54) three studies involved the Infancia y Medio Ambiente (INMA) cohort from Spain (42, 55, 56) and two studies involved the Center for the Health Assessment of Mothers and Children of Salinas (CHAMACOS) cohort from California (57, 58). The CPP studies from the 1960s, the Michigan Fish eaters cohort from the 1970s and 80s, and the North Carolina cohort from 1978–1982 are all characterized by high exposure levels to DDE which do not reflect current exposure in the EU. Three of the studies (40, 55, 56) identified consistent, dose-response relationships in early childhood, with increased rapid growth up to 6 months, (55, 56) overweight (BMI z-score > 85th percentile) at 14 months (55, 56) and change in weight for age z-score up to 24 months (40). In studies looking at older children up to 9 years, the panel identified five studies, of which four showed positive, gender-specific associations of prenatal DDE with obesity (42, 55, 58, 59). Of the two studies from the CHAMACOS cohort, an effect of prenatal DDE was found at nine years of age (58) but not at seven years of age (57). While some of the null studies observed higher exposure than currently identified in the EU (53, 54, 57)(one of the more recent longitudinal studies also failed to detect positive associations (60), or only reported positive associations of DDE only in combination with overweight mothers (59). The panel also noted the problem of multiple comparisons in some studies, which suggest a pattern but not the expected consistency of dose-response. The studies mostly controlled for appropriate confounders, though some studies did not control for pre/postnatal caloric intake, physical activity, or postnatal diet characteristics. Overall, the panel assessed moderate strength of the epidemiologic evidence for causation.

The panel found three published studies that focused on developmental DDT exposure and body weight and adiposity in rodents (see Appendix for further detail); taken together, the studies suggest that an endocrine mechanism is plausible but not yet fully demonstrated. Thus, the panel deemed toxicological evidence for obesity causation by DDT as moderate and, using the IPCC criteria, the probability of causation to be 40%–69%.

The panel used the ERR from the European pooled cohort analysis (40) (n = 2487) to extrapolate main estimates of attributable overweight at age 10. Extrapolating from these results (Table 1), increments of 0.004–0.06 in the change of weight-for-age Z-score were identified for DDE-exposed subpopulations in the EU, with resultant 0.12–1.94% increases in rapid infant weight gain. Of all cases of overweight in 10 year olds in the EU, 0.26% are attributable to DDE-mediated increases in rapid weight gain, with resultant social costs of €24.6 million. As an alternative input, the panel used data from a moderate size Spanish cohort (n = 1285), which identified a relative risk of 1.13 from a linear relationship between rapid weight gain and maternal serum DDE (55). Relative risks of rapid infant weight gain ranging from 1.04 to 1.17 are identified with increases in rapid infant weight gain from 1.01 to 4.30%. In this alternate scenario, 0.92% of all overweight
among 10-year old children was attributable to DDE-mediated increases in rapid infant weight gain, with associated social costs of €86.4 million.

**DDE-Attributable Adult Diabetes**

The panel identified five longitudinal studies focused on DDE exposure and diabetes in adulthood. Four of the studies reviewed showed no significant effect including studies from the CARDIA US cohort with relatively high exposures; (20) the PIVUS cohort of 75 year olds in Sweden; (61) a small cohort of Swedish women (62) and the larger US Nurses Health Study with a 20 year follow-up (46). One prospective study of male Great Lakes Sport Fish Consumers (n = 471) related exposure to DDE in early 1990s with follow up to 2005 to increased type 2 diabetes (OR 5.5) (48). The panel rated this study particularly strong because it had multiple DDE measurements and addressed the potential for reverse causality: the rate of decrease of DDE in serum was the same as rate of decrease in disease incidence in eight years. While the prospective studies were largely null, seventeen cross sectional studies were reviewed, of which thirteen showed positive associations. A meta-analysis was also performed of the prospective studies reviewed by our panel. Though no statistically significant association for DDE/DDT and adult diabetes was found (46), the direction of the association was positive with an OR of 1.25. Given the inconsistent association despite good control for confounding and a strong dose response relationship shown in the Turyk study (48), the panel assessed low strength of the epidemiologic evidence for causation.

The panel identified also four toxicological studies that provide evidence that DDT or DDE influences glucose metabolism (see results described in greater detail from Appendix references 20–23). While there was evidence for effects on glucose or insulin homeostasis following adult exposure, endocrine related mechanisms have not been elucidated, leading the panel to classify the toxicological evidence for DDT as an obesogen as moderate. Applying the IPCC criteria, the overall probability of causation is 20%–39%.

Serum DDE levels in the EU are estimated to range from 1.00 ng/mL in the 25–49th percentile to 9.41 ng/mL in the 90–99th percentile (Table 2). Using the meta-analysis as a basis for extrapolating DDE-attributable diabetes to the EU population, an additional 7.75 cases of newly incident diabetes per 10 000 person years are estimated to occur in
the 25% most highly exposed population, resulting in 28,200 additional cases each year. Using the Turyk results as an input to sensitivity analysis, an additional 15.5 cases/1,000 person years are estimated to occur in the same proportion of the population, resulting in 564,000 additional cases/ year. Social costs of DDE-attributable diabetes are estimated to range between €834 million–16.6 billion annually.

Phthalate-associated Adult Diabetes

The panel identified one prospective case-control study in which BPA and eight major phthalate metabolites were measured among incident type 2 diabetes cases (n = 971) from the Nurses’ Health Study (NHS; mean age 65.6) and NHSII (mean age 45.6) (51). The follow-up was 8–12 years, while phthalate exposures were measured at one time point. Total phthalate metabolites and total butyl phthalates were associated with T2D in the NHSII cohort only, with OR ratio rising nonmonotonically to 2.14 in the highest quartile for total phthalates. In the NHS cohort the OR ratio for the highest quartile was 0.87. The models used were adjusted for multiple confounders, including BMI, with models excluding BMI showing weaker associations. The differential findings between the two study populations may reflect real differences in risk by age. Despite the dose-response relationship, the panel evaluated the strength of the epidemiological evidence as low, given the paucity of prospective studies and uncertainty in exposure assessment.

Four in vivo studies supported toxic effects of DEHP on glucose and insulin metabolism through effects based on insulin signaling pathways (63), leading to the panel identifying strong toxicological evidence for causation. These studies are described in greater detail in the Appendix. Using the adapted IPCC criteria, the probability of causation was estimated at 40%–69%.

The panel suggested use of findings from the Nurses Health Study-II to extrapolate attributable burden of newly incident diabetes in adult women (51). The results were adapted as described to account for differences between the quantiles in the primary study and EU population data. A linear dose-response function was estimated using the median of the first quartile of the primary study as a threshold. The median urinary total phthalates in the 0–ninth, 10–24th and 25–49th percentiles estimated from DEMOCOPHES were less than the threshold (Table 4), and so no increments in diabetes risk were estimated for these groups. In the other groups, ORs of 1.05, 1.33 and 1.83 were applied to the other groups, with a total of 20,500 newly incident cases after accounting for preexisting diabetes. A total direct cost of €607 million annually.
was associated with phthalate-attributable diabetes in the EU.

**Phthalate-attributable adult overweight/obesity**

Though at least twenty cross-sectional studies have been published, only three longitudinal studies were available, (16) of which two had a relatively short follow up of 1–2 years (64, 65). One of these studies examined a Swedish cohort of seniors > 70 years of age in which serum levels of mono-isobutylphthalate were modestly but significantly associated with BMI, waist circumference, total fat mass and trunk fat mass by DXA after 2 years (64). In a second study of 387 Hispanic and Black New York City children between six and eight years at cohort enrollment (2004–2007), no significant associations were reported among urinary concentrations of nine phthalate metabolites (65). The most convincing prospective study was reported by Song et al in which the weight of adult females was followed for a period of 10 years (16). A modest positive association with annual weight gain and total phthalate concentrations in urine collected at one time point was found. The panel evaluated the strength of the epidemiological evidence as low, given only one truly prospective study and the lack of good exposure measurements.

The panel agreed that the toxicological data available for di-2-ethylhexylphthalate (DEHP) and obesity outcomes was convincing, as it showed mechanistic underpinning of effects based on the peroxisome proliferator activated receptor (PPARα and PPARγ), (66) master regulators of adipogenesis and lipid metabolism. The strong toxicological evidence (reviewed in greater detail in the Appendix) coupled with the low rating of the epidemiologic evidence produced a 40%–69% probability of causation using the adapted IPCC criteria.

The panel suggested use of findings from the Nurses Health Study to extrapolate attributable burden of obesity in adult women (16). The results were adapted as described to account for differences between the quantiles in the primary study and EU population data. A linear dose-response function was estimated using the median of the first quartile of the primary study as a threshold. The median urinary total phthalates in the 0–ninth, 10–24th and 25–49th percentiles estimated from DEMOCOPHES were less than the threshold (Table 3), and so no increments in weight gain were estimated for these groups. In the other groups, 0.08, 0.12 and 0.18 kg/yr annual weight gain were applied to the 50–75th, 75–90th and 90–99th percentile groups, resulting in an additional 53 900 cases of obesity. The direct attributable costs were €1.16 billion, while the indirect costs were €14.4 billion, totaling €15.6 billion in annual phthalate-attributable obesity-related social costs.

**BPA-attributable childhood obesity**

Three prospective studies were identified; all had two measures of urinary BPA in pregnancy, controlled for confounding and showed an ERR. In the Mexican-American CHAMACOS cohort an inverse relationship was identified for prenatal BPA with BMI and body fat at nine years of age, only in girls (67). Urinary BPA at 5y was not associated with overweight/obesity, though BPA at 9y was associated with overweight/obesity, BMI, waist circum-

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**Table 3. Phthalate-Attributable Adult Obesity, 2010**

<table>
<thead>
<tr>
<th>Expert Panel Evaluation of Epidemiologic Evidence</th>
<th>Low</th>
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</thead>
<tbody>
<tr>
<td>Expert Panel Evaluation of Toxicologic Evidence</td>
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<tr>
<td>Probability of Causation</td>
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</tr>
<tr>
<td>Percentile of Exposure</td>
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</tr>
<tr>
<td>Percentile Assumed</td>
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<tr>
<td>Urinary total phthalates, nmol/liter</td>
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<td>Annual weight gain, kg/yr</td>
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<tr>
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<tr>
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<td>Attributable direct costs</td>
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ference, fat mass at 9y. A recent US study by Braun et al showed a modest inverse but nonsignificant association with prenatal BPA and BMI at two years (68). Interestingly, growth between 2 and 5 years was accelerated in the highest exposure tertile of ages 1 and 2. A study in a Spanish birth cohort showed a positive association between prenatal BPA and age-specific z-scores for BMI and waist circumference at four years of age (52). The panel evaluated the evidence as low to very low due to inconsistency in the timing of BPA exposure associated with body mass across the three studies, and variability in direction of the ERR for exposure in pregnancy. The available studies had also averaged two measures to estimate exposure, which is problematic given the high temporal variability and thus may not accurately reflect the exposure over the specific critical window of vulnerability.

Fourteen toxicological studies published between 2001 and 2014 were considered: ten included perinatal exposure (69) while 4 focused on adult exposure (see results described in greater detail from Appendix references 32–45). All four postnatal exposure studies reported positive associations between prenatal BPA and age-specific z-scores for BMI and waist circumference at four years of age (52). The panel evaluated the evidence as low to very low due to inconsistency in the timing of BPA exposure associated with body mass across the three studies, and variability in direction of the ERR for exposure in pregnancy. The available studies had also averaged two measures to estimate exposure, which is problematic given the high temporal variability and thus may not accurately reflect the exposure over the specific critical window of vulnerability.

The main finding of our manuscript is that the potential impacts are large for these EDCs to the burden of obesity and diabetes in the European Union. While the magnitude of the burden is modest in proportion to diet and physical activity (70), with one recent estimate of diet-related ill health costs in the UK of £5.8 billion in 2006–7 (71), the costs of EDC-attributable obesity and diabetes are substantial to society, in the range of €18–29 billion annually. We have selected five exposures where we judge the evidence is strongest, but even so the epidemiological strength of evidence on its own is judged to be low in each case, in spite of generally strong evidence of causality from experimental data. For each, assuming a causal relationship we have estimated the attributable disease burden across Europe with attendant costs. While causality is not certain for each of these associations for people, other exposures already regulated under the Stockholm convention or with little or no epidemiology but persuasive toxicology were not included in this review, but we expect are

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**Table 4. Phthalate-Attributable Adult Diabetes, 2010**

<table>
<thead>
<tr>
<th>Expert Panel Evaluation of Epidemiologic Evidence</th>
<th>Low</th>
<th>Strong</th>
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<tbody>
<tr>
<td>Expert Panel Evaluation of Toxicologic Evidence</td>
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<tr>
<td>Probability of Causation</td>
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<td>40–69%</td>
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<tr>
<td>Percentile of Exposure</td>
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<td></td>
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<tr>
<td>Estimated urinary total phthalates, nmol/liter</td>
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<td></td>
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<tr>
<td>Odds ratio for newly incident diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increment in newly incident diabetes</td>
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<td></td>
</tr>
<tr>
<td>Annual attributable cases</td>
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<td></td>
</tr>
<tr>
<td>Annual attributable cases accounting for preexistent diabetes</td>
<td>20,500</td>
<td></td>
</tr>
<tr>
<td>Annual direct cost for attributable cases</td>
<td>607 million</td>
<td></td>
</tr>
</tbody>
</table>

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lating from the linear dose-response and using the 10th percentile in DEMOCOPHES as a reference level, 0.08–0.23 increments in BMI Z-score (Table 5) were identified in the most exposed half of the EU population. Increments in obesity prevalence ranged from 0.89–2.90%, with a total of 42,400 attributable cases of childhood obesity, of whom 21,200 are projected to remain obese as adults. A total of €454 million in direct BPA-attributable costs of childhood obesity were identified with an additional €1.08 billion in indirect costs, for a total of €1.54 billion in annual social costs.

**Discussion**

The main finding of our manuscript is that the potential impacts are large for these EDCs to the burden of obesity and diabetes in the European Union. While the magnitude of the burden is modest in proportion to diet and physical activity (70), with one recent estimate of diet-related ill health costs in the UK of £5.8 billion in 2006–7 (71), the costs of EDC-attributable obesity and diabetes are substantial to society, in the range of €18–29 billion annually. We have selected five exposures where we judge the evidence is strongest, but even so the epidemiological strength of evidence on its own is judged to be low in each case, in spite of generally strong evidence of causality from experimental data. For each, assuming a causal relationship we have estimated the attributable disease burden across Europe with attendant costs. While causality is not certain for each of these associations for people, other exposures already regulated under the Stockholm convention or with little or no epidemiology but persuasive toxicology were not included in this review, but we expect are
acting as other environmental causes of obesity and diabetes. Therefore the final list of compounds may change as knowledge accrues but the aggregate total attributable burden we estimate is a reasonable global estimate of the scale of impacts. This manuscript should therefore be considered a first assessment of metabolic disease costs associated with environmental pollutants, with a clear intent to set the foundation upon which future analyses can be built.

The strength of the approach taken includes the transparent use of available data to define dose-related outcomes and the distribution of exposures in EU countries. Such estimates will become more precise as better evidence becomes available. The causal attribution is supported by experimental data, and judgment in regard to impact of covariates, and steepness of the dose-dependence of the outcomes was based on consensus among the authors. Likewise, biomarker data were not available for all EU countries, and judgment was used in extrapolating to the EU as a whole. By this approach, the authors attempted to avoid underestimating the burden of disease simply because of insufficient or lacking data (72). On the other hand, the calculations could not take into account potential differences between exposure levels in the member states.

We did not quantify the obesogenic and diabetogenic effects of other EDCs that continue to contaminate the EU general population (eg, polychlorinated biphenyls and hexachlorobenzene) because they are banned under the Stockholm Convention (55, 73). The true cost of obesity and diabetes due to EDCs is likely to be substantially higher, and regulatory interventions aimed at decreasing their presence in animal and human food webs are likely to further reduce costs due to these banned, yet prevalent chemicals. DDE-attributable obesity and diabetes could be prevented through further reductions in DDT use globally, which is substantially relevant due to the current use of this chemical for malaria control and its long-range transport and persistence in the environment (74). The project’s focus on chemicals with the strongest evidence led us to exclude associations which were weaker with only sporadic epidemiologic data, which may nevertheless turn out to be positive, for example perfluoroalkylchemicals, which have been associated with obesity in one longitudinal cohort (75) but not another (76). We also excluded known obesogens for which animal data are strong, but human exposure data are limited, such as tributyltin and triflumizole (14, 28, 77, 78).

Models are only as good as their inputs; insofar as the positive studies used to estimate burden of disease suffer from residual confounding or from overadjustment, over- and underestimation can ensue, respectively. While panels were encouraged to consider nonmonotonicity, in practice the epidemiologic data used to generate estimates presumed monotonicity of the ERR. We made a consistent effort to choose conservative estimates from metaanalyses, and to present sensitivity analyses based upon studies with stronger ERRs. We did not consider joint indepen-
dent effects (eg, as identified by Sun et al (51)). Interactions may also be negative or antagonistic; if present among EDCs, they could also have contributed to overestimation.

While endocrine disruption is defined generally as chemical disruption of endocrine systems, (79) more than one mechanism of obesogenic and diabetogenic effects are likely (23). These chemicals are known to exert effects also through other pathways (such as altering microbiome status, circadian rhythms and immune status that could contribute to metabolic disorders) pathways (80) and it is plausible that EDC and non-EDC mechanisms are important. Our judgments were based on weight of evidence and biological plausibility. Even if endocrine disruption is just one broad type of mechanism leading to obesity and/or diabetes, each of the chemicals assessed is an endocrine disruptor; thus, our results support the substantial benefits to be gained from preventive policies that remove such obesogenic and diabetogenic exposures. The exposure-outcome relationships analyzed here are but a subset with the greatest evidence for obesogenicity and diabetogenicity; a more complete analysis would have yielded substantially higher disease burden and cost estimates. The total impact of EDC obesogens and diabetogens will increase substantially as evidence becomes available for human exposure to other known obesogens and diabetogens.

Accurate information on costs of illness can help focus preventive efforts (81–83). An additional reason to develop data on the costs of disease is to permit direct comparison with the costs of other categories of illness. Such an exercise may be useful in priority setting and allocation for prevention programs (84). Our findings should be considered by the European Union as well as other international entities alongside the costs of safer alternatives to chemical obesogens and diabetogens. The human and economic costs of these twin epidemics in Europe urge regulations to limit human exposure to EDCs.

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