

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 (EU). Exposure to endocrine-disrupting chemicals (EDCs) is increasingly recognized as a contributor, independent of diet and physical activity.

Objective: The objective was to estimate obesity, diabetes, and associated costs that can be reasonably attributed to EDC exposures in the EU.

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% to 69% probability of dichlorodiphenyldichloroethylene causing 1555 cases of overweight at age 10 (sensitivity analysis: 1555–5463) in 2010 with associated costs of €24.6 million (sensitivity analysis: €24.6–86.4 million). A 20% to 39% probability was identified for dichlorodiphenyldichloroethylene 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% to 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% to 69% probability of causing 20 500 new-onset cases of diabetes in older women with €607 million in associated costs. Prenatal bisphenol A exposure was identified to have a 20% to 69% probability of causing 42 400 cases of childhood obesity, with associated lifetime costs of €1.54 billion.

Conclusions: EDC exposures in the EU contribute substantially to obesity and diabetes, with a moderate probability of >€18 billion costs per year. This is a conservative estimate; the results emphasize the need to control EDC exposures. (*J Clin Endocrinol Metab* 100: 1278–1288, 2015)

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Abbreviations: AF, attributable fraction; BMI, body mass index; BPA, bisphenol A; CHAMACOS, Center for the Health Assessment of Mothers and Children of Salinas; CPP, US Collaborative Perinatal Project; DDE, dichlorodiphenyldichloroethylene; DDT, dichlorodiphenyltrichloroethane; EDC, endocrine-disrupting chemical; ERR, exposure-response relationship; EU, European Union; IPCC, Intergovernmental Panel on Climate Change; NHS, Nurses' Health Study; OR, odds ratio, RR, relative risk.

Obesity and diabetes are epidemic, affecting a substantial and increasing number of children and adults globally, including in the European Union (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, 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 and costs throughout the lifespan (10). In the EU, annual diabetes-attributable expenditures have been estimated to exceed \$100 billion and are 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, epidemiological and/or toxicological studies also suggest that environmental chemicals contribute to causing obesity and diabetes, independent of poor diet and physical inactivity; such chemicals include (but are not limited to) tributyltin (14), organophosphate pesticides, fungicides, phthalates (15–17), environmental phenols (18, 19), heavy metals, cigarette smoke, outdoor air pollutants, and persistent organic pollutants (20). Toxicological 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), and 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 for developmental perturbations in physiology with long-term and potentially lifelong consequences (27), although exposures across the lifespan are well documented to contribute to obesity and diabetes (23, 28).

Environmental contributions to obesity and diabetes can be prevented through proactive regulation. In the United States, the costs of BPA-attributable childhood

obesity were estimated to be \$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 (EDCs) 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 the economic impacts of environmentally mediated diseases (30, 31), the present article 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 because of uncertainties in the evidence (32), we 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 5 exposure-outcome relationships: prenatal dichlorodiphenyldichloroethylene (DDE) exposure with obesity, adult DDE exposure with diabetes, adult phthalate exposure and obesity, adult phthalate exposure and diabetes, and 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 the 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 article (35) in evaluating the strength of the epidemiological (using the World Health Organization GRADE Working Group criteria) (36, 37) and toxicological literature (using criteria consistent with those proposed in the EU roadmap for evaluating endocrine disruptors) (38, 39) and in assigning probability of causation (adapting the Intergovernmental Panel on Climate Change [IPCC] criteria) (33). The [Supplemental Appendix](#) describes exposure biomarker inputs used to model exposure in the EU and approaches to valuing costs of obesity and diabetes, and 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 (0–9th, 10th–24th, 25th–49th, 50th–74th, 75th–89th, and 90th–99th). The lowest grouping was treated as a reference category with no exposure, and the other groups were assumed to have levels corresponding to the lower value of the interval (eg, 10th percentile for all births in the 10th–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 the proportion of people with early infant weight gain (using the 0.67 cutpoint for rapid growth proposed by Monteiro and Victora [41]), assuming that the 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 Corp). Thus, for each percentile range group relative to the 0 to 9th 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 to 9th percentile. With use of 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). With their figure (odds ratio [OR] = 1.84, and the Levin formula [44]), the expected prevalence of overweight (aged 10 years) 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) and by population estimates of 10-year old children in each country, using 2010 population data from the United Nations (45).

Modeling DDE-attributable adult diabetes

The population of 50 to 64 year olds was divided into 0 to 9th, 10th to 24th, 25th to 49th, 50th to 74th, 75th to 89th, and 90th to 99th percentiles. The lowest grouping was assumed to have no exposure, whereas the other groups were assumed to have levels corresponding to the lowest extreme.

To extrapolate the 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 cases per 1000 person-years, from a large, recent and long-term longitudinal study of newly incident diabetes (European Prospective Investigation into Cancer and Nutrition [EPIC]) (47). The resultant increment in newly incident diabetes was applied to the 75th to 89th and 90th to 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 with ranges (<2.2, 2.2–3, 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 2 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 to 64 year olds for each of the EU countries from Eurostat to estimate the attributable annual increment in persons with newly incident diabetes (45). Recognizing that some 50 to 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 Organisation for Economic Cooperation and Development (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 EU. The population of 50- to 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 to 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 the 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 kilograms per year was then applied as a shift in body mass index (BMI) across the population of women (who comprised the study population from which the extrapolation was made), assuming a normal distribution. Mean BMI in each of the 28 EU countries in 2008 was identified from a previous publication and assumed to have an 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 addition of the corresponding weight gain, a new mean BMI was calculated corresponding to the appropriate increase in weight. Increments in obesity (BMI of >30 kg/m²) 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 to 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 OR was applied to the exposure distribution of the population subdivided into 0 to 9th, 10th to

24th, 25th to 49th, 50th to 74th, 75th to 89th, and 90th to 99th percentiles. Given that the effect measure was derived from a study population subdivided into percentile exposure groups, which did not match directly to the exposure groups available for the European population, the risks were linearly interpolated as follows. For published epidemiological results divided into quantiles, each was assigned an exposure value as the midpoint or median value in that group. The no effect level was taken to be the 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.

After calculation of the appropriate OR for each exposed group, the OR was multiplied against the annual incidence of diabetes identified in the EPIC cohorts between 1991 and 2007 from 8 of the 10 EPIC countries to calculate an incident rate in the presence of phthalate exposure (47). After subtraction of the baseline rate of diabetes, the incremental rate of diabetes was applied against the population estimate of 50 to 64 year olds (45).

Modeling BPA-attributable childhood obesity

The population of 4 year olds was divided into percentile ranges (0–9th, 10th–24th, 25th–49th, 50th–74th, 75th–89th, and 90th–99th). The lowest grouping was assumed to have no exposure, whereas the other groups were assumed to have levels corresponding to the lowest extreme (eg, 10th percentile for all children in the 10th–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 $\mu\text{g/L}$) was used as a reference level for estimating disease burden. Increments in the BMI Z score calculated from the linear dose-response relationship for each quantile of the population and shifts in the 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 13 longitudinal observational studies of developmental DDE exposure and weight-related outcomes in childhood. A number of the studies showed results in the same cohorts: 2 studies were from the US Collaborative Perinatal Project (CPP) from the early 1960s (53, 54), 3 studies involved the Infancia y Medio Ambiente (INMA) cohort from Spain (42, 55, 56), and 2 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 to 1982 are all characterized by levels of high exposure to DDE, which do not reflect current exposure in the EU. Three of the studies (40, 55, 56) identified consistent, dose-response relation-

ships in early childhood, with increased rapid growth up to 6 months (55, 56), overweight (BMI Z score of >85 th 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 5 studies, of which 4 showed positive, sex-specific associations of prenatal DDE with obesity (42, 55, 58, 59). Of the 2 studies from the CHAMACOS cohort, an effect of prenatal DDE was found at 9 years of age (58) but not at 7 years of age (57). Whereas 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 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, although some studies did not control for pre/postnatal caloric intake, physical activity, or postnatal diet characteristics. Overall, the panel assessed moderate strength of the epidemiological evidence for causation.

The panel found 3 published studies that focused on developmental dichlorodiphenyltrichloroethane (DDT) exposure and body weight and adiposity in rodents (see the Supplemental Appendix for further detail); taken together, the studies suggest that an endocrine mechanism is plausible but not yet fully demonstrated. Thus, the panel deemed the toxicological evidence for obesity causation by DDT as moderate and, with the IPCC criteria, the probability of causation to be 40% to 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. By extrapolating from these results (Table 1), increments of 0.004 to 0.06 in the change of weight-for-age Z score were identified for DDE-exposed subpopulations in the EU, with resultant 0.12% to 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-sized Spanish cohort ($n = 1285$), which identified an RR of 1.13 from a linear relationship between rapid weight gain and maternal serum DDE (55). RRs 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.

Table 1. DDE-Attributable Childhood Obesity, 2010

| | | | | | | |
|---|---------------|-------|-------|-------|--------|--------|
| Expert panel evaluation of epidemiological evidence | Moderate | | | | | |
| Expert panel evaluation of toxicological evidence | Moderate | | | | | |
| Probability of causation, % | 40–69 | | | | | |
| Percentile of exposure | 0–9 | 10–24 | 25–49 | 50–74 | 75–89 | >90 |
| Percentile assumed | 0 | 10 | 25 | 50 | 75 | 90 |
| Cord serum DDE, ng/g | <LOD | 10.62 | 22.47 | 50.25 | 112.36 | 211.54 |
| Increment in change in weight for age Z score (main estimate) | 0.00 | 0.00 | 0.004 | 0.01 | 0.03 | 0.06 |
| RR of rapid infant weight gain (sensitivity analysis) | 1.00 | 1.00 | 1.04 | 1.09 | 1.13 | 1.17 |
| Attributable increment in rapid weight gain (main estimate), % | 0.00 | 0.00 | 0.12 | 0.39 | 0.99 | 1.94 |
| Attributable increment in rapid weight gain (sensitivity analysis), % | 0.00 | 0.00 | 1.01 | 2.15 | 3.33 | 4.30 |
| Attributable fraction of overweight at age 10 (main estimate), % | 0.26 | | | | | |
| Attributable fraction of overweight at age 10 (sensitivity analysis), % | 0.92 | | | | | |
| Attributable cases of overweight (main estimate) | 1555 | | | | | |
| Attributable cases of overweight (sensitivity analysis) | 5463 | | | | | |
| Costs of attributable overweight (main estimate) | €24.6 million | | | | | |
| Costs of attributable overweight (sensitivity analysis) | €86.4 million | | | | | |

Abbreviation: LOD, limits of detection.

DDE-attributable adult diabetes

The panel identified 5 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 (NHS) with a 20-year follow-up (46). One prospective study of male Great Lakes Sport Fish Consumers ($n = 471$) related exposure to DDE in the 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 the rate of decrease in disease incidence in 8 years. Whereas the results of the prospective studies were largely null, 17 cross-sectional studies were reviewed, of which 13 showed positive associations. A meta-analysis of the prospective studies reviewed by our panel was also performed. Although 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 epidemiological evidence for causation.

The panel also identified 4 toxicological studies that provide evidence that DDT or DDE influences glucose metabolism (see results described in greater detail in Supplemental Appendix Refs. 20–23). Although there was evidence for effects on glucose or insulin homeostasis after adult exposure, endocrine-related mechanisms have not been elucidated, leading the panel to classify the toxicological evidence for DDT as an obesogen as moderate. By

applying the IPCC criteria, the overall probability of causation is 20% to 39%.

Serum DDE levels in the EU are estimated to range from 1.00 ng/mL in the 25th to 49th percentile to 9.41 ng/mL in the 90th to 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 per 1000 person-years are estimated to occur in the same proportion of the population, resulting in 564 000 additional cases per year. The social costs of DDE-attributable diabetes are estimated to range between €834 million and 16.6 billion annually.

Phthalate-associated adult diabetes

The panel identified one prospective case-control study in which BPA and 8 major phthalate metabolites were measured among individuals with incident type 2 diabetes ($n = 971$) from the NHS (mean age, 65.6 years) and NHSII (mean age, 45.6 years) (51). The follow-up was 8 to 12 years, whereas phthalate exposures were measured at one time point. Total phthalate metabolites and total butyl phthalates were associated with type 2 diabetes in the NHSII cohort only, with the OR rising nonmonotonically to 2.14 in the highest quartile for total phthalates. In the NHS cohort, the OR 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 2 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,

Table 2. DDE-Attributable Adult Diabetes, 2010

| | | | | | | |
|--|---------------|--------|--------|--------|---------|---------|
| Expert panel evaluation of epidemiological evidence | Low | | | | | |
| Expert panel evaluation of toxicological 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/mL | <LOD | 0.47 | 1.00 | 2.24 | 5.00 | 9.41 |
| Increment in diabetes cases applied annually (main estimate) | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0008 | 0.0008 |
| Increment in diabetes cases applied annually (sensitivity analysis) | 0.0000 | 0.0000 | 0.0000 | 0.0000 | 0.0155 | 0.0155 |
| Annual attributable cases (main estimate) | 0 | 0 | 0 | 0 | 18 800 | 11 300 |
| Annual attributable cases (sensitivity analysis) | 0 | 0 | 0 | 0 | 376 000 | 226 000 |
| Annual attributable cases accounting for preexistent diabetes (main estimate) | 28 200 | | | | | |
| Annual attributable cases accounting for preexistent diabetes (sensitivity analysis) | 564 000 | | | | | |
| Annual direct cost for attributable cases (main estimate) | €835 million | | | | | |
| Annual direct cost for attributable cases (sensitivity analysis) | €16.6 billion | | | | | |

Abbreviation: LOD, limits of detection.

given the paucity of prospective studies and uncertainty in exposure assessment.

Four *in vivo* studies supported the toxic effects of di-2-ethylhexylphthalate 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 Supplemental Appendix. By using the adapted IPCC criteria, the probability of causation was estimated at 40% to 69%.

The panel suggested use of findings from the NHSII to extrapolate the 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 to 9th, 10th to 24th, and 25th to 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, 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

Although at least 20 cross-sectional studies have been published, only 3 longitudinal studies were available (16), of which 2 had a relatively short follow-up of 1 to 2 years (64, 65). One of these studies examined a Swedish cohort of elderly individuals aged >70 years, in whom serum levels of mono-isobutylphthalate were modestly but significantly associated with BMI, waist circumference, total fat mass, and trunk fat mass by dual-energy x-ray absorp-

tiometry after 2 years (64). In a second study of 387 Hispanic and black New York City children between 6 and 8 years of age at cohort enrollment (2004–2007), no significant associations were reported among urinary concentrations of 9 phthalate metabolites (65). The most convincing prospective study was reported by Song et al (16) in which the weight of women was followed for a period of 10 years. 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 and obesity outcomes was convincing, as it showed mechanistic underpinning of effects based on the peroxisome proliferator-activated receptor (PPAR α and PPAR γ) (66), master regulators of adipogenesis and lipid metabolism. The strong toxicological evidence (reviewed in greater detail in the Supplemental Appendix) coupled with the low rating of the epidemiological evidence produced a 40% to 69% probability of causation using the adapted IPCC criteria.

The panel suggested use of findings from the Nurses' Health Study to extrapolate the attributable burden of obesity in 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 to 9th, 10th to 24th, and 25th to 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/y annual

Table 3. Phthalate-Attributable Adult Obesity, 2010

| | | | | | | |
|---|---------------|--------|--------|--------|---------|---------|
| Expert panel evaluation of epidemiological evidence | Low | | | | | |
| Expert panel evaluation of toxicological evidence | Strong | | | | | |
| Probability of causation, % | 40–69 | | | | | |
| Percentile of exposure | 0–9 | 10–24 | 25–49 | 50–74 | 75–89 | >90 |
| Percentile assumed | 0 | 10 | 25 | 50 | 75 | 90 |
| Urinary total phthalates, nmol/L | 0 | 144.43 | 241.63 | 420.45 | 1226.06 | 2361.08 |
| Annual weight gain, kg/y | 0.00 | 0.00 | 0.00 | 0.08 | 0.12 | 0.18 |
| Attributable cases of obese, females | 53 900 | | | | | |
| Direct cost per obese adult | €21 500 | | | | | |
| Indirect cost per obese adult | €268 000 | | | | | |
| Attributable direct costs | €1.16 billion | | | | | |
| Attributable indirect costs | €14.4 billion | | | | | |
| Attributable total costs | €15.6 billion | | | | | |

weight gains were applied to the 50th to 75th, 75th to 90th, and 90th to 99th percentile groups, resulting in an additional 53 900 cases of obesity. The direct attributable costs were €1.16 billion, whereas 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 2 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 9 years of age, only in girls (67). Urinary BPA at 5 years was not associated with overweight/obesity, although BPA at 9 years was associated with overweight/obesity, BMI, waist circumference, and fat mass. A recent US study by Braun et al (68) showed a modest inverse but nonsignificant association with prenatal BPA and BMI at 2 years. 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 4 years of age (52). The panel evaluated the evidence as low to very low because of the inconsistency in the timing of BPA exposure associated with body mass across the 3 studies, and variability in direction of the ERR for exposure in pregnancy. The available studies had

also averaged 2 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: 10 included perinatal exposure (69) and 4 focused on adult exposure (see results described in greater detail from Supplemental Appendix Refs. 32–45). All 4 postnatal exposure studies reported positive associations between BPA exposure and obesity/diabetes, whereas 7 of 10 perinatal studies reported positive associations and 3 others reported negative or divergent effects based on sex or no demonstrable association between BPA exposure and obesity endpoints. The Supplemental Appendix presents a summary of the context regarding the negative studies, which supported a rating of strong toxicological evidence for causation.

In the above studies, using the IPCC criteria, the panel identified a 20% to 69% probability of causation.

The panel used the findings from Valvi et al (52), who conducted a prospective study of prenatal BPA exposure, to extrapolate the burden of disease given the probability of causation. With extrapolation from the linear dose-response and use of the 10th percentile in DEMOCOPHES as a reference level, 0.08 to 0.23 increments in BMI Z-score (Table 5) were identified in the most exposed half of the EU population. Increments in obesity preva-

Table 4. Phthalate-Attributable Adult Diabetes, 2010

| | | | | | | |
|---|--------------|---------|--------|---------|---------|---------|
| Expert panel evaluation of epidemiological evidence | Low | | | | | |
| Expert panel evaluation of toxicological evidence | Strong | | | | | |
| Probability of causation, % | 40–69 | | | | | |
| Percentile of exposure | 0–9 | 10–24 | 25–49 | 50–74 | 75–89 | >90 |
| Estimated urinary total phthalates, nmol/L | 0 | 144.431 | 241.63 | 420.446 | 1226.06 | 2361.08 |
| OR for newly incident diabetes | 1.00 | 1.00 | 1.00 | 1.05 | 1.33 | 1.83 |
| Increment in newly incident diabetes | 0 | 0 | 0 | 0.00016 | 0.00103 | 0.00258 |
| Annual attributable cases | 21 900 | | | | | |
| Annual attributable cases accounting for preexistent diabetes | 20 500 | | | | | |
| Annual direct cost for attributable cases | €607 million | | | | | |

Table 5. BPA-Attributable Childhood Obesity, 2010

| | | | | | | |
|---|-----------------|-------|-------|--------|--------|--------|
| Expert panel evaluation of epidemiological evidence | Very low-to-low | | | | | |
| Expert panel evaluation of toxicological evidence | High | | | | | |
| Probability of causation, % | 20–69 | | | | | |
| Percentile of exposure | 0–9 | 10–24 | 25–49 | 50–74 | 75–89 | >90 |
| Percentile assumed | 0 | 10 | 25 | 50 | 75 | 90 |
| Urinary BPA, ng/mL | 0 | 0.46 | 1.00 | 1.94 | 3.70 | 6.70 |
| Increment in BMI Z score | 0.00 | 0.00 | 0.00 | 0.08 | 0.16 | 0.23 |
| Increment in obesity at age 4, % | 0.00 | 0.00 | 0.00 | 0.89 | 1.88 | 2.90 |
| Attributable cases of childhood obesity | 0 | 0 | 0 | 11 900 | 15 000 | 15 400 |
| Attributable cases of adult obesity | 0 | 0 | 0 | 5960 | 7520 | 7720 |
| Direct costs per case | €48 700 | | | | | |
| Indirect costs per case | €17 800 | | | | | |
| Attributable direct costs | €454 million | | | | | |
| Attributable indirect costs | €1.08 billion | | | | | |
| Attributable total costs | €1.54 billion | | | | | |

lence ranged from 0.89% to 2.90%, with a total of 42 400 children with 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 study is that the potential impacts of these EDCs on the burden of obesity and diabetes in the EU are large. Although 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 (£8.0 billion) in 2006 to 2007 (71), the costs of EDC-attributable obesity and diabetes are substantial to society, in the range of €18–29 billion annually. We have selected 5 exposures for which we judge the evidence to be strongest, but even so the epidemiological strength of evidence on its own is judged to be low in each case, despite 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. Although causality is not certain for each of these associations for people, other exposures already regulated under the Stockholm Convention or with little or no epidemiological but persuasive toxicological evidence 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 article 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 extrapolation to the EU as a whole. By this approach, we 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 that were weaker with only sporadic epidemiological data, which may nevertheless turn out to be positive, for example, perfluoroalkylchemicals, which have been associated with obesity in one lon-

gitudinal 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, overestimation and underestimation, respectively, can ensue. Although the panels were encouraged to consider non-monotonicity, in practice the epidemiological data used to generate estimates presumed monotonicity of the ERR. We made a consistent effort to choose conservative estimates from meta-analyses and to present sensitivity analyses based upon studies with stronger ERRs. We did not consider joint independent 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.

Whereas endocrine disruption is defined generally as chemical disruption of endocrine systems (79), more than one mechanism for the obesogenic and diabetogenic effects is likely (23). These chemicals are also known to exert effects through other pathways (such as altering microbiome status, circadian rhythms, and immune status, which could contribute to metabolic disorders) (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 comparisons 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 EU as well as other international entities alongside the costs of safer alternatives to chemical obesogens and diabetogens. The large human and economic costs of these twin epidemics attributable to EDCs in Eu-

rope speak to an urgent need for regulations to limit human exposure to EDCs.

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