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The benefits of removing toxic chemicals from plastics

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More than 16,000 chemicals are incorporated into plastics to impart properties such as color, flexibility, and durability. These chemicals may leach from plastics, resulting in widespread human exposure during everyday use. Two plastic-associated chemicals—bisphenol A (BPA) and di(2-ethylhexyl) phthalate (DEHP)—and a class of chemicals—brominated flame retardants [polybrominated diphenyl ethers (PBDEs)]—are credibly linked to adverse health and cognitive impacts. BPA exposures are associated with ischemic heart disease (IHD) and stroke, DEHP exposure with increased all-cause mortality among persons 55 to 64 y old, and prenatal PBDE exposures in mothers with IQ losses in their children. We estimate BPA, DEHP, and PBDE exposures in 38 countries containing one-third of the world's population. We find that in 2015, 5.4 million cases of IHD and 346,000 cases of stroke were associated with BPA exposure; that DEHP exposures were linked to approximately 164,000 deaths among 55-to-64 y olds; and that 11.7 million IQ points were lost due to maternal PBDE exposure. We estimate the costs of these health impacts to be $1.5 trillion 2015 purchasing power parity dollars. If exposures to BPA and DEHP in the United States had been at 2015 levels since 2003, 515,000 fewer deaths would have been attributed to BPA and DEHP between 2003 and 2015. If PBDE levels in mothers had been at 2015 levels since 2005, over 42 million IQ points would have been saved between 2005 and 2015.

health effects of plastics | costs of plastics consumption | toxic chemicals in plastics

Significance

Endocrine-disrupting and neurotoxic chemicals in plastics pose serious threats to human health. By examining exposures to three toxic chemicals found in plastics and their estimated health impacts, we provide evidence of the health benefits of reducing chemical exposures in plastics. For the year 2015, we estimate that eliminating exposures to BPA and DEHP in countries constituting one-third of the world's population would have saved approximately 600,000 lives. Reducing PBDEs to threshold levels in 2015 for women giving birth in countries accounting for 20 percent of global births would have saved approximately 11.7 million Intelligence Quotient (IQ) points. We estimate that the economic benefit in 2015 of reductions in exposures to these chemicals is $1.5 trillion 2015 PPP dollars.

Plastics are extraordinary materials that have supported significant advances in construction, electronics, aerospace, sports, and medicine. It is increasingly clear, however, that the benefits of plastics come at heretofore unrecognized costs to human health, the environment, and the economy.

Modern plastics are complex materials made from more than 16,000 chemicals (1, 2). Many of these chemicals are toxic and are linked to diverse health impacts (3, 4). A key concern of the UN Global Plastics Treaty currently under negotiation is to address the toxicity of chemicals in plastics (5).

In this paper, we focus on two chemicals of known toxicity used in large quantities in plastic manufacture—bisphenol A (BPA) and di(2-ethylhexyl) phthalate (DEHP)—and a class of brominated flame retardants, the polybrominated diphenyl ethers (PBDEs). Each of these chemicals is used almost exclusively in plastics (6–8). Bisphenols such as BPA are found in food packaging and beverage containers. DEHP, a phthalate, is used in industrial food processing and food packaging and also in household goods and electronics. PBDEs are flame retardants used in computers as well as in synthetic textiles, furniture, carpets, and other household products (3). All of these chemicals can leach out of plastics and enter the human body through ingestion, inhalation, or dermal absorption (3, 9). PBDEs contaminate household dust, resulting in exposure.

An extensive epidemiologic literature links each of these chemicals and chemical classes to adverse health effects. BPA is an endocrine-disrupting chemical linked to type II diabetes, polycystic ovary syndrome, obesity, hypertension, and heart disease (4, 10). DEHP is an endocrine disruptor linked to birth defects of the male reproductive organs and decreased serum testosterone as well as to increased blood pressure, heart disease, asthma, and all-cause mortality (11). PBDEs are neurotoxic and are linked to hypothyroidism, increased risk of asthma, diabetes, and decline in reproductive ability. Maternal exposure to PBDEs during pregnancy results in negative birth outcomes and neurodevelopmental disorders in their offspring, including cognitive impairment (IQ loss) (12).

In this paper, we estimate the levels of BPA and DEHP in adults and the levels of PBDEs in women of childbearing age in 38 countries containing one-third of the world's population: 28 countries for BPA, 23 for DEHP, and 15 for PBDEs; 22 of these countries are in Europe, 5 in Asia, and 4 in North America. The remaining 7 are in the Middle East, Africa, and Oceania. These exposure estimates come from national biomonitoring studies, from birth

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cohort studies, and from epidemiological studies designed to measure the health effects of BPA, DEHP, and PBDEs. We join estimates of exposure to dose–response functions to derive prevalence estimates for the relevant health endpoints. Building on findings from prior epidemiological and toxicological studies, we focus on the impacts of BPA on heart disease and stroke, on the association between DEHP and all-cause mortality among persons 55 to 64 y of age, and on the impact of maternal PBDE levels during pregnancy on their children's cognitive function, as measured by IQ (3). We focus on these endpoints because they are each well established in the biomedical literature and because their associated economic costs are substantial.

We then estimate the burden of adverse health outcomes attributable to each set of substances in each country and value them, using data for 2015. Thus, for each health endpoint, we calculate the fraction of cases attributable to estimated exposure levels (e.g., the fraction of strokes attributable to BPA) and then use baseline information for the year 2015 (baseline cases of stroke) to calculate the number of stroke cases attributable to BPA in that year. We value mortality associated with cardiovascular disease and stroke and all-cause mortality associated with DEHP for persons 55-to-64 using a Value per Statistical Life approach. For PBDE, we value children's IQ losses associated with maternal PBDE levels in pregnancy using the present discounted value of lost output. We view these costs as estimates of the potential benefits of removing these substances from plastics, so long as regrettable substitutions are avoided.

Attempts have been made in Europe, the United States, and Canada to reduce population exposures to BPA, DEHP, and PBDEs and to prevent harmful health effects by regulating production (see *SI Appendix* for details). Thus, beginning in 2010, several countries in the European Union banned BPA in infant feeding bottles, pacifiers, and food materials aimed at children. Similarly, in 2010, Canada banned the importation and sale of all polycarbonate baby bottles containing BPA. In 1998, European nations began to ban phthalates in children's toys and in 1999, an EU-wide ban went into effect. Canada began phthalate regulation in 1994 with a ban on its use in cosmetics and restrictions on use in children's toys.

PBDEs have been subject to especially stringent regulations because they are persistent organic pollutants that are stored for years in the human body in adipose tissue. Currently, most PBDE congeners (tetraBDE, pentaBDE, hexaBDE, heptaBDE, octaBDE, and decaBDE) are banned under the Stockholm Convention (13). In the United States, a voluntary corporate action ended the production of the most widely used PBDE mixtures (c-pentaBDE and c-octaBDE) in 2004.

To assess the health and economic impacts of these restrictions on the manufacture of BPA, DEHP, and PBDEs, we obtained time series exposure data for three countries—the United States, Canada, and South Korea—from 2003 onward. In many cases, exposure levels have dropped over time. We estimate the impacts of these exposure reductions on the incidence and prevalence of ischemic heart disease (IHD) and stroke, premature mortality, and lost IQ points, as well as on health-related costs. We interpret these estimates as the benefits of reducing exposure to these chemicals in plastics.

Ours is not the first study to estimate the economic costs of endocrine-disrupting substances in plastics. Work by Trasande and coauthors has estimated the costs of these substances in the United States (14, 15), Canada (16), and Europe (17). We add to this literature by focusing on four health endpoints with serious economic effects—IHD, stroke, premature mortality, and lost IQ points—and by gathering estimates of exposure from multiple countries throughout the world.

Materials and Methods

Health Effects of BPA and DEHP. Multiple, high-quality epidemiological studies over the past decade have explored associations between BPA and cardiovascular disease. Three of these studies (18–20) use data from multiple waves of the NHANES survey to link urinary BPA concentrations to various cardiovascular outcomes: coronary heart disease (CHD), IHD, congestive heart failure, and stroke, while controlling for other risk factors associated with cardiovascular disease. We use ref. 18 to estimate the impacts of BPA on the prevalence of IHD and the incidence of stroke. Applying propensity score matching (PSM) to the 2003 through 2016 waves of NHANES the authors estimate the odds of developing IHD and stroke to be a linear function of the natural logarithm (ln) of creatinine-adjusted BPA, whereby each natural logarithm unit increase is associated with odds ratios of 1.16 (CI: 1.06–1.27) for IHD and 1.15 (CI: 1.03–1.29) for stroke.*

We use the PSM results from ref. 18 together with the distribution of urinary BPA levels in the adult population of each country to calculate the fraction of IHD and stroke cases attributable to BPA, as described in *SI Appendix*. The attributable fraction of IHD cases in 2015 is multiplied by the baseline cases of IHD in 2015 for each country (21) to calculate the number of cases (disease burden) of IHD attributable to BPA. Likewise, the fraction of strokes attributable to BPA is applied to the incidence of stroke cases in each country (21) in 2015 to calculate cases of stroke attributable to BPA.

We use ref. 22 to estimate the impact of MEOHP, a DEHP metabolite, on all-cause mortality for persons 55-to-64 y old.† In ref. 22, the authors estimate the impact of phthalate metabolites, focusing on high-molecular-weight metabolites (HMW) and DEHP, on all-cause and cardiovascular mortality in the United States. Using data from the 2001-2010 waves of NHANES, the authors estimate Cox proportional hazard models relating the natural logarithm of urinary phthalate concentrations to cardiovascular and all-cause mortality for 55-to-64 y olds, controlling for various cardiovascular risk factors. They find that ln MEOHP is linearly related to all-cause mortality (OR = 1.09; CI: 1.02–1.17) for each natural log unit increase in MEOHP. We calculate the fraction of all-cause mortality for 55-to-64 y olds attributable to MEOHP for each country for which the distribution of MEOHP is available. This is multiplied by the number of deaths in the 55-to-64-y-old age group in each country (21) in 2015 to calculate the burden of deaths attributable to MEOHP in 2015.

We assume that removing BPA from plastics would reduce all BPA exposures to the threshold level, 1 μg/g, and thus reduce the attributable fractions of IHD and stroke due to BPA to zero. We likewise assume that removing DEHP from plastics would reduce all MEOHP exposures to the threshold level, 3.2 μg/L (22), and thus reduce the attributable fractions of all-cause mortality due to MEOHP to zero.‡

Measuring Exposure to BPA and MEOHP. Our exposure estimates come from a variety of sources. Few countries regularly monitor BPA and DEHP using a representative sample of the population and make their data publicly available. Exceptions are the United States (24), Canada (25), and South Korea (26). BPA and DEHP have also been monitored in national studies in China (27) and France (28). The DEMOCOPHES project in the EU (29) has monitored BPA and DEHP in mother-child pairs in some European countries. These and other biomonitoring results are available in the EU Biomonitoring database (30).

There is also a large epidemiological literature that measures exposure to BPA and DEHP in order to estimate their health impacts; however, many studies focus on persons who are occupationally exposed or are case–control studies that compare exposure levels of persons with a specific condition (e.g., diabetes) to persons without the condition. Using a database of 1,710 epidemiological studies compiled in a recent systematic evidence map (31), we identified studies that measured adult exposure to BPA or DEHP in the general population. Exposure estimates in these studies range from estimates in the late 1990s to 2018. Fifty percent of studies come from 2010 to 2014 (*SI Appendix*, Fig. S1), with the median year of estimates being 2013 for BPA and 2011 for DEHP.

*These odds ratios pertain to creatinine-adjusted BPA. Odds ratios for BPA samples not creatinine adjusted are 1.13 for IHD (CI = 1.04-1.24) and 1.13 for stroke (CI =1.01-1.26). We apply a no-effect threshold for BPA of 1 μg/g, following Moon et al. (18).

†Zeng et al. (23) also find significant impacts of DEHP metabolites on all-cause and cardiovascular mortality using the 2003-2014 waves of the NHANES survey.

‡We note that BPA and DEHP have half-lives of less than 24 h.

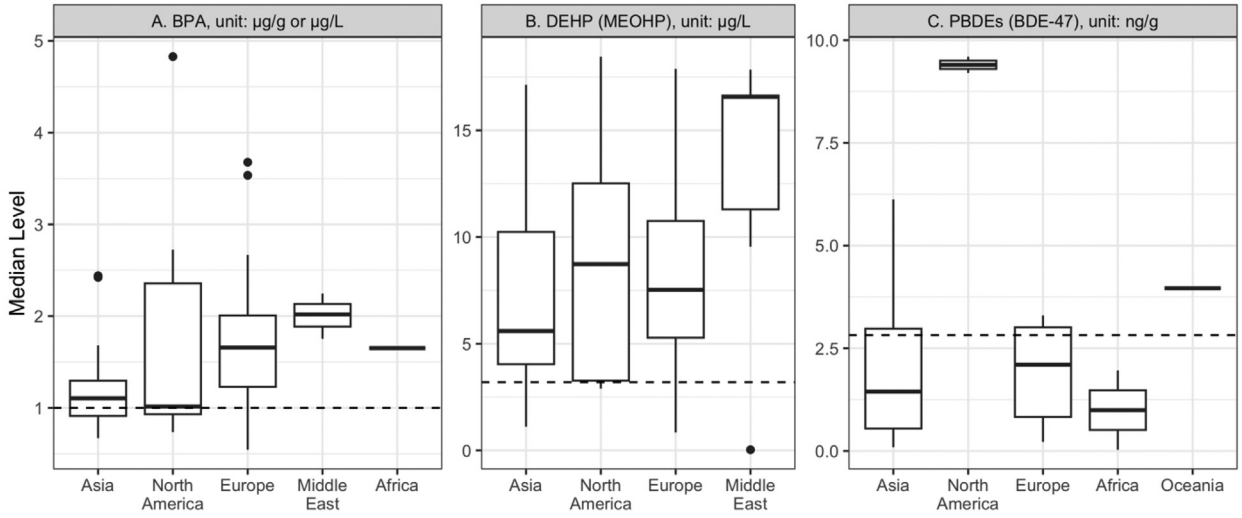

Fig. 1. Distribution of sample median estimates of BPA, MEOHP, and PBDEs. Note: The dashed lines represent the threshold levels of exposure [1 µg/g and µg/L for BPA, 3.2 µg/L for DEHP and 2.82 ng/g for BDE-47 (PBDE)].

To estimate the health effects of BPA or MEOHP, we must know the distribution of exposures to these chemicals in the study population. Although many articles provide estimates of median exposure, few provide estimates of the exposure distribution. We retained all studies that provided multiple quantiles of the exposure distribution and used these to estimate the mean and SD of exposure, assuming it to be lognormally distributed.[§] The average BPA study in our database contains 4.83 quantiles of the exposure distribution; the average DEHP study presents 4.64 quantiles of the exposure distribution.

Panel *A* of *SI Appendix*, Tables S1 and S2 describes exposure distributions of BPA and MEOHP for each of the 61 BPA and 85 MEOHP samples used in our 2015 analysis. This table includes the location of each study, the number of quantiles reported in the study, sample size, age group, and year of the sample. Based on the parameters of the lognormal distribution that we calculate for each study, we report the proportion of each sample in excess of the exposure threshold, median exposure in the sample, and the 90th percentile of exposure. Panel *B* of *SI Appendix*, Tables S1 and S2 presents the exposure distributions for BPA and MEOHP in various years for the United States, Canada, and South Korea.

To show graphically how the distributions of BPA and MEOHP vary by region, Fig. 1 *A* and *B* presents box plots showing the distribution of sample median estimates of BPA and MEOHP by region. The dotted horizontal line in each graph represents the threshold level of exposure. 80.9% of BPA and 85% of MEOHP samples have a median exposure exceeding the threshold, implying that at least half the sampled population will be affected by BPA (MEOHP) exposure.

Estimating and Valuing Health Effects: BPA and DEHP. To compute attributable fractions of IHD and stroke due to BPA and 55-to-64 all-cause mortality due to MEOHP, we use the distribution of the chemical in each sample and the formulas in *SI Appendix* to calculate the fraction of each health outcome attributable to the relevant pollutant. Panel *A* of *SI Appendix*, Tables S1 and S2 summarize the attributable fractions of each health endpoint due to BPA (*SI Appendix*, Table S1) and MEOPH (*SI Appendix*, Table S2).[¶] To calculate attributable fractions at the country level, we average values for samples within each country, weighting by sample size. Attributable fractions by country appear in *SI Appendix*, Tables S4–S6.

We value deaths associated with BPA and MEOHP using the Value per Statistical Life (VSL)–the amount that individuals will pay for small reductions in risk of death that together sum to one statistical life. (See *SI Appendix* for more detail.) We transfer estimates of the VSL for the year 2015 from the Organization for Economic Cooperation and Development (OECD), $3.8 million 2015 purchasing power parity (PPP) dollars, to individual countries using per capita Gross National Income (GNI) and an income elasticity of the VSL equal to one. This is equivalent to using a VSL equal to 100 times the per capita GNI of each country. We express all damages in 2015 international dollars. We do not monetize the direct costs of IHD and stroke; hence, our estimates of the costs of BPA and DEHP are lower bounds to social costs.

Health Effects of PBDEs. Prospective, longitudinal, birth cohort studies have linked PBDE levels in the blood of pregnant women to decreases in their children's IQ, finding that higher maternal levels of PBDEs are associated with lower IQ scores in children, and also negatively associated with other neurodevelopmental and behavioral indices (32–34). A meta-analysis of these studies (35) finds a statistically significant negative relationship between levels of BDE-47 in mothers' blood during pregnancy (indicating prenatal fetal exposure) and children's IQ. Specifically, a one-unit increase in $\log_{10}$ BDE-47 is associated with a 3.7-point reduction in IQ at age 5 (CI = 0.83-6.56). We apply this measure to BDE-47 levels in excess of 2.82 ng/g, which we treat as the BDE-47 threshold following Attina et al. (14). We use this relationship together with exposure estimates to calculate the number of IQ points lost per 100,000 births. These are multiplied by the size of the 2015 birth cohort (21) to estimate the number of IQ points lost to PBDE exposure in each country in 2015.

We assume that reducing BDE-47 exposure would reduce all exposures to the threshold level of 2.82 ng/g and thus reduce estimated lost IQ points to zero.[#]

Measuring PBDE Exposure. To our knowledge, NHANES is the only national biomonitoring study that regularly monitors PBDE congeners in human blood. Serum estimates of PBDEs have been obtained in national biomonitoring studies in France (2014-16) (28) and Canada (2007-09) (25). Other estimates of exposure include birth cohort studies and other epidemiological studies, in which PBDE congeners are measured in blood. We limit our analysis to studies that measured BDE-47 in either cord blood or maternal serum. We selected the BDE-47 congener as our measure of PBDE exposure because it is one of the most commonly measured congeners in studies of health effects, and in exposure and biomonitoring studies.[||] Additionally, to estimate the lognormal distribution of BDE-47 in the study population, we required studies to report multiple quantiles of BDE-47 distribution. The studies we use, on average, reported 3.47 exposure quantiles.

The studies used to estimate BDE-47 exposure are described in Panel *A* of *SI Appendix*, Table S3. Data similar to those for BPA and MEOHP are reported for 15 samples. We also report observed median exposure for 15 samples which did

[§]BPA and DEHP are lognormally distributed in the US population (24).

[¶]In the tables, we report the 95 percent CIs for each attributable fraction, based on the 95 percent CIs for each dose–response function. For BPA, the 95 percent CIs of the odds ratios for IHD and stroke due to (creatinine adjusted) BPA are reported as [1.06, 1.27] and [1.03, 1.29], respectively, in ref. 18. We use these to construct lower and upper bounds of relative risks to compute the lower and upper bounds of the fraction of IHD and stroke cases attributable to BPA. Similarly, we calculate the 95 percent CIs for all-cause mortality cases attributable to MEOHP, using CI of [1.02, 1.17] from ref. 22.

[#]The half-life of BDE-47 is between 0.4 and 3 y. Our analyses of the benefits of exposure reduction are "what if" analyses. If in US women of childbearing age in (e.g.) 2005 BDE-47 had been lower than measured, what would IQ losses have been?

[||]The epidemiological studies on which our estimates of IQ impacts are based use either mother's blood or cord blood as measures of exposure and BDE-47 levels as the measure of PBDE exposure.

Table 1. Health effects associated with BPA in 2015

Region	Number of Countries	Attributable fraction of IHD due to BPA	IHD prevalence cases attributable to BPA in 2015 (thousands)	IHD deaths attributable to BPA in 2015 (thousands)	Welfare costs of deaths (billions of 2015 PPP$)	Attributable fraction of stroke due to BPA	Stroke incidence cases attributable to BPA in 2015 (thousands)	Stroke deaths attributable to BPA in 2015 (thousands)	Welfare costs of deaths (billions of 2015 PPP$)
Asia	3	0.073 [0.026, 0.121]	3,046.0 [1,105.4, 5,047.9]	125.0 [45.3, 207.5]	172.3 [62.3, 286.1]	0.071 [0.011, 0.129]	249.5 [37.2, 456.0]	144.1 [21.5, 263.3]	198.8 [29.4, 363.6]
North America	4	0.079 [0.031, 0.125]	827.8 [326.0, 1,318.9]	44.0 [17.4, 70.3]	181.0 [70.6, 292.4]	0.075 [0.015, 0.132]	36.0 [7.4, 64.4]	14.5 [3.0, 26.0]	59.0 [12.1, 107.6]
Europe	18	0.098 [0.037, 0.158]	1,517.3 [571.1, 2,449.2]	64.8 [24.5, 104.7]	238.3 [90.1, 384.7]	0.095 [0.016, 0.168]	57.2 [9.8, 101.8]	34.6 [5.7, 61.5]	124.5 [20.6, 221.6]
Middle East	2	0.113 [0.046, 0.177]	42.3 [17.0, 66.4]	1.8 [0.7, 2.8]	3.8 [1.5, 5.9]	0.107 [0.023, 0.188]	1.4 [0.3, 2.5]	0.5 [0.1, 0.9]	1.4 [0.3, 2.4]
Africa	1	0.082 [0.033, 0.132]	14.3 [5.7, 22.9]	0.8 [0.3, 1.3]	0.2 [0.1, 0.4]	0.078 [0.017, 0.140]	1.4 [0.3, 2.6]	0.8 [0.2, 1.4]	0.2 [0.0, 0.4]
Total			5,447.8 [2,025.2, 8,905.3]	236.5 [88.2, 386.6]	595.6 [224.6, 969.6]		345.6 [55.0, 627.3]	194.4 [30.4, 353.1]	383.9 [62.4, 695.6]

not have sufficient quantile information to allow us to estimate parameters of the lognormal distribution. Fig. 1*C* presents box plots of median BDE-47 exposure for each region. The proportion of samples with median exposure in excess of the BDE-47 threshold is extremely small for Europe, but very high for North America and Oceania.

Estimating and Valuing Health Effects: PBDEs. To estimate IQ points lost due to BDE-47 exposure, we used the dose–response function in ref. 35 for the 15 samples for which we were able to estimate the lognormal distribution of BDE-47. (See *SI Appendix* for details.) In cases where only median exposure was reported, we relied on econometric modeling to extrapolate results from studies with complete information about the exposure distribution. For 52 studies for which we were able to estimate the lognormal exposure distribution, we regressed IQ point loss on median exposure ($R^2 = 0.933$). The results of this equation were used to predict IQ loss in the remaining 15 samples in *SI Appendix*, Table S3.**

We estimate the economic cost of lost IQ points using foregone output over the lifespan of exposed children. Following the *Lancet* Commission (36), we estimate output produced between the ages of 15 and 64 which we discount to birth (see *SI Appendix* for details). We assume, following the literature, that one IQ point reduces the present value of lifetime output by 1.1%, noting that recent studies have used values between 0.9% (37) and 1.4% (38).

Results

Benefits of Reducing Exposure to BPA, DEHP, and BDE47 in 2015. Country-specific estimates of the cases of IHD and stroke attributable to BPA, and IHD and stroke deaths attributable to BPA in 2015 are presented in *SI Appendix*, Tables S4 and S5. These tables also monetize the economic costs of deaths attributable to IHD and stroke. In Table 1, we aggregate these estimates to the region level, weighting results for each country by country population.

Our estimates of the impact BPA on IHD and stroke (Table 1) cover countries containing one-third of the world's population. Although the risks attributable to BPA for different countries come from exposure data for different years, there is no significant correlation between IHD risk and the beginning year of data collection. The attributable fraction of IHD due to BPA is highest in the Middle East (0.113), followed by Europe (0.098), Africa (0.082), North America (0.079), and Asia (0.073). Attributable fractions of stroke due to BPA follow a similar pattern, with attributable fractions being highest in the Middle East (0.107) and Europe (0.095), followed by Africa, North America, and Asia.

Exposure estimates, translated into cases, indicate that 5.4 million cases of IHD and 346,000 cases of stroke were associated with BPA exposure in 2015 in the countries included in Table 1. These incident cases resulted in approximately 431,000 deaths—237,000 deaths due to IHD and 194,000 due to stroke—valued at $0.980 billion 2015 international dollars. The largest number of IHD deaths attributable to BPA occurred in China, followed by the United States, Germany, Mexico, and Italy. Stroke deaths were highest in China, followed by the United States, Italy, Germany, and France (*SI Appendix*, Tables S4 and S5).

Estimates of DEHP exposure (Table 2) also cover countries containing one-third of the world's population. The ranking of the attributable fraction of mortality associated with DEHP for persons 55-to-64, by region, is similar to that for BPA: attributable fractions are highest in the Middle East (0.121) and Europe (0.100), followed by Asia (0.071) and North America (0.059). We calculate that DEHP exposures led to approximately 164,000 deaths in 2015 among 55-to-64-y-olds in the countries studied, resulting in welfare losses of $398 billion 2015 international dollars. Attributable deaths were largest in China, followed by Japan, the United States, Mexico, France, and Poland (*SI Appendix*, Table S6).

Due to more limited availability of data on PBDE levels in either cord blood, or serum of pregnant women or women of childbearing age, we have estimates of BDE-47 exposure for women in only 15 countries (Table 3 and *SI Appendix*, Table S7). Impacts on IQ loss are calculated for each of six percentiles of the BDE-47 distribution; however, if the 90th percentile of the distribution lies below the no-effect threshold, no IQ points are estimated to be lost. The countries with the largest impact of PBDEs on children's IQ are the United States and Canada, over 150,000 points lost per 100,000 births in 2015, followed by Australia and South Korea (approximately 50,000 points lost per 100,000 births). The five countries in Europe average 7,298 points lost per 100,000 births. Out of 28 million children born in the 15 countries we study in 2015, 11.7 million IQ points were lost due to maternal PBDE exposure. Our estimate of the present value of productivity losses associated with PBDE exposure to children born in the countries we study in 2015 is over 80 billion 2015 international dollars.

**The 52 studies used a variety of exposure media, including placenta and breast milk. Coefficients for sample source were insignificant in the regression. Our prediction equation includes only median BDE-47 and a constant term. We do not include all 52 studies in *SI Appendix*, Table S3 because the epidemiological studies in ref. 35 rely solely on serum samples.

Table 2. All-cause mortality, 55 to 64 y olds, associated with DEHP (MEOHP) in 2015

Region	Number of Countries	Attributable fraction of 55-to-64-y-old deaths Due to DEHP	All-cause deaths (55 to 64) attributable to DEHP in 2015 (thousands)	Welfare costs of deaths (billions of 2015 PPP$)
Asia	4	0.071 [0.017, 0.124]	103.3 [24.8, 180.2]	180.3 [43.9, 310.8]
North America	4	0.059 [0.014, 0.103]	25.6 [6.1, 45.1]	92.0 [21.4, 165.6]
Europe	13	0.100 [0.024, 0.171]	31.6 [7.7, 54.3]	110.3 [26.9, 189.5]
Middle East	2	0.121 [0.030, 0.205]	2.9 [0.7, 5.0]	14.7 [3.6, 24.9]
Total			163.6 [39.4, 284.9]	398.3 [96.1, 692.8]

Benefits of Exposure Reduction in Canada, Korea, and the United States. National biomonitoring surveys in Canada, Korea, and the United States, which are conducted regularly, make it possible to examine time trends in exposures to BPA and DEHP. The attributable fractions of IHD and stroke associated with BPA have fallen sharply in both Canada and the United States as population exposures to BPA and DEHP in these countries have declined. In the United States (Fig. 2 and *SI Appendix*, Table S1), attributable fractions of IHD associated with BPA fell by 59%—from .129 in 2003 to 0.053 in 2015 and attributable fractions of stroke also fell by 59%—from 0.122 to 0.050. Annual deaths associated with BPA due to IHD and stroke (Table 4) fell by over 60%: from 94,000 in 2003 to 35,900 in 2015. In Canada (Fig. 2 and *SI Appendix*, Table S1), BPA-associated risks of IHD fell by 64%—from 0.074 in 2007 to 0.027 in 2019 for IHD and from 0.070 to 0.025 for stroke, leading to a 42% reduction in associated annual deaths. The situation in Korea (Fig. 2 and *SI Appendix*, Table S1) was somewhat different: BPA-related attributable fractions for both IHD and stroke increased from 0.036 in 2010 to 0.060 in 2019.

Table 4 and *SI Appendix*, Table S1 also enable calculation of the aggregate benefits of reducing BPA exposures in the United States and Canada: Had exposure levels in the United States in 2003 been equal to the lower levels seen in 2015, more than 355,000 deaths due to IHD and stroke attributable to BPA would have been averted between 2003 and 2014. In Canada, reducing 2007 exposure levels to 2019 levels would have reduced IHD and stroke deaths attributable to BPA by 2,740.

In all three countries, exposure to DEHP (MEOHP) has fallen (Fig. 2 and *SI Appendix*, Table S2). In the United States, the attributable fraction of mortality due to MEOHP for 55-to-64-y-olds fell from 0.122 in 2003 to 0.035 in 2015. Attributable fractions in Canada fell from 0.063 in 2009 to 0.021 in 2019. In Korea, attributable fractions fell from 0.127 in 2011 to 0.068 in 2019. Had exposure levels in the United States been at 2015 levels each year between 2003 and 2014, there would have been 159,000 fewer deaths in that time period attributable to DEHP.

The United States has monitored blood PBDE levels since 2005 (*SI Appendix*, Table S3) and has found declining population exposure levels over that time. In 2005, IQ losses attributable to PBDEs exceeded 324,000 per 100,000 births. In 2015, IQ losses had fallen to 175,600 per 100,000 births, as shown in Fig. 2. If PBDE levels in mothers had been at 2015 levels since 2005, over 42 million IQ points would have been saved between 2005 and 2015 (Table 4).

Discussion

Estimating the health effects of toxic chemicals in plastics is challenging even when these chemicals can be measured in the human body and when plastics consumption is the main source of exposure. Few countries conduct national biomonitoring studies, so we have had to rely on individual studies conducted in a range of countries. We view the variation in exposure studies within a country as sampling variation and therefore average estimates calculated based on these exposures in proportion to sample size to estimate effects at the country level.

There is also uncertainty in the estimated health effects of BPA, MEOHP, and BDE-47. Our analyses rely on health impacts and effect sizes derived from observational research, as we do not have experimental exposure studies in humans, and assume a causal relationship underlying observed association between exposure and outcome. The source studies each involve large well-designed epidemiological cohorts, direct measurement of individual exposure in stored biosamples, and analyses that consider and adjust for potential confounding factors. Evidence for associations between chemicals and disease is especially convincing when multiple epidemiologic

Table 3. IQ losses and associated productivity losses due to PBDEs (BDE-47) in 2015

Region	Number of Countries	IQ point losses in points per 100,000 births	IQ points lost in 2015 birth cohort (thousands)	Total PDV of lost productivity in billions of 2015 PPP$
Asia	5	17,733.5 [3,978.1, 31,297.2]	3,181.7 [713.7, 5,615.3]	6.5 [1.5, 11.5]
North America	2	173,913.2 [39,013.0, 306,933.2]	7,534.0 [1,690.1, 13,296.5]	72.5 [16.3, 128.0]
Europe	5	7,298.0 [1,637.1, 12,880.0]	102.4 [23.0, 180.8]	0.7 [0.1, 1.2]
Africa	2	18,806.2 [4,218.7, 33,190.4]	653.3 [146.6, 1,153.0]	0.2 [0.0, 0.3]
Oceania	1	53,094.2 [11,910.3, 93,704.0]	161.9 [36.3, 285.8]	1.1 [0.2, 1.9]
Total			11,633.4 [2,609.7, 20,531.4]	81.0 [18.2, 142.9]

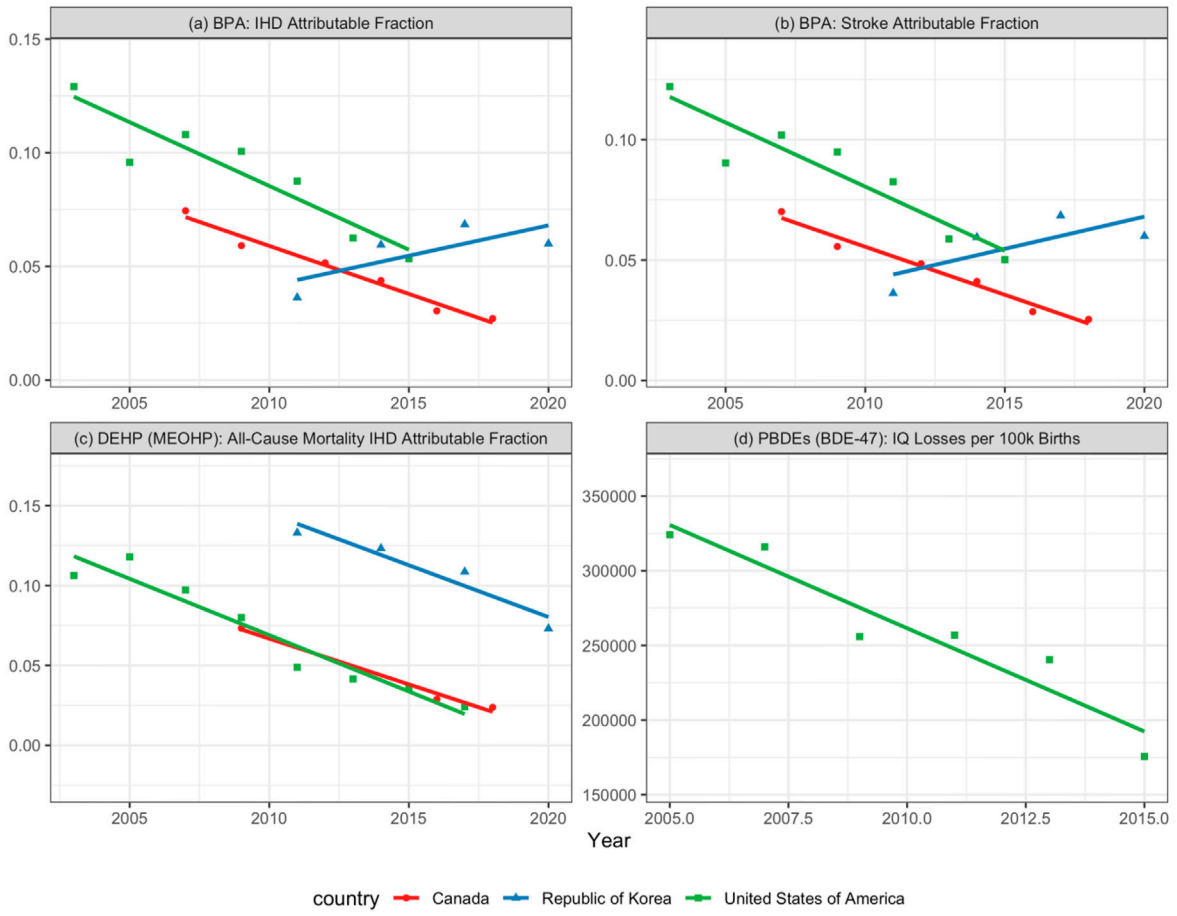

Fig. 2. Trends in attributable fractions associated with BPA and DEHP and IQ losses associated with PBDEs

studies in different populations yield consistent results. Observational studies may, however, be subject to residual confounding or reverse causal pathways that could impact the strength of the causal evidence and/or the estimated effect sizes that we rely upon here.

Subject to these caveats, we have two main results. First, we find that exposures to the plastics chemicals, BPA and DEHP, and to PBDEs are widespread and that these exposures are associated with significant morbidity and mortality in the countries studied. The economic costs of this disease burden are very high. In 2015, 5.4 million cases of IHD and 346,000 cases of stroke were associated with BPA exposure, DEHP exposures were linked to approximately 164,000 deaths among 55-to-64-y-olds, and 11.7 million IQ points were lost due to maternal PBDE exposure in pregnancy. The costs associated with these diseases and premature deaths were estimated at 1.46 trillion 2015 international dollars.

Our second main finding is that exposures to BPA, DEHP, and PBDEs have fallen significantly in the United States since 2003-2005 due to a combination of regulatory and voluntary actions. Similar trends are seen for BPA and DEHP in Canada since 2007. Had exposure to BPA in the United States been at 2015 levels between 2003 and 2014, we estimate that 355,000 fewer deaths would have been attributed to IHD and stroke associated with BPA over this period. Had exposure to DEHP been at 2015 levels between 2003 and 2014, we estimate that 159,000 fewer deaths would have been attributed to DEHP exposure. Similar but smaller gains would have occurred in Canada for both BPA and DEHP and in South Korea for DEHP. Had PBDE levels in women of childbearing age been equal to 2015 levels in 2005, over 42 million IQ points would have been saved in children born between 2005 and 2014 (Table 4). These findings demonstrate that BPA, DEHP, and PBDEs can be successfully removed from plastics and that such reductions are likely to result in major health benefits and substantial economic gains.

We emphasize that our estimates in Tables 1–3 are underestimates of the full benefits of reducing BPA, DEHP, and PBDE exposures in 2015. These estimates do not include health effects other than those we have quantified, and they cover only one-third of the world's population. Another source of underestimation is that our estimates cover only 1 y. However, the aggregate economic benefit of removing a harmful chemical from plastic is the sum of all the years in which the toxic chemical is no longer present. PBDEs began to be used as flame retardants in the 1970s and plastic bottles containing BPA replaced glass bottles in the United States in the 1970s, implying a long history of health impacts that we cannot measure. We also cannot estimate—with the exception of the United States, Canada, and South Korea—how exposures have varied over time. Even for these three countries, we have no information on exposures prior to 2003.

We note that the health hazards of the chemicals and chemical classes we study here were not recognized until many years after their introduction to US and Canadian markets and that many more years elapsed before actions were taken to reduce these exposures. Even after studies emerged in the 1970s and 1980s about the health effects of these substances, it took many years for government regulations to follow, producers to voluntarily withdraw production of some substances (e.g., PBDEs), and public pressure to lower sales of products containing BPA (*SI Appendix*). In the United States, these actions did not take

Table 4. Trends in BPA, DEHP, and PBDE outcomes in the United States

	BPA		DEHP (MEOHP)		PBDEs (BDE-47)	
Year	Deaths due to IHD and Stroke (thousands)	Reduction in deaths due to IHD and stroke if exposures were at 2015 levels (thousands)	All-cause mortality, 55-to-64 y olds due to DEHP (thousands)	Reduction in all-cause mortality, 55-to-64 y olds due to DEHP if exposures were at 2015 levels (thousands)	IQ points lost in the birth cohort (millions)	IQ points saved if exposures were at 2015 levels (millions)
2003	94.0 [34.4, 149.7]	55.2 [20.9, 84.5]	27.8 [6.7, 48.0]	18.5 [4.6, 31.0]		
2004	90.5 [33.1, 144.2]	53.1 [20.1, 81.4]	28.2 [6.8, 48.7]	18.8 [4.7, 31.4]		
2005	66.5 [23.7, 108.3]	29.4 [10.9, 46.1]	32.5 [7.9, 55.5]	22.7 [5.7, 37.6]	13.5 [3.0, 23.9]	6.2 [1.4, 11.0]
2006	65.0 [23.2, 105.9]	28.8 [10.6, 45.1]	33.2 [8.1, 56.7]	23.2 [5.8, 38.4]	13.9 [3.1, 24.5]	6.4 [1.4, 11.2]
2007	71.6 [25.7, 115.6]	36.2 [13.5, 56.3]	28.0 [6.7, 48.7]	17.7 [4.4, 29.9]	13.5 [3.0, 23.8]	6.0 [1.3, 10.6]
2008	71.0 [25.5, 114.7]	35.9 [13.4, 55.9]	28.7 [6.9, 49.9]	18.2 [4.5, 30.7]	13.2 [3.0, 23.3]	5.9 [1.3, 10.3]
2009	65.0 [23.2, 105.5]	30.5 [11.3, 47.7]	24.3 [5.8, 42.8]	13.5 [3.3, 23.0]	10.4 [2.3, 18.3]	3.3 [0.7, 5.7]
2010	64.4 [23.0, 104.6]	30.2 [11.2, 47.3]	24.8 [5.9, 43.7]	13.8 [3.4, 23.5]	10.1 [2.3, 17.9]	3.2 [0.7, 5.6]
2011	56.5 [20.0, 92.7]	22.1 [8.1, 34.8]	15.8 [3.6, 28.6]	4.3 [1.0, 7.5]	10.1 [2.3, 17.9]	3.2 [0.7, 5.7]
2012	56.7 [20.0, 93.0]	22.1 [8.1, 34.9]	16.1 [3.7, 29.1]	4.4 [1.0, 7.7]	10.1 [2.3, 17.8]	3.2 [0.7, 5.6]
2013	40.8 [14.2, 68.2]	6.0 [2.1, 9.6]	14.0 [3.2, 25.5]	2.0 [0.5, 3.5]	9.5 [2.1, 16.8]	2.6 [0.6, 4.5]
2014	41.2 [14.3, 68.8]	6.0 [2.2, 9.7]	14.4 [3.3, 26.3]	2.1 [0.5, 3.6]	9.6 [2.2, 16.9]	2.6 [0.6, 4.6]
2015	35.9 [12.3, 60.3]	0.0 [0.0, 0.0]	12.7 [2.9, 23.2]	0.0 [0.0, 0.0]	6.9 [1.6, 12.2]	0.0 [0.0, 0.0]
Total		355.6 [132.3, 553.3]		159.0 [39.4, 267.8]		42.4 [9.5, 74.8]

place until the early 2000s—30 or more years after the first recognition of hazard.

We also note that more than 70% of the chemicals incorporated into plastics have never been tested for safety or toxicity and that their possible harms to human health are not known (39). We consider it highly likely that there are chemicals in wide use in plastics today whose toxicity has not yet been recognized. It is likely that these chemicals are responsible for still undiscovered harms to health and for unquantified economic losses.

The absence of premarket testing of the majority of chemicals in plastics and the long delays between recognition of these chemicals' hazards and preventive intervention reflect the current state of national policies for chemicals management. The US Toxic Substances Control Act (TSCA) of 1976 only rarely requires manufacturers to test new or existing chemicals for toxicity. The burden is placed on government to prove that a chemical causes harm. In consequence, only a handful of chemicals have been banned in the nearly 50 y since TSCA's passage (39). In the EU, the chemicals management law—Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)—is ostensibly more protective of health than TSCA and states that it operates on the principle of "no data, no market" (40). In reality, however, premarket screening of chemicals in the EU relies heavily on toxicity data provided by the chemical industry, and these data are accepted with few quality controls. To date, restrictions have been applied to only 73 chemicals and chemical classes in European markets.

Protection of human health against the hazards of chemicals in plastics will require a paradigm shift in national chemical law in multiple countries including the United States, Canada, and the EU. It will require a more precautionary approach that prioritizes the protection of human health and no longer presumes that chemicals are safe. Under these new laws, chemicals would be allowed to enter plastic products and remain on markets only if their manufacturers can establish through independent hazard testing that they are safe. Such an approach has been the norm in pharmaceutical regulation since the 1970s.

At a global level, a key strategy for confronting the health impacts caused by toxic chemicals in plastics could be the inclusion of legally binding standards on chemical safety in the Global Plastics Treaty in current negotiation under UN auspices. These standards could require independent toxicity testing of all chemicals in plastics and full disclosure to national regulatory authorities of information on their chemical composition and health hazards. Inclusion of international standards on plastics chemicals in the Global Plastics Treaty will be especially important for protecting the health of vulnerable populations in low-income and middle-income countries, where 50% of the world's plastics are now consumed (41).

Data, Materials, and Software Availability. All study data are included in the article and/or *SI Appendix*.

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