Preterm birth attributable to exposure to chemicals used in plastic materials: a global estimate

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Summary

Background Phthalates, widely used as plasticizers, have been associated with adverse pregnancy outcomes, including preterm birth (PTB). This analysis quantifies the global burden of PTB associated with exposure to di (2-ethylhexyl) phthalate (DEHP) and diisononyl phthalate (DINP).

Methods A disease burden model was constructed using 2018 exposure estimates from available population-level biomonitoring surveys and meta-analyses in regions lacking such surveys. Hazard ratios (HRs) for PTB associated with phthalate exposure were derived from a previous cohort study and applied to regional exposure distributions, and a search from 2016 to 2026 was completed to identify uncertainty intervals for effect estimates. PTB-attributable outcome estimates were obtained from the Institute for Health Metrics and Evaluation's. Phthalate-associated PTB outcomes were calculated using a population attributable fraction approach.

Findings In 2018, 1.97 million DEHP-attributable PTBs (8.74% of global PTBs) were estimated, alongside 74,000 deaths, 6.69 million years of life lost (YLLs) and 1.22 million years of life lived with disability (YLDs). 1.93 million of these incident PTBs, 72,500 deaths, 6.56 million YLLs, and 1.20 million YLDs could be linked to plastics. The highest absolute burden was estimated in the Middle East and South Asia, representing over 54% of estimated attributable PTBs, followed by Africa at 26%. Attributable morbidity and mortality trends differed in accordance with underlying regional patterns of burden. Estimates were similar for DiNP (64,000 deaths, 1.88 million PTB cases, 5.77 YLLs, 1.35 YLDs, and PAF of 8.32%). To account for uncertainties in extrapolating effect estimates from the US, effect estimates from four previous global meta-analyses were also used to calculate uncertainty intervals. Uncertainty intervals revealed as low as 4 times lower estimates for DEHP, and 10 times lower DiNP estimates, highlighting the need for further investigation to refine DiNP associated morbidity and mortality.

Interpretation This model presents the first global estimate of the PTB burden linked to exposure to certain phthalates. Burden was estimated to be disproportionate in South Asia, the Middle East, and Africa. Implementing regulatory measures to limit exposure to phthalates as a class could help reduce the global PTB burden, particularly in and areas with high PTB risk, limited regulations, and growing plastics industries.

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Keywords: Phthalates; Plastics; DEHP; DiNP; Preterm birth

Introduction

Preterm birth (PTB, delivery of a child before 37 weeks of gestation) is a leading global health challenge.[1] Globally, more than 13 million infants were born prematurely in 2020, accounting for more than one-in-ten live births.[1] PTB is the leading cause of death worldwide in children under 5, and is the cause of approximately 1 million deaths of neonates per year.[2–4] The highest rates of preterm birth have been observed in Africa and South Asia,[1] but other regions such as the United States of America (USA) also have high PTB rates.[5] PTB can cause long-term health effects for survivors.[2]

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Research in context

Evidence before this study

Before conducting this study, a review of the literature was undertaken using databases such as Web of Science and PubMed. Search terms included combinations of "DEHP," "DiNP," "phthalates," "preterm birth," "preterm," "PTB," "plastic exposure," "endocrine disruptors," and "maternal and child health." Previous studies link phthalate exposure with increased risk of preterm birth, largely through mechanisms involving endocrine disruption, inflammation, and placental dysfunction. However, prior research was limited to individual studies or regional cohorts. To the authors' knowledge, no model to date had estimated the global burden of preterm birth attributable to DEHP or any of its replacements. Furthermore, no analysis had provided pooled global or region-specific estimates that incorporated percentile-based exposure distributions, examined inequality in exposure-related risk, or compared morbidity and mortality burden.

Added value of this study

This study provides the first global quantification of preterm births associated with exposure to two different phthalates estimating that more than 1.9 million PTBs, 74,000 deaths, 6.6 million YLLs, and 1.2 million YLDs in 2018 were linked to DEHP exposure. In addition to estimating the total burden of preterm birth incidence, this model also estimated deaths and years of life lost to PTB as well as years of life lived with disability attributable to PTB. The model also offers region-specific estimates that identify large disparities in estimated risk. Regions such as The Middle East, South Asia, and Africa were estimated to bear the highest burden of phthalate-associated PTB, both in absolute terms and by attributable fraction of preterm births. The analysis also incorporates several important secondary analyses. It estimates burden attributable to DiNP, a DEHP replacement not often studied, estimating almost equivalent burden. It also includes an effect-estimate uncertainty interval based on a systematised literature review of meta-analyses, producing a range for all estimates. These findings offer novel evidence that can support public health decision-making, particularly in regions experiencing rapid industrialisation, high underlying risk for PTB, and high rates of plastic waste and utilization. These findings provide a foundation for future global disease burden modelling, addressing a significant gap in the current body of literature.

Implications of all the available evidence

Taken together, this model and the broader body of literature highlights phthalate exposure as a potentially under-recognised contributor to adverse reproductive outcomes. These global estimates demonstrate that according to available evidence, a proportion of the global PTB burden may be avertable through plastics pollution mitigation strategies. These findings point to the urgent need for international action to reduce exposure to phthalates as a class, especially in regions with high burden and limited regulatory protections. Intra-regional disparities in exposure further underscore the importance of targeting the most highly exposed subpopulations within high-burden regions. Strengthened national regulations, improved waste management, and expansion of biomonitoring programs are essential steps to control and mitigate these risks. Future research should aim to include additional plastic-associated chemicals to further elucidate global burden of disease attributable to plastics and should support increased global biomonitoring of these chemicals in regions of the world lacking robust chemical monitoring systems.

Individuals who were born preterm have been shown to be at an increased risk for respiratory distress syndrome and neurodevelopmental deficits during infancy, and adverse health outcomes later in life.[6,7]

A bourgeoning body of research has identified the contribution of environmental exposures to PTB. Endocrine-disrupting chemicals (EDCs) interfere with hormonal regulation critical to the healthy course of pregnancy and foetal development.[8] One such class of EDCs, phthalates, are a group of synthetic chemicals frequently encountered in daily life due to their widespread use as plasticizers in personal care items, food packaging, and other products.[9] Human exposure to phthalates is ubiquitous, occurring primarily through ingestion, inhalation, and dermal absorption.[9] Phthalates have been found in maternal prenatal urine samples, amniotic fluid, and cord blood.[10–12] Toxicological studies demonstrate that phthalates can disrupt endocrine pathways and upregulate inflammation, can alter placental development, and induce oxidative stress in the reproductive system. These processes have all been implicated in PTB,[13–15] and a body of epidemiological literature has linked phthalate exposure directly to PTB outcomes.[16,17] The global epidemiologic literature exploring phthalate exposure's association with PTB is substantial, including single-cohort studies from north America,[16] Europe,[18,19] Mexico,[20] and China.[21–25] Notably, these studies focus on di-2-ethylhexyl phthalate (DEHP), with sparse inclusion of a common replacement, diisononyl phthalate (DiNP). Other conditions identified in human studies associated with phthalate exposure include childhood obesity and impaired glucose tolerance, among other health outcomes.[26]

Talks to negotiate a legally binding agreement aimed at ending plastic pollution internationally among the United Nations Environment Assembly have recently concluded, but work is ongoing.[27] Estimating the global

burden of disease attributable to prenatal phthalate exposure is critical to informing future discussions and policy changes both on the global and regional levels. Therefore, we aim to estimate global PTB outcomes linked to phthalate exposure through a globally inclusive burden of disease model.

Methods

Study population

This analysis included 203 countries or territories with PTB data from the Institute for Health Metrics and Evaluation (IHME's) 2021 Global Burden of Diseases Study.[28] A complete list, along with their UN standardized geographic regions and PTB-attributable disease burden estimates can be found in Supplement 1.

Estimation of exposures

Seven phthalate metabolites of interest were identified in this analysis. Four were Di (2-ethylhexyl) phthalate (DEHP) metabolites: Mono(2-ethylhexyl) phthalate (MEHP), Mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), Mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and Mono(2-ethyl-5-carboxypentyl) phthalate (MECPP). Three were Diisononyl Phthalate (DiNP) metabolites: Monocarboxy-isooctyl phthalate (MCOP), Mono-oxo-isononyl phthalate (MOiNP), and Mono-hydroxy-isononyl phthalate (OH-MiNP).

This analysis relied on 2018 estimates of phthalate exposure from a previous meta-analysis. Acevedo et al. estimated DEHP and DiNP exposures in areas of the world which suffer from lack of centralized or publicly available biomonitoring data including Africa, South Asia and the Middle East (Asia–MESA), East Asia and the Pacific (Asia-EPA), Australia, and Latin America.[29] Key results of this analysis were predicted mean and standard deviation of phthalate metabolite concentrations in 2018 for the 10th, 25th, 50th, 75th, and 95th population percentiles of exposure, derived from linear models of exposure changes over time. Details of analytic procedures used in meta-analysis can be found in Acevedo et al., 2025.[29] In the present model, available 2018 phthalate concentrations from Acevedo et al., 2025 were assigned to countries based on the UN statistics division standardized country geographic regions,[30] with the exception of Australia (being considered its own region), and New Zealand and countries in the sub-regions of Melanesia, Micronesia, and Polynesia being classified within Asia-EPA.

Where possible, exposure data was obtained directly from population-level biomonitoring survey databases. Metabolite concentrations for Canada, the United States of America (USA), and Europe were sourced from the Canadian Health Measures Survey (CHMS),[31] the USA's National Health and Nutrition Examination Survey (NHANES),[32] and the European Consortium to Perform Human Biomonitoring on a European Scale (COPHES)/DEMOCOPHES project.[33] Exposure data was extracted for all ages and both genders, without adjustments for urinary dilution. NHANES data is publicly available, and 2017–2018 cycle data was extracted from the Centers for Disease Control and Prevention National Center for Health Statistics NHANES webpage. Environmental NHANES sample weights were applied to calculate exposure percentiles while respecting complex survey design. A data request was necessary to access European data. In an approach adapted from previous analysis,[34] using STATA version 18.5 (Stata Corporation: College Station, Texas, USA), available median values and standard deviations from country-level samples were used to calculate a standard error-weighted regression model. Regional concentration estimates at the 10th, 25th, 50th, 75th, and 95th percentiles were then calculated using the inverse of the normal cumulative distribution for the specified mean and standard deviation. Lastly, CHMS data from cycle 6 (2018–2019) was publicly available through the Canadian Biomonitoring Dashboard, excepting the 25th and 75th exposure percentiles of the population. To obtain dashboard data, each biomarker was entered into the "Chemical Biomarker" field, "Matrix" was specified as urine, the collection period was set to "2018–2019," and the selected "Statistics" included the geometric mean, and 10th, 50th, and 95th percentiles. The 25th and 75th percentile concentrations were requested from the CHMS team.

Any missing exposure data (3.13% of DEHP data, and 29.2% of DiNP data) was imputed by calculating the ratio of an average global concentration of a reference metabolite to global concentrations of the missing metabolite and then multiplying this ratio by the concentration of the reference metabolite in the region with missing data. For DEHP, a reference metabolite of MEOHP was utilized, while for DiNP, MCOP was used. To ensure biologically plausible exposure distributions, in the case of any violations of monotonicity, individual percentile values were re-imputed using a smoothed ratio curve derived from regions with complete data. This curve represented the average percentile-wise ratio between the target and reference metabolites and was applied to the reference metabolite values in the region with missing data. Imputation of DiNP metabolites in the Australian region was not possible and thus was excluded from analysis.

Estimated metabolite concentrations for each chemical in each world region can be found in Supplement 2. Imputed estimates for metabolite concentrations are indicated by an asterisk in Supplement 2.

Estimating phthalate-related hazard

After obtaining chemical concentration estimates, molar sums were calculated for DEHP metabolites ($\sum$DEHP): MEHP, MEHHP, MEOHP, MECPP, and DiNP metabolites ($\sum$DiNP): MCOP, MOiNP, and OH-MiNP. Each compound's concentration was divided by

its molecular weight (g/mol) and then summed. This process was repeated for each region, and each target quantile of exposure within each region (10th, 25th, 50th, 75th, and 95th).

To calculate hazard ratios (HRs) for preterm birth across different quantiles of exposure to DEHP metabolites, exposure–outcome relationships were extrapolated from Trasande et al., 2024, an investigation on preterm birth in the Environmental influences on Child Health Outcomes research program which estimated the concentration of phthalate metabolites in urine of pregnant individuals and studied its effect on preterm birth longitudinally.[16] When considering the global literature on effect size estimation for phthalates and preterm birth, while statistical significance is heterogeneous, the direction of the associations remains consistent. DEHP effect sizes are often comparable or even more pronounced than those effects estimated in Trasande et al., 2024. In addition, other investigations are not inclusive of DiNP. In Trasande et al., 2024, the HR for continuously measured, $\log_{10}$ transformed DEHP metabolite concentration (prior HR) was 1.45. In order to create a threshold for hazard at which HR would be set to one, the 10th percentile value of NHANES 2017–2018 was utilized, as a threshold below which no effects were assumed. According to these estimations, the DEHP exposure level of the 10th percentile was 0.016 μmol/L. DiNP calculations used a hazard ratio of 2.25 with a threshold exposure of 0.009 μmol/L.

For each parent compound, if the calculated value of the molar sum exceeded the threshold, the HR for preterm birth for each phthalate exposure quantile in each region was estimated:

$$HR_{Region,Quantile} = Prior\ HR^{\log_{10}\left(\frac{molar\ sum_{Region,Quantile}}{10th\ percentile\ threshold}\right)}$$

Estimated HRs for preterm birth for each world region can be found in Supplement 3a.

Preterm birth data

In order to characterize PTB burden, four metrics were considered: preterm birth incidence, preterm birth-related deaths, preterm birth-related years of life lost (YLL), and preterm birth-related years of life lived with disability (YLD). The IHME global health index VizHub results tool was searched for "GBD Estimate: Cause of Death or Injury," "Measure: Deaths, Incidence, YLL, and YLD" "Cause: Neonatal preterm birth," "Location: Select all countries and territories," "Age: All ages," "Sex: Both," and "Year: 2018".[28] This dataset includes estimated number of incident PTBs, & deaths, YLLs, and YLDs attributable to PTB in each country, estimated through models created by the IHME from country-level and international health records.

Calculation of phthalate-attributable outcomes

A population attributable fraction (PAF) approach was utilized in the present model. The PAF can be understood as the theoretical proportion of disease that could be eliminated if a given environmental exposure was removed.[35] PAFs can be useful for estimation of the quantity of disease potentially attributable to an environmental exposure. PAF was derived from exposure quantile and hazard ratios using:

$$PAF_{country,quantile} = \frac{Quantile\ of\ exposure \cdot (HR_{region,quantile} - 1)}{(Quantile\ of\ exposure \cdot (HR_{region,quantile} - 1) + 1)}$$

Baseline metrics of preterm birth incidence, preterm birth-related deaths, years of life lost, and years of life lived with disability were calculated by multiplying country-specific metrics by exposure quantiles. Lastly, phthalate-attributable metrics for each country and quantile were derived by multiplying the PAF to these calculated baseline metrics.

The lowest 10th percent of the population in phthalate exposure was considered a control group and assigned no phthalate-attributable PTB. In these analyses, the 10th percentile phthalate exposure was applied to the 11th–25th percentile of country-level populations, 25th to the 26–50th, 50th to the 51–75th, 75th to the 76th–95th, and 95th to the 96th–100th percentile. Sums of attributable outcomes across percentiles calculated total number of PTBs in each country, and sums across countries calculated regional estimates. A worked example of estimations can be found in Supplement 5.

This analysis primarily estimates PTB morbidity and mortality associated with exposure to DEHP. In recent years however, DEHP has been replaced by other chemically similar phthalates, such as DiNP. While literature indicates that simultaneous exposure to multiple phthalates may have amplified adverse effects,[36] in the present model, competing exposures are considered as overlapping risks as opposed to additive in order to keep with conservative estimation, and because DEHP and DiNP may be correlated given their often shared exposure sources. Previous work utilizing PAFs suggest that environmental exposures often do not act as sole causes of disease but may instead contribute to, or amplify, existing cases.[35] This framework was applied in this analysis to estimate the disease burden associated with DiNP.

Calculation of uncertainty ranges

A second analysis was conducted to account for uncertainties in extrapolating US effect estimates. To determine the lower and upper ranges of possible

effect estimates, a systematized review of the literature encompassing 2016–2026 was conducted in PubMed, Embase, and Web of Science. Details of each search strategy are provided in Supplement 4. Four meta-analyses, each incorporating multiple studies, were selected,[37–40] and the lowest and highest effect estimates across these meta-analyses were used to establish the range, inclusive of prior HRs from main analyses. For DEHP, effect estimates ranged from 1.1 to 1.5, and for DiNP, effect estimates ranged from 1.1 to 2.25. HRs for preterm birth for each world region, including uncertainty intervals, can be found in Supplement 3b.

Additional analyses

A set of cost burden analyses was also undertaken to estimate the cost of attributable mortality. The social cost of a year of life lost (SCYLL) was comparatively set at $50,000 United States Dollars (USD, a USA-extrapolated value) and a more conservative $1000 USD/YLL.[41] A purchasing power parity correction was not conducted as this implies difference of value of years of life based on location.[42] The cost of deaths was estimated through value of statistical life (VSL) approach based on 2018 definitions,[43] compared to the 2006 U.S. Environmental Protection Agency's (EPA) value of mortality risk reduction.[44]

In addition, a plastic attributable fraction for DEHP exposure of 98% was utilized to estimate plastics-attributable burden, based on previous published estimates.[45] Estimated phthalate-associated PTB outcomes were multiplied by the plastics-attributable fraction to calculate these values.

Sensitivity analysis

Lastly, sensitivity analysis (SA) accounting for uncertainties in exposure models was performed. As alternative inputs for exposure, centiles of phthalate exposure derived from the quadratic models in Acevedo et al., 2024, which assumed nonlinear change over time in exposures, were used as exposure inputs.[29]

Ethics

Only summary-level data was used; therefore, no ethical approval for human subject research was required. The principal investigator signed a New York University Grossman School of Medicine Institutional Review Board attestation form documenting the nature of the research activity conducted as research non involving humans.

Role of the funding source

Funding sources for this study had no role in model design, data collection, analysis, and interpretation of findings, writing of the manuscript, nor decision to submit the paper for publication.

Results

DEHP-attributable PTB, main estimates

Across all regions assessed, exposure to DEHP phthalates was associated with an estimated 1.97 million PTBs in 2018, corresponding to a global population-weighted attributable fraction (PAF) of 8.74%. Under this disease burden model, the burden of DEHP-associated PTB was not evenly distributed across regions (Table 1 and Fig. 1). Estimates for the Middle East and South Asia were the highest with 1.07 million PTBs associated with DEHP (PAF 10.7%; 54.1% of the global total). Other highly-burden regions included Africa, with approximately 511,000 cases (PAF 7.30%; 25.9% of the global total), and East Asia and the Pacific, with approximately 226,000 cases (PAF 7.93%; 11.5% of the global total). In contrast, certain high-income regions such as Canada and Australia were estimated to have had the smallest burdens, with approximately 1480 and 2190 DEHP-associated preterm births (0.08% and 0.11% of the global total), respectively, with more middling results for Europe and the US, with an approximate 16,700 and 35,600 DEHP-associated preterm births (0.85% and 1.80% of the global total), respectively. Model estimations for DEHP are detailed in Table 1 with global distributions shown in Fig. 1.

Exposure to DEHP was also estimated to contribute to a global total of 74,300 deaths of neonates, 6.69 million YLL attributable to premature mortality resulting from PTB, and 1.23 million YLD. Regional trends generally mirrored that of PTB statistics, with the Middle East and South Asia estimated to bear the majority of burden (38,500 neonatal deaths, 3.47 million YLL, and approximately 845,000 YLD), with Africa following (25,400 deaths, 2.29 YLL and approximately 122,000 YLD). Notably, the African continent was estimated to have experienced a much higher global proportion of deaths and YLL (34.2%) than of PTB incidence (25.9%) or YLD (9.90%) indicating that mortality burden was heightened in this region when compared to morbidity. Alternatively, this model estimated that the Middle East and South Asia had a much higher proportion of the global total of YLD (68.8%) when compared to its global proportion of PTB incidence (54.1%), neonatal deaths (51.8%), and YLL (51.9%).

From these estimates, after applying the DEHP plastics-related fraction, it was estimated that a total of approximately 1.93 million PTBs, 72,900 neonatal deaths, 6.55 million YLL, and 1.20 million YLD could be attributed to DEHP use in plastics.

DiNP-attributable PTB, main estimates

Analyses revealed comparable total burden of PTB linked to DiNP, though differing from DEHP-attributable burden in spatial distribution. DiNP-attributable estimates are detailed in Tables 2 and 3.

	Preterm births					Years of life lost (% of global)						Year of life lived with disability (% of global)						Deaths						% Attributable Fraction of Preterm Birth (% of global)					
World region	10	25	50	75	95	Total (% of global total)	10	25	50	75	95	Total (% of global total)	10	25	50	75	95	Total (% of global total)	10	25	50	75	95	Total (% of global total)	10	25	50	75	95	Population-weighted average
AUS	142	631	784	585	45	2,187 (0.11%)	111	493	614	458	35	1,711 (0.03%)	140	618	769	574	44	2,145 (0.17%)	1	5	7	5	0	18 (0.02%)	3.13	8.32	10.35	9.656	2.989	7.215
Africa	0	37,746	239,816	215,709	18,519	511,790 (25.94%)	0	168,601	1,071,176	963,497	82,717	2,285,991 (34.19%)	0	8,966	56,965	51,239	4,399	121,569 (9.90%)	0	1,876	11,922	10,723	921	25,442 (34.21%)	0.00	2.15	13.68	15.380	5.281	7.298
Asia-EPA	21,060	67,957	77,366	55,601	4,173	226,157 (11.46%)	55,911	180,419	205,398	147,614	11,080	600,422 (8.98%)	13,457	43,426	49,438	35,530	2,667	144,518 (11.77%)	622	2,006	2,284	1,641	123	6,676 (8.98%)	4.92	9.53	10.85	9.748	2.927	7.93
Asia-MESA	109,817	327,285	358,424	253,209	19,023	1,067,758 (54.13%)	356,586	1,062,726	1,163,836	822,192	61,771	3,467,111 (51.85%)	86,928	259,070	283,718	200,433	15,058	845,207 (68.84%)	3,964	11,814	12,938	9,140	687	38,543 (51.83%)	7.32	13.08	14.33	12.651	3.802	10.67
Canada	0	308	507	614	55	1,484 (0.08%)	0	316	519	629	56	1,520 (0.02%)	0	296	487	590	53	1,426 (0.12%)	0	4	6	7	1	18 (0.02%)	0.00	2.78	4.57	6.928	2.465	3.347
Europe	0	8,071	14,563	11,976	971	35,581 (1.80%)	0	8,215	14,822	12,189	988	36,214 (0.54%)	0	6,701	12,091	9,943	806	29,541 (2.41%)	0	91	165	136	11	403 (0.54%)	0.00	4.20	7.58	7.796	2.528	4.633
Latin America	9,741	33,026	38,322	27,807	2,110	111,006 (5.63%)	23,919	81,097	94,102	68,280	5,181	272,579 (4.08%)	6,019	20,406	23,678	17,181	1,304	68,588 (5.59%)	266	902	1,046	759	58	3,031 (4.08%)	4.82	9.80	11.38	10.319	3.132	8.239
USA	0	2,901	6,553	6,563	712	16,729 (0.85%)	0	3,740	8,447	8,460	918	21,565 (0.32%)	0	2,560	5,783	5,792	628	14,763 (1.20%)	0	42	94	94	10	240 (0.32%)	0.00	2.30	5.20	6.510	2.824	3.319
Total	140,760	477,925	736,335	572,064	45,608	1,972,692 (100.00%)	436,527	1,505,607	2,558,914	2,023,319	162,746	6,687,113 (100.00%)	106,544	342,043	432,929	321,282	24,959	1,227,757 (100.00%)	4,853	16,740	28,462	22,505	1,811	74,371 (100.00%)	4.158	8.472	13.052	12.675	4.042	8.742

Outcome estimates are shown, as well as percent attributable fraction of preterm births associated with DEHP exposure in each region and quantile of the exposed population. Global totals represent the sum of linear estimates across all regions. Average percent attributable preterm birth for each region, and globally, was calculated by dividing the total number of attributable PTBs in the given world region by the total number of expected baseline PTBs per the IHME in that world region, and multiplying by 100. Global percent attributable preterm birth for each percentile was calculated by dividing the total number of global attributable PTBs in the given percentile by the total number of globally expected baseline PTBs per the IHME in that percentile of the population, and multiplying by 100. Baseline expected PTBs for specific percentiles were calculated by multiplying total number of expected PTBs per the IHME by each percentile's given weight in this analysis (0.15 for the 10–24th percentile, 0.25 for the 25–49th percentile, 0.25 for the 50–74th percentile, 0.2 for the 75–94th percentile, and 0.05 for the 95–100th percentile). Outcome estimates have been rounded to the nearest whole number, and percent attributable fraction values have been rounded to three decimal places.

Table 1: **Aggregate preterm birth associated with DEHP (main linear estimates), presented alongside the percent of global outcome experienced in each region.**

Exposure to DiNP was estimated to be associated with an estimated 1.88 million PTBs globally, representing a population-weighted PAF of 8.32%. Regional disparities in DiNP-attributable PTB were even more pronounced in Asia–MESA, where over 1.23 million DiNP-associated cases were estimated (PAF of 12.3%; 65.5% of the global total). This was followed by Asia-EPA (approximately 177,000 PTBs, PAF of 6.20%, representing 9.43% of the global total), and Africa (168,000 PTBs, PAF of 2.40%, representing 8.95% of the global total).

In total, approximately 64,000 neonatal deaths and 5.77 million DiNP-associated years of life lost were estimated globally. Of these, approximately 44,400 of these deaths and 3.99 million of these YLLs (69.3 and 69.2% of these global totals, respectively) were borne by Asia–MESA, followed by approximately 8360 deaths and 751,000 YLLs (13.0% of these global totals) borne by Africa. DiNP was estimated to be associated with 1.34 million YLD, with Asia–MESA contributing approximately 974,000 of these years (72.2% of the global total), followed by Asia-EPA contributing approximately 113,000 YLD (8.4% of the global total). Notably, Africa was estimated to bear 13.0% of the global total of deaths and YLL, but only 2.96% of global YLD. Europe experienced higher morbidity burden relative to mortality, bearing 4.2% of the global PTB burden, 4.9% of the YLD loss, and only 1.4% of global deaths and YLL.

Uncertainty ranges for DEHP and DiNP estimates

Inclusion of effect estimate ranges derived from global meta-analyses reveals broader possible ranges of burden estimates. After systematized review of the existing literature, a range of effect estimates for DEHP on preterm birth was identified to be 1.1–1.5, and a lower estimate for DiNP of 1.1 was identified. As the literature was sparse for DiNP, only a lower range was feasibly extracted, with the upper range of 2.25 taken from Trasande et al., 2024.[16] Using these ranges as alternative hazard ratio priors for linear exposure model calculations resulted in an approximate global 17,000–82,000 prenatal deaths, 1.57–7.37 million YLL, 289,000–1.35 million YLD, and 463,000–2.17 million incident preterm births attributable to DEHP. DiNP low ranges were estimated to be an approximate global 6500 deaths, 590,000 YLL, 138,000 YLD, and 192,000 PTBs. Detailed full ranges of regional and country-level estimates can be found in Supplements 9a and b. The evident wide ranges, spanning as low as 4 times lower and 1.14 times higher estimates for DEHP and as low as 10 times lower for DiNP than main models, reveals higher uncertainty for DiNP estimates compared with DEHP estimates.

Cost estimation

Ranging SCYLL from 1000$ to 50,000$ USD, social costs of plastic-associated preterm birth mortality based on linear, main models would range between 6.69

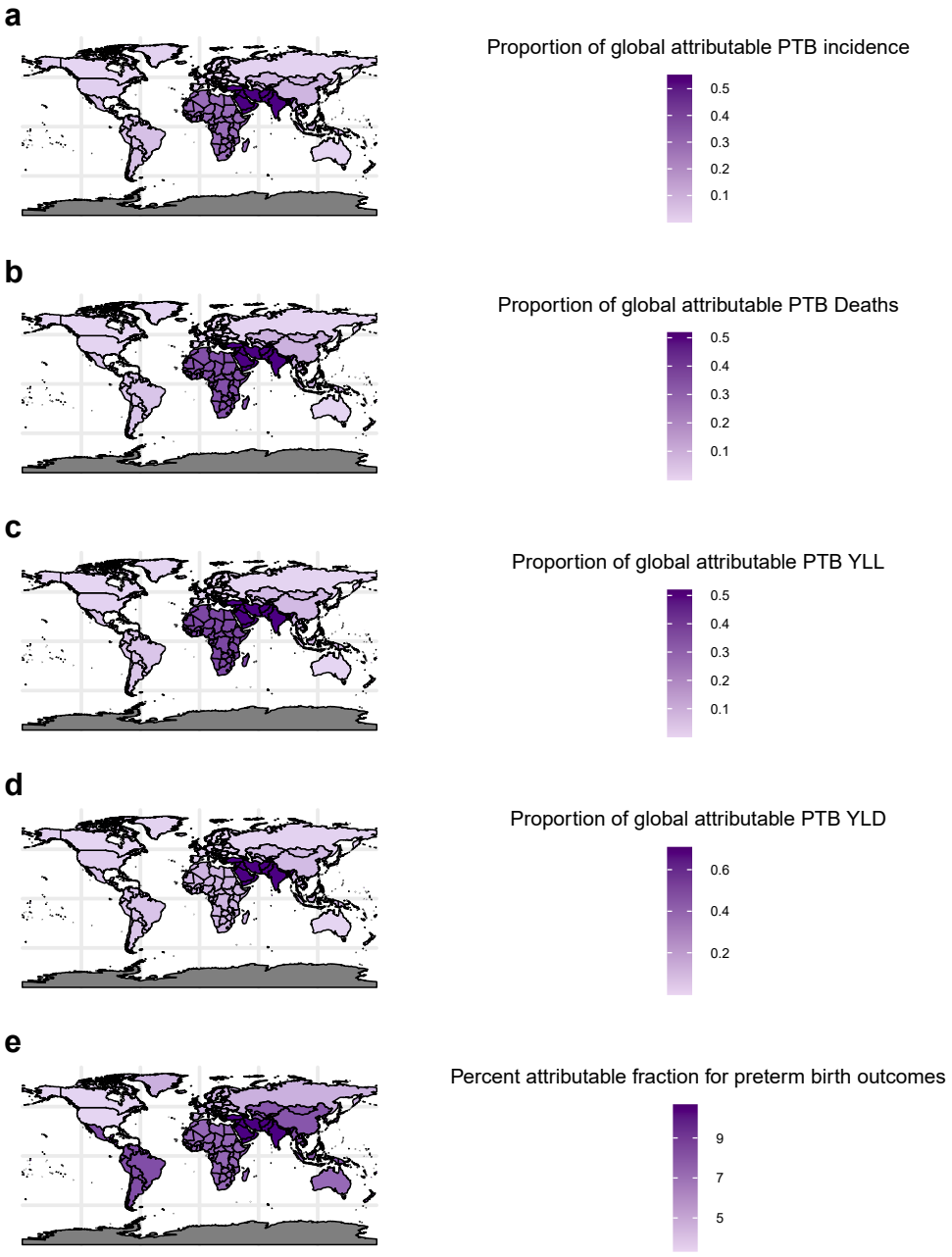

Fig. 1: **Aggregate DEHP-attributable PTB morbidity and mortality world maps among eight world regions.** In each plot, the legend gradient represents the global range of the given metric. Plot labelled a. represents proportion of global DEHP-attributable incident preterm births, or "global share" of PTB incidence burden in each region. Plot labelled b. represents proportion of global DEHP-attributable PTB-related deaths, plot labelled c. represents proportion of global DEHP-attributable PTB-related YLL, and plot labelled d. represents proportion of global DEHP-attributable PTB-related YLD. Plot labelled e. represents a map of the average percent of preterm birth outcomes in each region attributable to DEHP.

million and 334 billion USD linked to DEHP and 5.77 billion and 288 billion USD linked to DiNP. Comparing a VSL approach to the 2006 U.S. Environmental Protection Agency's value of mortality risk reduction, the total cost would range between 550 billion USD and 781 billion USD associated with DEHP and 474 billion and 673 billion associated with DiNP. When the lowest ranges of cost estimates are calculated, costs remain considerable, totaling 1.5 billion USD linked to DEHP-related YLLs, 590 million USD linked to DiNP-related YLLs, 126 billion USD to DEHP-related neonatal deaths and 48 billion USD to DiNP-related deaths.

	Preterm births						Years of life lost						Year of life lived with disability						Deaths						% Attributable Fraction of Preterm Birth					
World region	10	25	50	75	95	Total (% of global total)	10	25	50	75	95	Total (% of global total)	10	25	50	75	95	Total (% of global total)	10	25	50	75	95	Total (% of global total)	10	25	50	75	95	Population-weighted average
AUS	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Africa	0	0	0	151,709	16,435	168,144 (8.95%)	0	0	0	677,632	73,409	751,041 (13.03%)	0	0	0	36,036	3,904	39,940 (2.96%)	0	0	0	7,542	817	8,359 (13.04%)	0.0	0.000	0.00	10.82	4.687	2.398
Asia-EPA	0	36,017	71,123	64,034	5,808	176,982 (9.43%)	0	95,619	188,822	170,001	15,419	469,861 (8.15%)	0	23,015	45,448	40,918	3,711	113,092 (8.39%)	0	1,063	2,099	1,890	171	5,223 (8.15%)	0.0	5.052	9.98	11.23	4.073	6.206
Asia-MESA	0	221,260	517,142	448,658	42,759	1,229,819 (65.49%)	0	718,454	1,679,210	1,456,837	138,844	3,993,345 (69.26%)	0	175,144	409,355	355,146	33,847	973,492 (72.21%)	0	7,987	18,667	16,195	1,543	44,392 (69.24%)	0.0	8.844	20.67	22.42	8.546	12.289
Canada	0	0	0	276	91	367 (0.02%)	0	0	0	283	93	376 (0.01%)	0	0	0	266	87	353 (0.03%)	0	0	0	3	1	4 (0.01%)	0.0	0.000	0.00	3.12	4.096	0.828
Europe	0	15,590	33,320	27,702	2,341	78,953 (4.20%)	0	15,867	33,912	28,194	2,382	80,355 (1.39%)	0	12,944	27,665	23,000	1,943	65,552 (4.86%)	0	176	377	313	26	892 (1.39%)	0.0	8.119	17.35	18.03	6.095	10.28
Latin America	3,913	42,127	61,748	45,522	3,622	156,932 (8.36%)	9,608	103,444	151,625	111,781	8,894	385,352 (6.68%)	2,418	26,029	38,152	28,127	2,238	96,964 (7.19%)	107	1,150	1,686	1,243	99	4,285 (6.68%)	1.9	12.506	18.33	16.89	5.376	11.647
USA	131	14,394	25,877	23,237	2,914	66,553 (3.54%)	169	18,555	33,358	29,954	3,756	85,792 (1.49%)	115	12,704	22,839	20,508	2,572	58,738 (4.36%)	2	206	371	333	42	954 (1.49%)	0.17	11.42	20.54	23.05	11.562	13.204
Total	4,044	329,388	709,210	761,138	73,970	1,877,750 (100.00%)	9,777	951,939	2,086,927	2,474,682	242,797	5,766,122 (100.00%)	2,533	249,836	543,459	504,001	48,302	1,348,131 (100.00%)	109	10,582	23,200	27,519	2,699	64,109 (100.00%)	0.119	5.839	12.571	16.865	6.556	8.321

Outcome estimates are shown, as well as percent attributable fraction of preterm births associated with DiNP exposure in each region and quantile of the exposed population. Global totals represent the sum of linear estimates across all regions. Average percent attributable preterm birth for each region, and globally, was calculated by dividing the total number of attributable PTBs in the given world region by the total number of expected baseline PTBs per the IHME in that world region, and multiplying by 100. Global percent attributable preterm birth for each percentile was calculated by dividing the total number of global attributable PTBs in the given percentile by the total number of globally expected baseline PTBs per the IHME in that percentile of the population, and multiplying by 100. Baseline expected PTBs for specific percentiles were calculated by multiplying total number of expected PTBs per the IHME by each percentile's given weight in this analysis (0.15 for the 10–24th percentile, 0.25 for the 25–49th percentile, 0.25 for the 50–74th percentile, 0.2 for the 75–94th percentile, and 0.05 for the 95–100th percentile). Outcome estimates have been rounded to the nearest whole number, and percent attributable fraction values have been rounded to three decimal places.

Table 2: **Aggregate preterm birth associated with DiNP exposure (main linear estimates), presented alongside the percent of global outcome experienced in each region.**

Sensitivity analysis

Burden estimates under quadratic exposure models can be found detailed in Supplement 6. DEHP-associated global mortality (YLL and deaths) was 3.09% higher using quadratic models when compared to linear models of exposure. Similarly, YLD was estimated to be 2.4% higher and PTB incidence 2.9% higher. It was estimated that DiNP-associated global mortality was 28.1% lower, YLD 21.0% lower, and PTB incidence 25.1% lower under quadratic exposure as compared to linear models. Aside from these global differences in estimates, there were some notable regional differences as well, most notably in DiNP models. In sensitivity analysis, Africa was estimated to bear much less global burden than under linear models, with 36,584 preterm births (PAF of 0.522%, representing 2.60% of the global total) estimated under quadratic exposure. In fact, while in linear models Africa was estimated to be the region with the second highest contribution to DiNP-associated mortality, under quadratic models, the second highest contributor was estimated to be Asia-EPA (3986 deaths and 358,499 YLL, totalling a respective 8.65 and 8.64% of the global total).

Discussion

Main findings of this disease burden model estimate that plastic exposure (through one phthalate, DEHP) contributes to approximately of 8.74% of global PTB (uncertainty interval: 2.05–9.63%), with attributable YLL loss of 6.69 million (uncertainty interval: 1.57–7.37 million), YLD loss of 1.23 million (uncertainty interval: 288,000–1.35 million) and 74,300 deaths (uncertainty interval: 17,400–82,000). Estimates for DiNP suggest similar burden, at 8.32% of PTB (uncertainty interval lower limit: 0.85%), with attributable YLL loss of 5.77 million (uncertainty interval lower limit: 590,000), YLD of 1.34 million (uncertainty interval lower limit: 138,000), and neonatal deaths of 64,000 (uncertainty interval lower limit: 6500). The burden of plastic-attributable PTB is largely borne by in the Middle East, South Asia, and Africa across both morbidity and mortality (Table 3 and Supplement 9a and b).

When considering that an estimated 98% of DEHP use is for the plastics industry, these findings help to inform cost-benefit considerations of using and producing plastics in various areas of the world. A higher estimated burden in certain regions could be linked to growing plastics industrialization, higher level of deposited plastics waste, weaker plastic regulations, and higher baseline risk of PTB. Of note, DiNP was estimated to be a roughly equivalent contributor to PTB globally, though these estimates were more uncertain. In addition, patterns of DiNP-related burden over regions differed from DEHP, with the highest raw burden estimated in the Asia–MESA, followed by Asia-EPA, and mortality by Africa, potentially due to

World region	Preterm births		Years of life lost		Year of life lived with disability		Deaths	
	DEHP contribution	DiNP contribution	DEHP contribution	DiNP contribution	DEHP contribution	DiNP contribution	DEHP contribution	DiNP contribution
AUS	2187	ND	1711	ND	2145	ND	18	ND
Africa	511,790	168,144	2,285,991	751,041	121,569	39,940	25,442	8359
Asia-EPA	226,157	176,982	600,422	469,861	144,518	113,092	6676	5223
Asia–MESA	1,067,758	1,229,819	3,467,111	3,993,345	845,207	973,492	38,543	44,392
Canada	1484	367	1520	376	1426	353	18	4
Europe	35,581	78,953	36,214	80,355	29,541	65,552	403	892
Latin America	111,006	156,932	272,579	385,352	68,588	96,964	3031	4285
USA	16,729	66,553	21,565	85,792	14,763	58,738	240	954
Global	1,972,692	1,877,750	6,687,113	5,766,122	1,227,757	1,348,131	74,371	64,109

Health burden estimates associated with phthalate exposure for presented for four health outcomes across global regions. Effects of phthalates are considered overlapping, rather than additive.

Table 3: **Phthalate-specific contributions to preterm birth by region: main burden estimates, summed over quantiles.**

differences in patterns of chemical use in different regions. Regulating chemicals individually as compared to a class risks delaying progress in curbing health burdens, as demonstrated by the considerable burden estimates associated with both DEHP and DiNP exposure.

Spatial patterns in this model are consistent with known hotspots of plastic production and waste accumulation, as high plastic emissions and widespread use of DEHP-inclusive materials in regions such as Sub-Saharan Africa and Southeastern Asia has been documented.[46,47] Regions identified in this analysis as bearing the highest burden from phthalate exposure also exhibit the highest baseline rates of preterm birth.[1] Environmental exposures contribute to heightened biological susceptibility, resulting in a double-burden scenario when situated within populations impacted by adverse social determinants of health, as is the case in countries which suffer from high baseline high neonatal and infant mortality rates.

Uncertainty analyses provide a foundation for future models and meta-analyses, helping to identify and refine plausible ranges of estimates. Based on these analyses, the range of effect for DiNP was broader than that of DEHP. However, the ranges for both phthalates were ultimately in the same direction, with all meta-analyses consistently finding a positive association between phthalate exposure and preterm birth. The lowest estimates for both DiNP and DEHP came from the earliest of those meta-analyses in a systematized literature search of global literature, and recent studies have refined these values and reported stronger associations. The initial analysis also concluded that this relationship was not statistically significant, citing high heterogeneity among studies included from the Asia–Pacific region. However, subsequent meta-analyses have refuted these findings, likely due to advancements in knowledge, the inclusion of more individual cohorts, and a rapidly expanding body of literature. DiNP has been less widely included in meta-analyses, and unfortunately, hazard estimates for DiNP were only available in this earliest meta-analysis.[40] These early values require validation, as more recent pooled region-specific analyses suggest significantly higher risks associated with DINP exposure.[16] In addition to heterogeneity in effect estimates for DiNP exposure on preterm birth, quadratic model sensitivity analyses also point to greater regional variability in DiNP effects compared to DEHP, and DiNP data has higher missingness in the global literature when compared to DEHP. This highlights an overall higher level of uncertainty when modelling effects of DiNP exposure, and the need for an increased number of studies inclusive of DINP and other phthalate replacements. Given wide uncertainty intervals, especially for DiNP, additional studies are necessary, including comprehensive meta-analysis that generates universal effect estimates after pooling results from all previously conducted cohort studies and meta-analyses.

Costs of phthalate-attributable preterm birth morbidity and mortality are estimated to be considerable, with the highest estimate being 781 billion in 2018 alone. These estimates are taken alongside the figures of $3.74 trillion in costs linked to DEHP-attributable cardiovascular mortality.[48] These considerable costs can be viewed as a de facto subsidy to the chemical industry, with costs shifted from polluters to governments and the public.

The current regulatory framework limiting use of phthalates is insufficient. While many countries in 2018 had already instituted regulations curbing DEHP use in specific sectors, such as Japan,[49] the European Union,[50–52] Canada,[53] the United States,[54] and Australia,[55] regulatory coverage remains inconsistent. Regulations in the food packaging sector in India and banning of foreign plastics waste in China were only implemented after 2018,[56,57] and following recognition of DEHP's adverse health effects in recent years, many manufacturers have simply replaced DEHP with similar compounds like DiNP. In

certain regions, DiNP has become even more prevalent than DEHP.[58] Many countries have started to put in place regulations on DiNP, but the landscape remains heterogenous.[59] New regulations focusing on phthalates as a class of EDCs are needed.

While this model represents the most robust approach available at this time, uncertainty is present. To create a global model, it was necessary to rely on decentralized datasets. Outside the US, Canada and EU, we relied on a meta-analysis of available biomonitoring studies. In some cases, and especially for DiNP, it was necessary to impute estimates for missing metabolites. This may introduce uncertainty in specific regions. We also note that previous analyses have used differing methods in estimating DEHP-attributable PTB in the USA, with the present model finding a lower value (16,728) than the previously estimated 24,003–56,595 PTBs attributable to DEHP.[16] The previous analysis leveraged available data on GA distribution. Had such data been available the attributable burden estimates may well have been higher. Taken together, there is a need for continued study including multi-site biomonitoring studies with harmonized methods and confirmatory global models.

Uncertainty exists in interpretation of model results. The model is based on an epidemiological study that indicates a higher risk associated with DiNP compared to DEHP.[16] However, prior meta-analyses suggest that DiNP may have a weaker effect on preterm birth,[40] and toxicological research has indicated that DEHP may be a more potent reproductive toxicant than DiNP.[60] Nevertheless, both exhibit dose-dependent reproductive effects, and further research is needed to better understand DiNP's distinct reproductive toxicities.[60–62] Additionally, DEHP and DiNP might not solely reflect their specific toxicological effects but could also serve as indicators of exposure to microplastics. Recent studies have identified microplastics and nanoplastics within human preterm placentas, with limited evidence linking these exposures to preterm birth.[63–69] This raises the possibility that the similar contribution of DEHP and DiNP to the burden of preterm birth might be related to their role as proxies for microplastic exposure. Since DEHP may represent broader microplastic exposure within populations, our estimation could partially account for the potential effects of microplastics on preterm birth.

Several assumptions were also undertaken in this modelling technique. Exposure–response relationships as well as effect thresholds used to calculate hazard ratios were primarily derived from studies conducted in the United States,[16] with sensitivity analyses using priors derived from global meta-analyses with a higher number of studies from the USA and Asia-EPA. These effect estimates may not fully reflect country-specific risk patterns or may be biased towards epidemiological estimates found in regions which more heavily contribute to the literature. While existing literature is supportive of the effect size and direction utilized to build this model for DEHP,[19,37–39] the authors acknowledge several studies in which statistical significance was not achieved, including one meta-analysis which attributed this variability to heterogeneities in study design.[19,21,40,70] Additional cohort studies are needed in other regions of the world in order to truly elucidate reliable region-specific effect sizes, and will further refine the estimates presented here. This model also utilized exposure estimates from the general population, as exposure estimates among only pregnant individuals were not widely available. Another assumption was made in order to utilize PAF-based methods to estimate attributable burden. Causality of the relationship between phthalate exposure and preterm birth outcome in Trasande et al., 2024 was assumed,[16] therefore assuming no unmeasured confounding in the prior study. This assumption is backed by both epidemiological and toxicological studies; however, due to the limited availability of epidemiological research on DiNP, further studies focusing on DEHP replacements are necessary. Additionally, this analysis generated ranges of effect estimates based on findings from various global meta-analyses. However, while this study applied a $\log_{10}$ transformation to ensure a conservative approach, global meta-analyses did not consistently clarify whether the odds ratios reported corresponded to a specific logarithmic change in exposure, introducing potential variability.

This study also did not assess exposure to other plastic-associated chemicals or compounds, including bisphenols and microplastics, which may also contribute to preterm birth, nor did it account for co-exposures between phthalates that may increase risk when compared to individual phthalates alone.[71] Additionally, preterm birth, like other health outcomes, can be affected by many covariates such as access to prenatal care and preexisting comorbidities within individuals.[72] As this model used regional level aggregate data, it was not able to consider differential risk in subpopulations.

Having described important limitations, this analysis helps to estimate the potential preterm-birth related costs of the plastic industry. It utilized international datasets to estimate the global burden of preterm birth morbidity and mortality attributable to phthalate exposure, providing estimates for DEHP and DiNP, and capturing regional differences in burden in regions previously understudied. As treaty negotiations to regulate phthalates move forward, further estimation of the vast costs of the plastics industry are needed, and strong regulatory measures to phthalates as a class should be considered.

Contributors

Ms. Sara Hyman contributed to all aspects of analysis and sections of the manuscript, excluding funding acquisition. Mr. Jonathan Acevedo contributed to data curation and review & editing of the manuscript. Dr.

Leonardo Trasande contributed to project conceptualization, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, and writing of the manuscript in the review and editing stages. Ms. Sara Hyman and Dr. Leonardo Trasande accessed and verified all underlying data. All authors read and approved the final version of the manuscript.

Data sharing statement

No individual-level data was utilized in this analysis. The majority of data is publicly available through the data publisher's websites, and there is no published end date to availability. In order to access data from their global burden of diseases study, the IHME necessitates users to sign a data agreement upon requesting access. Data from the European COPHES/DEMOCOPHES project is available to the public at request of the project staff. Data from Health Canada and NHANES is available on a publicly accessible webpages. This study was not associated with an institutional protocol, and no consent was required.

Editor note

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Declaration of interests

Leonardo Trasande, MD. MPP has received royalties or licenses from Houghton Mifflin Harcourt, Audible, Paidos and Kobunsha, unrelated to the present project. He has received support for meetings to travel from the Endocrine Society, World Health Organization, the United Nations Environment Programme, Japan Environment and Health Ministries, and the American Academy of Pediatrics, unrelated to the present project. He has served in leadership or fiduciary roles at Beautycounter, Ahimsa, and Grassroots Environmental Education and Footprint, unrelated to the present project. The remaining authors have no interests to declare. Funding for this study came from Beyond Petrochemicals and National Institutes of Health grant number: P2CES033423. This study is independent and is not necessarily representative of the views of the National Institutes of Health.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.eclinm.2026.103842.

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