From:	Evans, Ashley
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Cc:	Davies, Holly G (DOH); Tan, Shirlee; Laurie Valeriano; Erika Schreder (eschreder@toxicfreefuture.org)
Subject:	Study for the Phthalates Action Plan process
Date:	Monday, March 21, 2022 2:39:17 PM
Attachments:	Ahren_2022_Medication_PrePub.pdf

Hi Irina,

This study came into my inbox today establishing a link between phthalates and childhood cancer. See attached.

A plastic chemical you can't escape is linked to cancer in children | Salon.com

> Now, a recent study of unprecedented scope has revealed that phthalates are linked to childhood cancers.
>
> Lead by scientists at the University of Vermont Cancer Center and published in the *Journal of the National Cancer Institute,* researchers compiled data on nearly 1.3 million live births in Denmark between 1997 and 2017. Within that group, there were 2,027 cases of childhood cancer. They also assessed phthalate exposure by seeing whether mothers had filled prescriptions for medications formulated with phthalates either during their pregnancies (to measure gestational exposure) and for their children up until they were 19 years old (to measure childhood exposure).
>
> The researchers found that "childhood phthalate exposure was strongly associated with incidence of osteosarcoma" and identified correlations with other cancers like lymphoma "driven by associations with Hodgkin and non-Hodgkin lymphoma, but not Burkitt lymphoma." They also found that "associations were apparent only for exposure to low-molecular phthalates, which have purportedly greater biological activity."

Thanks,
Ashley

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Responding to COVID-19 - We are doing what we can to protect everyone in King County during the COVID-19 outbreak, including making changes in some of our services.
To get the latest updates visit the King County central service change update page or add your name to our interest list by emailing us at haz.waste@kingcounty.gov.

Medication-Associated Phthalate Exposure and Childhood Cancer Incidence

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Keywords

Phthalates; pediatric cancer; epidemiology; pharmaceuticals; neoplasms; lymphoma; leukemia; osteosarcoma; cohort study

ABSTRACT

Background

Human phthalate exposure is widespread through contact with myriad consumer products. Exposure is particularly high through medications formulated with phthalates. Phthalates disrupt normal endocrine signaling and are associated with reproductive outcomes and incidence of some cancers. We measured associations between gestational and childhood medication-associated phthalate exposures and the incidence of childhood cancers.

Methods

We identified all live births in Denmark between 1997–2017, including both children and birth mothers. Using drug ingredient data merged with the Danish National Prescription Registry, we measured phthalate exposure through filled prescriptions for mothers during pregnancy (gestational exposure) and for children from birth until age 19 years (childhood exposure). Incident childhood cancers were ascertained from the Danish Cancer Registry, and associations were estimated with Cox regression models.

Results

Among 1,278,685 children, there were 2,027 childhood cancer cases diagnosed over 13.1 million person-years of follow-up. Childhood phthalate exposure was strongly associated with incidence of osteosarcoma (HR=2.78, 95% CI: 1.63, 4.75). We also observed a positive association with incidence of lymphoma (HR=2.07, 95% CI: 1.36, 3.14), driven by associations with Hodgkin and non-Hodgkin lymphoma, but not Burkitt lymphoma. Associations were apparent only for exposure to low-molecular phthalates, which have purportedly greater biological activity.

Conclusions

Childhood phthalate exposure was associated with incidence of osteosarcoma and lymphoma before age 19 years. Lingering questions include which specific phthalate(s) are responsible for these associations, by what mechanisms they occur, and to what extent childhood cancer cases could be avoided by reducing or eliminating the phthalate content of medications and other consumer products.

Nearly 16,000 cases of cancer are expected to be diagnosed among US children and adolescents in 2021,[1] and an estimated 11.5 million disability-adjusted life-years were lost to childhood cancer globally in 2017.[2] While incidence of childhood malignancy has slowly increased in recent decades, few exogenous causes have been identified for the majority of pediatric cancers.[3,4] It is especially unclear to what extent maternal and childhood environmental exposures modify risk, and therefore to what extent childhood cancers could be preventable through these factors. A survey by the Children's Cancer Group found that the potential etiologic role of environmental exposures in their child's disease was the most prominent concern expressed by parents of childhood cancer patients.[5]

Phthalates are plastic additives that increase flexibility, transparency, durability, and longevity.[6] They are found in children's toys, medical tubing, food storage containers, building materials, furniture, and clothing.[6] Since they are not covalently bound with other constituents, phthalates readily leach out of products.[7] Human exposure is widespread through ingestion, inhalation, and absorption of leached phthalate residues. The U.S. National Health and Nutrition Examination Survey (NHANES) found that over 75% of U.S. adults had detectable levels of ≥1 urinary phthalate metabolite.[8] Phthalate metabolites are also detectable in human amniotic fluid.[9] Phthalates mimic hormones and interfere with normal endocrine signaling pathways,[10] and may therefore affect hormonally-mediated health outcomes including fertility, fetal/ child development, and cancer.[6,11]

Phthalates are used in the formulation of many pharmaceuticals, particularly those requiring an enteric coating to control drug release.[12] Users of phthalate-

containing medications represent a highly exposed population, having metabolite burdens up to 50-fold higher than people with only environmental phthalate exposure.[13]

Studying phthalate health effects is difficult for several reasons: (1) the short half-life of phthalate metabolites requires longitudinal measurements to characterize exposure history;[6] (2) phthalate metabolite assays are prohibitively expensive at the scale of adequately-sized epidemiologic studies; and (3) accurate measurement of phthalate metabolites requires urine specimens,[14] which are rarely collected in epidemiologic cohorts. To overcome these obstacles we capitalized on the high relative exposure among users of phthalate-containing medications to examine associations between gestational and childhood phthalate exposure and childhood cancer incidence in a Danish nationwide cohort.

Methods

Ethics approval

This study was approved by the Institutional Review Board at the University of Vermont and by the Danish Children's Cancer Group. This study was also registered with the Danish Data Protection Board and adhered to the European Union's General Data Protection Regulations.

Danish population-based registries

Denmark has a tax-supported universal healthcare system with free access to primary care, inpatient and outpatient clinics, and emergency care.[15] As part of this system, Denmark maintains a network of population-based registries to record

information on health, employment, vital status, and emigration.[15] We enumerated our study population from several Danish registries with linkage *via* the unique Central Personal Register (CPR) code assigned to all legal residents.[16]

Phthalates in prescription medications

Since 1995 the Danish Medicines Agency has maintained a database of all pharmaceutical products marketed in Denmark. Records include the following data fields: the VNR code (a unique identifier assigned to medicinal agents distinguished by manufacturer, active ingredient, formulation, dose, and package size), the Anatomical Therapeutic Chemical (ATC) code, dates of market entry and removal, and a listing of active and inactive ingredients. Ingredient data include the mass of each constituent per unit of medication (*e.g.*, milligrams per capsule). We searched drug ingredient fields for Danish and English text strings encompassing a comprehensive set of phthalate compounds. We then prepared a data set of oral medications formulated with at least one phthalate,[17,18] and merged this with the Danish National Prescription Registry (DNPR).[19] The DNPR records information about every community pharmacy transaction in Denmark since 1995, including transaction date, the ATC and VNR codes of the prescribed drug, and the quantity dispensed.

Study population and data collection

Our source population included all live births in Denmark between 1997–2017, ascertained from the Danish Medical Birth Registry (DMBR).[20] The DMBR records data from all live births in Denmark since 1973, including home deliveries. Each birth record

contains the delivery date, mode of delivery (vaginal *vs.* cesarean section), type of pregnancy (singleton *vs.* multiple), mother and infant CPR numbers, maternal data (*e.g.*, age, height, weight, smoking status, and parity), and infant data (*e.g.*, gestational age, birth weight, and presence of congenital malformations). We included both mothers and infants in the live birth cohort and ascertained their exposure to phthalate-containing medications by linkage with the ingredient-augmented DNPR. We identified cases of incident childhood cancer through age 19 years in the Danish Cancer Registry (ICD-10 codes appear in **Supplementary Table 1**).[21] We retrieved vital status from the Danish Civil Registration System.[16]

Definitions of analytic variables

We defined separate phthalate exposure groups for gestational and childhood time periods. Gestational exposure was characterized by phthalate-containing drug formulations dispensed to mothers. Childhood exposure was characterized by phthalate-containing drug formulations dispensed to children. Gestational exposures comprised the nine-month window preceding delivery dates and were initially divided into estimated trimesters. Childhood phthalate exposure was initially defined as the cumulative milligrams of phthalates ingested *via* medications. Data sparsity required simplifying these exposures as dichotomous variables. Phthalate exposures were defined both overall (exposure to any phthalate) and by specific compounds [*i.e.*, dibutyl phthalate (DBP), diethyl phthalate (DEP), cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), and hydroxypropyl methylcellulose phthalate (HPMCP)]. We also defined exposure to phthalate polymers (CAP, HPMCP, and PVAP–considered

biologically inactive) and to low molecular weight phthalates (DBP and DEP–suspected endocrine disruptors). Phthalate exposure was considered positive if at least one prescription was filled with a phthalate-containing drug product. We conducted a sensitivity analysis in which exposure required at least two phthalate-containing drug fills.

Follow-up began at birth and continued until attainment of 19 years of age, first cancer diagnosis, death from any cause, emigration from Denmark, or January 1, 2018–whichever came first. We studied incidence of any childhood cancer as well as incidence of 16 specific cancer types or groups [leukemia (overall, acute lymphocytic, and acute myeloid), lymphoma (overall, Hodgkin, non-Hodgkin, and Burkitt), brain/CNS, neuroblastoma, retinoblastoma, kidney, liver, osteosarcoma, soft tissue sarcoma, reproductive organ cancers, and other/unclassified cancers]; see Supplemental Table 1 for ICD-10 codes.

We defined child and maternal covariables with known or suspected associations with either childhood cancer or medication-associated phthalate exposure. Child-level covariables included natal sex,[22] birth year, gestational age,[23] birth weight,[24,25] small for gestational age, and presence of congenital malformations or chromosomal abnormalities.[26] Maternal-level covariables included age at delivery,[27–29] pre-pregnancy BMI (available since 2004),[30] mode of delivery,[31–33] type of pregnancy,[34] parity,[35] and smoking status during pregnancy.[36] Detailed definitions of categorical variables appear in **Table 1**.

Statistical analysis

We tabulated the frequency and proportion of child and maternal characteristics according to overall phthalate exposure status. We fit crude and multivariable Cox regression models to estimate associations between gestational and childhood phthalate exposures and incidence of childhood cancer (overall and type-specific). Gestational exposure and childhood exposure were modeled as separate, mutually adjusted exposures. Childhood exposure was modeled as a time-varying factor, and was characterized as 'unexposed' until 6 months after meeting the exposure definition. The 6-month lag allowed a reasonable amount of time for the exposure to exert an effect on the outcome. We increased the lag to 12 months in a sensitivity analysis to better protect against reverse causation bias. We also carried out sensitivity analyses in which users of azathioprine were excluded, given this drug's association with cancer.[37] Models of type-specific cancers censored follow-up upon diagnosis with another cancer. We carried out pre-planned stratified analyses according to natal sex and follow-up periods based on child's age. Table cells with fewer than 5 individuals are reported as "<5" in accordance with Danish privacy law. Associations were estimated as hazard ratios with accompanying 95% confidence limits. To guard against potentially spurious findings across the 16 evaluated cancer sites, we subjected our associations to semi-Bayes shrinkage[38] using a conservative variance of 0.125 (consistent with a 4-fold hypothetical range across all phthalate/cancer associations). Analyses were carried out with SAS version 9.4 (SAS Institute, Cary, NC); plots were created with the 'ggplot2' package for R.[39] No hypothesis testing was performed.[40–43]

Results

Searching the Danish Medicines Agency database revealed 430 marketed drug products (representing 29 medications) formulated with at least one phthalate. None of the phthalate-containing drug products appeared on the Danish Medicines Agency's listing of over-the-counter medications.[44] Cohort members filled prescriptions for 25 of the 29 medications, all of which were also represented by phthalate-free formulations (**Supplementary Table 2**). We identified 1,278,685 children, of whom 113,529 (8.9%) were exposed to at least one medication-associated phthalate during gestation and/or childhood. **Table 1** reports the distribution of child and maternal characteristics according to phthalate exposure status. Children with any phthalate exposure were more likely to be born earlier in the study period (consistent with the time trend in the prevalence of phthalates in medication formulations[17]) and were more often exposed to clarithromycin, erythromycin, ibuprofen, and naproxen. Mothers of children with any phthalate exposure were more likely than mothers of unexposed children to have filled prescriptions for clarithromycin and erythromycin during pregnancy.

Tables 2 and 3 report results from our main analyses. Over 13.1 million person-years of observation, 2,027 cases of childhood cancer were diagnosed. The combined rarity of phthalate exposure and type-specific cancer incidence precluded fitting complex multivariable models. We were able to fit simpler multivariable models with mutual adjustment of gestational and childhood phthalate exposures and adjustment for birth year and specific medication exposures (*i.e.*, the imbalanced factors in **Table 1**). Cancers diagnosed among children exposed to phthalates were somewhat more likely to be metastatic at diagnosis (43% of cases among phthalate-exposed and 33% of cases among phthalate-unexposed; prevalence ratio=1.29, 95% CI: 0.93, 1.67). **Table 2**

reports associations between specific phthalate exposures and incidence of any childhood cancer. Exposure to any phthalate during childhood was associated with an approximately 20% higher hazard of childhood cancer (HR=1.19, 95% CI: 0.97, 1.47), with a median time between first phthalate exposure and cancer diagnosis of 3.3 years. Exposure to any phthalate during gestation was not associated with overall childhood cancer incidence (HR=0.87, 95% CI: 0.60, 1.24). Associations between childhood phthalate exposure and incidence of any cancer varied by the specific type of phthalate. We saw evidence for positive associations with exposure to DEP (HR=1.67, 95% CI: 1.16, 2.41), CAP (HR=2.31, 95% CI: 0.74, 7.20), and PVAP (HR=4.70, 95% CI: 0.66, 33.30). We observed a near-null association with exposure to HPMCP (HR=1.16, 95% CI: 0.94, 1.44). The association between childhood DBP exposure and childhood cancer incidence was not estimable due to very low exposure frequency. Childhood exposure to phthalate polymers (CAP, HPMCP, and PVAP) was weakly associated with childhood cancer (HR=1.18, 95% CI: 0.96, 1.46). Childhood exposure to low molecular weight phthalates (DBP and DEP) was associated with a 66% higher hazard of childhood cancer (HR=1.66, 95% CI: 1.15, 2.39). No type of gestational phthalate exposure was associated with incidence of any childhood cancer, with the possible exception of CAP (HR=1.59, 95% CI: 0.51, 4.91). Phthalate-specific associations were essentially unchanged after further adjustment for birth year (data not shown).

Table 3 reports associations between gestational and childhood phthalate exposures and incidence of specific cancers or cancer groups from models with a 6-month exposure lag. Several associations were not estimable due to sparse data. While most estimable associations were near-null or null-centered, we observed a positive

association between childhood phthalate exposure and osteosarcoma (HR=2.78, 95% CI: 1.63, 4.75). Childhood phthalate exposure was also associated with combined lymphoma (HR=2.07, 95% CI: 1.36, 3.14), driven by associations with both non-Hodgkin lymphoma (HR=2.29, 95% CI: 1.33, 3.92) and Hodgkin lymphoma (HR=2.04, 95% CI: 1.01, 4.12). The osteosarcoma association persisted after further adjustment for birth year and for childhood exposure to clarithromycin, erythromycin, ibuprofen, and naproxen (HR_{adj}=2.78, 95% CI: 1.63, 4.76). It was also similar under the 12 month exposure lag (HR=2.91, 95% CI: 1.70, 4.98) and after excluding azathioprine users from the analysis (HR=2.65, 95% CI: 1.53, 4.60). Lymphoma associations were similarly robust to multivariable adjustment, increasing the exposure lag to 12 months, and excluding azathioprine users. Associations between childhood phthalate exposure and type-specific cancers were not substantially changed after semi-Bayes shrinkage (**Supplementary Table 3**) or by requiring two filled prescriptions to define exposure (**Supplementary Figure 1**). Associations between gestational phthalate exposure and type-specific cancer incidence were either not estimable or near-null.

Our data could not support sex-stratified analyses of type-specific cancer associations nor of phthalate-specific associations. However, we observed no modification by natal sex of the hazard ratios associating gestational or childhood phthalate exposure and incidence of any childhood cancer (**Figure 1**). The osteosarcoma association was slightly stronger in natal females than in natal males (**Figure 1**). Type-specific models for leukemia, combined lymphoma, and osteosarcoma were generated for age-specific follow-up periods (age 0-5 *vs.* 6-19 years for leukemia, and age 0-9 *vs.* 10-19 years for lymphoma and osteosarcoma; **Figure 2**). The near-null

leukemia association was not substantially modified by age at diagnosis. The positive association between childhood phthalate exposure and incidence of combined lymphoma (**Table 3**; HR=2.07, 95% CI: 1.36, 3.14) was apparent in both the 0-9 year and 10-19 year follow-up periods (**Figure 2**). The positive association between childhood phthalate exposure and osteosarcoma was also apparent in both follow-up periods.

Discussion

Childhood phthalate exposure was strongly associated with incidence of osteosarcoma. This association was slightly stronger for natal females, did not vary according to follow-up period, and was robust to adjustment for birth year and exposure to clarithromycin, erythromycin, ibuprofen, and naproxen–the only measured factors that differed between phthalate-exposed and unexposed children. Exclusion of azathioprine users did not materially affect the osteosarcoma association, nor did semi-Bayes shrinkage or requiring 2 phthalate-containing prescriptions to define exposure. The association also persisted when the exposure lag period increased from 6 to 12 months, providing assurance that the association cannot be explained by use of analgesics or antibiotics to manage symptoms of subclinical disease such as bone/joint pain or infection. Osteosarcoma may have a hormonal etiology since its sex-specific incidence patterns track closely with puberty onset, and because of its link with childhood growth hormone exposure.[22,45] It is therefore plausible that endocrine disruption by phthalates could increase osteosarcoma risk. This association is also consistent with evidence

linking phthalate exposure with early onset of puberty,[46–48] which has in turn been linked with osteosarcoma.[49]

We also observed a positive association between childhood phthalate exposure and incidence of lymphoma, driven by associations with both Hodgkin and non-Hodgkin lymphoma. These associations were robust to multivariable adjustment, increase to a 12-month exposure lag, exclusion of azathioprine users, semi-Bayes shrinkage, and requiring 2 phthalate-containing prescriptions for exposure. The potential mechanisms underlying the lymphoma association are unclear, and warrant further study.

Exposure to any phthalate during childhood was associated with an approximately 20% higher incidence hazard for any childhood cancer. Combined childhood exposure to DBP and DEP–low molecular weight phthalates with purportedly greater biological activity[6]–was more strongly associated with cancer incidence than childhood exposure to high molecular weight phthalate polymers.

Most associations between gestational phthalate exposure and site-specific childhood cancers were near-null, and all were measured with poor precision. While some of these associations appeared protective–and were therefore of oppositive direction to childhood exposure associations (*i.e.*, for combined lymphoma and osteosarcoma)–their imprecision precluded meaningful comparison.

Ours is the first study to measure associations between gestational and childhood phthalate exposures and childhood cancer incidence. Others have studied phthalate exposure in relation to adult hormone-related malignancies such as thyroid, prostate, and breast cancer.[50–56] Two studies reported positive associations between urinary DEHP metabolites and thyroid cancer incidence.[55,56] DEHP, butyl-benzyl

phthalate (BBzP), and di-isobutyl phthalate (DiBP) were all positively associated with prostate cancer incidence in abdominally obese men.[54] We could not assess these specific phthalates, as they were not used in any pharmaceuticals marketed in Denmark. Breast cancer findings are inconsistent, with only modest agreement across studies.[50–53] Our group recently studied the impact of medication-associated phthalate exposure on breast cancer incidence in a Danish cohort of >1 million women.[57] We observed a twofold higher hazard for estrogen receptor-positive breast cancer among women with high exposure to DBP, which mimics estrogen *in vitro*.[57,58] Another Danish study reported associations between high cumulative exposure to DBP and DEP and incident colorectal cancer.[59]

Key strengths of our study are its large size, virtual immunity from selection bias, completeness of follow-up, and high-validity cancer registry data.[15,60] Most limitations of our study are a consequence of sparse data resulting from the combination of rare exposures with rare outcomes. While we initially divided gestational exposures into trimesters, the categories were too sparse to support estimation and were ultimately combined. This may have masked true associations by mixing etiologically relevant and etiologically inert exposure windows. We also sought to cross-classify gestational and childhood exposures so we could assess their interdependence, but this approach was abandoned due to model fitting issues. Sparse data also limited our ability to specify complex multivariable models for all cancer outcomes to control for the comprehensive set of measured maternal and child factors that could potentially confound phthalate/childhood cancer associations. Most outcome models could not accommodate any covariables beyond the two terms for gestational and childhood phthalate

exposures. Nonetheless, we noted a high degree of balance in most measured candidate confounders between phthalate exposure groups. Such balance is expected because receipt of a phthalate-containing drug formulation instead of a phthalate-free formulation is essentially random–a function of which specific drug product was available at the pharmacy when the patient presented. Adjusting regression models for the few factors that showed imbalances between exposure groups did not change our estimates. We are therefore confident that the associations we observed were not generated by uncontrolled confounding.

Two important sources of measurement error warrant consideration. First, our medication-based classification scheme could not capture phthalate exposure through other environmental sources. Our reference group of phthalate-unexposed participants is therefore certain to contain individuals with exposure from non-medication sources, which could have biased association estimates toward the null. Since phthalate exposure is near-ubiquitous in modern society, it would be impossible to enumerate a truly unexposed reference group. Nonetheless, the considerably higher exposure observed among people who ingest phthalate-containing medications compared with those exposed only through background sources[13] provides reassurance that non-differential exposure misclassification would not be sufficient to mask true associations. Second, our classification scheme inherently assumed that filled prescriptions were ingested by mothers and children, which we were not able to confirm. However, a prescription record in the DNPR indicates that a patient presented to a pharmacy and tendered a copay for the filled prescription, implying intent to adhere to the medication order. Finally, we did not have information on the specific indication(s) for which

phthalate-containing medications were prescribed. However, all phthalate-containing drug classes were also well represented by phthalate-free formulations, and presence or absence of phthalates in a relevant prescription fill was expected to be random. This is also expected to be true for extended release drug formulations, as phthalates are not the only excipient used to impart this property. Together, these features provide reassurance that our associations are not likely attributable to confounding by indication or by active drug ingredients.

In summary, we observed positive associations between childhood phthalate exposure and the incidence of osteosarcoma and lymphoma in a Danish nationwide cohort. Lingering questions include which specific phthalate(s) are responsible for these associations, by what mechanism(s) they occur, the impact of dose and timing, and to what extent childhood cancer cases could be avoided by reducing or eliminating the phthalate content of medications and other consumer goods.

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Author contributions: Conceptualization (TPA, PD, LGS); Funding acquisition (TPA);

Data curation (PD, DC, HTS, BOE, SPU, KE); Formal analysis & Software (BOE, SPU, KE); Methodology (TPA, DC, TLL, LGS); Supervision (TPA, DC); Visualization (TPA); Writing – original draft (TPA); Writing – review and editing (TPA, LGS, PD, BOE, TLL, HTS, DC).

Data Availability

Danish registry data, including those used for this study, are protected by Danish privacy law and are accessible only through application to appropriate Danish authorities.

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Tables

Table 1. Characteristics of mothers and children, all live births in Denmark, 1997-2017, according to medication-associated phthalate exposure status during gestation or childhood.

Characteristics	Any phthalate exposure No. (%) (n=113,529)	No phthalate exposure No. (%) (n=1,165,156)
Child characteristics		
Natal sex		
Female	53,841 (47)	568,638 (49)
Male	59,688 (53)	596,518 (51)
Birth year		
1997-2002	36,694 (32)	342,801 (29)
2003-2007	30,659 (27	284,379 (24)
2008-2012	32,500 (29)	266,379 (23)
2013-2017	13,676 (12)	271,597 (23)
Gestational age, weeks		
<34	2,420 (2.1)	23,607 (2.0)
34-36	5,889 (5.2)	53,824 (4.6)
37-41	98,974 (87)	1,024,467(88)
≥42	6,246 (5.5)	63,258 (5.4)
Birth weight category		
Extremely low (<1000g)	318 (0.3)	4,186 (0.4)
Very low (1000-1499g)	672 (0.6)	6,173 (0.5)
Low (1500-2499g)	5,337 (4.7)	49,629 (4.3)
Normal (2500-3999g)	86,520 (76.5)	889,878 (76.7)
High (≥4000g)	20,190 (17.9)	209,804 (18.1)
(Missing)	492	5,486
Small for gestational age		
Yes	11,317 (10.0)	114,720 (9.9)
No	101,720 (90.0)	1,044,950 (90.1)
(Missing)	492	5,486
Congenital malformations		
Nervous system	228 (0.2)	1,587 (0.1)
Maxillofacial	282 (0.2)	2,215 (0.2)
Circulatory system	1,543 (1.4)	12,306 (1.1)
Respiratory system	305 (0.3)	2,434 (0.2)
Cleft lip/palate	300 (0.3)	2,014 (0.2)
Digestive system	839 (0.7)	7,843 (0.7)
Reproductive organs	687 (0.6)	6,199 (0.5)

Urinary tract	366 (0.3)	3,513 (0.3)
Musculoskeletal	2,385 (2.1)	21,554 (1.8)
Chromosomal abnormalities	272 (0.2)	1,289 (0.1)
Medication exposures		
Bisacodyl	723 (0.6)	1,720 (0.1)
Budesonide	67 (0.1)	399 (0.03)
Clarithromycin	81,732 (72.0)	23,248 (2.0)
Colestipol	<5	<5
Diclofenac	2,088 (1.8)	12,014 (1.0)
Dipyridamole	<5	<5
Duloxetine	190 (0.2)	461 (0.04)
Erythromycin	36,900 (32.5)	143,846 (12.3)
Esomeprazole	2,091 (1.8)	12,491 (1.1)
Fluoxetine	449 (0.4)	2,840 (0.2)
Ibuprofen	11,557 (10.2)	81,271 (7.0)
Lithium	32 (0.03)	80 (0.01)
Mesalazine	166 (0.1)	920 (0.1)
Mianserin	22 (0.02)	148 (0.01)
Multienzymes	189 (0.2)	96 (0.01)
Mycophenolic acid	7 (<0.01)	47 (<0.01)
Naproxen	8,742 (7.7)	42,361 (3.6)
Pentoxyverine	76 (0.1)	565 (0.1)
Propantheline	127 (0.1)	863 (0.1)
Rabeprazole	14 (0.01)	8 (<0.01)
Sulfasalazine	101 (0.1)	93 (<0.01)
Theophylline	76 (0.1)	132 (0.01)
Valproic acid	1,046 (0.9)	4,029 (0.3)
Verapamil	17 (0.01)	82 (<0.01)
Maternal characteristics		
Age at delivery, years		
<20	1,661 (1.5)	15,595 (1.3)
20-24	13,394 (12)	131,073 (11)
25-29	37,381 (33)	388,657 (33)
30-34	40,248 (35)	414,131 (36)
35-39	17,735 (16)	182,337 (16)
≥40	3,110 (2.7)	33,363 (2.9)
Pre-pregnancy BMI, kg/m^2		
Underweight (<18.5)	2,967 (4.4)	32,837 (4.4)
Normal (18.5-24.9)	41,183 (60.7)	458,351 (62.0)
Overweight (25-29.9)	14,839 (21.9)	156,011 (21.1)
Obese (≥30)	8,880 (13.1)	92,511 (12.5)
(Missing)[a]	45,660	425,446
Mode of delivery		
Vaginal	88,442 (77.9)	930,350 (79.8)
Cesarean section	25,087 (22.1)	234,806 (20.2)
Type of pregnancy		

Singleton	108,997 (96.0)	1,117,295 (95.9)
Twins	4,440 (3.9)	46,830 (4.0)
Triplets or greater	92 (0.1)	1,031 (0.1)
Parity		
1	47,622 (41.9)	496,409 (42.6)
2 or 3	60,331 (53.1)	608,788 (52.2)
≥4	5,576 (4.9)	59,959 (5.1)
Smoking during pregnancy		
Non-smoker	84,636 (82.0)	907,165 (84.6)
Quit during pregnancy	2,803 (2.7)	27,689 (2.6)
Smoked during pregnancy	15,772 (15.3)	137,553 (12.8)
(Missing)	10,318	92,749
Medication exposures		
Bisacodyl	2,655 (2.3)	18,408 (1.6)
Budesonide	950 (0.8)	5,786 (0.5)
Clarithromycin	21,260 (18.7)	130,624 (11.2)
Colestipol	107 (0.1)	717 (0.1)
Diclofenac	48,146 (42.4)	422,126 (36.2)
Dipyridamole	243 (0.2)	1,221 (0.1)
Duloxetine	4,527 (4.0)	33,070 (2.8)
Erythromycin	44,897 (39.5)	301,785 (25.9)
Esomeprazole	9,299 (8.2)	66,885 (5.7)
Fluoxetine	4,291 (3.8)	33,164 (2.8)
Ibuprofen	89,112 (78.5)	834,784 (71.6)
Lithium	753 (0.7)	5,022 (0.4)
Mesalazine	2,370 (2.1)	14,032 (1.2)
Mianserin	3,149 (2.8)	24,382 (2.1)
Multienzymes	155 (0.1)	938 (0.1)
Mycophenolic acid	20 (0.02)	126 (0.01)
Naproxen	20,556 (18.1)	176,297 (15.1)
Pentoxyverine	208 (0.2)	1,220 (0.1)
Propantheline	470 (0.4)	3,741 (0.3)
Rabeprazole	455 (0.4)	3,124 (0.3)
Sulfasalazine	2,277 (2.0)	11,017 (0.9)
Theophylline	566 (0.5)	2,624 (0.2)
Valproic acid	1,233 (1.1)	8,765 (0.8)
Verapamil	870 (0.8)	5,247 (0.5)

[a]Body mass index (BMI) data were only available from 2004 onward.

Table 2: Associations between specific phthalate exposures and incidence of any childhood cancer. Live births in Denmark, 1997-2017.

Phthalate	Exposure period	No. of cases	Person-years	Hazard ratio (95% CI) [a]
Any phthalate	Gestation			
	Unexposed	1,997	12,878,437	1.00 (Referent)
	Exposed	30	232,311	0.87 (0.60, 1.24)
	Childhood			
	Unexposed	1,923	12,516,243	1.00 (Referent)
	Exposed	95	594,504	1.19 (0.97, 1.47)
Cellulose acetate phthalate (CAP)	Gestation			
	Unexposed	<5	13,098,472	1.00 (Referent)
	Exposed	<5	12,276	1.59 (0.51, 4.91)
	Childhood			
	Unexposed	<5	13,103,506	1.00 (Referent)
	Exposed	<5	7,241	2.31 (0.74, 7.20)
Dibutyl phthalate (DBP)	Gestation			
	Unexposed	<5	13,095,380	1.00 (Referent)
	Exposed	<5	15,367	0.89 (0.22, 3.55)
	Childhood			

	Unexposed	2,018	13,109,090	1.00 (Referent)
	Exposed	<5	1,658	Not estimable
Diethyl phthalate (DEP)	Gestation			
	Unexposed	2,002	12,904,083	1.00 (Referent)
	Exposed	25	206,665	0.81 (0.55, 1.20)
	Childhood			
	Unexposed	1,988	12,982,931	1.00 (Referent)
	Exposed	30	127,816	1.67 (1.16, 2.41)
Hydroxypropyl methylcellulose phthalate (HPMCP)	Gestation			
	Unexposed	2,006	12,937,462	1.00 (Referent)
	Exposed	21	173,285	0.81 (0.53, 1.25)
	Childhood			
	Unexposed	1,927	12,524,945	1.00 (Referent)
	Exposed	91	585,802	1.16 (0.94, 1.44)
Polyvinyl acetate phthalate (PVAP)	Gestation			
	Unexposed	2027	13,110,318	1.00 (Referent)
	Exposed	<5	429	not estimable
	Childhood			
	Unexposed	<5	13,109,241	1.00 (Referent)

	Exposed	<5	1,507	4.70 (0.66, 33.30)
Phthalate polymers (CAP, HPMCP, and PVAP)	Gestation			
	Unexposed	2,003	12,925,172	1.00 (Referent)
	Exposed	24	185,575	0.86 (0.58, 1.29)
	Childhood			
	Unexposed	1,924	12,517,554	1.00 (Referent)
	Exposed	94	593,193	1.18 (0.96, 1.46)
Low molecular weight phthalates (DBP and DEP)	Gestation			
	Unexposed	2,000	12,889,001	1.00 (Referent)
	Exposed	27	221,746	0.82 (0.56, 1.20)
	Childhood			
	Unexposed	1,988	12,981,592	1.00 (Referent)
	Exposed	30	129,156	1.66 (1.15, 2.39)

[a] Gestational and childhood phthalate exposures were modeled as independent terms (*i.e.* mutually-adjusted) in Cox regression models. CI = confidence interval.

Table 3. Associations between exposure to any phthalate (with 6-month lag period) and incident childhood cancer. Live births in Denmark, 1997-2017.

Cancer type	Exposure period	Number of cases	Median duration of pre-diagnosis exposure, years [a]	Hazard ratio (95% CI) [b]
Leukemia – combined	Gestation			
	Unexposed	673		1.00 (Referent)
	Exposed	12		1.07 (0.60, 1.89)
	Childhood			
	Unexposed	663		1.00 (Referent)
	Exposed	22	2.5	0.85 (0.55, 1.30)
Leukemia – acute lymphocytic	Gestation			
	Unexposed	518		1.00 (Referent)
	Exposed	11		1.27 (0.70, 2.31)
	Childhood			
	Unexposed	512		1.00 (Referent)
	Exposed	17	2.5	0.81 (0.50, 1.32)
Leukemia – acute myeloid	Gestation			
	Unexposed	<5		1.00 (Referent)
	Exposed	<5		0.66 (0.09, 4.70)
	Childhood			
	Unexposed	<5		1.00 (Referent)
	Exposed	<5	3.4	1.22 (0.44, 3.37)
Lymphoma – combined	Gestation			
	Unexposed	<5		1.00 (Referent)
	Exposed	<5		0.65 (0.21, 2.03)
	Childhood			
	Unexposed	218		1.00 (Referent)
	Exposed	25	4.9	2.07 (1.36, 3.14)
Lymphoma – non-Hodgkin	Gestation			
	Unexposed	<5		1.00 (Referent)
	Exposed	<5		1.10 (0.35, 3.45)

	Childhood			
	Unexposed	138		1.00 (Referent)
	Exposed	15	2.6	2.29 (1.33, 3.92)
Lymphoma – Hodgkin	Gestation			
	Unexposed	69		1.00 (Referent)
	Exposed	<5		Not estimable
	Childhood			
	Unexposed	60		1.00 (Referent)
	Exposed	9	7.7	2.04 (1.01, 4.12)
Lymphoma – Burkitt	Gestation			
	Unexposed	21		1.00 (Referent)
	Exposed	<5		Not estimable
	Childhood			
	Unexposed	<5		1.00 (Referent)
	Exposed	<5	Not reportable	0.90 (0.12, 6.75)
Brain/CNS	Gestation			
	Unexposed	263		1.00 (Referent)
	Exposed	5		1.10 (0.45, 2.67)
	Childhood			
	Unexposed	256		1.00 (Referent)
	Exposed	9	1.2	0.84 (0.43, 1.65)
Neuroblastoma	Gestation			
	Unexposed	<5		1.00 (Referent)
	Exposed	<5		0.59 (0.08, 4.25)
	Childhood			
	Unexposed	<5		1.00 (Referent)
	Exposed	<5	1.2	1.57 (0.49, 5.04)
Retinoblastoma	Gestation			
	Unexposed	<5		1.00 (Referent)
	Exposed	<5		1.48 (0.37, 6.03)
	Childhood			
	Unexposed	93		1.00 (Referent)
	Exposed	<5	Not reportable	Not estimable

Kidney	Gestation			
	Unexposed	<5		1.00 (Referent)
	Exposed	<5		0.61 (0.08, 4.36)
	Childhood			
	Unexposed	<5		1.00 (Referent)
	Exposed	<5	Not reportable	1.17 (0.37, 3.72)
Liver	Gestation			
	Unexposed	37		1.00 (Referent)
	Exposed	<5		Not estimable
	Childhood			
	Unexposed	<5		1.00 (Referent)
	Exposed	<5	Not reportable	1.18 (0.16, 8.86)
Osteosarcoma	Gestation			
	Unexposed	<5		1.00 (Referent)
	Exposed	<5		0.46 (0.06, 3.27)
	Childhood			
	Unexposed	90		1.00 (Referent)
	Exposed	16	6.5	2.78 (1.63, 4.75)
Soft tissue sarcoma	Gestation			
	Unexposed	<5		1.00 (Referent)
	Exposed	<5		1.17 (0.29, 4.76)
	Childhood			
	Unexposed	<5		1.00 (Referent)
	Exposed	<5	3.8	0.98 (0.36, 2.69)
Reproductive organ	Gestation			
	Unexposed	57		1.00 (Referent)
	Exposed	<5		Not estimable
	Childhood			
	Unexposed	<5		1.00 (Referent)
	Exposed	<5	2.1	0.38 (0.05, 2.78)
Other or unclassified	Gestation			
	Unexposed	<5		1.00 (Referent)
	Exposed	<5		0.73 (0.24, 2.30)

Childhood			
Unexposed	203		1.00 (Referent)
Exposed	11	5.6	0.95 (0.52, 1.75)

[a] Median time elapsed from receipt of first phthalate-containing prescription drug product until cancer diagnosis (applicable only to time-varying childhood exposure).

[b] Gestational and childhood phthalate exposures were modeled as independent terms (*i.e.* mutually-adjusted) in Cox regression models.

Figure Legends

Figure 1: Sex-stratified associations between gestational and childhood exposure to any phthalate and incidence of any childhood cancer and osteosarcoma. Cross mark (×) denotes an association that was not estimable due to sparse data. Error bars represent the 95% confidence intervals (CIs). Age is in years.

Figure 2. Associations between gestational or childhood exposure to any phthalate and incidence of leukemia, brain/CNS cancer, lymphoma (combined), and osteosarcoma, stratified by age (years) of the modeled at-risk period. Cross marks (×) denote associations that were not estimable due to sparse data. Error bars represent the 95% confidence intervals (CIs).