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Urinary Phthalate Metabolite Concentrations and Cancer Mortality in NHANES,

1999-2006

A Thesis Presented

by

AMY BRADSHAW KAISER

Submitted to the Graduate School of the
University of Massachusetts Amherst in partial fulfillment
of the requirements for the degree of

MASTER OF SCIENCE

May 2015

Public Health

Department of Biostatistics and Epidemiology

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ACKNOWLEDGEMENTS

ABSTRACT

URINARY PHTHALATE METABOLITE CONCENTRATIONS AND CANCER

MORTALITY IN NHANES, 1999-2006

MAY 2015

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Four in ten people in the US will be diagnosed with cancer during their lifetime. Environmental exposures are important determinants of cancer risk, causing as many as 19% of cancers worldwide. Phthalates are a group of chemicals used to increase the flexibility of plastics and vinyl in household materials such as food packaging, plastic toys, wood finishes and adhesives. Some phthalates may act as endocrine disruptors with hypothesized links to endometriosis, breast cancer, and reproductive outcomes. However, no research yet exists on phthalate exposure and all-cancer mortality. We investigated the relationship between seven urinary phthalate metabolites among 5,205 adults in National Health and Nutrition Examination Survey (NHANES), from 1999 to 2006 with mortality data through 2011. Urinary phthalate metabolites were measured in spot urine samples using HPLC-MS/MS and HPLC-ESI-MS/MS. Cox proportional hazard regressions were conducted to calculate hazard ratios and 95 percent confidence intervals for all-cancer mortality, stratified by gender. Mean creatinine adjusted

metabolite concentrations ranged from 0.03 – 3.86 ug/mg in males and 0.07 – 4.37 ug/mg in females. Age-adjusted and multivariate Cox proportional hazard models did not yield statistically significant results for any metabolites. Hazard ratios in the multivariate model for continuous, creatinine adjusted, log transformed metabolite concentrations, ranged from 0.90 to 1.27 in men and 0.86 to 1.07 in women. There was no evidence for a dose-response relationship in the quartile analyses, with p-values for trend above 0.12. This research contributes to the limited cancer literature on phthalate exposure that helps direct future regulations on plasticizers in consumer products.

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CHAPTER 1

INTRODUCTION

In 2014, the rate of cancer in the US was 460.4 per 100,000 with an average 5-year survival rate of 66.1 percent. Since 1992, the incidence and mortality rates of cancer have been slowly decreasing, but it is still one of the most burdensome diseases in the country. The three most common cancer sites are breast, lung, and colorectal, which together account for about 40 percent of all new cancer cases.[1] Risk factors for cancer are extremely broad, and depend on the cancer site, and in some cases, the histological type. In general, they include lifestyle factors, such as smoking, diet, alcohol, and exercise; genetics; psychological stress; radiation and magnetic field exposure, including CT scans, x-rays, radon; infectious agents such as human immunodeficiency virus, Human papillomavirus, and H. pylori; and chemical or environmental exposures, including asbestos, formaldehyde, some pesticides, and possibly bisphenol A and phthalates.[2]

Phthalates are a family of chemicals ubiquitous in countless industrial products. They hold color and fragrance and add gloss to personal care products; provide time releasing for some pharmaceuticals; and most commonly, add flexibility to polyvinyl chloride (PVC).[3] Higher molecular weight phthalates, including di-(2-ethylhexyl) phthalate (DEHP), di-isodecyl phthalate (DiBP), and di-isononyl pthalate (DiNP) are most common in construction material, clothing, children's toys, household furnishings, and as a plasticizer in PVC. Lower molecular weight phthalates, dibutyl phthalates (DBP), dimethyl phthalate (DMP), and diethyl phthalate (DEP), are typically used as solvents in adhesives, pharmaceuticals, waxes, inks, and cosmetics (Table 1).[4, 5]

Humans have opportunity to be exposed to phthalates through ingestion, inhalation, intravenous injection, and skin absorption. Phthalates are not covalently bound to the PVC plastics, and tend to leach, migrate or evaporate into the environment. [3, 6] The most common route of exposure is ingestion (through food, medicine, or children's toys), inhalation (house dust and indoor air), intravenous (medical tubing), and dermal absorption (direct contact with clothing, waxes, cleaning products, cosmetics).[5] Medical devices are a particularly common source of exposure. Phthalates (particularly DEHP) are used as softeners for medical tubing or medical bags used for administering blood and nutritional formulas, as well as gases for respiratory treatments, and are in medicine packaging and coatings of supplements and herbal treatments. Therefore, individuals undergoing medical treatment have phthalate exposure associated with each treatment (e.g. intravenous exposure to DEHP from a blood transfusion in a trauma patient is about 8.5 mg/kg/day)[5].

Phthalates are quickly metabolized in the body into monoesters, and then depending on the phthalate, further metabolized into oxidative products of their lipophilic aliphatic side chain, then excreted in urine and feces[3]. According to the National Health and Nutrition Examination Survey (NHANES), several phthalate metabolites are detectable in the urine of 97 percent of the total US population,[7] and adult women have particularly high levels of metabolites associated with phthalates used in cosmetics and personal care products.[8] Phthalates are suspected to act as endocrine disruptors in humans, which may be associated with infertility, endometriosis, and some endocrine related cancers, possibly by mimicking naturally occurring hormones, blocking endogenous hormones from binding, or altering the production of hormones in the body.[9]

The National Toxicology Project has classified one phthalate DEHP as Group 2B, possibly carcinogenic to humans, based on sufficient evidence for carcinogenicity in animal studies. [10]

Physiology of Phthalate−Cancer Relationship

The carcinogenic mechanism for phthalates is unclear and the specific carcinogenic mechanism and metabolism of endocrine disruptors is poorly understood. Endocrine disrupters are typically considered compounds that bind to steroid hormone receptors to mimic or block the transcriptional activation elicited by naturally circulating steroid hormones. Hsieh et al. demonstrated that phthalates could induce proliferation, migration, invasion, and tumor formation and initiate a cascade of events that facilitates cancer, specifically ER-negative breast cancer. [11]

They can also act as hormone sensitizers by inhibiting histone deacetylase activity and can stimulate mitogen-activated protein kinase activity. Additionally, they may have effects on receptors other than ER, AR, and thyroid hormone receptor and can have genome-wide effects on DNA methylation. [12]

Epidemiology of Phthalate−Cancer Relationship

The association between phthalate exposure and all cancer mortality has not been previously been studied. However, three studies have examined breast cancer and exposures to phthalates or endocrine disruptors, and one study examined lung cancer and occupational exposures, including phthalates.

Two occupational case-control studies evaluated breast cancer. Aschengrau et al. [13] evaluated occupational exposure to 18 estrogenic chemicals assigned according to job description, and risk of breast cancer among 261 employees compared to 753 population

controls. Cases only exposed to butylbenzyl phthalate (BBzP) (n=4 cases) had an adjusted odds ratio of 0.9 (95% CI: 0.3-2.9) compared to controls with the same exposure. Combined exposure to BBzP phthalate and other xenoestrogens (defined as any of 33 substances with estrogenic properties in E-SCREEN bioassay), had an adjusted OR of 0.7 (95% CI: 0.4-1.2) compared to controls with the same exposure. Brophy et al. 2012 [14] conducted compared occupational work history of 1,005 breast cancer cases with 1,146 community controls. They reported that women in jobs with high exposures to endocrine disruptors had elevated breast cancer risk (OR=1.42, 95% CI: 1.18-1.73), with particularly elevated risks among automotive plastics manufacturing (OR=2.68, 95% CI: 1.47-4.88).

A third occupational case-control study[15] compared 43 cases that died of lung cancer from 1976 to 1979 to community controls that died in the same time period. Cases were more likely to work in a plant that produced phthalates (OR=5.2), but the plant also produced large levels of soot. The analysis adjusted for age and smoking, but not soot exposures.

These studies are limited by misclassification of exposure and lack of individual exposure. Since exposure assessment was based on work history, it is not clear exactly which chemicals are responsible for the increased risk. Especially in cases where participants held multiple jobs over a lifetime, results could be confounded by other occupational exposures. Records-based occupational studies also may not have comprehensive, reliable covariate data which introduces unadjusted confounding or residual confounding. There could also be recall bias, typical of case-control studies, or chance findings.

Lopez Carrillo et al.[16] conducted a case-control study of breast cancer, with 233

cases and 221 age-matched controls, and assessed phthalate exposure through urine

metabolites. For the sum of all metabolites, the authors reported slightly increased odds

of breast cancer in the third tertile compared to the first tertile, which was not statistically

significant (OR=1.09, 95% CI=0.69-1.71). They also reported statistically significant

increased odds of breast cancer in the third tertile compared to the first tertile in some

metabolites: DEP metabolites, OR=2.20, 95% CI=1.33-3.63; DEHP metabolites,

OR=1.68, 95% CI=1.01-2.78. However, they also found statistically significant

protective effects when comparing the third tertile to the first: BBzP metabolites,

OR=0.46, 95% CI=0.27-0.79; DOP metabolites, OR=0.44, 95% CI: 0.24-0.80. These

results demonstrate the importance of assessing individual compounds, since each

phthalate does not affect risks of breast cancer equally; this study found that most either

have no effect or a protective effect on risk. Additionally, the effect sizes in this study

may be overestimated because phthalates are found in medical equipment and

medications. Therefore, cases will have higher exposure to phthalates than controls due to

their cancer treatments, not because their exposure increased their risk of cancer.

Summary of Significance and Innovation

Given the high percentage of Americans exposed to phthalates on a daily basis,

further research on the health implications of these substances is increasingly important.

The existing literature suggests possible health implications of phthalates and the possible

carcinogenicity of endocrine disruptors. However, cancer incidence or mortality has not

been adequately assessed. This study is significant given the prevalence of phthalates in

consumer products, and its suspected carcinogenicity and is innovative by evaluating the

association between urinary phthalate metabolites and cancer mortality in a large

population with a verified exposure assessment.

CHAPTER 2

METHODS

Study Design

Using a prospective cohort design, we conducted a mortality analysis to assess the

association between urinary phthalate metabolites and all cancer mortality using four

National Health and Nutrition Examination Survey (NHANES) series from 1999-2006,

linked with mortality data through 2011. NHANES is a national survey from the National

Center for Health Statistics, part of the Center for Disease Control and Prevention (CDC).

The assessment included an interview component to collect sociodemographic, household

and medical information; as well as a mobile examination component (MEC) for blood

and urine samples which was conducted for a random sample of one third of the

participants. The NHANES interview team included physicians, medical technicians and

health interviewers. The interviews were conducted in the participants' houses, and the

MECs were conducted in mobile centers.[17]

Study Population

The NHANES survey is the longest ongoing survey of the US population. The

survey began in the 1960s, with the continuous series beginning in 1999. Each NHANES

series includes 2 years and enrolls about 10,000 participants each series. Participants are

randomly selected through a complex survey design, designed to be representative of

civilian, noninstitutionalized US population; African Americans, Mexican Americans,

infants, children, and the elderly were oversampled to ensure the sample was fully

representative. [17] The public-use linked mortality files provide linkage with the National

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Death Index (NDI) and Social Security Administration (SSA) databases for vital status

and cause of death data. Mortality data are available through December 31, 2011.[18]

NHANES surveyed about 41,400 participants over the four series. Participants

were eligible for our study if they were adults (more than 20 years old) who underwent

the MEC assessment and were randomly selected for the phthalate assessment of the

MEC assessment (n=5205, evenly distributed between each series)[1]. We further excluded

participants who died within 12 months of the MEC assessment (n=67), who were ever

diagnosed with a cancer other than melanoma (n=434), or who were pregnant at time of

MEC assessment (n=378), to eliminate confounding by prevalent cancers or conditions,

increased medicalization or changes in phthalate metabolism. We also excluded

participants who had incomplete mortality follow-up (n=8). Our final study population

included 5,205 participants (Table 2).

<u>Urinary Phthalate Metabolite Assessment</u>

Phthalate metabolites were measured on a random one-third sample of the MEC

assessment participants, starting in 1999. One spot urine sample was collected from each

participant, stored at -20°C and then shipped to Division of Environmental Health

Laboratory Sciences, National Center for Environmental Health, Centers for Disease

Control and Prevention for analysis. We included include metabolites that were assessed

for at least three NHANES series from 1999 to 2006, and that had more than 60 percent

of samples above the level of detection: MBzP, MnBP, MEHP, MEP were measured

starting in 1999 and are associated with BzBP, DBP, DEHP and DEP, respectively;

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[1] About 18,850 of the surveyed participants had missing follow-up data. However, 15,162
of these were also missing phthalate data and 1,202 of them were less than 20 years old.
Therefore, only 8 were eligible for our study, and later excluded.

MiBP, MCPP, MEHHP, MEOHP and were measured starting in 2001 and are associated with DBP, DnOP, DEHP, and DEHP, respectively. In the 1999-2000 series, the MnBP and MiBP metabolites were not differentiated, so these measurements were combined in subsequent series for consistency. Samples below the LOD were assigned the value of the LOD divided by the square root of two by the laboratory conducting the analyses. Each value was natural log transformed, and adjusted for urine dilution by dividing by creatinine concentration.

Validation of Urinary Phthalate Metabolite Assessment

Due to decisions made by NHANES, two different methods were used to assess phthalate concentration. From 1999 to 2002, urine was analyzed using high-pressure, liquid chromatography tandem mass spectrometry (HPLC-MS/MS). From 2003 to 2006, phthalate metabolites were analyzed using high performance liquid chromatography-electrospray ionization-tandem mass spectrometry (HPLC-ESI-MS/MS). The precision of this method was evaluated by repeated measures of quality control pools over time and CVs were provided (Table 1).[19-22] Urinary creatinine was also measured in each participant and used to adjust for urinary dilution.

Cancer Mortality Assessment

NHANES participants were linked with mortality data through December 31, 2011 by the National Center for Health Statistics (NCHS). Participants were matched to death certificates, National Death Index (NDI) records, SSA records, and Centers for Medicare and Medicaid Services, and then cause of death data was ascertained from the NDI and death certificates. Matches were determined using 12 matching variables and a probabilistic algorithm.[18] Cause of death was recoded into 10 general categories for this

dataset. The code "002", any malignant neoplasm, was used for this analysis. Although we do not have site-specific cancer data, based on previous mortality data available through 2010, the most common cancers contributing to mortality were trachea, bronchus and lung cancer; colon, rectum and anus cancer; and non-Hodgkin's lymphoma.

To take advantage of data available in NHANES, we used cancer mortality as a proxy for cancer incidence. However, cancer mortality does not adequately capture survivable cancers which will be missed in this analysis, while aggressive cancers will be over-represented.

<center>Validation of Cancer Mortality</center>

The National Center for Health Statistics (NCHS) completed a calibration study to verify their linkage methodology for mortality follow-up.[23] They used the NHANES I Epidemiologic Follow-up survey (conducted from 1971 to 1992), which includes participants for whom vital status was known. A sample was submitted to the NDI for match searches, and matches were compared with each other. Of the decedents, 96.1 percent were correctly classified as deceased and correctly matched with a death certificate. Among non-decedents, 99.4 percent were correctly classified as alive. In total, 98.5 percent of NHEFS respondents were correctly classified.

The NDI has documented cause of death data since 1979, and is the accepted source for mortality data for large studies. A validation study of the NDI cause of death data compared NDI underlying cause of death to the cause of death assigned by two nosologists. They provided discrepancy rates using the NCHS code as the reference. The discrepancy rate for all causes of death combined was four percent for NDI Plus codes and six percent to seven percent for the study nosologists' original codes. The

discrepancy rate for specific cancer sites was one percent for NDI Plus codes and three percent for the final study codes.[24] Cancer mortality was assessed as a dichotomous variable.

<div align="center">Covariate Assessment</div>

We considered as possible covariates demographic, lifestyle, and health factors available from data obtained during the demographic or household section of the NHANES questionnaire. Age at home visit, family poverty-income ratio (PIR), BMI, and age at menarche, were assessed as continuous variables. Categorical variables included: race (Mexican American, other Hispanic, Non-hispanic White, Non-hispanic Black, other race/multi-race), gender (male, female), education (less than high school, high school graduate or GED, some college or AA degree, college graduate or above), country of birth (born in the US, born in Mexico, or born elsewhere), and marital status (married/living with partner, never married, widowed/divorced/separated), smoking status (smoker, non-smoker), menopausal status (pre- or post- menopausal), alcohol intake (none, light, moderate, heavy).

Smoking status (dichotomous) was ascertained using the question "smoked at least 100 cigarettes in lifetime?" to reduce missing data. For the last 2 series, subjects were considered postmenopausal if the answer to the question "what is the reason that you have not had regular periods in past 12 months?" was "menopause/hysterectomy." For the first 2 series they were considered postmenopausal if their answer this question was "going-gone through menopause or their answer to "have you had a hysterectomy?" was yes.   Alcohol intake was coded as light for 1-2 drinks per day, moderate for 3-4 drinks per day, and heavy for more than 4 drinks per day. These were been identified

based existing literature on risk factors for cancer mortality and possible association with phthalate exposure (Table 2).

Data Analysis

Each phthalate metabolite was standardized by urinary creatinine levels to account for urinary dilution, and natural log transformed.   We calculated Pearson correlation coefficients were calculated for continuous variables and anova for categorical variables to assess crude correlations between each phthalate metabolite and covariates.

Multivariable Cox proportional hazards regression was used to model the association between urinary creatinine-adjusted phthalate metabolite concentrations (continuously and in quartiles) and cancer mortality. Person-time was measured in months starting from MEC exam. Participants were right censored at of time of death from non-cancer cause or administrative censoring in December 2011.

Two models were considered for each metabolite, each stratified by sex: model 1 was adjusted for age, and model 2 was a multivariate analysis adjusted for age, BMI, PIR, race, smoking, education, country of birth, marital status and alcohol intake. In the female strata, model 2 was also adjusted for menopausal status and parity. Risk factors for cancer are abundant, and vary greatly between cancer sites. When choosing covariates, we took into account common risk factors for most prevalent cancers (cancers of the colon, breast and lung),[2] literature on phthalates, and results from our bivariate analyses.

For all statistical analyses, SAS 9.3 was used.

CHAPTER 3

RESULTS

Our study population was approximately 51% male and 49% female. The average

age at entry was 48 years for men and 50 years for women and about 49% were non-

Hispanic White, 22% were Mexican American, and 20% were Black. About 30% had

less than a high school education, and 20% of men were college graduates for more,

while 17% of women were college graduates. Among women, 65% were post-

menopausal (Table 3). Mortality follow-up yielded 132 cancer deaths, 81 among men and

51 among women (Table 4).

Metabolites MBzP, MEHP, and MEP were measured in 2,654 males and 2,511

females; metabolites MCPP, MEHHP, MEOHP and MnBP were measured in 2,042

males and 1,896 females. In general, women had higher concentrations than men, with

the biggest difference in mean for MEP (males: 3.86 ug/mg, females: 4.37 ug/mg). Males

had a slightly higher mean concentration of MBzP, but larger standard deviation (SD)

(males: 0.17 ug/mg, SD: 2.14; females: 0.15 ug/mg; SD: 0.25 ug/mg) (Table 5).

Bivariate analyses showed that age was statistically significantly associated with

most phthalate metabolites for men and women. Race was significantly associated with

MEHP, MnBP, MEHHP, MEOHP, and MCPP in men, and with MBZP, MnBP and

MCPP in women, with Hispanics having the highest levels overall. Participants who were

never married had higher concentrations than married or divorced/widowed participants,

and marital status was associated with every metabolite except MEHP and MEOHP in

men, and MEHP and MnBP in women. Among women, parity was not associated with

any metabolite, while premenopausal women had overall higher concentrations (Table 6, 6a, 7, 7a).

Due to missing data, Cox proportional hazard regressions in men included 2,359 subjects and 59 events for MEHP, MBZP and MnBP, and 1,886 participants and 43 events for MEHHP, MEOHP, and MCPP; and 2358 participants and 59 events for MEP. Results of the age-adjusted analysis of continuous metabolites were mostly null with hazard ratios ranging from 0.87 to 1.29. The multivariate analysis of continuous metabolites, adjusted for age, BMI, PIR, race, smoking, education, place of birth, marital status, and alcohol intake, yielded hazard ratios ranging from 0.90 to 1.26, with confidence intervals including 1. The quartile analysis yielded similar results, with p-values for trend much large than 0.05, with the exception of MEP, which had reducing risk estimates with higher exposure, and a p-value of 0.06.

In women, Cox proportional hazard regressions results included 2,025 subjects and 38 events for MEHP, MBZP and MnBP; 1,576 participants and 26 events for MEHHP, MEOHP, and MCPP; and 2,022 participants and 37 events for MEP. Results of the age-adjusted and multivariate analyses of continuous metabolites were mostly null with hazard ratios ranging from 0.86 to 1.07. Some quartile analyses were suggestive of increased risks with exposure, but the trends were not approaching significance (lowest p-trend=0.12).

Results for a fully adjusted Cox proportional hazard regression for men and women combined did not yield meaningfully different results (not shown).

CHAPTER 4

DISCUSSION

We found no evidence of an association between urinary phthalate metabolites and all-cancer mortality. Results for multivariate Cox proportional hazard regressions were null, as were analysis of exposure in quartiles. As expected, we observed differences in exposure between men and women, races and age, and between individual phthalates.

Overall, previous literature is limited to case-control studies from occupational settings that lack individual exposure assessment or exposure to specific compounds. The single study that does have results for individual compounds, Lopez Carillo et al.[16] reported increased odds of breast cancer for DEP metabolites (MEP) and DEHP metabolites (MEHP, MEHHP, MEOHP) protective effects for BzBP metabolites (MBzP) and DnOP metabolites (MCPP). We were unable to reproduce these results, and found that in men, MBzP actually had the highest hazard ratio.

This study has several strengths. We used a cohort design with individual exposure assessment and specific phthalate compounds with mortality follow-up to conduct a time-to-event analysis which allowed us to take into account person-time for the entire cohort. Our data for exposure, outcome and covariates was reliable, and residual confounding is unlikely due to measurement error. One possible exception is confounding due to unmeasured medication use. We were unable to account for medication use in our analyses, which could increase phthalate metabolite levels. [7] To reduce the chances of including very ill individuals in our analysis, we excluded participants who died within 1 year of baseline. Lastly, NHANES is a random selection

of the U.S. population, so selection bias in the overall dataset was unlikely and our results could be are broadly generalizable.

Our study had several limitations. First, we used cancer mortality as a proxy for cancer incidence; however, many cancers are survivable: overall, cancers have an on average a 61.1 percent 5-year survival rate, [25] while many of the most prevalent cancers have even higher rates. Therefore, many incident cancer cases likely went undetected in our analysis because participants either survived or survived past end of follow-up. Additionally, we could not assess site-specific cancer mortality, and missed the opportunity to analyze cancers likely to be associated with phthalate exposure (hormone-related cancers).

Secondly, phthalate exposure was assessed through spot urine samples, collected at different times of the day for each participant. Phthalates are quickly metabolized in the body, so a single urine sample will only reflect recent (<1 day) exposures. We are unsure if a single urine sample is representative of a participant's current actual phthalate exposure, and what the likelihood is that that sample can represent longer term phthalate exposures. In study among men of reproductive age, the day-to-day variance ranged from 27.2% to 58.1%, 30-day cycle variances ranged from 1.5% to 16.3%, so the authors concluded that day-to-day variance accounts for most of the variance within 30 days. [26] There is substantial variance in phthalate exposure that will not be captured by a single urine sample and limits the ability of our samples to adequately estimate true exposures.

The authors also assessed the predictability of a single spot urine sample in relation to 3-month average in tertiles. They reported sensitivities of 0.56 (MEHP), 0.63 (MBzP), 0.63 (MEP), and 0.67 (MBP).[26] These are very modest sensitivities, and

suggest that only 55-70 percent of samples were correctly classified into tertiles, so our quartile analyses only slightly increase the accuracy of the exposure assessment.

Misclassification of exposure is likely, especially if each sample is intended to estimate long-term exposures. This is a moderate non-differential misclassification of exposure that will affect subjects regardless of outcome and bias the results toward the null. In general, ability of a spot sample to predict average exposure varies by metabolite; MEP and MBP are more representative, while MEHP, MEHHP, DEHP, are less representative. [26, 27]

Additional misclassification of exposure may persist due to urine concentration, despite adjusting for creatinine. Creatinine adjustment is not appropriate for compounds secreted through tubular secretion, which is suggested to be the case for phthalates, and creatinine varies by factors such as age, BMI, exercise, and diet. Alternative methods used are specific gravity and urinary osmolality. [26, 27] However, creatinine is what is recommended in the NHANES dataset.

Another related concern is the temporal relationship between exposure and cancer. Our study had between 5 and 11 years of follow-up on each participant. Since cancers tend to have long latency periods, it is likely that a longer follow-up period would capture more events. Additionally, we also did not take into account periods of sensitivity; exposure *in utero*, during puberty or during childhood which could have a larger effect on risk of cancer than exposure in other times of life. Lastly, this analysis is likely underpowered to detect effects. The sample size was small after exclusions, and events were lost in the regressions due to missing data in covariates.

CHAPTER 5

CONCLUSION

We did not observe associations between all-cancer mortality and phthalate

metabolites (MBzP, MCPP, MEHHP, MEHP, MEOHP, MEP, MnBP) in age-adjusted or

multivariate Cox proportional hazard regressions, stratified by gender. Our study was

limited by power, mortality data instead of cancer incidence data, and misclassification of

exposure. However, it contributed longitudinal data with individual exposure assessment

to the existing literature on potential carcinogenicity of phthalates. Our study was

inconclusive, and warrants additional epidemiological, as well as toxicological, research

on the subject. We were unable to assess site-specific cancers, which would be essential

for further research. We also do not know how much our results were affected by

confounding due to exposure to medical devices or if our exposure assessment was

adequately precise. It is also possible that our study missed the window of sensitivity for

this exposure-outcome mechanism. Given the high percentage of Americans exposed to

phthalates on a daily basis, further research on the health implications of these substances

is increasingly important.

APPENDIX

TABLES

Table 1: Sources of exposure, metabolites and analytical data for assessed phthalates

Parent Compound	Sources of Exposure[a]	Metabolite	Series	CV (99-00)[b]	CV (01-02)[c]	CV (03-04)[d]	CV (05-06)[e]
Benzylbutyl phthalate (BzBP)	Floorings, paints, carpet backings, adhesives, wood finishers, wallpaper, PVC products	Mono-benzyl Phthalate (MBzP)	1999-2006	9.6-12.8%	5.4-14.2%	6.3-6.4%	6.8-8.9%
Di-butyl phthalate (DBP)	Deodorants, perfumes, personal care products, aftershave, cosmetics, pharmaceutical/herbal coating, chemiluminescent glow sticks	Mono-n-butyl Phthalate (MnBP)	1999-2006	7.2-22.1%	4.0-17.2%	7-7.4%	7.5-17.4%
		Mono-isobutyl Phthalate (MiBP)	2001-2006		7.2-8.3%	5.8-8.6%	7.3-13.2%
Di 2-ethylhexyl phthalate (DEHP)	PVC containing medical tubing, medical devices, food packaging, indoor air, plastic toys, tablecloths, floor tiles, furniture upholstery, shower curtains, garden hoses, rainwear, baby pants, dolls, shoes, automobile upholstery and tops, and sheathing for wire and cable	Mono-(2-ethyl)-hexyl Phthalate (MEHP)	1999-2006	10.5%-18.2%	8.6-15.8%	7.6-10.5%	6.3-12.0%
		Mono-(2-ethyl-5-hydroxyhexyl) Phthalate (MEHHP)	2001-2006		8.6-15.8%	6.7-8.4%	3.8-5.7%
		Mono-(2-ethyl-5-oxohexyl) Phthalate (MEOHP)	2001-2006		4.8-6.0%	6.6-9.6%	3.3-4.4%
Diethyl phthalate (DEP)	Deodorants, perfumes, personal care products, aftershave, cosmetics, pharmaceutical/herbal coating, insecticide	Mono-ethyl Phthalate (MEP)	1999-2006	4.9-10.0%	4.7-10.6%	5.1-6.0%	2.9-5.2%
Di-n-octyl phthalate (DnOP)	Medical tubing and blood storage bags, wire and cables, carpetback coating, floor tile, and adhesives, cosmetics and pesticides	Mono-(3-carboxypropyl) phthalate (MCPP)	2001-2006		4.1-4.3%	10.9-12.3%	14.0-15.5%

[a] Adapted from: Sathyanarayana S. Phthalates and Children's Health. Curr Probl Pediatr Adolesc Health Care 2008;34 49.

[b] CDC/National Center for Environmental Health. Laboratory Procedure Manual, Phthalate Monoesters in Urine, NHANES 1999-2000. http://www.cdc.gov/nchs/data/nhanes/nhanes_99_00/PHPYPA_met_phthalates.pdf . 2010. 3-29-2015.

[c] CDC/National Center for Environmental Health. Laboratory Procedure Manual, Phthalate Monoesters in Urine, NHANES 2001-2002. http://www.cdc.gov/nchs/data/nhanes/nhanes_01_02/PHPYPA_b_met_phthalates.pdf . 2010. 3-29-2015.

[d] CDC/National Center for Environmental Health. Laboratory Procedure Manual, Phthalate Monoesters in Urine, NHANES 2003-2004. http://www.cdc.gov/nchs/data/nhanes/nhanes_03_04/l24ph_c_met.pdf. 2013. 3-29-2015.

e CDC/National Center for Environmental Health. Laboratory Procedure Manual, Phthalate Monoesters in Urine, NHANES 2005-2006. http://www.cdc.gov/nchs/data/nhanes/nhanes_05_06/PHTHTE_D_met.pdf. 2013. 3-29-2015.

Table 2: Number and percent in final study sample, NHANES 1999-2006

Original Study Sample (adults eligible for follow up and phthalate data)	6059	%
Incomplete follow up	8	0.1%
Died within 12 months of baseline	67	1.1%
Ever diagnosed with cancer (except non-melanoma skin)	434	7.2%
Pregnant at time of MEC	378	6.2%
Final Sample Size	5205	86%

Table 3: Distribution of covariates, NHANES 1999-2006

	Males (n=2669; 51%)			Females (n=2536, 49%)		
	M	SD	missing	M	SD	missing
Age (years)	48.61	17.7	0	50.05	18.1	0
BMI (kg/m2)	28.16	5.7	56	28.85	7.1	44
Ratio of family income to poverty	2.73	1.6	181	2.62	1.6	209
	N	%	missing	N	%	missing
Race			0			0
Mexican American	595	22.3		563	22.2	
Other hispanic	115	4.3		113	4.5	
Non-Hispanic White	1327	49.7		1221	48.2	
Non-Hispanic Black	545	20.4		546	21.5	
Other Race /multi-race	87	3.3		93	3.7	
Smoking			1			3
Smoked > 100 cigarettes in lifetime	1518	56.9		976	38.5	
Smoked< 100 cigarettes in lifetime	1150	43.1		1557	61.5	
Education level			5			4
Less than high school	840	31.5		777	30.7	
High school grad/GED or Equivalent	626	23.5		581	23.0	
Some college or AA degree	665	25.0		727	28.7	
College Graduate or above	533	20.0		447	17.7	
Born in US or abroad			2			2
Born in US	2001	75.0		1986	78.4	
Born in Mexico	382	14.3		324	12.8	
Born elsewhere	284	10.7		224	8.8	
Marital status			67			61
Married /living with partner	1764	67.8		1384	55.9	
Never married	448	17.2		351	14.2	
Widowed, divorced, separated	390	15.0		740	29.9	
Menopausal status						102
Premenopausal	---	---	---	1192	49.0	
Post menopausal	---	---	---	1242	51.0	
Parity						352
Nulliparous	---	---	---	255	11.7	
1 live birth	---	---	---	327	15.0	
More than 1 live birth	---	---	---	1602	73.4	
Alcohol intake			0			0
None	337	12.6		780	30.8	
Light (1-2 drinks/day)	1435	53.8		1420	56.0	
Moderate (3-4 drinks/day)	457	17.1		237	9.4	
Heavy (>4 drinks/day)	440	16.5		99	3.9	

Table 4: Distribution of cancer mortality, NHANES 1999-2006 with follow-up through 2011

	All	Males	Females
Cancer mortality	132	81 (61%)	51 (39%)

Table 5: Distribution of creatinine adjusted, phthalate metabolite concentration (ug/mg), NHANES 1999-2006

	Males			Females		
	Mean	SD	N	Mean	SD	N
MBzP	0.17	2.14	2654	0.15	0.25	2511
MCPP	0.03	0.10	2042	0.04	0.15	1896
MEHHP	0.41	1.01	2042	0.45	1.13	1896
MEHP	0.07	0.21	2654	0.07	0.24	2511
MEOHP	0.25	0.60	2042	0.29	0.69	1896
MEP	3.86	10.29	2653	4.37	17.95	2507
MnBP	0.35	3.23	2042	0.43	1.55	1896

Table 6: Distribution of creatinine adjusted, log transformed phthalate metabolite concentration (ug/mg) and coefficients, males, NHANES 1999-2006

	MEHP	MEP	MBzP	MnBP	MEHHP	MEOPH	MCPP
	Coefficient (p-value)	Coefficient (p-value)	Coefficient (p-value)	Coefficient (p-value)	Coefficient (p-value)	Coefficient (p-value)	Coefficient (p-value)
Age (years)	-0.13 (<.01)	0.02 (0.32)	-0.04 (0.04)	0.05(0.04)	-0.05(0.03)	-0.02(0.32)	0.11(<.001)
Body Mass Index (kg/m^2)	-0.02 (0.33)	0.05(0.02)	0.01 (0.62)	-0.02(0.28)	0.07 (<0.01)	0.07(<0.00)	0.01(0.66)
Family PIR	0.03 (0.17)	-0.03(0.15)	-0.12 (<0.01)	-0.12(<0.01)	0.07 (<0.01)	0.08(<0.01)	0.00(0.83)
	MEHP	MEP	MBzP	MnBP	MEHHP	MEOHP	MCPP
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Race							
Mexican American	0.03 (3.22)	1.40 (4.22)	0.06 (2.69)	0.19 (2.23)	0.15 (2.97)	0.10 (2.8)	0.02 (2.34)
Other hispanic	0.04 (3.9)	1.60 (4.35)	0.08 (2.64)	0.21 (1.9)	0.20 (3.00)	0.12 (2.86)	0.02 (2.34)
Non-Hispanic White	0.03 (3.35)	0.98 (4.39)	0.07 (2.77)	0.18 (2.25)	0.18 (3.22)	0.12 (3.10)	0.02 (2.39)
Non-Hispanic Black	0.03 (3.67)	1.48 (4.06)	0.07 (2.77)	0.19 (2.20)	0.17 (3.22)	0.11 (3.06)	0.01 (2.56)
Other Race /multi-race	0.02 (2.89)	0.72 (3.82)	0.06 (2.97)	0.21 (2.89)	0.14 (2.92)	0.08 (2.80)	0.01 (2.53)
ANOVA p-value	0.01	0.08	<0.01	0.12	0.01	0.01	<0.01
Smoking							
Smoker	0.03 (3.39)	1.21 (4.62)	0.07 (2.80)	0.18 (2.32)	0.17 (3.22)	0.11 (3.10)	0.02 (2.51)
Non-smoker	0.03 (3.42)	1.12 (3.94)	0.07 (2.69)	0.17 (2.14)	0.18 (3.03)	0.11 (2.92)	0.02 (2.32)
ANOVA p-value	0.50	0.09	0.20	<0.01	0.13	0.15	0.07

Table 6a: Distribution of creatinine adjusted, log transformed phthalate metabolite concentration (ug/mg) and coefficients, males, NHANES 1999-2006, continued

	MEHP	MEP	MBzP	MnBP	MEHHP	MEOHP	MCPP
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Education level							
Less than high school	0.02 (3.13)	1.32 (4.66)	0.07 (2.89)	0.20 (2.29)	0.14 (2.92)	0.09 (2.80)	0.02 (2.44)
High school grad or equivalent	0.02 (3.53)	1.25 (4.18)	0.07 (2.56)	0.18 (2.18)	0.18 (3.10)	0.11 (3.03)	0.02 (2.44)
Some college or AA	0.03 (3.67)	1.12 (4.18)	0.07 (2.75)	0.18 (2.25)	0.19 (3.25)	0.12 (3.10)	0.02 (2.51)
College graduate or above	0.03 (3.39)	0.95 (4.01)	0.06 (2.77)	0.17 (2.18)	0.19 (3.29)	0.12 (3.16)	0.02 (2.36)
ANOVA p-value	0.03	<0.01	<0.01	<0.01	<0.01	<0.01	0.38
Born in US or abroad							
Born in US	0.03 (3.46)	1.11 (4.31)	0.07 (2.75)	0.18 (2.23)	0.18 (3.22)	0.11 (3.10)	0.02 (2.48)
Born in Mexico	0.03 (3.10)	1.54 (4.14)	0.06 (2.72)	0.19 (2.29)	0.15 (2.92)	0.09 (2.75)	0.02 (2.16)
Born elsewhere	0.03 (3.46)	1.2 (4.35)	0.06 (2.80)	0.23 (2.23)	0.16 (2.97)	0.1 (2.80)	0.02 (2.53)
ANOVA p-value	0.10	<0.01	<0.01	<0.01	0.01	0.01	0.22
Marital status							
Married /living with partner	0.03 (3.32)	1.17 (4.31)	0.06 (2.75)	0.18 (2.23)	0.17 (3.13)	0.11 (2.97)	0.02 (2.41)
Never married	0.03 (3.82)	1.08 (3.86)	0.07 (2.80)	0.18 (2.27)	0.18 (3.46)	0.11 (3.29)	0.02 (2.56)
Widowed, divorced, separated	0.02 (3.29)	1.28 (4.9)	0.08 (2.69)	0.20 (2.29)	0.17 (2.94)	0.11 (2.92)	0.02 (2.39)
ANOVA p-value	0.01	<0.01	0.24	0.11	0.98	0.97	<0.01
Alcohol intake							
None	0.02 (3.29)	1.19 (4.44)	0.07 (2.48)	0.18 (2.27)	0.15 (2.72)	0.1 0(2.61)	0.02 (2.51)
Light (1-2 drinks/day)	0.03 (3.35)	1.13 (4.39)	0.07 (2.80)	0.18 (2.23)	0.18 (3.03)	0.11 (2.92)	0.02 (2.39)
Moderate (3-4 drinks/day)	0.03 (3.67)	1.25 (3.97)	0.07 (2.48)	0.18 (2.16)	0.18 (3.6)	0.11 (3.46)	0.02 (2.39)
Heavy (>4 drinks/day)	0.03 (3.42)	1.21 (4.39)	0.07 (3.13)	0.19 (2.39)	0.17 (3.35)	0.10 (3.16)	0.02 (2.53)
ANOVA p-value	0.79	0.14	0.53	0.99	0.11	0.19	0.01

Table 7: Distribution of creatinine adjusted, log transformed phthalate metabolite concentrations (ug/mg), females, NHANES 1999-2006

	MEHP	MEP	MBzP	MnBP	MEHHP	MEOPH	MCPP
Pearson coefficient	Coefficient (p-value)	Coefficient (p-value)	Coefficient (p-value)	Coefficient (p-value)	Coefficient (p-value)	Coefficient (p-value)	Coefficient (p-value)
Age (years)	-0.09 (<0.01)	-0.06 (0.01)	-0.06 (0.01)	0.00 (0.85)	-0.04 (0.13)	-0.04 (0.07)	0.11 (<0.1)
Body Mass Index (kg/m^2)	-0.08 (<0.01)	0.04 (0.11)	0.06 (0.01)	-0.04 (0.13)	0.05 (0.04)	0.05 (0.02)	-0.02 (0.40)
Family PIR	0.02 (0.38)	-0.04 (0.07)	-0.16 (<0.01)	-0.09 (<0.01)	0.04 (0.07)	0.05 (0.05)	-0.02 (0.33)
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**
Race	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)	M(SD)
Mexican American	0.03 (2.97)	2.03 (3.35)	0.08 (2.77)	0.29 (2.29)	0.19 (2.69)	0.13 (2.56)	0.02 (2.41)
Other hispanic	0.03 (2.97)	2.2 (3.49)	0.1 (2.41)	0.39 (2.12)	0.25 (2.51)	0.16 (2.59)	0.03 (2.18)
Non-Hispanic White	0.03 (3.10)	1.26 (3.63)	0.09 (2.69)	0.26 (2.25)	0.21 (2.92)	0.14 (2.86)	0.02 (2.32)
Non-Hispanic Black	0.03 (3.13)	1.88 (3.56)	0.09 (2.69)	0.28 (2.16)	0.22 (2.94)	0.14 (2.89)	0.02 (2.41)
Other Race /multi-race	0.03 (3.10)	0.93 (4.39)	0.08 (2.97)	0.28 (2.27)	0.18 (3.06)	0.12 (2.86)	0.02 (2.89)
ANOVA p-value	0.82	0.06	<0.01	<0.01	0.11	0.37	<0.01
Smoking							
Smoker	0.03 (2.94)	1.54 (3.74)	0.09 (2.80)	0.29 (2.29)	0.20 (2.66)	0.13 (2.64)	0.02 (2.41)
Non-smoker	0.03 (3.13)	1.55 (3.6)	0.08 (2.66)	0.26 (2.2)	0.21 (3.00)	0.14 (2.89)	0.02 (2.39)
ANOVA p-value	0.12	<0.01	<0.01	0.6	0.51	0.15	0.59
Menopausal status							
Premenopausal	0.04 (3.29)	1.68 (3.67)	0.09 (2.61)	0.28 (2.23)	0.22 (3.13)	0.15 (3.03)	0.02 (2.39)
Postmenopausal	0.03 (2.86)	1.43 (3.63)	0.08 (2.77)	0.27 (2.25)	0.20 (2.64)	0.13 (2.59)	0.02 (2.41)
ANOVA p-value	<0.01	0.10	0.79	0.01	0.01	<0.01	<0.01
Parity							
Nulliparous	0.03 (3.00)	1.45 (3.97)	0.07 (2.77)	0.26 (2.12)	0.24 (2.89)	0.16 (2.80)	0.02 (2.39)
1 live birth	0.03 (3.10)	1.77 (3.78)	0.08 (2.66)	0.28 (2.18)	0.21 (2.97)	0.14 (2.97)	0.02 (2.32)
More than 1 live birth	0.03 (3.06)	1.52 (3.56)	0.09 (2.72)	0.28 (2.29)	0.20 (2.86)	0.13 (2.75)	0.02 (2.41)
ANOVA p-value	0.55	0.15	0.35	0.17	0.16	0.08	0.21

Table 7a: Distribution of creatinine adjusted, log transformed phthalate metabolite concentrations (ug/mg), females, NHANES 1999-2006, continued

	MEHP	MEP	MBzP	MnBP	MEHHP	MEOPH	MCPP
Pearson coefficient	Coefficient (p-value)	Coefficient (p-value)	Coefficient (p-value)	Coefficient (p-value)	Coefficient (p-value)	Coefficient (p-value)	Coefficient (p-value)
Education level							
Less than high school	0.03 (3.13)	1.72 (3.67)	0.09 (2.94)	0.28 (2.29)	0.19 (2.86)	0.13 (2.75)	0.02 (2.64)
High school grad or Equivalent	0.03 (3.00)	1.67 (3.56)	0.09 (2.53)	0.28 (2.20)	0.21 (2.83)	0.14 (2.77)	0.02 (2.25)
Some college or AA degree	0.03 (3.00)	1.49 (3.71)	0.09 (2.61)	0.26 (2.14)	0.20 (2.83)	0.13 (2.75)	0.02 (2.29)
College Graduate or above	0.03 (3.16)	1.22 (3.53)	0.07 (2.69)	0.27 (2.39)	0.23 (3.03)	0.15 (2.97)	0.02 (2.41)
ANOVA p-value	0.6	0.01	0.27	<0.01	0.02	0.07	0.65
Born in US or abroad							
Born in US	0.03 (3.29)	1.48 (3.63)	0.09 (2.72)	0.27 (2.23)	0.21 (2.89)	0.14 (2.83)	0.02 (2.39)
Born in Mexico	0.03 (3.03)	2.01 (3.25)	0.07 (2.80)	0.28 (2.27)	0.18 (2.92)	0.12 (2.69)	0.02 (2.44)
Born elsewhere	0.03 (3.10)	1.65 (4.26)	0.07 (2.46)	0.34 (2.27)	0.19 (2.61)	0.13 (2.56)	0.02 (2.34)
ANOVA p-value	0.34	<0.01	<0.01	<0.01	0.02	0.08	0.03
Marital status							
Married /living with partner	0.03 (3.13)	1.49 (3.67)	0.08 (2.75)	0.26 (2.29)	0.20 (2.97)	0.13 (2.92)	0.02 (2.36)
Never married	0.03 (3.16)	1.75 (3.32)	0.08 (2.86)	0.28 (2.25)	0.23 (2.92)	0.15 (2.80)	0.02 (2.34)
Widowed, divorced, separated	0.03 (2.92)	1.58 (3.74)	0.09 (2.59)	0.30 (2.12)	0.21 (2.64)	0.14 (2.59)	0.02 (2.48)
ANOVA p-value	0.09	0.02	<0.01	0.14	0.03	0.02	<0.01
Alcohol intake							
None	0.03 (3.00)	1.52 (3.39)	0.09 (2.69)	0.26 (2.20)	0.18 (2.72)	0.12 (2.64)	0.02 (2.36)
Light (1-2 drinks/day)	0.03 (3.06)	1.52 (3.82)	0.08 (2.72)	0.27 (2.29)	0.22 (2.92)	0.14 (2.86)	0.02 (2.36)
Moderate (3-4 drinks/day)	0.03 (3.22)	1.82 (3.42)	0.10 (2.66)	0.31 (1.93)	0.21 (2.92)	0.14 (2.83)	0.02 (2.53)
Heavy (>4 drinks/day)	0.03 (3.49)	1.54 (4.10)	0.13 (2.56)	0.38 (2.29)	0.26 (2.92)	0.18 (2.89)	0.02 (2.75)
ANOVA p-value	0.68	<0.01	0.17	0.01	<0.01	0.01	0.24

Table 8. Adjusted hazard ratios and 95% confidence intervals for cancer mortality and creatinine adjusted, log transformed urinary phthalate metabolite concentration (ug/mg), males, NHANES 1999-2006

		N	Events	Model 1[a]			Model 2[b]		
				HR	95% CI LB	95% CI UB	HR	95% CI LB	95% CI UB
MEHP									
	Continuous	2359	59	0.99	0.78	1.24	0.97	0.77	1.23
	1st quartile (referent)			1.00	----	----	1.00	----	----
	2nd quartile			1.33	0.69	2.56	1.29	0.67	2.51
	3rd quartile			1.22	0.60	2.49	1.09	0.53	2.25
	4th quartile			1.09	0.50	2.37	1.06	0.48	2.33
	p-trend			0.79			0.92		
MEP									
	Continuous	2358	59	0.91	0.77	1.08	0.89	0.75	1.06
	1st quartile (referent)			1.00	----	----	1.00	----	----
	2nd quartile			0.70	0.35	1.40	0.64	0.32	1.30
	3rd quartile			0.67	0.33	1.37	0.61	0.30	1.27
	4th quartile			0.60	0.30	1.20	0.51	0.25	1.05
	p-trend			0.13			0.06		
MBzP									
	Continuous	2359	59	1.29	1.01	1.66	1.27	0.98	1.64
	1st quartile (referent)			1.00	----	----	1.00	----	----
	2nd quartile			1.45	0.70	3.02	1.30	0.62	2.74
	3rd quartile			2.16	1.07	4.38	2.23	1.09	4.55
	4th quartile			1.25	0.56	2.80	1.13	0.50	2.55
	p-trend			0.30			0.38		
MnBP									
	Continuous	1886[c]	43	1.08	0.74	1.58	1.07	0.73	1.56
	1st quartile (referent)			1.00	----	----	1.00	----	----
	2nd quartile			0.98	0.45	2.14	0.98	0.44	2.17
	3rd quartile			1.15	0.52	2.57	1.04	0.46	2.35
	4th quartile			0.73	0.29	1.83	0.69	0.27	1.76
	p-trend			0.66			0.54		
MEHHP									
	Continuous	1886[c]	43	0.90	0.68	1.19	0.92	0.70	1.21
	1st quartile (referent)			1.00	----	----	1.00	----	----
	2nd quartile			0.90	0.44	1.86	0.97	0.46	2.03
	3rd quartile			0.30	0.10	0.88	0.32	0.11	0.95
	4th quartile			0.82	0.37	1.84	0.82	0.36	1.88
	p-trend			0.21			0.23		
MEOHP									
	Continuous	1886[c]	43	0.87	0.64	1.17	0.89	0.67	1.20
	1st quartile (referent)			1.00	----	----	1.00	----	----
	2nd quartile			0.94	0.45	1.96	1.05	0.50	2.22
	3rd quartile			0.40	0.15	1.09	0.44	0.16	1.23
	4th quartile			0.83	0.37	1.88	0.82	0.35	1.88
	p-trend			0.29			0.31		
MCPP									
	Continuous	1886c	43	0.94	0.67	1.32	0.92	0.66	1.30
	1st quartile (referent)			1.00	----	----	1.00	----	----
	2nd quartile			0.54	0.22	1.33	0.56	0.22	1.42
	3rd quartile			0.87	0.40	1.88	0.87	0.39	1.91
	4th quartile			0.76	0.34	1.72	0.76	0.33	1.75
	p-trend			0.70			0.72		

[a] Age-adjusted Cox proportional hazard regression
[b] Cox proportional hazard regression, adjusted for age, BMI, ratio of family income to poverty, race, smoking, education, diabetes status, place of birth,
[c] Assessed for 3 out of 4 series

Table 9. Adjusted hazard ratios and 95% confidence intervals for cancer mortality and creatinine adjusted, log transformed urinary phthalate metabolite concentration (ug/mg), females, NHANES 1999-2006

		N	Events	Model 1[a]			Model 2[b]		
				HR	95% CI LB	95% CI UB	HR	95% CI LB	95% CI UB
MEHP									
	Continuous	2025	38	0.94	0.69	1.27	0.98	0.72	1.34
	1st quartile (referent)			1.00	----	----	1.00	----	----
	2nd quartile			0.86	0.38	1.94	0.94	0.41	2.17
	3rd quartile			0.28	0.09	0.89	0.31	0.10	1.00
	4th quartile			0.91	0.39	2.09	1.05	0.44	2.47
	p-trend			0.42			0.63		
MEP									
	Continuous	2022	37	1.06	0.83	1.35	1.07	0.84	1.37
	1st quartile (referent)			1.00	----	----	1.00	----	----
	2nd quartile			0.53	0.20	1.39	0.53	0.20	1.41
	3rd quartile			0.56	0.21	1.47	0.59	0.22	1.59
	4th quartile			1.11	0.49	2.55	1.19	0.50	2.83
	p-trend			0.66			0.54		
MBzP									
	Continuous	2025	38	0.98	0.71	1.35	1.01	0.71	1.42
	1st quartile (referent)			1.00	----	----	1.00	----	----
	2nd quartile			0.68	0.29	1.61	0.67	0.28	1.60
	3rd quartile			0.32	0.11	0.90	0.32	0.11	0.92
	4th quartile			0.76	0.34	1.70	0.82	0.36	1.88
	p-trend			0.33			0.43		
MnBP		1576[c]	26						
	Continuous			0.86	0.53	1.38	0.92	0.56	1.50
	1st quartile (referent)			1.00	----	----	1.00	----	----
	2nd quartile			1.91	0.49	7.39	2.07	0.53	8.10
	3rd quartile			1.28	0.32	5.12	1.55	0.38	6.33
	4th quartile			1.38	0.38	5.01	1.62	0.44	6.01
	p-trend			0.95			0.73		
MEHHP		1576[c]	26						
	Continuous			0.95	0.63	1.42	0.94	0.62	1.42
	1st quartile (referent)			1.00	----	----	1.00	----	----
	2nd quartile			1.15	0.41	3.23	1.15	0.40	3.29
	3rd quartile			0.66	0.21	2.05	0.66	0.21	2.07
	4th quartile			0.63	0.19	2.05	0.64	0.19	2.12
	p-trend			0.27			0.29		
MEOHP									
	Continuous	1576[c]	26	0.87	0.56	1.34	0.86	0.56	1.33
	1st quartile (referent)			1.00	----	----	1.00	----	----
	2nd quartile			1.70	0.59	4.89	1.60	0.54	4.77
	3rd quartile			0.84	0.27	2.63	0.84	0.26	2.70
	4th quartile			0.45	0.11	1.88	0.42	0.10	1.80
	p-trend			0.12			0.12		
MCPP		1576[c]	26						
	Continuous			0.91	0.56	1.45	0.90	0.55	1.49
	1st quartile (referent)			1.00	----	----	1.00	----	----
	2nd quartile			0.29	0.06	1.50	0.28	0.05	1.45
	3rd quartile			1.52	0.54	4.29	1.50	0.52	4.34
	4th quartile			0.53	0.16	1.75	0.52	0.15	1.80
	p-trend			0.79			0.84		

[a] Age-adjusted Cox proportional hazard regression

[b] Cox proportional hazard regression, adjusted for age, BMI, ratio of family income to poverty, race, smoking, education, place of birth,

[c] Assessed for 3 out of 4 series

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