



Published in final edited form as:

J Occup Environ Med. 2014 June ; 56(6): 573–578. doi:10.1097/JOM.000000000000167.

Prenatal exposure to air toxics and risk of Wilms' tumor in 0-5 year old children

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Abstract

Objective—To study prenatal air toxics exposure and Wilms' tumor in children.

Methods—We identified 337 Wilms' tumor cases among children <6 years (1988-2008) from the California Cancer Registry, randomly selected 96,514 controls from California birth rolls in 20:1 ratio matched to all cancer cases, then linked birth addresses to air monitors within 15 miles to assess exposures. Multiple logistic regressions were applied to estimate effects.

Results—Children prenatally exposed to formaldehyde, polycyclic aromatic hydrocarbons, perchloroethylene, or acetaldehyde in the third trimester had an increased odds of Wilms' tumor per interquartile increase in concentration (OR [95%CI]: 1.28 [1.12, 1.45], 1.10 [0.99, 1.22], 1.09 [1.00, 1.18], 1.25 [1.07, 1.45] respectively).

Conclusions—We found positive associations for four air toxics. This is the first study of this kind. Future studies are needed to confirm our findings.

Background

Wilms' tumor or nephroblastoma is an embryonal tumor that represents 95% of all renal cancers diagnosed in children and 6% of all cancers among children under 15 years of age, with the highest incidence during 0-5 years of age.¹ Advancements in diagnosis and treatment have dramatically improved 5-year survival rates, which are now as high as 90%.² However, treatments have short- and long-term adverse effects and little is known about disease etiology. The sporadic nature of occurrence in the majority of cases (98-99%)³ and high incidence in early childhood suggest prenatal and early childhood contributions to its etiology possibly involving environmental exposures during these periods.

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Conflict of Interest: The co-authors declare no conflict of interest.

At the molecular level, Wilms' tumor is characterized by multiple genetic and epigenetic aberrations. These include mutations in *WT1*, a tumor suppressor gene located on chromosomal band 11p13 (in < 20% of sporadic cases), and the *CTNNB1/β-catenin* gene (5-15% of cases); loss of heterozygosity (LOH) at Wilms' tumor 2 (*WT2*) locus on chromosomal band 11p15, a growth regulatory region (in up to 40% of sporadic cases); loss of imprinting (LOI) resulting in bi-allelic expression of insulin-like growth factor 2 gene (*IGF2*) in 26-77% of cases; and hypermethylation leading to silencing of *H19* genes in 26-75% of tumors without LOH. These events suggest that Wilms' tumor etiology involves factors that affect very early pregnancy or even the preconceptional period.⁴

Both animal and human studies indicate that certain air pollutants such as benzo[a]pyrene—a type of polycyclic aromatic hydrocarbon (PAH), carbon monoxide and chromium (more VI compounds than III compounds) can cross the placenta.^{5,6,7} Moreover, animal studies have shown that transplacental exposures disrupt fetal development and in humans, such exposures have been linked to adverse birth outcomes.⁸ Higher levels of ambient PAHs have been found to be associated with elevated levels of PAH-DNA adducts in blood from adults, children, and in cord blood.^{5,9,10,11,12,13} Moreover, the fetus is more susceptible than adults to various pollutants including PAHs and metals.¹⁴ Studies examining PAH- and aromatic-DNA adducts and somatic gene mutations in mothers and cord blood of newborn babies showed similar or higher adduct formation and mutations in newborns compared to mothers even though estimates from experimental studies suggested that the PAH exposure reaching the fetus is 10 times lower compared to the mothers.^{5,13,15}

Traffic-related air toxics such as benzene, benzo[a]pyrene, formaldehyde, and 1,3-butadiene have been classified by the International Agency for Research on Cancer (IARC) as human carcinogens (Group 1), and several other traffic-related toxics (e.g. ethyl benzene, dibenz[a, h]anthracene, benzo[b]fluoranthene, benzo[*l*]fluoranthene) are classified as probable (Group 2A) or possible (Group 2B) carcinogens.^{16,17,18,19} In addition, some organic solvents and heavy metals (e.g. trichloroethylene, perchloroethylene, and hexavalent chromium compounds) originating from industry in California are also classified as human carcinogens or probable or possible carcinogens by IARC. Moreover, some air toxics including formaldehyde and PAHs have pro-mutagenic or mutagenic properties, with benzo[a]pyrene being one of the more potent pro-mutagens, having the ability to convert into an atmospheric mutagen by reacting with hydroxyl (OH⁻) and nitrate radicals (NO₃⁻).^{20,21,22,23}

Occupational exposures to toxics such as formaldehyde, trichloroethylene, perchloroethylene, lead, and PAHs have been associated with increased risk of kidney and bladder cancers in adults.^{24,25,26} Studies of these pollutants' potential associations with any type of childhood cancer have been limited in number as well as by methodological approach. Some epidemiological studies observed increased risk of Wilms' tumor among children with paternal occupational exposure to hydrocarbons and lead during the preconceptional and pregnancy periods, and maternal prenatal exposure to pesticides.⁴ No studies to date have examined the relationship between exposure to any air toxics during pregnancy and Wilms' tumor development in children. In this exploratory study, we address this gap by reporting associations between various air toxic exposures during pregnancy and Wilms' tumor development in children < 6 years of age.

Methods

Study Population

We conducted a large population-based case-control study that included all incident cases diagnosed during 1988-2008 among children ages 0-5 in the California Cancer Registry (CCR).²⁷ Here, we report on Wilms' tumor cases (n=769) and controls only. Using first name, last name, date of birth, and social security number when available, we were able to match 89% of all childhood cancer cases to a California birth certificate (1986-2007). Controls, frequency matched to all cancer cases on birth year at a 20:1 ratio, were randomly selected from the California birth registry (n=209,700). Controls were cancer free up to age six or the age attained by 2008 if younger than six. Using a custom geocoder,²⁸ cases and controls were mapped based on the maternal addresses at delivery provided on birth certificates from 1998 onwards, and on zip code area of residence at birth for children born in earlier years. Each geocoded residence or zip code area was linked to the closest air monitor that met our minimum air monitoring data requirements for the pregnancy period, as discussed further below. We excluded infants with implausible birth weights (<500g, >5250g) and gestational ages (<20 weeks, > 44 weeks), and children born outside California. We restricted our analyses to subjects with residential addresses within a 15 mile radius of an air monitoring site, which was a compromise between sufficient sample size and accuracy of exposure assessment, leaving us with 337 cases diagnosed from 1990-2008, who were born between 1990 and 2007, and 96,514 controls with the same birth years. Institutional review board approvals were obtained from the University of California Los Angeles and the California Committee for the Protection of Human Subjects.

Outcome and covariate assessment

Cancer-related information including Wilms' tumor diagnosis, histology and year of diagnosis were obtained from the CCR. Cases were those assigned site group of VIa in the International Classification of Childhood Cancer, 3rd edition (ICCC-3)²⁹ and were assigned histological code of 8960/3 from the International Classification of Disease for Oncology, 3rd edition (ICD-O-3). Prenatal and perinatal data including birth weight, gestational age at birth, parental age at delivery, maternal race/ethnicity, and other demographic information were collected from birth registry records. Socioeconomic status was measured using an area-level socioeconomic status index which was created by combining seven census block group indicators: education index, median household income, percent living 200% below poverty level, percent blue-collar workers, percent older than 16 years in the workforce without a job, median rent, and median housing value.³⁰

Exposure assessment

We obtained daily (24-hour) average concentrations of air toxics measured every 12 days at monitoring sites throughout California from the California Air Resources Board (CARB). Since the start of air toxics monitoring network in major urban areas in 1985, CARB has continued to expand its list of pollutants as well as areas covered for monitoring. The CARB monitors around 60 to 70 air toxics at any given time point, although they have collected up to 189 in the past. We obtained air toxic concentration values for all pollutants monitored between 1990 and 2008 measured at 35 air monitoring sites located within 7 air basins¹, but

selected 20 air toxics *a priori* based on their classification as human carcinogens or probable or possible carcinogens as determined by IARC and the availability of sufficient air monitoring data to construct exposure estimates to examine their potential relationship with Wilms' tumor (see supplemental digital content (SDC) 1 for the complete list). To estimate pregnancy period exposures, we first calculated average air toxics concentrations corresponding to each subject's months of pregnancy (i.e., a 30 gestational day period). Trimester specific and entire pregnancy average exposures were then calculated based on the monthly average values. Trimesters were based on date of birth and gestational age from the birth certificates—first trimester (estimated first day of last menstrual period through day 90), second trimester (days 91-180), third trimester (day 181 through birth). We included one measurement in each 30 day (month) period in a given pregnancy period and since pregnancy is rarely exactly 9 months in length, at least one measurement within the last 30 days of pregnancy, to calculate average toxic concentrations for each trimester and the entire pregnancy period.

The pregnancy period average values for PAHs were calculated from the sum of average monthly values for the following six highly correlated toxics: benzo[a]pyrene, benzo[b]fluoranthene, benzo[ghi]perylene, benzo[k]fluoranthene, dibenz[a, h]anthracene, and indeno[1, 2, 3-c,d]pyrene. We also examined benzo[a]pyrene separately because it is an established carcinogen.

Data Analysis

First, we examined correlations between the 20 selected toxics within and across pregnancy periods. Next, we conducted factor analyses using varimax rotation among the control group to explore potential patterns among exposures within each pregnancy trimester and the entire pregnancy period. We relied on logistic regression models for each air toxic separately to estimate odds ratios (ORs) and 95% confidence intervals (95% CI) per inter-quartile range (IQR) increase in exposure average for each pregnancy period. Adjusted models included the following covariates selected based on literature review and directed acyclic graphs (DAGs): maternal age at delivery, parity, maternal race/ethnicity (non-Hispanic white, Hispanic of any race, other), census-based socioeconomic status (SES, 1 being of lowest level and 5 being of highest level), and birth year. We further explored associations within 10 mile and 5 mile radii to see whether exposure assessments were sensitive to buffer distance. For the toxics that showed consistent positive associations in initial analyses, we performed additional analyses: 1) adjusting for multiple air toxics, and 2) mutually adjusting for all three trimester averages – to assess whether any of the toxics or the trimester periods may emerge as most important. All analyses were carried out using SAS version 9.3 (Cary, North Carolina, USA).

Results

Demographic characteristics for cases and controls were similar except for child's sex, maternal age at child's birth, and SES. Slightly more cases (54%) were females compared to

¹Air monitors located within the following seven air basins were included in this study: Sacramento Valley, San Francisco Bay Area, San Joaquin Valley, South Central Coastal, South Coast, San Diego, and Salton Sea.

controls (49%). More mothers of cases were 30 years or older at the time of delivery (44%) compared to controls (39%). In contrast, slightly more mothers of controls belonged to the lowest SES group (28% compared to 23% among cases). Detailed demographic characteristics are presented in Table 1.

Five out of six constituents of PAHs were highly positively correlated with each other (Pearson $r = 0.82 - 0.99$) within each pregnancy period examined (only dibenz[a,h]anthracene was less highly correlated with other PAHs, Pearson $r=0.56-0.84$). Similarly, other traffic-related air toxics—benzene, 1,3-butadiene, ethyl benzene, ortho-xylene, and toluene were highly correlated with each other (Pearson $r: 0.83-0.93$) but weakly to moderately correlated (Pearson $r: -0.01-0.76$) with the rest of the toxics we examined (data not shown). In terms of pregnancy trimesters, most toxics were weakly to moderately correlated across pregnancy periods (Pearson $r: -0.26$ to 0.68 , see SDC 2). On the other hand, some toxics such as lead showed consistently moderate correlations across the entire pregnancy period (Pearson $r > 0.6$), indicating little temporal variation. Factor analysis results mirrored these correlation patterns. Three factors emerged with loadings of ≈ 0.5 that seem to represent common sources of air toxics emissions. Factor 1 mainly included traffic-related pollutants (e.g, benzene, toluene, ortho-xylene and PAH); factor 2 consisted of emissions from industrial sources such as dry cleaners, cement manufacturing, cooling towers, petroleum processing, coal and oil combustion, and sewage incineration (e.g. trichloroethylene, lead, acetaldehyde); and factor 3 of emissions representing a combination of atmospheric reaction by-products, refrigerants and pharmaceutical manufacturing, coating degreasing agents, incomplete combustion, and oil refineries (e.g. formaldehyde, chloroform). Several of the toxics are emitted by multiple sources as reflected by high loading on two separate factors (e.g. benzene, toluene, styrene from both traffic and industrial sources, and perchloroethylene coinciding with all other industrial emissions possibly due to the more distributed nature of its source i.e. the dry cleaning industry). Correlation coefficients for pregnancy periods and interquartile ranges (IQR) for each air toxic in the control group are provided in SDC 2 and 3. Factor analysis results are provided in SDC 4.

Two-thirds of all mothers (66%) resided in the South Central and South Coast Air Basins during their pregnancy. The rest represented Sacramento and San Joaquin valleys, the San Francisco Bay Area and a small number (<1%) were from the Salton Sea, Mexicali and Tijuana. The IQR values in all pregnancy periods for benzo[a]pyrene and PAHs were the highest in the San Joaquin Valley (0.40-0.45 and 2.43-2.61 nanogram per meter cubed (ng/m^3) respectively). The IQR values for formaldehyde were higher in the San Joaquin Valley (1.62-1.64 part per billion by volume (ppbV)) and in the South Coast Air Basin (1.79-1.91 ppbV). Chloroform, ortho- and para-dichlorobenzene concentrations were low (IQR values ranging from 0.01 to 0.09 ppbV) and homogeneously distributed across all sites. The South Coast Air Basin had the highest measured IQRs for the remaining toxics.

Out of 20 air toxics we examined, we report findings on four representing the three factors we identified—total PAHs, acetaldehyde, formaldehyde, and perchloroethylene. For all four toxics we estimated positive associations between exposure during the third trimester of pregnancy and Wilms' tumor with associations ranging from a 28% increase in the odds

ratio for Wilms' tumor for every interquartile increase in formaldehyde concentration (95%CI: 1.12, 1.45) to a 9% increase in the odds ratio for Wilms' tumor for perchloroethylene (95% CI: 1.00, 1.18) after adjusting for all covariates (Table 2). These positive associations were found consistently across all analyses we carried out, including models in which we restricted residential distance to air monitors to 5 and 10 mile radii as well as models in which air toxics measures for all three trimesters were considered simultaneously, however, smaller radii resulted in wider confidence intervals and slightly attenuated point estimates (data not shown). No associations were observed for first or second trimester exposures to any of the air toxics examined except for hexavalent chromium which indicated a positive association during the second trimester. However, since it is an established carcinogen, one should take this finding with caution and keep in mind that the association we observed here may be merely due to chance. Findings for the remaining toxics are provided in SDC 5.

Discussion

This is the first study to examine associations between prenatal exposure to air toxics and Wilms' tumor. From the selected 20 air toxics with known or potential carcinogenic properties, we found a small positive association with third trimester exposures to formaldehyde, acetaldehyde, PAHs, and perchloroethylene and Wilms' tumor in young children. Our findings for these specific toxics are provocative but warrant replication in other studies. Estimates did not change much when we included only women living within 5 and 10 mile radii from monitoring stations, except for a loss of precision and some attenuation in the case of perchloroethylene at the 5 mile radius. Our findings suggest that the third trimester pregnancy period may be important in the etiology for Wilms' tumor development. Findings from another recent study of ambient pollutants and childhood cancer also suggest that prenatal exposure to air pollutants may be important in development of Wilms' tumor (OR[95%CI]: 1.15[0.82,1.63]).³¹

Several air toxics, including formaldehyde and PAHs, have been implicated in DNA damage in fetuses and also been associated with increased risk of kidney cancer or kidney damage in adults (e.g. formaldehyde, hexavalent chromium, and lead).^{5,6,7,25,26,32} Moreover, some toxics including formaldehyde and PAHs have been shown to be carcinogenic with some inducing renal cancer in experimental studies.^{7,26} A few epidemiological studies have examined parental occupation-related lead exposure during preconceptional, prenatal, or postnatal periods and Wilms' tumor in children, but findings to date have been inconsistent.²⁶ It is possible that these toxics also increase susceptibility to renal cancers such as Wilms' tumor in children, particularly during early stages of life since this developmental period is believed to be more vulnerable to DNA damage and to higher absorption of toxics than in adulthood.^{5,26} The four toxics we report here are well established carcinogens and some occupational studies have shown these toxics to increase kidney cancer in adults.^{24,32} Moreover, the timing of exposure for which we observe positive associations is plausible from a developmental prospective as formation of functional kidney during fetal development is completed by week 36 of gestation.

Air toxics monitoring data show a steady decline in pollution levels over the past two decades in California.³³ However, ambient concentrations for some toxics such as formaldehyde and acetaldehyde have been constant over the years and we selected known carcinogens that continue to be of concern for human health. Incidence rates for Wilms' tumor in the US have been fairly constant for the past four decades.³⁴ Similarly, in California, annual incidence rates for kidney and renal pelvis cancer among children of ages 1-4 did not change much during this study period.³⁵ Exposures in our study were based on about 20 years of routine measurements of ambient air toxic concentrations at monitoring sites located throughout California. Therefore, these measures reflect both spatial and temporal variations in air toxics concentrations. We relied on population-based cases and controls from registries and routine monitoring only, thus minimizing both selection and recall bias.

Many toxics we examined are products of automobile combustion. However, some including benzene, formaldehyde and perchloroethylene have multiple sources of emissions (e.g. motor vehicles, oil refineries, dry cleaning, degreasing, etc.) or are by-products of atmospheric reactions (e.g. formaldehyde and acetaldehyde). Thus, both emission sources and their stability in the atmosphere determine their spatial, daily, and seasonal variation. In addition, seasonal variations in ambient concentrations allowed us to consider period specific effects during pregnancy. For example, formaldehyde concentrations peak in California during the winter and dip to their lowest levels during summer (except for in the South Coast Air Basin, where peaks occur during both winter and summer). This seasonal difference is reflected by negative correlations between the first and the third trimester concentrations for some of the air toxics. There are also some strong spatial gradients in our data, with the highest concentrations of formaldehyde measured in the South Coast Air Basin and the lowest in the San Francisco Bay Area. Benzo[a]pyrene, on the other hand, has the highest concentrations in Sacramento and the lowest in the south central coastal area. The point estimates we report here are for the entire state and thus, the positive associations we observed may reflect the outcomes driven by either populous regions or regions with very high or low concentrations of toxics. At the same time, we may have failed to find weak or moderate associations due to our limited case number.

If our findings are verified elsewhere, they may inform clean air policies designed to protect pregnant women and their fetuses. In California, air pollution standards and routine air monitoring are in place to minimize and control emission levels from vehicles and industrial sources, as well as to encourage use of more fuel efficient vehicles.³³ A steady decline in the levels of several of these ambient toxics over the past two decades could be attributed to these standards. Further reductions may be achieved by increasing access to public transportation and by continual efforts of the California state agencies especially the California Air Resources Board to revise air toxics standards according to new scientific data on health effects.

We relied on subjects residing within a 15 mile radius of the monitoring sites as a compromise between sample size and exposure misclassification concerns. For some persistent and stable or ubiquitous toxics (e.g. formaldehyde, benzene, benzo[a]pyrene, and perchloroethylene), distance from an air pollution measurement site may have only a small

impact on actual exposure while, for other toxics that are highly reactive and can rapidly convert to non-toxic by-products (e.g. 1,3-butadiene), this buffer distance may introduce bias in exposure assessment.^{21,23,36,37,38} Our study lacked information on mothers' residential location for the entire pregnancy period, which can be another source of bias in exposure assessment if many mothers in this study moved during the pregnancy period. However the 15-mile buffer makes this less likely. A recent review of 7 studies in the US found that only small number of pregnant women moved during pregnancy (9% - 32%), most of them moved during the second trimester, and the median distance of moving was <10km.³⁹ Other limitations of the study include a lack of data on indoor air quality and addresses of maternal job sites, which could reduce accuracy in exposure assessment. These factors may have resulted in confounding or additional misclassification of exposures. Finally, most sources release multiple air toxics simultaneously. Thus, some of the toxics could potentially be proxies for other unmeasured toxics originating from the same sources.

In summary, we found positive associations between Wilms' tumor in children and third trimester exposure to formaldehyde, acetaldehyde, perchloroethylene, and PAHs, all known carcinogens. In addition, the timing of exposure coincides with the final stage in kidney formation, thus supporting the early life origin of the tumor. Future studies are needed to confirm these findings, to examine exposure response associations and to identify biological mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Source of Funding: This study was funded by grants from the National Institute of Environmental Health Sciences (R21ES018960, R21ES019986, P30ES007048).

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Table 1

Frequency distribution of birth and demographic characteristics across cases and controls

Variable name	Residing within 15 miles of an air monitor	
	Cases (n=337) Frequency (%)	Controls (n=96,514) Frequency (%)
Child's gender		
Male	154 (45.7)	49165 (50.9)
Female	183 (54.3)	47349 (49.1)
Birth type		
Singleton	328 (97.3)	94014 (97.4)
Multiple birth	9 (2.7)	2500 (2.6)
Maternal age at child birth		
<20	39 (11.6)	10133 (10.5)
20-29	150 (44.5)	48628 (50.4)
30-34	101 (30.0)	23218 (24.1)
35	47 (14.0)	14524 (15.0)
Missing	0 (0.0)	11 (0.0)
Maternal race/ethnicity		
Non-Hispanic white	107 (31.8)	27079 (28.1)
Hispanic of any race	161 (47.8)	47693 (49.4)
Other (black, Asian/Pacific Islander, other)	68 (20.2)	21284 (22.0)
Missing	1 (0.3)	458 (0.5)
Parity		
Nulliparous	138 (41.0)	38540 (39.8)
One child	100 (29.7)	30119 (31.2)
Two or more children	99 (29.4)	27945 (29.0)
Census-based SES *		
1 (Lowest)	77 (22.9)	27212 (28.2)
2	78 (23.2)	22230 (23.0)
3	68 (20.2)	18235 (18.9)
4	64 (19.0)	15359 (15.9)
5 (Highest)	50 (14.8)	13445 (13.9)
Missing	0 (0.0)	33 (0.0)

PI, Pacific Islander; SES, socioeconomic status.

* Index created by combining 7 census block group indicators: education, median household income, percent living <200% poverty level, percent blue-collar workers, percent > 16 years in workforce without job, median rent, and median housing value.

Table 2

Odd ratios and 95% CIs from logistic regression models for Wilms' tumor and selected air toxics measured¹ at monitors within a 15 miles radius of mother's address at child delivery

Variable name ²	Unadjusted ³					Adjusted ⁴				
	First Trimester Cases OR (95% CI)	Second Trimester Cases OR (95% CI)	Third trimester Cases OR (95% CI)	Entire pregnancy Cases OR (95% CI)	First Trimester Cases OR (95% CI)	Second Trimester Cases OR (95% CI)	Third trimester Cases OR (95% CI)	Entire pregnancy Cases OR (95% CI)	Third trimester Cases OR (95% CI)	Entire pregnancy Cases OR (95% CI)
<i>Per interquartile range (IQR) increase in average value</i>										
Factor 1										
Polycyclic aromatic hydrocarbons ⁵ (PAH)	0.99 (0.87, 1.12)	1.06 (0.98, 1.15)	1.09 (0.99, 1.21)	1.14 (1.01, 1.30)	0.99 (0.88, 1.12)	1.06 (0.98, 1.15)	1.10 (0.99, 1.22)	1.15 (1.02, 1.31)	1.10 (0.99, 1.22)	1.15 (1.02, 1.31)
Number of cases	242	242	242	242	241	241	241	241	241	241
Factor 2										
Acetaldehyde	1.04 (0.89, 1.21)	1.04 (0.89, 1.22)	1.19 (1.02, 1.39)	1.12 (0.95, 1.32)	1.08 (0.93, 1.27)	1.08 (0.92, 1.26)	1.25 (1.07, 1.45)	1.19 (1.00, 1.40)	1.25 (1.07, 1.45)	1.19 (1.00, 1.40)
Number of cases	308	308	307	308	307	307	306	307	306	307
Perchloroethylene	0.99 (0.87, 1.13)	0.95 (0.82, 1.09)	1.08 (0.99, 1.18)	1.01 (0.86, 1.19)	1.00 (0.88, 1.14)	0.97 (0.84, 1.11)	1.09 (1.00, 1.18)	1.04 (0.88, 1.22)	1.09 (1.00, 1.18)	1.04 (0.88, 1.22)
Number of cases	304	304	304	304	303	303	303	303	303	303
Factor 3										
Formaldehyde	1.01 (0.88, 1.15)	1.04 (0.91, 1.19)	1.24 (1.10, 1.41)	1.12 (0.98, 1.27)	1.03 (0.90, 1.18)	1.07 (0.93, 1.23)	1.28 (1.12, 1.45)	1.16 (1.02, 1.32)	1.28 (1.12, 1.45)	1.16 (1.02, 1.32)
Number of cases	308	308	307	308	307	307	306	307	306	307

¹ Average values per trimester or entire pregnancy

² Units of measure: all particulates, PAH was measured in nanogram/meter cubed and the rest (all gases) were measured in part per billion by volume. Point estimates reflect odds of having Wilms tumor per inter-quartile increase in the mean concentration of the respective air toxic.

³ Adjusted for birthyear

⁴ Adjusted for the following variables: birth year, maternal age, maternal race/ethnicity, parity, census-based socioeconomic status

⁵ Includes sum of average concentrations of six hydrocarbons: benzo[a]pyrene, benzo[b]fluoranthene, benzo[k]fluoranthene, dibenz[a,h]anthracene, and indeno[1,2,3-c,d]pyrene