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Para-Dichlorobenzene Exposure Is Associated with Thyroid Dysfunction in US Adolescents

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Objective To examine the association between exposure to para-dichlorobenzene, measured as urinary concentrations of 2,5-dichlorophenol (2,5-DCP), and thyroid function in US adolescents.

Study design A nationally representative subsample of 618 adolescents aged 12-19 years in the 2007-2008 and 2011-2012 National Health and Nutrition Examination Survey was analyzed for the association of urinary 2,5-DCP with serum thyroid function measures using multivariate logistic and general linear regression models.

Results After adjusting for potential confounders, we found a significantly positive association between urinary concentrations of 2,5-DCP and serum levels of thyroid-stimulating hormone and thyroglobulin in adolescents. Furthermore, urinary 2,5-DCP was associated with an increased prevalence of hypothyroidism in the study population.

Conclusions This study demonstrates a potential relationship between para-dichlorobenzene exposure, measured as urinary 2,5-DCP, and thyroid dysfunction in adolescents; however, further studies are needed to confirm our findings and to elucidate mechanisms of action. *(J Pediatr 2016;177:238-43).*

Thyroid hormones play a vital role in many physiological processes, particularly growth and development in fetal life and childhood.[1] A growing body of evidence from human, animal, and in vitro studies has revealed that exposure to environmental chemicals could affect thyroid function through a number of potential mechanisms.[2-8] These thyroid-disrupting chemicals may trigger autoimmune thyroiditis, the most common cause of hypothyroidism, and mimic thyroid hormone action by modulating the binding of these hormones to their receptors or transport proteins, potentially leading to thyroid dysfunction.[3,4,8,9]

Para-dichlorobenzene (*p*-DCB) is a chlorinated, highly volatile organic compound that is widely used as an environmental pesticide and a room deodorant. People may be exposed to this chemical on a daily basis by inhaling vapors from *p*-DCB–containing products (up to 99%) used in the home and in public buildings, such as moth balls, some air fresheners, and toilet deodorizer blocks.[10,11] In experimental studies, exposure to *p*-DCB caused a reduction in plasma thyroxine levels in rats[12,13] and an increase in thyroid gland follicular cell hyperplasia in male mice.[14]

Limited information is available on the thyroid actions of *p*-DCB in humans. A recent study that measured endocrine actions of pesticides in adolescents aged 14-15 years residing in the Flanders region of Belgium found an association between urinary 2,5-dichlorophenol (2,5-DCP), a reliable biomarker for measuring *p*-DCB exposure,[15] and serum thyroid measures.[16] In previous studies, we found associations between urinary concentrations of 2,5-DCP and obesity, metabolic syndrome, and diabetes among participants in the US National Health and Nutrition Examination Survey (NHANES).[17-20] A significant and dose-dependent association between urinary 2,5-DCP and obesity was observed in children and adolescents.[17] In addition to our findings, other studies have reported associations between urinary 2,5-DCP and body weight measures in children and adolescents,[21] and with early age of menarche in females aged 12-17 years.[22]

These findings led us to hypothesize that exposure to *p*-DCB may affect body development, body weight, and metabolism in the growing child by disrupting endocrine function. To explore this hypothesis, we investigated the relationship between urinary concentrations of 2,5-DCP and serum thyroid function measures in adolescents aged 12-19 years who participated in the 2007-2008 and 2011-2012 NHANES. Because an underactive thyroid gland could lead to a slow rate of metabolism and subsequent obesity, we evaluated the association between urinary 2,5-DCP and underactive thyroid as well.

2,4-DCP	2,4-Dichlorophenol
2,5-DCP	2,5-Dichlorophenol
BMI	Body mass index
FT_3	Free triiodothyronine
FT_4	Free thyroxine
LOD	Limit of detection
NHANES	National Health and Nutrition Examination Survey
p-DCB	Para-dichlorobenzene
Tg	Thyroglobulin
TSH	Thyroid-stimulating hormone

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Methods

The NHANES is an ongoing cross-sectional survey of a nationally representative sample of the noninstitutionalized US civilian population conducted by the National Center for Health Statistics of the Ceneters for Disease Control and Prevention.[23] The NHANES has been conducted continuously and released in 2-year cycles since 1999. To obtain survey estimates with greater precision, we combined the 2 data collection cycles of 2007-2008 and 2011-2012 for the present study. Participants were selected using a complex multistage stratified probability sampling design. All procedures were approved by the National Center for Health Statistics' Research Ethics Review Board, and all participants provided written informed consent.

Data from different components of the NHANES, including the questionnaire, laboratory tests, and physical examination, were used in the study. Participants were interviewed and followed by a detailed physical examination and collection of urine and blood samples in a mobile examination center by trained health technicians. Urinary 2,5-DCP was measured in a random one-third subsample of the NHANES participants aged 6 years and older. For the present study, we included adolescent participants aged 12-19 years who had 2,5-DCP measurements.

Urinary concentrations of 2,5-DCP were used to determine the level of exposure to *p*-DCB. Spot urine samples were collected from study participants and stored at −20°C until analysis. The urine samples were analyzed for chlorophenols using solid-phase extraction coupled online to high-performance liquid chromatography and tandem mass spectrometry. Details of urine sample collection and analyses are provided elsewhere.[24] Urinary 2,5-DCP was detected in 97.9% of the urine samples of NHANES participants during the study period. For urinary 2,5-DCP concentrations below the limit of detection (LOD; 2.1% of participants), a value of 0.14 μg/L (LOD divided by the square root of 2) was assigned in the NHANES dataset.

Data on serum thyroid function measures, including thyroid-stimulating hormone (TSH), free thyroxine (FT_4), free triiodothyronine (FT_3), and thyroglobulin (Tg), were extracted from the dataset. The FT_3 values in traditional units (pg/mL) were converted to SI units (pmol/L) by multiplying by 1.536. The thyroid function panel was measured in serum samples using various immunoenzymatic assays as described elsewhere.[24] In 2003, the American Association of Clinical Endocrinologists' guidelines changed the normal range for TSH to 0.3-3.04 μIU/mL.[25] Based on these guidelines, in the present study underactive thyroid (hypothyroidism) was defined as serum levels of TSH >3.0 μIU/mL and FT_4 <10 pmol/L or FT_3 <3.5 pmol/L.

We considered the age, sex, race/ethnicity, poverty status, body mass index (BMI), physical activity, serum cotinine (used as a biomarker of exposure to environmental tobacco smoke), and urinary iodine of the participants as poteintial confounders. Race/ethnicity was categorized as non-Hispanic white, non-Hispanic black, Hispanic (Mexican American and other Hispanic), and other (Asian and other, including multiracial). Poverty status was classified as a family income to poverty level ratio of <1 vs ≥1. Physical activity was categorized as self-reported moderate or vigorous physical recreational activity vs none.

Statistical Analyses

Statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, North Carolina). Because the population was selected using a complex probability sample procedure, sample weights were incorporated into the analysis to obtain proper estimates and 95% CIs of estimates, according to the NHANES guidelines.[26] A multivariate general linear model was constructed to examine changes in serum thyroid function measures in association with quartiles of urinary concentrations of 2,5-DCP. Considering the highly skewed distribution of serum levels of TSH, FT_4, FT_3, and Tg, we log-transformed these values when conducting linear regression analyses. Study participants were then categorized into those with hypothyroidism, as defined earlier according to the American Association of Clinical Endocrinologists' guidelines, and those without hypothyroidism (the remaining participants). A multivariate logistic regression analysis was conducted to evaluate the association of quartiles of 2,5-DCP with hypothyroidism. The logistic and general linear models were adjusted for age, sex, race/ethnicity, poverty status, BMI, physical activity, serum cotinine, and urinary iodine. To control for urine dilution in spot urine samples, the analyses were also adjusted for urine creatinine as a covariate. Because the distributions of serum cotinine, urinary iodine, and urinary creatinine levels were highly skewed, the values of these covariates were log-transformed when adjusting as continuous variables. Results were considered statistically significant at an α level of 0.05, and all statistical tests were 2-sided.

To analyze for specificity of the association, we used another dichlorophenol compound, 2,4-dichlorophenol (2,4-DCP), which is chemically similar to 2,5-DCP, and examined associations of urinary concentrations of this compound with serum thyroid measures in the regression models as well. 2,4-DCP is used primarily as intermediate in the manufacturing of the herbicide 2,4-dichlorophenoxyacetic acid and has not been associated with metabolic disorders.[17-20,22] 2,4-DCP was detected in urine of 88.9% of the NHANES participants. Similarly, a value of 0.14 μg/L was assigned to participants with a urinary 2,4-DCP below the LOD (11.1% of participants) in the NHANES dataset. Analyses for 2,4-DCP were conducted as described above for 2,5-DCP.

Results

During the study periods of 2007-2008 and 2011-2012, a total of 789 adolescents, aged 12-19 years, had available data on 2,5-DCP. We excluded female participants who were pregnant (n = 0) and participants with missing values for any thyroid