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Associations between blood BTEXS concentrations and hematologic parameters among adult residents of the U.S. Gulf States

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ABSTRACT

Background: Studies of workers exposed to benzene at average air concentrations below one part per million suggest that benzene, a known hematotoxin, causes hematopoietic damage even at low exposure levels. However, evidence of such effects outside of occupational settings and for other volatile organic compounds (VOCs) is limited.

Objective: To investigate associations between ambient exposures to five VOCs, including benzene, and hematologic parameters among adult residents of the U.S. Gulf Coast.

Materials and methods: Blood concentrations of selected VOCs were measured in a sample of adult participants in the Gulf Long-term Follow-up Study (GuLF STUDY) during 2012 and 2013. Complete blood counts with differentials were also performed on a subset of participants (n = 406). We used these data together with detailed questionnaire data to estimate adjusted associations between blood BTEXS (benzene, toluene, ethylbenzene, o-xylene, m/p-xylene, and styrene) concentrations and hematologic parameters using generalized linear models.

Results: We observed inverse associations between blood benzene concentrations and hemoglobin concentration and mean corpuscular hemoglobin concentration, and a positive association with red cell distribution width among tobacco smoke-unexposed participants (n = 146). Among tobacco smoke-exposed participants (n = 247), we observed positive associations between blood VOC concentrations and several hematologic parameters, including increased white blood cell and platelet counts, suggestive of hematopoietic stimulation typically associated with tobacco smoke exposure. Most associations were stronger for benzene than for the other VOCs.

Conclusions: Our results suggest that ambient exposure to BTEXS, particularly benzene, may be associated with hematologic effects, including decreased hemoglobin concentration, mean corpuscular hemoglobin concentration, and increased red cell distribution width.

1. Introduction

The volatile organic compounds (VOCs) benzene, toluene, ethylbenzene, xylene, and styrene (BTEXS) are important as fuel additives, solvents, and industrial intermediates, and can be found in a diverse array of consumer products. Because these compounds are highly volatile and emission sources are widespread, they are present at detectable concentrations in most human environments, though the most common source of population exposure in the United States is tobacco smoke (ASTDR, 2010; Lin et al., 2008; Weisel, 2010). Exposures to these compounds are associated with a range of adverse health effects (ATSDR, 2007a, b; Hack et al., 2005; WHO, 2000), including hematotoxic effects of benzene exposure (ATSDR, 2007a; Galbraith et al., 2010; IARC, 2011). Briefly, benzene is metabolized to

Abbreviations: 2,5-DMF, 2,5-dimethylfuran; BTEXS, benzene, toluene, ethylbenzene, xylene, and styrene; CBC, complete blood count; CDC, Centers for Disease Control; CLIA, Clinical Laboratory Improvement Amendments; Est, effect estimate; GuLF STUDY, Gulf Long-term Follow-up Study; LOD, limit of detection; MCHC, mean corpuscular hemoglobin concentration; ln, natural log; MCV, mean corpuscular volume; NHANES, National Health and Nutrition Examination Survey; ppm, parts per million; RBC, red blood cell count; RDW, red cell distribution width; SE, standard error; VOCs, volatile organic compounds; WBC, white blood cell count

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several reactive metabolites that can damage hematopoietic progenitor cells and lead to depression of the bone marrow (Ross, 2000; Snyder and Hedli, 1996; Wang et al., 2012). This hematopoietic damage is upstream of blood cell formation and can manifest as reduced blood cell counts (cytopenia) and altered hematologic parameters, while prolonged exposure can lead to hematologic conditions including aplastic anemia, leukemia, and other hematologic cancers (ATSDR, 2007a; Galbraith et al., 2010; IARC, 2011).

Some (Koh et al., 2015; Lan et al., 2004; Qu et al., 2002), but not all (Collins et al., 1997; Swaen et al., 2010; Tsai et al., 2004), occupational studies have reported decreased blood cell counts and other hematologic abnormalities among workers exposed to benzene even at time-weighted average air concentrations at or below one part per million (ppm). The potential for hematologic effects at low occupational benzene levels raises the possibility that ambient and environmental exposures, though typically lower than occupational exposures, could produce similar effects (Bolden et al., 2015; Brugnone et al., 1998; Smith, 2010). Data on hematologic effects of ambient exposure to BTEXS, however, are very limited. In one ecological study, Lee et al. observed decreases in multiple blood cell types among children living near a petrochemical production and processing site (n = 97) compared to suburban controls (n = 95) (Lee et al., 2002). Another ecological study of 158 adult females in Taiwan found associations between distance from a freeway and abnormal white blood cell count (WBC) and hemoglobin concentration; however, the authors observed low correlations between measured air VOC concentrations and distance from freeway, suggesting that the observed associations may be at least partially due to other factors (Jeng et al., 2006). More recently, Pelallo-Martinez et al. investigated hematologic effects among children exposed to a mixture of petrochemicals across multiple industrial sites in Mexico (Pelallo-Martinez et al., 2014). The authors observed no differences in hematologic parameters across study sites, representing a range of petrochemical exposures, but did observe negative correlations between certain hematologic parameters (including blood cell counts) and urinary metabolites of benzene and toluene among children from the most highly exposed site (n = 20). These studies suggest that ambient VOC exposures may be associated with adverse hematologic effects, though the evidence to date is limited by modest sample sizes, relatively crude quantification of exposure, and little or no control for potential confounding.

This study was carried out in conjunction with the Gulf Long-Term Follow-up Study (GuLF STUDY), a prospective cohort study of individuals who participated in the *Deepwater Horizon* oil spill cleanup and comparison subjects who did not (Kwok et al., 2017). Blood concentrations of a range of VOCs, including BTEXS, were measured for a sample of Gulf state residents approximately three years after the spill to address community concerns about reports of high levels of these chemicals in some residents. Because BTEXS is rapidly metabolized and excreted (α-phase half-lives of less than an hour) (Ashley et al., 1996; Ashley and Prah, 1997), these measurements represent contemporary exposures and not exposures related to clean-up work. Complete blood counts (CBCs) with differentials were also performed on a random subset of study participants. We investigated associations between measured levels of BTEXS in blood and hematologic cell counts and parameters.

2. Methods

2.1. Study population

The GuLF STUDY is described in detail elsewhere (Kwok et al., 2017). In brief, GuLF STUDY investigators used administrative records to identify and enroll individuals who were involved in any aspect of *Deepwater Horizon* oil spill work and/or completed worker safety training in anticipation of performing spill-related work. Eligible individuals were at least 21 years of age at time of enrollment and capable of completing an interview in English, Spanish, or Vietnamese. Between March 2011 and March 2013, 32,608 participants completed a detailed telephone enrollment. All cohort members who lived in one of the Gulf States (Alabama, Florida, Louisiana, Mississippi, and eastern Texas) and spoke English or Spanish were invited to participate in a home visit; home visits were completed for 11,193 cohort members between May 2011 and May 2013. The present study includes 406 participants, oversampled for non-smokers, women, and clean-up workers, who provided additional blood samples during their home visit for measurement of VOCs and CBCs for substudies nested within the main study.

Participants provided written informed consent. The study was approved by the Institutional Review Board of the National Institute of Environmental Health Sciences. The Centers for Disease Control and Prevention's (CDC) role was limited to analysis of coded specimens and was determined to not constitute engagement in human subjects research.

2.2. Home visit and biological specimen collection

During the home visit, trained field agents interviewed participants about health status, sociodemographic and lifestyle characteristics, and other factors. These agents also collected blood samples that included 10 mL for measurement of VOCs and 2 mL for CBC. Blood samples for VOC measurement were collected using glass blood collection tubes containing potassium oxalate sodium fluoride anticoagulant that were fitted with butyl rubber stoppers, which had been pre-treated by the CDC laboratory to remove VOC residue to minimize pre-collection contamination (Chambers et al., 2005, 2008). Blood samples were stored in a 4 °C refrigerator prior to being shipped overnight on cold packs to the central study lab, where they were sent in biweekly batches to either the Centers for Disease Control and Prevention in Atlanta, Georgia for VOC analysis or to a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory for CBC analysis.

2.3. Analysis of biological samples

Blood samples were analyzed for concentrations of VOCs using previously published methods (Blount et al., 2006; Chambers et al., 2005, 2006). Briefly, investigators used isotopically labeled analog internal standardization and headspace solid phase microextraction extraction/gas chromatography/mass spectrometry (SPME/GC/MS) to measure concentrations of 46 VOCs, including BTEXS and 2,5-dimethylfuran (2,5-DMF; a biomarker of exposure to tobacco smoke) (Chambers et al., 2011; Charles et al., 2008). Limit of quantitation was defined as the concentration where both blank-level sample false positive and detection-level sample false negative results fell below 5% (Armbruster and Pry, 2008). A portion of ethylbenzene measurements were affected by a coeluting column-bleed interferent and were excluded. We excluded one participant with multiple aberrantly high blood VOC concentrations from this analysis. For all statistical analyses, we imputed blood VOC concentrations below the limit of detection (LOD) as the LOD divided by the square root of two (Lubin et al., 2004) and natural log (ln)-transformed blood BTEXS concentrations.

A central CLIA-certified laboratory carried out complete blood counts with leukocyte differential using routine clinical laboratory procedures. The following hematologic parameters were measured: red blood cell count (RBC, ×10E6/uL), hemoglobin concentration (g/dL), hematocrit (%), mean corpuscular volume (MCV, fL), mean corpuscular hemoglobin concentration (MCHC, g/dL), red cell distribution width (RDW, %), platelets (×10E6/uL), white blood cell count (WBC, ×10E3/uL), neutrophils (%), lymphocytes (%), and monocytes (%), and eosinophils (%). Derived hematologic parameters include hematocrit (the ratio of the volume of red blood cells to total blood volume), MCHC (the quotient of hemoglobin concentration divided by hematocrit), and RDW (a measure of variability of RBC size, equal to the