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Blood/air distribution of volatile organic compounds (VOCs) in a nationally representative sample

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ABSTRACT

Volatile organic compounds (VOCs) in human blood are an effective biomarker of environmental exposure and are closely linked to health outcomes. Unlike VOC concentrations in air, which are routinely collected, blood VOC data are not as readily available. This study aims to develop the quantitative relationship between air and blood VOCs by deriving population-based blood/air distribution coefficients (popKs) of ten common VOCs in the general U.S. population. Air and human blood samples were collected from 364 adults aged 20–59 years in 1999–2000 National Health and Nutrition Examination Survey (NHANES). Determinants of popKs were identified using weighted multivariate regression models. In the non-smoking population, median popKs ranged from 3.1 to 77.3, comparable to values obtained in the laboratory. PopKs decreased with increasing airborne VOC concentrations. Smoking elevated popKs by 1.5–3.5 times for aromatic compounds, but did not affect the popKs for methyl *tert*-butyl ether (MTBE) or chlorinated compounds. Drinking water concentration was a modifier of MTBE's popK. Age, gender, body composition, nor ethnicity affected popKs. PopKs were predictable using linear models with air concentration as the independent variable for both adults and children. This is the first study to estimate blood/air distribution coefficients using simultaneous environmental and biological monitoring on a national population sample. This study was also the first to determine the blood/air distribution coefficient of *p*-dichlorobenzene, a compound frequently found in indoor environments. These results have applications in exposure assessment, pharmacokinetic analysis, physiologically-based pharmacokinetic (PBPK) modeling, and uncertainty analysis.

1. Introduction

Exposures to airborne volatile organic compounds (VOCs) may cause a variety of adverse health effects including sensory irritation symptoms, allergies, asthma, neurological and liver toxicity, and cancers (Casset and de Blay, 2008; Rumchev et al., 2004). VOCs are diverse groups of volatile hydrocarbons emitted by a wide array of sources, and constitute the majority of "hazardous air pollutants (HAPs)" or "air toxics" regulated by the U.S. Environmental Protection Agency (US EPA, 1990). While, numerous studies have measured VOC concentrations in indoor and ambient air, e.g., the TEAM study and RIOPA study (Weisel et al., 2005) in the U.S., and the European EXPOLIS study (Jantunen et al., 1998), adverse effects are associated with the amount of the chemical absorbed by humans rather than the environmental concentration. A better measure of exposure is the absorbed (internal) dose determined via biological monitoring (Escher and Hermens, 2004). Blood VOCs represent the actual dose of these compounds as they pass the human absorption barrier (alveoli) and get distributed systemically, thus they are regarded as one of best surrogates of exposure to air pollution (NRC, 1991). They provide a scientifically sound basis for extrapolating dose–response relationship (Dahl, 1990), and show promising applications in clinical practice (Probert et al., 2009).

Obtaining representative measurements of blood VOCs is difficult. VOCs tend to degrade or transform quickly in the human body, e.g., the half lives ($t_{1/2}$) are only a few hours for common terpenoid, aromatic, aliphatic and chlorinated compounds (Pleil et al., 1998; Wallace et al., 1997). Furthermore, participation rates are often low because obtaining blood samples is invasive and unpleasant. Other factors may impact or confound blood VOC levels in the general population; these include age, exposure level and duration (K. Abraham et al., 2005), respiratory rate, metabolic rate, body mass, body fat (Ashley and Prah, 1997), smoking (Ashley et al., 1995), and measurement techniques (Ashley et al., 1994). With abundant monitoring (Bortnick and Stetzer, 2002) and modeling (US EPA, 2010) data available for airborne VOCs, but limited data on blood VOCs, there is a critical need for researchers to be able to estimate blood VOC concentrations using air concentrations.

Bioavailability connects blood concentrations to environmental exposures. It is defined as the fraction of the concentration of a

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chemical in contact with a body portal-of-entry that enters the systemic circulation and may interact with various target tissues and organs. Blood/air partition coefficient (K_{BA}) is an important bioavailability parameter that indicates blood/air distribution of volatile chemicals (Nong and Krishnan, 2006). K_{BA} is defined as the ratio of concentrations of a specific VOC achieved between air and human blood at equilibrium:

$$K_{BA} = C_B/C_A \quad (1)$$

where C_B = blood concentration (mg L^{-1}), and C_A = air concentration (mg L^{-1}) of the VOC. Similar to other partition coefficients, K_{BA} is unitless and often expressed as logK_{BA} (base 10). K_{BA}'s were initially measured for anesthetics, and then gradually expanded to cover over 100 endogenous VOCs in the 1970s and 1980s (Pierce et al., 1996). They are typically measured at the equilibrium of the high concentration of individual compounds or simple mixtures between air and human or animal blood in the controlled laboratories. Laboratory-based K_{BA}'s (denoted as "labK"), however, do not account for the large variability among different individuals and various air concentrations. Similar to K_{BA}, a real-world blood/air distribution coefficient can be defined as the ratio of the VOC concentrations in blood and air measured in the field. Such coefficients will allow using environmental exposure measurements to determine biological exposure without the need to conduct invasive blood sampling. To date, no study has reported distribution coefficients measured in uncontrolled environments and in a representative sample of the general population.

The 1999–2000 National Health and Nutrition Examination Survey (NHANES) measured personal exposures to and blood concentrations of VOCs in a nationally representative sample. Personal exposure is a better exposure indicator than air concentrations obtained via area sampling (indoors or outdoors), because of large temporal and spatial variations, as well as variation in amount of time humans spend in different microenvironments. Distribution coefficients of the predominant VOCs can be estimated using these datasets, which are currently the only available simultaneous measurements of airborne and blood VOCs in a population-based sample. The goal of this paper is to derive blood/air distribution coefficients (denoted as "popKs") based on the NHANES population data for common VOCs. It also seeks to compare popKs with labKs, identify physiological, behavioral and demographic determinants, and develop predictive models of popKs for estimating real-world blood VOC concentrations.

2. Methods

2.1. Sampling and analytical methods

NHANES collects health-related information including demographic, socioeconomic, physiological, and environmental questions and measurements on a two-year cycle. The Centers for Disease Control and Prevention (CDC) has detailed documentation of NHANES samples and methods (CDC, 2007). In the 1999–2000 NHANES, airborne and blood VOC concentrations were measured in a subsample of 851 persons aged 20–59 years. Personal exposure was measured using passive badge-type 3M 3520 Organic Vapor Monitors (OVM, 3M Corporation, St. Paul, MN, USA). Participants wore the badges for 48–72 h, starting when they left the mobile examination center (MEC), and ending when they returned the badges to the MEC or the field office. During the return visit, whole-blood samples were drawn for various tests, including VOC measurements. Air samples were analyzed using gas chromatography/mass spectrometry (GC/MS) for 10 VOCs: benzene, toluene, ethyl benzene, *m,p*-xylene, *o*-xylene, chloroform, trichloroethene, tetrachloroethene, *p*-dichlorobenzene and methyl *tert*-butyl ether (MTBE). Method detection limits (MDLs) ranged from 0.29 to 7.1 μg/m^3 for a nominal 48-h sampling period (Weisel et al., 2005). Details of sample collection and laboratory analyses were described in CDC's technical report (CDC, 2005) and a previous study (Chung et al., 1999a,b). Blood VOC concentrations were measured using headspace solid-phase microextraction (SPME) followed by GC/MS analysis (Blount et al., 2006). The analyses targeted 16 VOCs, 10 of which were the same as those measured in air. Detection limits were below 50 ppt (pg/mL) for a majority of the VOCs tested. Protocols for recruitment, field sampling and laboratory analysis were approved by the NHANES Institutional Review Board (Protocol #98-12).

2.2. Data sources and data cleaning

Data and documentation were acquired from the 1999–2000 NHANES database (http://www.cdc.gov/nchs/nhanes/nhanes1999-2000/nhanes99_00.htm). Personal exposure data were obtained from the "Lab 21 Volatile Organic Compounds" dataset, which also contained housing and personal characteristics that might influence personal exposures. The blood VOC concentrations were obtained from "Lab 04 Volatile Organic Compounds in Blood and Water". Demographic variables were extracted from the "DEMO" dataset. These datasets were merged by the respondent sequence number. The merged dataset had a total of 851 participants, of which 182 were non-respondents (i.e., weight = 0) and were then excluded. Outliers were excluded by examining the probability distributions (Jia et al., 2008). We excluded 23 respondents from Lab 21 dataset, including 14 with measurements of all the 10 VOCs missing, 2 with extremely high ethylbenzene and toluene concentrations ($>2000\ \mu g\ m^{-3}$), and 7 with insufficient sampling durations (<2000 min). We also excluded 294 respondents that had missing measurements for all the 10 VOCs in the Lab 04 dataset. The final dataset had 364 respondents, representing 81,757 weighted observations.

2.3. Statistical analyses

All statistical analyses employed sampling weights and sampling design variables to take into account the complex, multistage, probability sampling design of NHANES (CDC, 2009). Measurements below the method detection limits (MDLs) were replaced with MDLs/$\sqrt{2}$ (CDC, 2005, 2006). Detection frequencies (DFs) were calculated as percentages of detectable concentrations in samples. Probability distributions of VOC concentrations were identified and confirmed using Anderson-Darling tests in Crystal Ball® (Decisioneering, Inc., Denver, CO, USA).

Blood/air distribution of VOCs was quantified as the ratio of blood to air concentrations for each VOC in NHANES. To distinguish between experimentally determined coefficients and those inferred from population-based observations, we use the term "population-based blood/air distribution coefficient" (popK) for a coefficient derived from the population data, as the population-based blood/air distribution is likely to be more relevant to exposure estimations of members of the general population. To avoid large uncertainty in undetectable values, popKs were calculated based on VOC concentrations above the MDLs in both air and blood samples. The numbers of such air and blood sample pairs varied from 11 to 256, depending on VOC species. The exclusion of missing, undetectable and outlier measurements did not change the demographic distribution of the retained population (Table A1). Determinants of popKs were identified using weighted regression analyses. The potential determinants included air concentration (measured as personal exposure), drinking water concentration (for MTBE and chloroform), gender, age, body mass index (BMI), body weight, race/ethnicity, and smoking status. PopKs and concentrations were log-transformed (base = 10) in regression analyses as they generally showed lognormal distributions (see Results and discussion). Accordingly, predictive models of