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Development/verification of methods for measurement of exhaled breath and environmental e-vapor product aerosol

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ABSTRACT

Concerns have been raised about the potential health effects of potential bystander exposure to exhaled aerosols from e-vapor products (EVPs). An exhaled breath collection system (EBS) was developed and analytical methods were verified for collection and analysis of exhaled breath from users of EVPs. Analytical methods were adapted and verified for collection of environmental air samples during EVP use in an exposure chamber. Analysis of constituents in exhaled breath focused on nicotine, propylene glycol, and glycerin (because these are reported as the major constituents in EVPs) and selected carbonyl compounds (acetaldehyde, acrolein, and formaldehyde). Analysis of environmental samples included nicotine, propylene glycol, glycerin, 12 volatile organic compounds (VOCs), 15 carbonyl compounds and 4 metals. The EBS and analytical methods used were found to be suitable for collection and analysis of the target constituents in exhaled breath. Environmental sampling for background levels of VOCs and carbonyl compounds found only acetone, acetaldehyde, benzene, ethylbenzene, formaldehyde, isoprene, methyl ethyl ketone, hexaldehyde, propionaldehyde, and toluene above the limit of quantification in some samples. None of the targeted metals were detected. Background levels of VOCs and carbonyl compounds were consistent with levels previously reported for ambient air.
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1. Introduction

Concerns have been raised about the potential health effects of potential bystander exposure to exhaled aerosols from e-vapor products (EVPs; also known as e-cigarettes or ENDS – electronic nicotine delivery systems) (Riker et al., 2012; Lippi et al., 2014; Offermann, 2014; Torjesen, 2014; Hess et al., 2016). In order to understand every possible situation that an individual could be exposed to exhaled EVP aerosol (e.g., car, home, etc.) numerous controlled studies would need to be conducted. Conducting numerous experimental studies to address each situation where human exposure to exhaled EVP aerosol could occur is inefficient and unlikely to provide necessary information in a timely manner. The US Environmental Protection Agency (EPA) has utilized various modeling approaches when evaluating ambient or indoor air quality concerns (EPA, 2016a, b). Initial efforts of modeling exhaled EVP aerosols (Burstyn, 2014) have used various assumptions based upon EVP emissions generated using machine puffing (Offerman, 2015) or used estimates of the amount of a specific chemical (nicotine) that might be in the exhaled EVP aerosol (Colard et al., 2015). Based upon sensitivity analysis in their modeling work, Colard et al. (2015) concluded that the amount of exhaled constituent was the most important parameter when modeling potential aerosol exhaled from EVP use.

A few studies (Long, 2014; Marko and Grimalt, 2015; St. Helen

Abbreviations: DNPH, 2,4-dinitrophenylhydrazine; EBS, exhaled breath collection system; EC, exposure chamber; EPA, U.S. Environmental Protection Agency; EVP, e-vapor product; GC-FID, gas chromatograph equipped with a flame ionization detector; GC-MS, gas chromatography with mass spectrometry; HPLC-UV, high performance liquid chromatography with ultraviolet detection; HVAC, heating, ventilation, air conditioning; ICP-MS, inductively coupled plasma mass spectrometry; IPA, isopropyl alcohol; ISO, International Organization for Standardization; LOD, limit of detection; LOQ, limit of quantification; PG, propylene glycol; R^2, coefficient of determination; SIM, selective ion monitoring.

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et al., 2016; Gallart-Mateu et al., 2016) quantified selected constituents in the exhaled breath of EVP users. Long (2014) collected three replicate exhaled breath samples from 10 subjects who used two different disposable EVPs and measured water, glycerin, nicotine, and selected phenolic and carbonyl compounds by modifying a method used for collection of cigarette smoke with an exhaled breath collection system (EBS). The method required vacuum assistance due to the pressure drop of the collection system, which used a single filter to collect water, glycerin, nicotine, and selected phenolic compounds while dual 2,4-dinitrophenyhydrazine (DNPH)-coated filters were used to collect selected carbonyl compounds. Marko and Grimalt (2015) reported using the Bio-VOCs exhaled air sampler (Markes International Ltd., Llantrisant, UK) to study volatile organic compounds (VOCs) in exhaled breath of EVP users. They accounted for potential metabolic differences between subjects by measuring constituents in exhaled breath 20 min after EVP use. With a single inhalation from an EVP, the concentration of exhaled constituents declines with each subsequent breath due to dilution. For modeling purposes, the breath that is immediately exhaled by EVP users is most relevant for potential exposure to exhaled EVP aerosol. To determine the retention of nicotine, propylene glycol (PG), and glycerin in 13 EVP users, St. Helen et al. (2016) collected their exhaled breath in three gas-washing bottles connected in series, and they also collected blood samples. They determined that 93.8%, 91.7%, and 84.4% of the inhaled nicotine, propylene glycol, and glycerin were retained, respectively. Other investigators studied EVP aerosols generated using machine puffing and hypothesized the potential exposure to exhaled EVP aerosols neglecting the effect of aerosol deposition in the respiratory tract of the EVP users (McAuley et al., 2012; Pellegrino et al., 2012; Zhang, et al., 2012; Czogala et al., 2014; Bekki et al., 2014; Geiss et al., 2015). Schripp et al. (2013) indicated that consideration of exhaled EVP aerosol is critical for determining its potential influence. Other investigators incorporated respiratory tract deposition into their studies by reporting levels of selected constituents from environmental samples collected in a room where EVP use had occurred (Romagna et al., 2012; Czogala et al., 2014; Ballbe et al., 2014; Schober et al., 2014; Maloney et al., 2016). Some studies also measured biomarkers in individuals exposed to exhaled aerosol from EVP users (Flouris et al., 2012; 2013; Tzatzarakis et al., 2013) or lung function (Chorti et al., 2012). Yet, none of the available studies provide a combined measurement of constituent levels in the immediately exhaled breath of EVP users together with constituent levels in the environmental air of a room with EVP users that can be used for modeling purposes.

In support of a planned clinical trial, the purpose of this work was to develop and verify simplified sampling methods for the detection of selected chemical constituents in the exhaled breath of EVP users and in environmental air from a room with EVP users. The clinical trial was designed to collect exhaled breath and environmental sampling data for modeling the potential exposure to exhaled aerosols from EVP users. Details of the clinical trial are reported separately (Sarkar et al., 2017; Rostami et al., 2016).

2. Material and methods

Sampling techniques were developed, and analytical methods were adapted, to measure selected constituents in the exhaled breath of experienced adult EVP users. Collection efficiency of the selected constituents was determined using mainstream EVP aerosol generated by a smoking machine. The feasibility of environmental sampling during 3 h was assessed in an office space using a smoking machine to generate EVP aerosol prior to performing environmental sampling at the clinical trial site. Based upon this feasibility work, a new derivatization method was developed and verified to improve the recovery and detection of aerosolized glycerin in ambient air. The environmental sampling techniques and improved analytical methods were employed at the clinical trial site to collect environmental air samples for measurement of selected constituents in a room at several time points during 4 h of prescribed and *ad lib* EVP use. The clinical trial site was a mobile environmental exposure chamber (EC; Inflamax Research Inc., Ontario, Canada) that was located in the warehouse of Highpoint Clinical Trial Center located in High Point, NC. The EC was a mobile, self-contained (having an independent and controllable heating, ventilation, air conditioning [HVAC] system) unit measuring 113 m^3 (6.25 × 6.25 × 2.89 m; width × length × height). Similar exposure chambers have been used in human allergen exposures (Bernstein et al., 2012; Meyer et al., 2013; Patel et al., 2013). All work was performed by Enthalpy Analytical, Inc. (Durham, NC) as a subcontract to the clinical contractor Inflamax Research Inc. All samples were analyzed using reference methods accredited by the Louisiana Department of Environmental Quality to the National Environmental Laboratory Accreditation Conference Standard. The reference methods used in this study included (1) Compendium Method TO-11A, Determination of Formaldehyde in Ambient Air Using Adsorbent Cartridge Followed by High Performance Liquid Chromatography (HPLC) [Active Sampling Methodology] (EPA, 1999a); (2) EPA Draft Method 325B, Volatile Organic Compounds from Fugitive and Area Sources (EPA, 2015); (3) EPA Method 18, Measurement of Gaseous Organic Compound Emissions by Gas Chromatography (40 CFR Part 60, Appendix A) (EPA, 1991); (4) EPA Method 29, Determination of Metals Emissions from Stationary Sources (EPA, 1992).

2.1. Exhaled breath collection

The EBS consisted of an RTube™ (Respiratory Research, Austin, TX) connected to dual, in series, filter holders, each containing a Respirgard II™ filter. The RTube™ portion of each EBS was cooled by an insulated aluminum jacket that had been kept on dry ice for at least 10 min prior to sample collection. The following chemical compounds were targeted for measurement because they have been reported as major constituents in the exhaled breath from EVP users: nicotine, PG, glycerin, acetaldehyde, acrolein, and formaldehyde. Two separate collections were performed. The first collection used the EBS with uncoated Respirgard II™ filters for nicotine, PG, and glycerin. The second collection was for carbonyl compounds using the EBS with the Respirgard II™ filters that had been pretreated with DNPH, which was used in other studies to collect carbonyl compounds (Moldoveanu and St. Charles, 2007; Moldoveanu et al., 2007).

In order to determine collection efficiency of the EBS, machine-generated mainstream aerosol samples from EVPs were first collected using validated methods. For all testing of the EBS, EVPs were smoked using an SM450 20-port linear analytical smoking machine (Cerulean Inc., Richmond, VA). Consistent with previous work (Flora et al., 2016), the puffing regime was one puff every 30 s with a duration of 4 s and a puff volume of 55 mL collected using a constant flow rate “square” wave profile. Aerosol was generated from the prototype device Green Smoke® EVP (Nu Mark LLC, Richmond, VA; 2.4% nicotine, 43.7% PG and 43.7% glycerol, 10% water, and 0.2% proprietary formulation) with 50 puffs taken on each new, unused device, which was fully charged before use and weighed before and after each set of 50 puffs.

Analyte yields obtained from a smoking machine were used as the basis in determining the target analyte recovery efficiency of the EBS. To simulate exhaled aerosol from EVP use, zero-grade compressed air was pushed through the ventilation hole of the prototype Green Smoke® EVP, which caused aerosol to exit the

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