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Characterization of potential impurities and degradation products in electronic cigarette formulations and aerosols

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ABSTRACT

E-cigarettes are gaining popularity in the U.S. as well as in other global markets. Currently, limited published analytical data characterizing e-cigarette formulations (e-liquids) and aerosols exist. While FDA has not published a harmful and potentially harmful constituent (HPHC) list for e-cigarettes, the HPHC list for currently regulated tobacco products may be useful to analytically characterize e-cigarette aerosols. For example, most e-cigarette formulations contain propylene glycol and glycerin, which may produce aldehydes when heated. In addition, nicotine-related chemicals have been previously reported as potential e-cigarette formulation impurities. This study determined e-liquid formulation impurities and potentially harmful chemicals in aerosols of select commercial MarkTen® e-cigarettes manufactured by NuMark LLC. The potential hazard of the identified formulation impurities and aerosol chemicals was also estimated. E-cigarettes were machine puffed (4-s duration, 55-mL volume, 30-s intervals) to battery exhaustion to maximize aerosol collection. Aerosols analyzed for carbonyls were collected in 20-puff increments to account for analyte instability. Tobacco specific nitrosamines were measured at levels observed in pharmaceutical grade nicotine. Nicotine-related impurities in the e-cigarette formulations were below the identification and qualification thresholds proposed in ICH Guideline Q3B(R2). Levels of potentially harmful chemicals detected in the aerosols were determined to be below published occupational exposure limits.

1. Introduction

The U.S. Food and Drug Administration (FDA) recently established a list of harmful and potentially harmful constituents (HPHCs) for currently regulated tobacco products (e.g., cigarettes) (FDA, 2012a). FDA guidance defined harmful and potentially harmful constituents as "any chemical or chemical compound in a tobacco product or in tobacco smoke: a) that is or potentially is inhaled, ingested, or absorbed into the body; and b) that causes or has the potential to cause direct or indirect harm to users or non-users of tobacco products" (FDA, 2011). Subsequently, a list of more than 90 HPHCs was communicated (FDA, 2012a).

However, there is a lack of in-house laboratory capabilities, a potential for large and unmanageable testing volumes in contract laboratories, and a lack of validated analytical test methods for all of the HPHCs listed on the established list (FDA, 2012a). Therefore, FDA published an abbreviated HPHC list for initial regulatory reporting requirements (FDA, 2012b). The abbreviated list comprises constituents for which analytical methods were thought to be established and which represent several different chemical classes. Table 1 shows the abbreviated list of HPHCs that are initially required by FDA to be reported for cigarette smoke and cigarette filler (i.e., tobacco that is a component of a cigarette).

FDA requires reporting the quantities of all HPHCs on the abbreviated list for a regulated tobacco product. Currently, the regulated tobacco products that require HPHC reporting are cigarettes (smoke and tobacco filler), smokeless tobacco, and roll-your-own tobacco.

E-cigarettes, also referred to as electronic nicotine delivery systems or e-vapor products, are gaining popularity in the U.S and other global markets. FDA (2014) published a proposed deeming rule that would extend the agency's regulatory authority to include e-cigarettes; at this time in manuscript preparation (June 2015), the

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Abbreviations

ACGIH	American Conference of Governmental Industrial Hygienists
B[a]P	benzo[a]pyrene
BLOQ	below the limit of quantitation
CFP	Cambridge filter pads
CO	carbon monoxide
CORESTA	Cooperation Centre for Scientific Research Relative to Tobacco
CRM	CORESTA-recommended method
DFG	Deutsche Forschungsgemeinschaft
DNPH	2,4-dinitrophenylhydrazine
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
GC	gas chromatography
GC-MS	gas chromatography-mass spectrometry
HCI	Health Canada Intense
HPHC	harmful and potentially harmful constituent
IC-CD	ion chromatography with a conductivity detector
ICP-MS	inductively coupled plasma mass spectrometry
ICH	International Conference on Harmonisation
ISO	International Organization for Standardization
LC-MS/MS	liquid chromatography-tandem mass spectrometry
LOD	limit of detection
LOQ	limit of quantitation
MDPH	Massachusetts Department of Public Health
MS/MS	tandem mass spectroscopy
NIOSH	National Institute of Occupational Safety and Health
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
NNN	N-nitrosonornicotine
NSRL	No Significant Risk Level
OEHHA	Office of Environmental Health Hazard Assessment
OSHA	Occupational Health and Safety Administration
PEL	permissible exposure limit
RfC	reference concentration
SIM	selected ion monitoring
SPE	solid-phase extraction
TLV	threshold limit value
TSNA	tobacco specific nitrosamine
TWA	time-weighted average
UPLC-MS/MS	ultra performance liquid chromatography-tandem mass spectrometry
UV	ultraviolet
VOC	volatile organic compound
WHO	World Health Organization

rule is under review and has not yet been finalized. E-cigarettes are available in both disposable and rechargeable formats. The rechargeable devices have either a refillable or disposable cartridge. When a user puffs on an e-cigarette, a liquid is heated, aerosolized, and inhaled. E-cigarette formulations (often called e-liquids) typically contain propylene glycol and/or glycerin, water, nicotine, and flavors.

The number of publications focusing on the chemical characterization of e-cigarette formulations and aerosols is increasing. Most studies seek to identify impurities in the formulation such as tobacco specific nitrosamines (TSNAs) and nicotine-related impurities (Cobb et al., 2010; Trehy et al., 2011; Westenberger, 2009), while other studies focus on identifying potentially harmful chemicals in the aerosol such as carbonyl compounds, volatile organic compounds (VOCs), TSNAs, metals, and silicates (Goniewicz et al., 2014; Tayyarah and Long, 2014; Williams et al., 2013).

Table 1
Abbreviated list of HPHCs in cigarette smoke and cigarette filler (FDA, 2012b).

HPHCs in cigarette smoke	HPHCs in cigarette filler
Acetaldehyde	Ammonia
Acrolein	Arsenic
Acrylonitrile	Cadmium
4-Aminobiphenyl	Nicotine (total)
1-Aminonaphthalene	NNK
2-Aminonaphthalene	NNN
Ammonia	
Benzene	
Benzo[a]pyrene	
1,3-Butadiene	
Carbon monoxide	
Crotonaldehyde	
Formaldehyde	
Isoprene	
Nicotine (total)	
NNK	
NNN	
Toluene	

HPHC, harmful and potentially harmful constituents; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N-nitrosonornicotine.

Additionally, a recent study investigated the impact of design parameters such as battery output voltage on the generation of potentially harmful chemicals such as carbonyl compounds in the e-cigarette aerosol (Kosmider et al., 2014).

One of the objectives of this research was to determine and quantify potential impurities and degradation products in the formulations and aerosols of four e-cigarettes (rechargeable with disposable cartridges) manufactured by Nu Mark LLC, an Altria company, and sold as MarkTen®. The other objective was to conduct a risk assessment analysis of these e-liquid formulation impurities and aerosol chemicals. Because the regulation of e-cigarettes has not yet been promulgated and no specific HPHC list exists for e-cigarette formulations and aerosols, this study focused on measuring chemicals that are listed for cigarette tobacco and smoke on the abbreviated HPHC list published by FDA (2012b) (Table 1) as well as chemicals identified in publications focused on analytical characterization of e-cigarette liquid formulations and aerosols (Cheng, 2014; Cobb et al., 2010; Etter et al., 2013; FDA, 2012b; Goniewicz et al., 2014; Kosmider et al., 2014; Tayyarah and Long, 2014; Trehy et al., 2011; Uchiyama et al., 2013; Westenberger, 2009; Williams et al., 2013).

2. Methods

2.1. E-cigarette test products

Four commercial e-cigarette products available in the U.S. marketplace (at the time of manuscript preparation) produced by Nu Mark LLC (an Altria company) under the MarkTen® brand name were included in all analytical evaluations. The commercial products were the MarkTen® Menthol and Classic sold in Indiana and Arizona during the first quarter of 2014, and all contained 1.5% nicotine by weight. The average nicotine delivery for these devices was 29 μg/puff under the machine smoking conditions discussed below and shown in Table 5 (4 s puffs, 55 mL puff volume, puffed in 20 puff increments to battery exhaustion).