Chemical Research in Toxicology

pubs.acs.org/crt Article

Emerging Chemicals of Health Concern in Electronic Nicotine Delivery Systems

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Cite This: Chem. Res. Toxicol. 2020, 33, 2637−2646

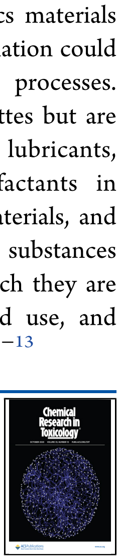
ABSTRACT: Electronic nicotine delivery systems (ENDS), by virtue of their highly engineered construction (plastics, glass, e-liquids), may contain a number of emerging chemicals of concern (ECCs), including phthalates, phenolic compounds, and flame retardants. Current knowledge regarding the safety of ENDS may underestimate the health risks from ECCs. In this study, we examined the types and levels of those three groups of chemicals in the components and parts of ENDS devices, including refill liquids, tanks/cartridges, atomizers, drip tips/mouthpieces, and sealing materials. Our results suggest that phthalates were the most prevalent chemicals in all tested samples, followed by parabens and organophosphate flame retardants (OPFRs). Particularly, all measured chemicals had significantly higher detection rates in cartridges/tanks, drip tips/mouthpieces, and sealing materials in contrast to e-liquids and coil samples. Among all those three types of ENDS components, phthalates generally had the highest concentrations (0.279−3790 ng/unit) in the drip tip/mouthpiece samples, followed by the sealing materials (0.380−508.8 ng/unit) and the empty tank/cartridge samples (up to 761.7 ng/unit). For parabens, highest concentrations were observed in drip tip/mouthpiece samples (1.152−130.1 ng/unit), followed by sealing materials (0.220−30.08 ng/unit) and the tank/cartridge samples (1.794−34.24 ng/unit). For OPFRs, tris(1,3-dichloro-2-propyl) phosphate had the highest concentrations (39.40−774.1 ng/unit) in all component samples. High concentrations (20.25−260.4 ng/unit) were also observed for several OPFRs in sealing materials and drip tip/mouthpiece samples. These findings will contribute to addressing the information gaps pertinent to the presence of ECCs in ENDS and will warrant further studies for understanding the potential negative health effects and to what extent those chemicals may cause potential negative health effects when using the ENDS. The findings will also contribute to developing evidence-based standards for the regulatory control of the types and levels of ECCs in ENDS products.

1. INTRODUCTION

Electronic nicotine delivery systems (ENDS) have been promoted and are often perceived by consumers as "safer" products than combustible tobacco products (e.g., cigarettes) in part because of lower toxic levels observed in ENDS aerosols compared with those identified in cigarette smoke.[1] ENDS are increasingly used in the United States (US)[2] and worldwide,[3] and they have especially become very popular with young people over the past few years.[4,5]

Current debate regarding the safety of ENDS has focused on the toxicants known to be present in cigarettes[6] that are absent or substantially reduced in ENDS (e.g., nitrosamines, polyaromatic hydrocarbons (PAHs), volatile organic compounds (VOCs), nitrogen oxides (NOxs), CO).[6] This may underestimate long-term novel health risks posed by several other types of emerging chemicals of health concern (ECCs), such as phthalate plasticizers, phenolic compounds, and flame retardants. The concern that ENDS may contain a number of ECCs arises from the engineered construction of ENDS devices. It specifically builds on the following observations: (1) ENDS are highly engineered and contain plastic parts (e.g., cartridge, mouthpieces, and sealing materials); (2) there is potential contamination of e-liquids by ECCs along the manufacturing and distribution process from production to sale; and (3) there is contamination of nonplastics materials used in ENDS, i.e., glass and metal parts. Contamination could also occur during manufacturing and packaging processes. Those ECCs are not typical in combustible cigarettes but are widely used as plasticizers, flame retardants, lubricants, preservatives, antifoaming stabilizers, and surfactants in plastics, electronics, medical devices, packaging materials, and other consumer goods.[7−11] Because many of these substances are not chemically bonded to the materials in which they are present, they can leach or outgas with time and use, and consequently, this can lead to human exposure.[7,11−13]

Received: July 15, 2020
Published: September 3, 2020



https://dx.doi.org/10.1021/acs.chemrestox.0c00281
Chem. Res. Toxicol. 2020, 33, 2637−2646

Identification of ECCs in consumable goods has prompted concerns about subsequent human exposure, and a number of studies have documented that ECC exposures are associated with adverse health outcomes, including carcinogenic activity, neurotoxicity, endocrine disruption, and reproductive and developmental abnormalities.[14−24] To date, information regarding the presence of ECCs in ENDS is limited to only a few studies.[25−29] Chung et al.[27] detected moderate to elevated levels of polybrominated diphenyl ethers (PBDEs), a class of flame retardants, in 5 out of the 13 ENDS aerosol samples. For instance, the level of BDE-47 in one brand was >180 ng/mL. The authors also made the argument that the potential source may be the PBDEs leaching from ENDS atomizers and the associated protective casing.

The Chung findings are lent further relevance by our recent study in which we found ENDS users had the highest detection rates for the metabolites of organophosphate flame retardants (OPFRs) in urine samples from the National Health and Nutrition Examination Survey (NHANES) during 2013−2014.[26] Among the measured metabolites, significantly higher urinary metabolite levels of tris(2-chloroethyl) phosphate (TCEP) were observed in ENDS users than in nonusers (p = 0.0124). TCEP is regarded as toxic and carcinogenic.[20,23] Limited data related to ENDSs in the NHANES precluded a full evaluation of other ECC biomarkers in ENDS users. Considering similar exposure pathways, co-occurrence of ECCs in ENDSs is possible and forms the main hypothesis to be examined in this research.

In this study, we examined phthalate plasticizers, phenolic compounds, and organophosphate flame retardants in the components and parts of ENDS devices, including refill liquids, tanks/cartridges, atomizers, drip tips/mouthpieces, and sealing materials. While further research is still needed to assess the potential adverse health effects that might be associated with the use of ENDS that contain ECCs in their components, the analytical results obtained in the present study will contribute to addressing the information gaps pertinent to the presence of ECCs in ENDS and to the development of evidence-based standards to regulate the types and levels of ECCs in ENDS.

2. EXPERIMENTAL PROCEDURES

2.1. Reagents and Standards. Native reference standards, including dibutyl phthalate (DBP), diethyl phthalate (DEP), di-2-ethylhexyl phthalate (DEHP), benzylbutyl phthalate (BBP), diisononyl phthalate (DiNP), di-*n*-octyl phthalate (DNOP), diisodecyl phthalate (DiDP), bis(2-butoxyethyl) phthalate (DBEP), dihexyl phthalate (DHP), di(2-ethylhexyl) terephthalate (DEHTP), dimethyl phthalate (DMP), di(isononyl) cyclohexane-1,2-dicarboxylate (DINCH), tris(1,3-dichloro-2-propyl)phosphate (TDCPP), tris(2-chloroethyl)phosphate (TCEP), tris(1-chloro-2-propyl)phosphate (TCPP), bis(1,3-dichloro-2-propyl)phosphate (BDCPP), tricresyl phosphate (TMPP), diphenyl phosphate (DPhP), triphenyl phosphate (TPhP), tributyl phosphate (TnBP), tri-isobutyl phosphate (TiBP), triethyl phosphate (TEP), tripropyl phosphate (TPP), tris(2-ethylhexyl)phosphate (TEHP), tris(2-butoxyethyl)phosphate (TBOEP), tris(2,3-dibromopropyl)phosphate (TDBPP), 2-ethylhexyl diphenyl phosphate (EHDPP), resorcinol bis(diphenyl phosphate) (RDP), tris(2,3-dibromopropyl)phosphate (TDBPP), trabromobisphenol A (TBBPA), and isotope labeled standards, including DHP-d4, DBP-d4, DEP-d4, DMP-d4, and DCHP-d4, were purchased from AccuStandard (New Haven, CT, USA). Native standards, including, methyl-, ethyl-, propyl-, and butyl-parabens, and isotopically labeled compounds, including TDCPP-d15, TPrP-d12, BBP-d4, TBP-d27, TEP-d51, TCPP-d18, TDBPP-d15, TPhP-d15, TCEP-d12, TBOEP-d27, butyl-d9, methyl-d4, and ethyl-d5 parabens, were purchased from Toronto Research Chemicals (North York, ON, Canada). All chemicals were used without further purification. Liquid chromatography−mass spectrometry (LC−MS) grade water, acetonitrile, methanol, formic acid, ammonium format, and USP-grade PG/VG were purchased from Fisher Scientific (Fairlawn, NJ, USA). Artificial saliva was purchased from Pickering Laboratories, Inc. (Mountain View, CA). TruView LC−MS Certified Glass inject vials were purchased from Waters (Milford, MA, USA). SPE (C18, 100 mg) columns were bought from Biotage (Charlotte, NC, USA). The Kinetex EVO C18 column (100 mm × 2.1 mm, particle size 2.6 μm) was purchased from Phenomenex (Torrance, CA, USA).

2.2. ENDS Samples. There are many types of ENDS products, and the product designs and materials used largely vary across brands. It is expected that types and levels of ECCs in ENDS products will largely vary across brands as well. We selected the brands of ENDS available in the US market based on the survey data from the Population Assessment of Tobacco and Health (PATH) Study,[2,30] with combination of the latest available report on sales of ENDS products in the US,[31] and purchased them either in local retail stores or online commercial sources during the period from October 2018 to January 2020. The brands that were reviewed and examined included VUSE, JUUL, NJOY, MarkTen, Halo Cigs, Mister-E-Liquid, Green Smoke, JoyeTech, Vaporfi, South Beach, White Cloud, Vapor4Life, KangerTech, Innokin, Aspire, ELeaf, ePuffer, Envii, VaporFi, Veppo, RI e-Cig & Vapes, and Element Vape. For each product, we only analyzed one manufacturer lot. Therefore, we did not examine lot-to-lot variability in this study. Samples were logged into a custom database categorized, kept in their original packages, and stored in Ziploc bags in a refrigerator (4 °C) until analysis. While not all types of brands were examined in this study, we believe that the results obtained by analyzing those most common brands available in US market will be meaningful for understanding the presence (types and levels) of ECCs in ENDS.

2.3. Standards and Sample Preparation. *2.3.1. Standard Solution Preparation.* The protocols for the preparation of the standard working solutions followed the International Conference on Harmonization guidelines[32] and common procedures described elsewhere.[25,33−35] Briefly, calibrators, quality control (QC) samples, and internal standard solution were prepared from serial dilutions of primary stock solutions with 60% methanol in water, and these solutions were stored in Teflon-capped amber glass vials at −20 °C. Twelve-point calibrators were prepared for each analyte encompassing concentrations ranging from 0.001 to 500 ng/mL. Three levels of QC samples, with their concentrations ranging from 0.15 to 500 ng/mL, were used to evaluate the accuracy of the results. A mixed spiking solution of 50 ng/mL for all internal standards was prepared and used for all analysis. Samples with concentrations exceeding the upper calibration standard were diluted, reprepared, and reanalyzed.

2.4. Sample Preparation. *2.4.1. E-Liquid Sample Preparation.* Detailed sample preparation protocol for measuring ECCs in e-liquids was reported in a previous study by Wei et al.[25] Briefly, 50 μL of internal standard solution (50 ng/mL for each isotope labeled standard) was first added into each LC injection vial. Then, 50 μL of each sample (e.g., e-liquids, QCs, calibrators, and laboratory control blanks) and 400 μL of methanol and water (v/v 60:40) were transferred into the same vial. After gently mixing, 10 μL of each sample was injected into the LC system.

2.4.2. Sample Preparation for Refillable Empty Cartridge/Tank, Coils, and Sealing Components. PG was used as the matrix to extract potential ECCs on ENDS parts, including refillable empty cartridges/tanks, coils, and sealing materials that have direct contact with e-liquids. Using PG as an extraction solvent provides comparable, although not fully identical, characteristics with e-liquids, in terms of solvent strength and extraction capability. We added and recorded the maximum volume of PG into each empty cartridge/tank sample along with 50 μL of internal standard solution. Coils and sealing materials were separately extracted with 5 mL of PG and 50 μL of internal standard solution. There is no standard testing method for quantifying ECCs presented on ENDS parts. Extraction was performed at room temperature for a duration of 30 min. This duration is similar to the

Table 1. Description of the E-Liquid Samples[a]

brand name	flavor	PG/VG	country of origin
ElementVape — A	American Red Premium American Tobacco	PG	USA with foreign ingredients
ElementVape — B	Vortex Vanilla Graham Custard	PG	USA with foreign ingredients
ElementVape — C	Kiwi Melon	30/70	MV Enterprises LLC, DBA OG Eliquids, USA
ElementVape — D	Blue Raspberry	20/80	JRU Inc., USA
ePuffer — A	Appletini	70/30	USA
ePuffer — B	Grape	70/30	USA
ePuffer — C	Menthol	70/30	USA
ePuffer — D	New London	70/30	USA
JoyTech — A	Tropical Blend	40/60	MyVapors Liquids, USA
JoyTech — B	Menthol	40/60	MyVapors Liquids, USA
JoyTech — C	Tobacco	40/60	MyVapors Liquids, USA
JoyTech — D	Orange Cream	40/60	MyVapors Liquids, USA
JUUL — A	Classic Tobacco	PG/VG	JUUL, USA
JUUL — B	Fruit	PG/VG	JUUL, USA
JUUL — C	Mint	PG/VG	JUUL, USA
JUUL — D	Mango	PG/VG	JUUL, USA
HaloCigs — A	Cherry	PG	Nicopure Laboratories LLC, USA
HaloCigs — B	Berry Blend	PG	Nicopure Laboratories LLC, USA
HaloCigs — C	Mint menthol	PG	Nicopure Laboratories LLC, USA
HaloCigs — D	Smooth Tobacco	PG	Nicopure Laboratories LLC, USA
Low Vis Liquids — A	Overcast	20/80	USA
Low Vis Liquids — B	Stratus	20/80	USA
MigCigs — A	It is Nuts	50/50	MigVapor, USA
MigCigs — B	Tobacco with a kick	50/51	MigVapor, USA
MigCigs — C	Caribbean Freeze	50/50	MigVapor, USA
Mister-E-Liquid — A	Psychobilly	30/70	Mister-E-Liquid LLC, USA
Mister-E-Liquid — B	Mister-E's Menthol	67/33	Mister-E-Liquid LLC, USA
Mister-E-Liquid — C	Neptune	67/33	Mister-E-Liquid LLC, USA
Mister-E-Liquid — D	Blue Voodoo	67/33	Mister-E-Liquid LLC, USA
Mister-E-Liquid — E	Dime Piece	67/33	Mister-E-Liquid LLC, USA
Mister-E-Liquid — F	Gray Matter	67/33	Mister-E-Liquid LLC, USA
RI e-Cig & Vapes — A	Tobacco	50/50	USA
RI e-Cig & Vapes — B	Grape Frost	50/50	USA
RI e-Cig & Vapes — C	Menthol	50/50	USA
RI e-Cig & Vapes — D	The Berg	30/70	InneVape Laboratories USA, USA
South Beach Smoke — A	unflavored	70/30	USA
South Beach Smoke — B	unflavored	70/31	USA
South Beach Smoke — C	unflavored	70/32	USA
VaporFi — A	flavoring ingredients listed, not specified	50/50	VaporFi, USA
VaporFi — B	flavoring ingredients listed, not specified	50/50	VaporFi, USA
VaporFi — C	flavoring ingredients listed, not specified	50/50	VaporFi, USA
Vapor4Life — A	Oasis	PG/VG, ratio not specified	USA
Vapor4Life — B	Refreshmint	PG/VG, ratio not specified	USA
Vapor4Life — C	Grape	PG/VG, ratio not specified	USA
Veppo — A	Tobacco	PG	China
Veppo — B	Menthol	PG	China
Veppo — C	My Burro	PG	China
White Cloud — A	Regular	PG/VG, ratio not specified	China
White Cloud — B	What a Melon	PG/VG, ratio not specified	White Cloud Electronic Cigarettes, USA
White Cloud — C	Cin	PG/VG, ratio not specified	China
White Cloud — D	Menthol	PG/VG, ratio not specified	China
The House of Vapor — A	Menthol Sensation	PG/VG, ratio not specified	The House of Vapor LLC, USA
The House of Vapor — B	Tobacco	PG/VG, ratio not specified	The House of Vapor LLC, USA
The House of Vapor — C	Ghostberry	PG/VG, ratio not specified	The House of Vapor LLC, USA

[a]Descriptions include brand name, flavor types, PG/VG ratio, and country of origin. Samples were purchased during the period from October 2018 to January 2020.

time used for the quantification of bisphenol A in plastic bottles in the ASTM standard method (D 7574-09).[36] Based on the actual sample volume, an appropriate volume of HPLC grade water was added to dilute the sample, yielding a maximum percentage of <15% for total organic constituents (mainly PG) in the solution. This is important to obtain a sufficient recovery on subsequent SPE extraction.[25] Samples were gently vortex-mixed and loaded onto SPE cartridges, equilibrated with 1.0 mL of methanol, 1.0 mL of acetonitrile, and 1.0 mL of water, and the solutions were pushed through the SPE under approximately 1.0 psi positive pressure. Samples were subsequently washed with 1.0 mL of water and 1.0 mL of methanol and water (v/v 15:85). After being dried for 15 min with nitrogen (25 psi), the samples were eluted with 1.0 mL of methanol, collected in 1.5 mL LC injection vials, and evaporated under a gentle nitrogen stream to dryness. The residuals were reconstituted in 100 μL of methanol and water (v/v 50:50) prior to analysis.

2.4.3. Sample Preparation for Drip Tips/Mouthpieces. Artificial saliva was used as the matrix to extract ECCs on ENDS drip tips/mouthpieces. We chose to use artificial saliva mainly because of the comparable characteristics with those of human saliva. It is also important to note that background levels of ECCs in artificial salvia can be well-controlled. To prepare the sample, each mouthpiece was put into 15 mL of artificial saliva and extracted for 30 min at a temperature of 37 °C, which is comparable to human body temperature. Extracted mouthpiece samples went through the same, complete SPE cleanup procedures for extracted ENDS component samples, except that artificial saliva extraction samples were not diluted with water prior to SPE cleanup.

2.5. Instrumentation Analysis. All pretreated samples were chromatographically resolved using a Kinetex EVO C18 column on a Shimadzu UPLC system (Columbia, MD, USA) and were analyzed by a Sciex triple quadrupole 6500+ mass spectrometer with a TurboIonSpray source (Foster City, CA, USA) under the conditions described in a previous study by Wei et al.[25] Analyst software (version 1.7.0) was used for chromatographic data acquisition, and MultiQuant (version 3.0.3) was employed to process the analytic data and to quantitate the sample concentrations. Calibration curves were constructed using peak area ratios of analytes to corresponding internal standards for each batch via linear least-squares regression with a $1/x$ weighting factor.

2.6. Quality Control and Quality Assurance Measures. The following quality control (QC) and quality assurance (QA) measures were used during the entire study period to ensure the reliability of the analytical data: (a) Calibration standard solutions were stored ≤−20 °C, and the calibration curves were evaluated every three months using standard solutions prepared from secondary production lots; (b) calibrators, QC samples, and laboratory control blanks were prepared and analyzed following the same preparation and analysis procedures used for the unknown samples in each analytical batch. Blank controls are especially vital when analyzing ECCs which could present in many common laboratory consumables and instruments. In addition to including blank control samples in each batch, efforts to minimize the contamination during analysis included using prescreened high purity solvents and using pretested glassware; (c) QC samples were prepared in PG or artificial saliva to correct for potential matrix effects, and sample concentrations were calculated using 12-point curves. (d) Instruments were evaluated to maintain high sensitivity prior to each batch analysis; (e) the following parameters were characterized to ensure the data quality, including retention time, ion ratio (qualitative/quantitative peak area), and acceptable thresholds (e.g., blank contamination, extreme concentration, calibration linearity, QC concentration range, and carry over).

3. RESULTS

3.1. Detection Rates and Characteristics. *3.1.1. E-Liquid Samples.* For e-liquid samples (detailed sample information provided in Table 1, n = 54), phthalates, including DMP, DBP, and DEP, were the most prevalent chemicals whose concentrations were at or higher than their limits of detection (LODs) (hereafter called detection rate) (Figure 1A). Other phthalates such as BBP, DCHP, DAP, and DEHP were detected in 6.3−28.6% of the samples. Among OPFRs measured in this study, TEP had the highest detection rate (44.4%) in e-liquids, followed by EHDPP (30.2%) and TBOEP (25.4%). Detection rates for other OPFRs were <21%. For parabens, methyl paraben was detected in 20.6% of e-liquid samples, followed by ethyl paraben (17.5%) and propyl paraben (3.2%). Butyl paraben was not detected in any samples.

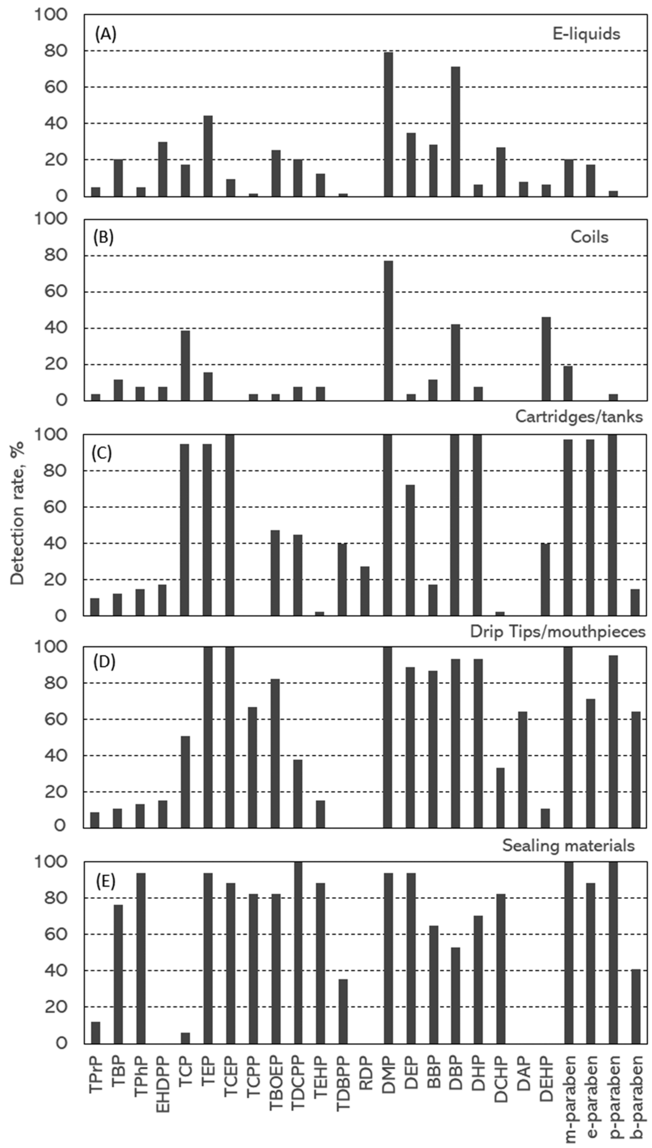


Figure 1. Detection rates of ECCs in e-liquids, cartridges/tanks, coils drip tips/mouthpieces, and sealing materials.

3.1.2. Coil Samples. For coil extraction samples (n = 20), phthalates were the most frequently detected chemicals. DMP had the highest detection rate of 76.9%, followed by DEHP (46.2), DBP (42.3%), DHP (7.7%), and DEP (3.8%) (Figure 1B). Neither DCHP nor DAP was detected in any samples. Among OPFRs, TCP had the highest detection rate of 38.5%, followed by TBP which was detected in 11.5% of the samples. Detection rates for other OPFRs were ≤11.5%. For parabens, only methyl- and propyl-parabens were detected in <20% samples.

3.1.3. Cartridges/Tanks. For cartridges/tanks (n = 40), phthalates including DMP, DBP, and DHP were detected in all extraction samples, followed by DEP and DEHP which were detected in 72.5 and 40% of samples (Figure 1C). Methyl-, ethyl-, and propyl-parabens were detected in ≥97.5% samples.

https://dx.doi.org/10.1021/acs.chemrestox.0c00281
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Table 2. Description of ENDS Products[a]

				component tested			
product description	purchase source	manufacturer	manufacturer location	drip tip	sealing material	coil	cartridge/ tank
Ultimo atomizer	JoyeTech.com	Joyetech Electronics Co., Ltd.	China	√	√	√	√
ProCore X atomizer	JoyeTech.com	Joyetech Electronics Co., Ltd.	China	√	√	√	√
ProCore Aries atomizer	JoyeTech.com	Joyetech Electronics Co., Ltd.	China	√	√	√	√
Topbox Mini Platinum	Kangeronline.com	KangerTech Technology Co., Ltd.	China	√			√
Subtank Mini-C	Kangeronline.com	KangerTech Technology Co., Ltd.	China	√	√		√
Toptank Mini/Topfill	Kangeronline.com	KangerTech Technology Co., Ltd.	China	√			√
CLOCC	Kangeronline.com	KangerTech Technology Co., Ltd.	China			√	
Clear Cartomizer	Kangeronline.com	KangerTech Technology Co., Ltd.	China				√
CC Clear Cartomizer	Kangeronline.com	KangerTech Technology Co., Ltd.	China				√
Dual Coil Unit	Kangeronline.com	KangerTech Technology Co., Ltd.	China			√	
Seal ring	Kangeronline.com	KangerTech Technology Co., Ltd.	China		√		
Mini Protank 3/EVOD Glassomizer	Kangeronline.com	KangerTech Technology Co., Ltd.	China	√			√
Refillable Mini Tank	Whitecloudcigs.com	White Cloud Electronic Cigarettes	China	√			√
Nord Pod	HaloCigs.com	Shenzhen IVPS Technology Co., Ltd.	China			√	√
Reactor Subohm Tank	HaloCigs.com	Nicopure Laboratories	USA	√			√
Journey to Infinity/K Lite Tank, Aspire	HaloCigs.com	Shenzhen Eigate Technology Co., Ltd.	China	√			√
Suorin Air Cartridge	HaloCigs.com	Shenzhen Bluemark Technology Co., Ltd.	China				√
Nautilus XS Tank Kit	Aspirecig.com	Shenzhen Eigate Technology Co., Ltd.	China	√	√	√	√
Nautilus XS (Mesh Coil)	Aspirecig.com	Shenzhen Eigate Technology Co., Ltd.	China			√	
K1 BVC Glassomizer	Aspirecig.com	Shenzhen Eigate Technology Co., Ltd.	China	√			
Breeze 2 Pod	Aspirecig.com	Shenzhen Eigate Technology Co., Ltd.	China				√
Lemo Drop atomizer	eleafus.com	iSmoka	China	√			√
iJust 2 atomizer	eleafus.com	Eleaf Electronics Co., Ltd.	China	√		√	√
Lyche atomizer	eleafus.com	Eleaf Electronics Co., Ltd.	China	√	√	√	√
Melo 4 atomizer	eleafus.com	Eleaf Electronics Co., Ltd.	China	√	√	√	√
Ello Duro atomizer	eleafus.com	Eleaf Electronics Co., Ltd.	China	√	√	√	√
GS Drive atomizer	eleafus.com	Eleaf Electronics Co., Ltd.	China	√			√
Rotor atomizer	eleafus.com	Eleaf Electronics Co., Ltd.	China	√	√	√	√
Nord Pod	Vaprzon.com	Shenzhen IVPS Technology Co., Ltd.	China				√
ROLO Badge Pod	Vaprzon.com	Shenzhen IVPS Technology Co., Ltd.	China				√
SMOK, Fit Kit	Vaprzon.com	Shenzhen IVPS Technology Co., Ltd.	China				√
Cobble Replacement Pod	Vaprzon.com	Shenzhen Eigate Technology Co., Ltd.	China				√
AVP (Mesh Coil)/Journey to Infinity/ AVP Pod	Vaprzon.com	Shenzhen Eigate Technology Co., Ltd.	China				√
Suorin Vagon Cartridge	Vaprzon.com	Shenzhen Bluemark Technology Co., Ltd.	China				√
Suorin Air	Vaprzon.com	Shenzhen Bluemark Technology Co., Ltd.	China				√
Suorin ishare	Vaprzon.com	Shenzhen Bluemark Technology Co., Ltd.	China	√			
Zero Pod	Vaprzon.com	Renova Vaporesso	China				√
Teros	Vaprzon.com	Joyetech Electronics Co., Ltd.	China				√
eGo AIO	VaporFi.com	Joyetech	China	√	√	√	√
Wotofo Profile unity RTA, nexMESH	VaporFi.com	Shenzhen Wotofo Technology Co., Ltd.	China	√			√
Go Max, Multi-Use Disposable Tank	VaporFi.com	Shenzhen Innokin Technology Co., Ltd.					√
vSIX Subohm Tank	VaporFi.com	VaporFi	China	√		√	
Crown IV Tank Checkmate	VaporFi.com	Shenzhen UWELL Technology Co., Ltd.	China	√	√	√	
Herakles III 24	VaporFi.com	Cigreat		√	√	√	

https://dx.doi.org/10.1021/acs.chemrestox.0c00281
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Table 2. continued

product description	purchase source	manufacturer	manufacturer location	component tested: drip tip	sealing material	coil	cartridge/tank
FreeMax, Fireluke M	VaporFi.com	Shenzhen Freemax Technology Co., Ltd.	China	√	√	√	
Zlide	VaporFi.com	Shenzhen Innokin Technology Co., Ltd.	China	√	√	√	
Scion II	VaporFi.com	Shenzhen Innokin Technology Co., Ltd.	China	√			
Hakutaku/Sxmini	VaporFi.com	YiHitech	China	√	√		√
Drip Tips	The House of Vapor		China	√			
Super Tank Mini Resin Tip	The House of Vapor		China	√			
Resin Tip	The House of Vapor			√			
Drip Tip Blue	The House of Vapor			√			
Profile Drip Tips Black	The House of Vapor			√			
Drip Tip	The House of Vapor			√			
Regis Mini Kit	The House of Vapor	Geekvape Technology Co., Ltd.		√			√
Kroma-A Zenith Kit	The House of Vapor	Shenzhen Innokin Technology Co., Ltd.	China	√			
Smoov	The House of Vapor	The House of Vapor	USA	√		√	√
Amulet Pod	The House of Vapor	Shenzhen UWELL Technology Co., Ltd.	China				√
Nord Pod	The House of Vapor	Shenzhen IVPS Technology Co., Ltd.	China	√			√
EQ Pod	The House of Vapor	Shenzhen Innokin Technology Co., Ltd.	China	√			
Arco HorizonTech Tank	The House of Vapor	Shenzhen Horizon Technology Co., Ltd.	China	√	√		

[a]Descriptions include product name, purchase source, manufacturer, country of production, and specific testing components. Samples were purchased during the period from October 2018 to January 2020.

Butyl-paraben was only detected in 15% of extraction samples. Among OPFRs, TCEP had the highest detection rate of 100%, followed by TCP (95%) and TEP (95%). Detection rates for other OPFRs were in the range 2.5–40%.

3.1.4. Drip Tip and Mouthpiece Samples. For drip tips/mouthpiece samples (Table 2, n = 41), parabens had the highest average detection rate among those three groups of chemicals, ranging from 64.4 to 100% (Figure 1D). DMP, DBP, DHP, BBP, and DEP were detected in above 86% of all extraction samples, and other phthalate analytes were detected in 11.1–64.4% of samples. Among OPFRs, TEP and TCEP were detected in all samples, followed by TBOEP, TCPP, TCP, and TDCPP which had the detection rates of 82.2, 66.7, 51.1, and 37.8%, respectively. Detection rates for EHDPP, TPhP, TBP, and TPrP were in a range 8.9–15.6%. Neither TDBPP nor RDP was detected in any samples.

3.1.5. Sealing Materials. For sealing samples (Table 2, n = 17), the trends for the detection rates for those three types of chemicals were similar to those for the drip tip/mouthpiece samples (Figure 1E). Parabens (methyl-, propyl-, and ethyl-parabens) had the highest average detection rate of 82.4%, followed by OPFRs (58.4%) and phthalates (57.4%).

3.2. Concentrations and Comparisons. For e-liquid samples (detailed sample information provided in Table 1), as the detection rates for the majority of the analytes were below 40%, except for TEP, DMP, and DBP, only blank-corrected 75% percentiles and maximum concentration values are presented (Table 3). Despite the general low detection rates, we observed that the concentrations of some chemicals in e-liquids can be remarkably high. For instance, the highest concentrations for TBOEP, TEHP, TDCPP, DMP, DCHP, DEHP, ethyl-, and propyl-parabens were all above 140 ng/mL. DBP, which was detected in 71.4% of e-liquids, had a median concentration of 149 ng/mL and a maximum concentration of 3539 ng/mL in those tested samples.

Because detection rates in those ENDS component samples, including cartridges/tanks, drip tips/mouthpieces, and the sealing materials, except for coil samples, were generally higher in contrast to those of e-liquid samples, blank-corrected 25%, 50%, and 75% percentiles and the maximum values with detection rates of >50% are presented in Tables 4 and 5. Among those three types of ENDS components, phthalates generally had the highest concentrations (0.279–3790 ng/unit) in the drip tip/mouthpiece samples (Table 4), followed by the sealing materials (0.380–508.8 ng/unit) and the empty tank/cartridge samples (<LOD–761.7 ng/unit). Similarly, for parabens, highest concentrations were observed in drip tip/mouthpiece samples (1.152–130.1 ng/unit), followed by sealing materials (0.220–30.08 ng/unit) and the tank/cartridge samples (1.794–34.24 ng/unit) (Table 4). Among those OPFRs measured in this study, TDCPP had the highest concentrations (39.40–774.1 ng/unit) in all ENDS component samples (Table 5). High concentrations (20.25–260.4 ng/unit) were also observed for TCEP, TBOEP, TEP, TBP,

Table 3. Blank-Corrected Percentiles for Phthalate and Paraben Concentrations in E-Liquid Samples (ng/mL)

	detection rate	percentile			
	%	25%	50%	75%	maximum
TPrP	4.8			0.153	0.271
TBP	20.6			7.995	44.03
TPhP	4.8			4.119	4.619
EHDPP	30.2			0.736	6.218
TCP	17.5			0.476	7.703
TEP	44.4			5.413	32.65
TCEP	9.5			0.938	10.25
TCPP	1.6			54.61	54.61
TBOEP	25.4			44.28	214.1
TDCPP	20.6			75.81	202.6
TEHP	12.7			151.2	241.0
TDBPP	1.6			17.37	17.37
RDP	0.0				
DMP	79.4	0.195	2.493	2.493	228.4
DEP	34.9			53.46	1825
BBP	28.6			2.979	52.92
DBP	71.4	11.03	149.1	149.1	3539
DHP	6.3			1.181	3.010
DCHP	27.0			67.39	155.9
DAP	7.9			0.270	0.304
DEHP	6.3			85.30	135.7
m-Paraben	20.6			3.598	1040
e-Paraben	17.5			10.26	149.0
p-Paraben	3.2			109.9	146.1
b-Paraben	0.0				

TPhP, and TEHP in sealing materials and drip tip/mouthpiece samples. Concentrations for TPrP, EHDPP, TCP, TDBPP, and RDP were generally <10 ng/unit in those four types of ENDS component samples.

4. DISCUSSION

Considering the highly engineered characteristics of ENDS which contain plastic, glass, and metal parts, as well as e-liquids which are packaged in similar materials, on the basis of our preliminary study, we performed this study and tested the hypothesis that ECCs, e.g., phthalate plasticizers, phenolic compounds, and flame retardants, that have been widely identified in consumable goods, are present in ENDSs. There is still limited research on types and levels of ECCs in ENDS, although a number of studies have documented other harmful or potentially harmful constituents (HPHCs),[6] e.g., metals, PAHs, VOCs, and TSNAs, in ENDS/e-liquids/aerosols. This study fills this information gap for the first time by examining the types and levels of ECCs in ENDS.

The samples under each brand/category were purchased first on the basis of popularity, and those with the highest user self-reported prevalence were considered and selected. As the main goal of the present study is to examine the presence (types and levels) of ECCs in ENDS, we did not evaluate whether specific ingredients (e.g., flavors and nicotine) in e-liquids are potential sources of ECCs, mainly because the types and levels of the ingredients utilized by different manufactures are diversified and, to some extent, complicated. Given available resources, we were unable to purchase and assay sufficient samples, especially those flavored products, to categorize and evaluate the influences of different flavors on the types and levels of ECCs. Eliminating the flavored products and only measuring nonflavored ones would not reflect the main portion of ENDS use.

In addition to aforementioned limitations, in this study, we did not evaluate whether the presence of those ECCs, regardless of their levels in ENDS products, will eventually lead to adverse health consequences in ENDS users. However, previous epidemiological and toxicological studies have shown that many of those measured ECCs are potentially endocrine disrupting chemicals (EDCs) which can mimic or interfere with the hormone functions even at low levels, consequently resulting in many adverse health consequences, including carcinogenic activity, neurotoxicity, endocrine disruption, and reproductive and developmental abnormalities.[14−24] Previously, we observed that there are significant associations between exposure to ECCs and the sex hormone levels in the general US population.[24] For instance, we observed that the adjusted geometric means of serum sex-hormone-binding globulin increased by more than 36% in female children and

Table 4. Blank-Corrected Percentiles for Phthalate and Paraben Concentrations in ENDS Extraction Samples (ng/Unit)

		phthalate								paraben			
		DMP	DEP	BBP	DBP	DHP	DCHP	DAP	DEHP	methyl	ethyl	propyl	butyl
empty tank/cartridge	25%	2.015	1.394		82.43	0.082				1.196	0.055	0.480	
	50%	4.815	5.418		144.8	0.119				3.840	0.092	1.273	
	75%	22.76	16.45	1.476	261.5	0.167			0.317	6.793	0.338	3.270	0.281
	max	333.5	82.79	5.962	761.7	0.504	39.26		0.756	34.24	1.843	14.63	1.794
coil	25%	0.139			4.310								
	50%	0.229			10.41					0.274			
	75%	0.674		2.760	24.30	0.484			0.326	0.378			
	max	5.492	1.531	2.840	510.7	0.560			0.470	0.904		0.467	
drip tip/mouthpiece	25%	2.696	2.068	0.212	20.85	0.095		0.034		26.06	0.094	0.352	0.030
	50%	9.874	5.208	0.340	42.97	0.143		0.058		28.14	0.230	0.765	0.055
	75%	21.58	11.75	0.600	62.31	0.253	18.38	0.110	2.447	32.75	0.398	3.427	0.083
	max	3790	75.64	3.344	275.4	2.583	32.64	0.279	2.759	130.1	1.152	78.32	2.851
sealing material	25%	5.858	1.799	0.167	6.646	0.141	3.701			6.549	0.130	1.800	
	50%	10.21	5.685	0.218	9.229	0.185	7.491			12.42	0.313	2.706	
	75%	40.77	19.87	0.558	16.32	0.282	10.12			15.88	0.422	5.386	0.128
	max	508.8	58.80	0.940	17.85	0.380	17.99			30.08	1.468	15.39	0.220

https://dx.doi.org/10.1021/acs.chemrestox.0c00281
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Table 5. Blank-Corrected Percentiles for OPFR Concentrations in ENDS Extraction Samples (ng/Unit)

	percentile	TPrP	TBP	TPhP	EHDPP	TCP	TEP	TCEP	TCPP	TBOEP	TDCPP	TEHP	TDBPP	RDP
coil	25%													
	50%			1.718										
	75%		0.573	2.039	1.170	0.046	0.202				597.1	88.67		
	maximum	0.004	0.769	2.359	1.250	0.143	0.513		35.50	24.69	774.1	110.8		
empty tank/cartridge	25%					0.043	0.410	0.050						
	50%					0.083	0.563	0.116						
	75%	0.044	2.520	0.500	0.449	0.176	1.374	0.213		8.865	26.08	1.938	0.135	0.355
	maximum	0.107	22.55	1.973	2.633	1.717	7.827	2.547		25.80	39.39	1.938	0.802	3.214
sealing material	25%		0.104	0.215				0.256	3.582	5.047	50.21	8.816		
	50%		0.124	0.562			5.036	0.345	8.177	13.07	106.8	14.10		
	75%	0.008	0.274	0.790			13.52	0.435	10.04	21.14	181.2	19.58	0.592	
	maximum	0.008	2.684	1.180		0.055	25.11	64.42	12.80	38.66	226.3	38.87	0.870	
drip tip/mouthpiece	25%					0.009	0.480	0.254	1.413	5.394				
	50%					0.032	1.271	0.412	6.963	14.41				
	75%		1.070	1.256	0.163	0.101	2.604	0.643	10.50	32.78	63.38	12.65		
	maximum	0.021	14.01	20.25	0.180	0.623	33.38	115.6	21.39	260.4	287.1	25.92		

female adolescents from the first to fourth quartiles of the urinary levels of diphenyl phosphate (DPhP), a metabolite of TPhP, bis(1,3-dichloro-2-propyl) phosphate (BDCPP), a metabolite of TDCPP, and dibutyl phosphate (DBuP), a metabolite of TBP. We also found that the adjusted GMs of serum estradiol (EST) decreased by more than 64% in female children and adolescents from the first to fourth quartiles of the urinary DBuP levels. As such, the findings obtained in this research warrant further toxicological and epidemiological studies for understanding the negative health effects and to what extent those chemicals may cause negative health effects when using the ENDS.

In June 2009, the FDA acquired the authority to regulate the manufacture, marketing, and distribution of cigarettes and smokeless and roll-your-own tobacco products to protect public health. In May 2016, the FDA extended its jurisdiction to all tobacco products, including ENDS, which gives the agency authority over the manufacturing, marketing, and distribution of e-cigarettes.[37] There is significant concern about the adverse health outcomes that are found to be associated with ECCs exposure.[14−22] The results of this study, specific to the types and levels of ECCs in different ENDS components, and of our previous work on biomarkers[26] indicate that ENDS can be a source of exposure to ECCs. Although specific guidelines are not in place for regulatory control of the types and levels of ECCs in ENDS products, authorities have begun to regulate certain ECCs in consumer and industrial goods. For instance, in 2012, the FDA's Center for Drug Evaluation and Research (CDER) released guidelines on the use of dibutyl phthalate (DBP) and di(2-ethylhexyl) phthalate (DEHP) in CDER-regulated drug and biologic products.[9] This and future research can contribute to the development of the evidence-based standards for the regulatory control of the types and levels of ECCs in ENDS. Given emerging data, ENDS manufacturers should evaluate their manufacturing and packaging practices and minimize or eliminate ECCs from their products.

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Funding

The research in this study was performed in Dr. Wei's laboratory at Roswell Park Comprehensive Cancer Center and was supported by the National Institute of Environmental Health Sciences (NIEHS) and the US FDA Center for Tobacco Products (CTP) (NIH Grant No. R21 ES030028). The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies.

Notes

The authors declare the following competing financial interest(s): M.L.G. received a research grant from Pfizer and served as a member of the scientific advisory board to Johnson&Johnson.

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https://dx.doi.org/10.1021/acs.chemrestox.0c00281
Chem. Res. Toxicol. 2020, 33, 2637−2646