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Vaped Humectants in E-cigarette are a Source of Phenols

Rachel El-Hage^{†,§}, Ahmad El-Hellani^{†,§}, Rola Salman^{‡,§}, Soha Talih^{‡,§}, Alan Shihadeh^{‡,§}, Najat Aoun Saliba^{†,§,*}

[†] Chemistry Department, Faculty of Arts and Sciences, American University of Beirut, Beirut, Lebanon

[‡] Mechanical Engineering Department, Maroun Semaan Faculty of Engineering and Architecture American University of Beirut, Beirut, Lebanon

[§] Center for the Study of Tobacco Products, Virginia Commonwealth University, Richmond, Virginia, USA

Abstract

Electronic cigarettes (ECIGs) have always been promoted as safer alternatives to combustible cigarettes. However, a growing amount of literature shows that while ECIGs do not involve combustion-derived toxicants, thermal degradation of the main constituents of ECIG liquid produces toxicants such as carbonyls. In this study, we report the detection of phenolic compounds in ECIG aerosols using a novel analytical method. The introduced method relies on liquid-liquid extraction to separate phenols from the major constituents of ECIG aerosol: propylene glycol (PG) and vegetable glycerol (VG). Phenol emissions from ECIGs were tested at different powers, puff durations, PG/VG ratios, nicotine benzoate concentrations, and flow rates to assess the influence of these operating parameters on phenol formation. The performance metrics showed that the analytical method has high specificity and reliability to separate and quantify phenolic compounds in ECIG aerosols. Increasing power and puff duration significantly increased all phenol emissions, while flow rate had no significant effects. The phenol profile in the ECIG aerosol was dominated by the unsubstituted phenol that reached comparable levels to those of IQOS, combustible cigarettes, and waterpipe. In contrast, low levels of the more toxic phenolic compounds, like catechol and hydroxyquinone, were quantified in ECIG aerosols. Emission of toxicants is presented, for the first time in this study, as the yield per unit of time, or flux ($\mu\text{g}/\text{sec}$), which is more suitable for inter-study and inter-product comparison. This work demonstrated a robust analytical method for isolating and quantifying phenol emissions in ECIG aerosols. Using this method, the study shows that phenols, which are not present in the simple solution of nicotine benzoate dissolved in mixtures of PG/VG, are formed upon vaping. Phenol emissions was independent of the nicotine benzoate concentration but significantly correlated with the PG/VG

* Corresponding Author: Najat A. Saliba, Tel: +961 1 350000/3992. ns30@aub.edu.lb.

Author Contributions

The first two authors contributed equally to the writing of the manuscript. The experimental work was done by RH and RS. All authors approved the final version of the manuscript.

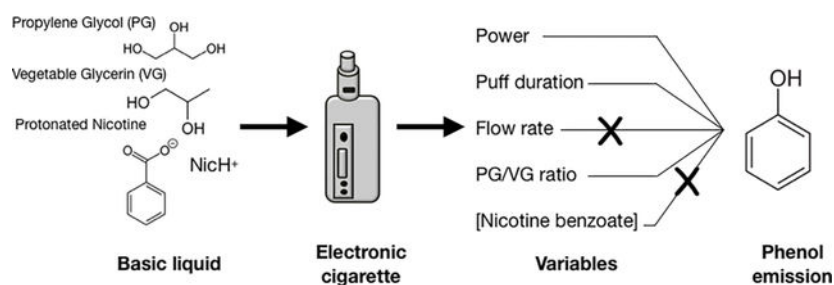
ASSOCIATED CONTENT

Supporting Information

A full comparison of all phenolic compounds obtained under different operating conditions is listed in Table S1.

ratio. It increased with power and puff duration, consistent with conditions that lead to a higher temperature and greater thermal degradation.

Graphical Abstract



Keywords

Electronic cigarette; phenol; toxicity; liquid-liquid extraction; GC-MS

INTRODUCTION

Electronic cigarette (ECIG) use has gained popularity among current smokers, former smokers, and nicotine-naïve users, particularly middle- and high-school students.^{1–2} It is usually advertised as a safer alternative to combustible cigarettes or as utterly safe by industry-funded researchers or ECIG advocates.^{3–6} Others claim that ECIGs may be useful tools in strategies to achieve tobacco harm reduction or smoking cessation.^{7–8} However, the recent outbreak of e-cigarette or vaping product use-associated lung injury (EVALI), which led to 68 casualties (February 2020), highlights the need for more pre-clinical, clinical, and longitudinal studies to evaluate the acute and chronic health risks associated with ECIG use.⁹

The ECIG literature has witnessed a surge in studies about toxicant emissions in ECIG aerosol.^{10–11} The most studied harmful or potentially harmful constituents (HPHCs) in ECIG aerosol are carbonyl compounds and reactive oxygen species (ROS); produced via several mechanisms the degradation and oxidation of PG/VG and other constituents in ECIG liquid, they can reach comparable levels to those observed in combustible cigarettes.^{12–14} Other reports addressed the detection and quantification of volatile organic compounds (VOCs), including aryl compounds like benzene.^{11, 15} Similarly, several reports detected phenols in general screenings of ECIG aerosols.^{16–21} Phenol species are commonly found in combustible tobacco smoke and are thought to be tumor promoters, genotoxic, and linked to cardiovascular risk.^{22–24}

Methods for detecting and quantifying phenols in tobacco smoke from cigarettes or waterpipe are well documented in the literature.^{25–28} The reported methods are usually based on the extraction of phenols from the tobacco matrix or smoke followed by analysis using GC- or HPLC-MS.^{29–33} The high affinity of phenol molecules to the primary constituents of ECIG aerosols, namely PG and VG, makes the available analytical methods unsuitable for analyzing phenols in ECIG aerosols. Here, a novel analytical method using

liquid-liquid extraction followed by GC-MS analysis permitted the quantification of phenol emissions in ECIG aerosols generated solely from heating the base constituents of ECIG liquids (humectants) under various operating conditions.

EXPERIMENTAL PROCEDURES

Materials

PG (99.5%; CAS No. 57–55-6) and VG (99%–101%; CAS No. 56–81-5) were procured from Sigma-Aldrich. A standard mixture containing phenol, o-cresol, m-cresol, p-cresol, catechol, resorcinol, and hydroquinone was purchased from Absolute Standards. A deuterated mixture of p-cresol-d8 and phenol-d6 was purchased from Absolute Standards and was used as an internal standard. Hydrochloric acid (HCl; 37%; CAS No. 7647–01-0), ascorbic acid (CAS No. 50–81-7) and sodium bicarbonate (CAS No. 144–55-8) were purchased from Sigma-Aldrich and Fluka, respectively. N,O-Bis(trimethylsilyl)trifluoroacetamide (BSTFA) with 1% trimethylchlorosilane (25561–30-2) was purchased from Fluka. HPLC-grade ethyl acetate was purchased from Sigma-Aldrich. Quartz filters (ADVENTEC, QR-100 47 mm) were purchased from the Pall Corporation. A Kangertech ECIG device (the Sub-Ohm MiniBox), stainless steel organic cotton coils (SSOC), and a nichrome coil (0.50 Ω resistance) were purchased from online vendors.

Study design

The liquids tested in this study are nicotine benzoate salt dissolved in PG/VG ratios of 30/70, 50/50, and 0/100. The ECIG device was operated at powers of 15, 30, and 45 W with puff durations of 1, 2, and 4 sec and puff flow rates of 5, 8, and 12 L/min. All conditions were cross-randomized except for the flow rate and nicotine concentration. The effect of flow rate was examined in a separate set of experiments, in which we fixed the PG/VG ratio, power, and puff duration at 30/70, 30 W, and 4 sec, respectively. A liquid formed solely of PG/VG (30/70) with no nicotine benzoate salt was tested for comparison. Each combination of conditions was tested in triplicate using a new coil for each test. Before sampling, the ECIG device was conditioned by filling the reservoir with liquid and allowing it to sit vertically for one h to ensure that the wick is saturated. Conditioning puffs were performed with a duration of 4 sec and a velocity of 16.7 ml/sec. Then, the remaining liquid in the reservoir was discarded and replaced with fresh liquid before puffing for the experiment.

Aerosol generation and sampling

The AUB Aerosol Lab Vaping Instrument (ALVIN) was used to generate ECIG aerosols. The generated aerosols were trapped on 47 mm quartz filters using the setup that was previously described.³⁴ Then, the total particulate matter (TPM) trapped on the filter was gravimetrically measured.

Extraction method

A solution of 0.3% HCl mixed with 0.1% (w/v) ascorbic acid (Sol A) and a solution of 5% (w/v) sodium bicarbonate (Sol B) were both prepared in deionized water and then used for the developed liquid-liquid extraction clean-up method. The quartz filter used to trap the aerosol sample was spiked with 1 μ l of a 100 μ g/ml stock solution of internal standard (IS),

soaked in 10 mL of Sol A, and shaken for 30 min. Then, 5 mL of ethyl acetate was added, and the vial was shaken again for 30 min to extract phenolic compounds and the non-ionized benzoic acid from the aqueous into the organic layer. PG, VG and nicotine are left in the aqueous medium at low pH. The collected organic layer was poured onto 5 mL of Sol B and shaken for 30 min to allow benzoic acid to react with sodium carbonate and then transfer the basic ionized soluble benzoate into the aqueous layer. The organic layer was separated and concentrated to 50 μ L under a nitrogen flow of 10 mL/min. Next, 50 μ L of BSTFA was added to the sample to derivatize the hydroxyl groups and was heated for 30 min at 70 °C before injection into GC-MS for analysis.

GC-MS method

The GC-MS analysis was performed on a Thermo Trace GC ITQ-900 instrument equipped with a thermostatically controlled AI 3000 auto-sampler and a TG-5MS Thermo Scientific fused silica capillary GC column (30 m \times 0.25 mm \times 0.25 μ m). The mass spectrometer ionization mode was electron ionization (EI) at 70 eV. The carrier gas was helium delivered at a flow rate of 1 mL/min. The injector temperature was 250 °C, with a split-less injection of 1 μ L using a single taper gooseneck, deactivated, glasswool free liner. The oven temperature program was as follows: hold at 70 °C for 1 min, ramp up 10 °C/min to 200 °C, ramp up 40 °C/min to 250 °C, and hold for 1 min. The total run time was 16.25 min, and the solvent delay time was 4.9 min. Quantification was performed using selected ion mass (SIM) monitoring with two qualifiers and one quantifier peak for each analyte, as shown in Table 1.

As part of the validation method, two types of blanks were used to verify that the detection of phenol in the vaped samples relate to a reaction happening during heating and not due to the contamination on the unused quartz filters or the original liquid solution. (nicotine benzoate in PG/VG mixtures). The Gas Chromatography results of Blank 1 (quartz filter spiked with IS) and blank 2 (a quartz filter spiked with the liquid used for vaping and IS), showed that the phenol concentrations in the two blank filters were below the detection limit. Blank 2 was subtracted from the sample data set and the points of the calibration curve (Table S1 in the Supplementary Information (SI)).

Statistical analysis

The multiple linear regression in SPSS was used to study the effect of the different operating parameters on phenol emissions. The ECIG power output, puff duration, puffing flow rate, PG/VG ratio, and nicotine benzoate concentration were studied as possible variables affecting phenol emissions in the particle phase of the aerosols.

RESULTS

The analytical method introduced to quantify phenolic emissions from ECIG was validated using lab-prepared standard solutions of phenols in a PG/VG matrix. The method showed a high analytical performance of the seven phenolic compounds, as shown in Table 2.

The results for the samples prepared with nicotine benzoate salt and various PG/VG ratios (30/70, 50/50, and 0/100) and operated at three different power levels (15, 30, and 45 W),

puff durations (1, 2, and 4 sec), and puff flow rates (5, 8, and 12 L/min) showed that the formation of phenols is dependent on power ($p < 0.002$) and puff duration ($p < 0.001$) and independent of the puff flow rate. The liquid composition affected the formation of only the unsubstituted phenol ($p < 0.004$). In an attempt to normalize variations among different devices, the phenol levels are presented as the yield per unit of time, or flux ($\mu\text{g}/\text{sec}$). The flux of the seven phenolic compounds showed that only the unsubstituted phenol is detected in the aerosol under mild operating conditions (e.g., low power and short puff duration). In contrast, all phenolic compounds, including higher levels of catechol, were detected under harsh conditions (e.g., high power and long puff duration), as shown in Table 3. Also, Table 3 shows that heating a PG/VG liquid with no nicotine benzoate yielded the same phenol profile as compared to the nicotine-containing counterpart at the same operating conditions. Unlike other phenolic compounds, the unsubstituted phenol flux was highly correlated (78%) with the total particle matter (TPM) flux emissions, as shown in Figure 1.

The range of the unsubstituted phenol flux calculated for ECIG emissions (0.01–0.27 $\mu\text{g}/\text{sec}$) was found to be comparable to that of IQOS (0.12 $\mu\text{g}/\text{sec}$) and waterpipe (0.13 $\mu\text{g}/\text{sec}$) under specific conditions but was much lower than that of combustible cigarettes (phenol fluxes of the other tobacco products were calculated from data extracted from references [26] and [35]). The highest phenol flux, which was obtained with high power and puff duration (i.e., 45 W and 4 sec), was almost one-third and one-fifth that of a reference cigarette and a Marlboro cigarette, respectively (0.71 and 1.24 $\mu\text{g}/\text{sec}$, respectively).^{26, 35} Similar comparisons for the seven phenolic compounds are shown in Table 3 (For the full data check Table S2 in SI). While the unsubstituted phenol is the major product in ECIGs, catechol and hydroquinone are significant contributors to phenol emissions in IQOS, waterpipe, and combustible cigarettes.

DISCUSSION

ECIG liquid is a challenging matrix for the detection and quantification of polar compounds due to interference from its major components, PG and VG. The introduced method separates phenolic compounds from the matrix due to the selective solubility of the analytes. A similar approach was previously reported by our group for analyzing nicotine and pyrazine in ECIG liquids and aerosols.^{36–37}

The literature has shown that the oxidation and thermal degradation of the main liquid components (PG and VG) led to the formation of carbonyl compounds, radicals, ROS, and other compounds.^{38–40} Per contra, the formation of other families of toxicants, like aryl compounds, could be attributed to the addition reactions of radicals or unsaturated hydrocarbon intermediates.^{11, 41} In this study, phenols are likely to be produced by addition/cyclization reactions of smaller molecules or intermediates (PG, VG, and their degradation products).

Statistical analysis of the presented data showed that power and puff duration are key parameters affecting phenols emission.³⁴ According to previous studies, power and puff duration are directly correlated with the temperature of the ECIG heating coil.¹⁰ This conclusion is corroborated by the increase of unsubstituted phenol flux with TPM flux,

with the latter being highly correlated with temperature.³⁴ This indicates that the formation of the phenolic compounds is an endothermic reaction that resulted from heating the base ECIG liquid components, PG and VG. The benzoate species are shown to be indifferent to phenol formation (Table S2) in agreement with the literature.⁴² Our statistical analysis showed that PG/VG ratio significantly affects the emission of the unsubstituted phenol, which could be explained by different mechanistic routes leading to this compound (Scheme S1). The addition of flavors might enhance the level and change the distribution profile of the different phenolic compounds, as was observed for other toxicants.^{12, 43}

The fact that nicotine benzoate concentration is independent of phenol emission is in line with a recent report that showed that benzoic acid remained stable up to 300 °C after heating for 10 min, unlike its derivatives (anthranilic, salicylic, and syringic acids) that initiated decomposition at much lower temperatures (~150 °C). As the temperature approached 350 °C, benzoic acid produced benzene and not phenol. Phenol was found to be the major degradation product of salicylic acid.⁴² Although some copper-activated thermal decomposition reactions of benzoic acid have been reported to produce unsubstituted phenol,^{44–45} our experimental results did not show catalyzed metallic induced transformations.

In this study, we found that toxicant flux is suitable for inter-study comparison of toxic emissions from ECIG, as it takes into consideration puffing variation and encompasses all other operating parameters.⁴⁶ Comparison of phenol emissions from ECIGs, under realistic use conditions, showed that ECIGs could emit levels of unsubstituted phenol comparable to IQOS, waterpipe, and combustible cigarettes. However, the phenol profile of ECIG aerosol was significantly different from that of the other tobacco products; the ECIG aerosol showed minimal amounts of the most toxic phenolic compounds, catechol, and hydroquinone,^{47–50} that were detected in the smoke of the other products. This could be attributed to different reaction mechanisms or different reactants, leading to phenols in the tobacco systems. For tobacco cigarettes and IQOS, phenols are produced from the thermal degradation of large molecules in tobacco like quinic acid, chlorogenic acid, and quercetin.^{27, 51–52} For the simple synthetic liquid mixture of nicotine benzoate dissolved in a mixture of PG and VG, phenols are emitted upon aerosolization and are likely produced by addition/cyclization reactions of the humectants or their degradation products.

This study reports a novel extraction method used to separate phenols from PG and VG in ECIG aerosols. The quantified phenols in ECIG aerosol were found to be statistically dependent on power, puff duration and PG/VG ratio but independent of the flow rate and the nicotine benzoate concentration. The examined ECIG emits the unsubstituted phenol, and not more toxic compounds, at a comparable flux to IQOS, waterpipe, and combustible cigarettes.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Funding Sources

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ABBREVIATIONS

ECIG	electronic cigarette
PG	propylene glycol
VG	vegetable glycerol
HPHC	harmful or potentially harmful compounds
ROS	reactive oxygen species
VOC	volatile organic compound
BSTFA	N,O-Bis(trimethylsilyl)trifluoroacetamide
TPM	total particle matter

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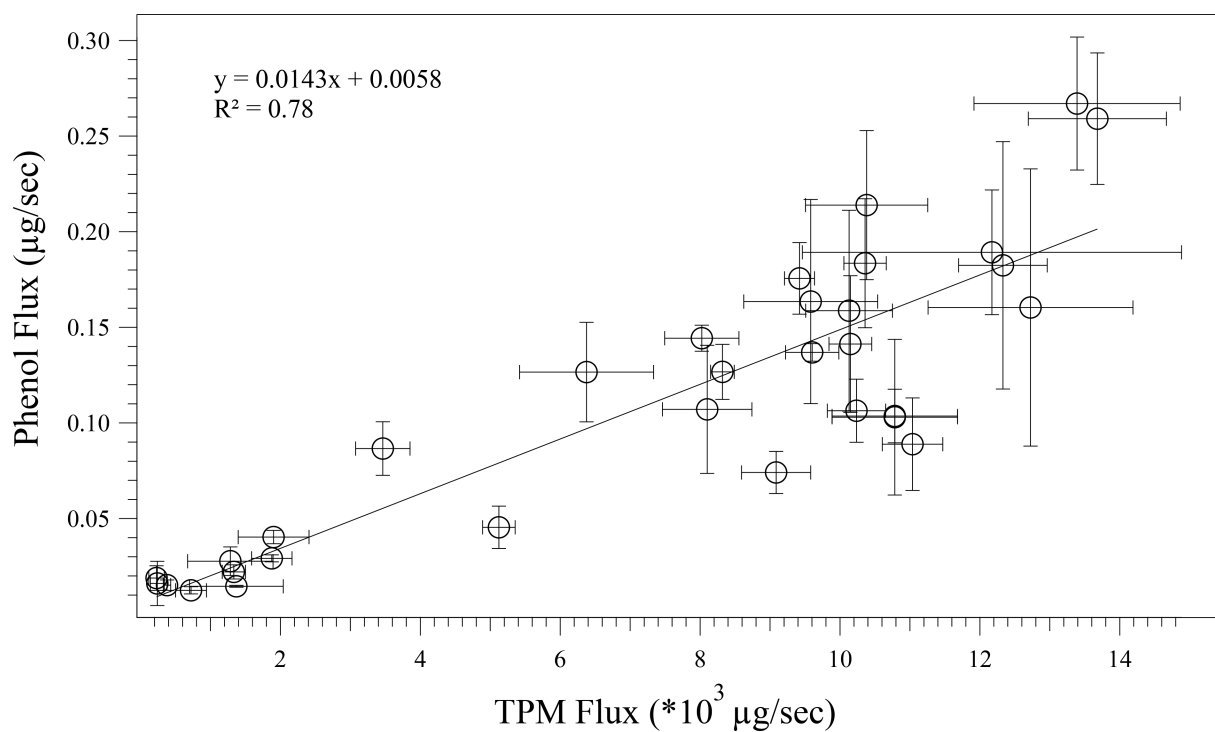


Figure 1.

A plot of phenol flux versus TPM flux in ECIG aerosol tested using only nicotine benzoate dissolved in solutions with various PG/VG ratios. Vertical and horizontal error bars are standard deviations for phenol flux and TPM flux, respectively.

Table 1.Qualifier and quantifier ions in GC-MS (m/z) of the O-trimethylsilyl derivatives of the analytes.

	Retention time (min)	Quantifier m/z	Qualifier 1 m/z	Qualifier 2 m/z
phenol	5.20	151	156	77
<i>o</i> -cresol	6.22	135	165	180
<i>m</i> -cresol	6.34	165	135	180
<i>p</i> -cresol	6.46	165	135	180
catechol	8.80	151	239	254
resorcinol	9.62	239	254	133
hydroquinone	9.86	239	254	133
phenol-d6	5.18	156	166	-
<i>p</i> -cresol-d8	6.43	172	98	-

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Table 2.

Analytical method validation parameters.

	LOQ ^a (µg/mL)	Recovery (%)	Range of calibration curve (µg/mL)	Repeatability (%RSD ^b)
phenol	0.50	90	0.5–8.0	11
<i>o</i> -cresol	0.19	90	0.5–8.0	4
<i>m</i> -cresol	0.14	90	0.5–8.0	3
<i>p</i> -cresol	0.46	90	0.5–8.0	10
catechol	0.60	50–70	0.5–8.0	12
resorcinol	0.30	90	0.5–8.0	6
hydroquinone	0.40	70–90	0.5–8.0	10

^a: Limit of quantification

^b: relative standard deviation.

Table 3.

Summary of the flux ($\mu\text{g}/\text{sec}$) of the seven phenolic compounds across ECIG operating conditions and comparison with IQOS, combustible cigarettes, and waterpipe.

Power (W)	Puff Duration (sec)	PG %	Flow rate (L/min)	Nic content (mg/mL)	Phenol flux ($\mu\text{g}/\text{sec}$)	o-cresol flux ($\mu\text{g}/\text{sec}$)	m-cresol flux ($\mu\text{g}/\text{sec}$)	p-cresol flux ($\mu\text{g}/\text{sec}$)	Catechol flux ($\mu\text{g}/\text{sec}$)	Resorcinol flux ($\mu\text{g}/\text{sec}$)	Hydroquinone flux ($\mu\text{g}/\text{sec}$)
15	4	0	8	15	0.0125 \pm 0.0019	0	0	0	0	0	0
15	4	30	8	15	0.0146 \pm 0.0005	0	0	0.0004 \pm 0.0003	0	0	0
30	4	0	8	15	0.1030 \pm 0.0407	0	0	0	0	0	0
30	4	30	8	15	0.1369 \pm 0.0046	0	0	0.0019 \pm 0.0032	0.0061 \pm 0.0055	0	0
30	4	50	8	15	0.1835 \pm 0.0337	0	0	0	0.0090 \pm 0.0156	0	0
45	2	0	8	15	0.1036 \pm 0.0140	0	0	0	0.0045 \pm 0.0078	0	0
45	2	30	8	15	0.1824 \pm 0.0647	0	0	0.0018 \pm 0.0031	0.0165 \pm 0.0062	0	0
45	2	50	8	15	0.2591 \pm 0.0344	0	0	0.0016 \pm 0.0027	0.0097 \pm 0.0089	0	0
45	4	0	8	15	0.1604 \pm 0.0725	0.0063 \pm 0.0110	0.0060 \pm 0.0104	0.0042 \pm 0.0073	0.4246 \pm 0.7040	0.0222 \pm 0.0385	0.0023 \pm 0.0040
45	4	30	8	15	0.2670 \pm 0.0348	0.0082 \pm 0.0018	0.0072 \pm 0.0015	0.0022 \pm 0.0038	0.2178 \pm 0.0952	0.0135 \pm 0.0022	0.0328 \pm 0.0053
45	4	50	8	15	0.1892 \pm 0.0326	0.0050 \pm 0.0065	0.0037 \pm 0.0064	0.0021 \pm 0.0036	0.1222 \pm 0.1504	0.0103 \pm 0.0148	0.0191 \pm 0.0330
30	4	30	5	15	0.1756 \pm 0.0187	0	0	0	0.0027 \pm 0.0047	0	0
30	4	30	8	15	0.2139 \pm 0.0390	0	0	0	0.0059 \pm 0.0102	0	0
30	4	30	12	15	0.1064 \pm 0.0165	0	0	0	0.0046 \pm 0.0080	0	0
15	2	30	8	0*	0.0137 \pm 0.0026	0	0	0	0.0006 \pm 0.0010	0.0003 \pm 0.0005	0
30	2	30	8	0*	0.0740 \pm 0.0187	0.0004 \pm 0.0007	0.0014 \pm 0.0022	0	0.0159 \pm 0.0172	0.0033 \pm 0.0035	0.0072 \pm 0.0046

Power (W)	Puff Duration (sec)	PG %	Flow rate (L/min)	Nic content (mg/mL)	Phenol flux (µg/sec)	o-cresol flux (µg/sec)	m-cresol flux (µg/sec)	p-cresol flux (µg/sec)	Catechol flux (µg/sec)	Resorcinol flux (µg/sec)	Hydroquinone flux (µg/sec)
45	4	30	8	0*	0.1457 ± 0.0993	0.0364 ± 0.0417	0.0062 ± 0.0059	0.0003 ± 0.0005	0.1178 ± 0.0913	0.0122 ± 0.0071	0.0582 ± 0.0205
					0.1225	0.0065	0.0035	0.0059	1.1667	0.0046	0.5458
					0.7091	0.2186	0.1927	0.4364	3.8227	0.0782	4.2955
					1.2389	0.3217	0.2406	0.5611	2.2611	0.0439	1.9222
					0.1305	0.0099	0.0105	0.0121	0.7110	0.0038	0.2490

*. PG/VG liquid with no nicotine benzoate.