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Brief report

Free Radical, Carbonyl, and Nicotine Levels Produced by Juul Electronic Cigarettes

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Abstract

Introduction: Free radicals and carbonyls produced by electronic cigarettes (e-cigs) have the potential to inflict oxidative stress. Recently, Juul e-cigs have risen drastically in popularity; however, there is no data on nicotine and oxidant yields from this new e-cig design.
Methods: Aerosol generated from four different Juul flavors was analyzed for carbonyls, nicotine, and free radicals. The e-liquids were analyzed for propylene glycol (PG) and glycerol (GLY) concentrations. To determine the effects of e-liquid on oxidant production, Juul pods were refilled with nicotine-free 30:70 or 60:40 PG:GLY with or without citral.
Results: No significant differences were found in nicotine (164 ± 41 µg/puff), free radical (5.85 ± 1.20 pmol/puff), formaldehyde (0.20 ± 0.10 µg/puff), and acetone (0.20 ± 0.05 µg/puff) levels between flavors. The PG:GLY ratio in e-liquids was ~30:70 across all flavors with GLY being slightly higher in tobacco and mint flavors. In general, when Juul e-liquids were replaced with nicotine-free 60:40 PG:GLY, oxidant production increased up to 190% and, with addition of citral, increased even further.
Conclusions: Juul devices produce free radicals and carbonyls, albeit, at levels substantially lower than those observed in other e-cig products, an effect only partially because of a low PG:GLY ratio. Nicotine delivery by these devices was as high as or higher than the levels previously reported from cigarettes.
Implications: These findings suggest that oxidative stress and/or damage resulting from Juul use may be lower than that from cigarettes or other e-cig devices; however, the high nicotine levels are suggestive of a greater addiction potential.

Introduction

Juul electronic cigarettes (e-cigs) have risen drastically in popularity during recent years, reaching 60%[1] of the e-cig market share in April 2018. These products are sold in a variety of flavors, including mint, tobacco, creme brulee, and fruit punch. Juul has gained ample news coverage for being used in schools.[2,3] In fact, a recent study using an online survey showed that 21% of the respondents between the ages of 15 and 17 recognized Juul with 6% reporting past 30-day use.[4] On April 24, 2018, the US Food and Drug Administration (FDA) announced enforcement actions to tackle youth use of e-cigs, particularly citing Juul.[5] The youth usage of these products emphasizes the need to know the amount of toxicants delivered from these devices and the characterization of the e-liquid in them. However, even if the FDA successfully combats the youth usage, the high market sales also suggest that many adult vapers are using this product, further stressing the need to know the potential harms related to Juul.

One potential harm that e-cigs have been suggested to inflict is oxidative stress, which, along with the resulting oxidative damage, plays a critical role in the development of many tobacco-related diseases including respiratory diseases[6] and cancer.[7] Free radicals[8,9] and carbonyls[10,11] are oxidants that have been shown to be present in the aerosols of other e-cigs; however, thus far, no study has characterized the oxidant output from Juul devices. To help understand the potential oxidative damage, it is important to consider the makeup of these products. By characterizing the e-liquid, we will also be able to determine what might be influencing the resulting oxidant yields. For example, the ratio of propylene glycol (PG) and glycerol (GLY) has been shown to influence both free radical and carbonyl yields,[9–11] and flavor additives have been shown to have a drastic effect on free-radical production.[8]

In addition to oxidant production, an important consideration for consumption is the amount of nicotine delivered from the product as users switching from cigarettes might adjust their behaviors to get their preferred nicotine consumption,[12] thus changing the amount of oxidants they receive. The amount of nicotine these products deliver is also of interest regarding youth use as the amount produced by Juul devices is likely to cause nicotine addiction as Juul e-cigs are advertised as being high in nicotine (5% strength) with one pod/cartridge being roughly equivalent to one pack of cigarettes.[13] One independent study has confirmed that the e-liquid contains upwards of 61.6 mg/mL nicotine,[14] much higher than the nicotine levels previously reported in other e-cigs.[15,16] As another study looking at a different e-cig showed that up to 60% of the nicotine in the cartridge can be transferred into the aerosol,[16] the high nicotine content of the e-liquid suggests a large amount of nicotine could potentially reach the vapers of Juul. Recently, one study found that the Juul has a low free-base nicotine fraction in its aerosols suggesting a decrease in the perceived harshness of the aerosol to the user and thus a greater abuse liability.[17]

In this study, we contribute to the literature by determining the levels of oxidants and nicotine produced by Juul e-cigs and the characteristic makeup of their e-liquids. To do this, we examined the aerosol for all four flavors that come in the Juul starter pack (tobacco, cool mint, fruit punch, and creme brulee) for free radical, carbonyl, and nicotine yields. We then determined the amounts of PG, GLY, and nicotine in the e-liquid as well as qualitatively determined the presence of other flavoring or characterizing chemicals to determine what factors are present that could be influencing the yields observed in the aerosol. To test the effects of changing the e-liquid, we tested the Juul device with 60:40 PG:GLY with and without citral. Citral was used as free radicals levels have been shown to increase when it is added to the e-liquid and was found in roughly 8% of commercial e-liquids measured.[8] Altogether, these findings will help researchers and policymakers to better understand the potential harms Juul vapers face and how they compare both with cigarette smokers and vapers using other e-cigs.

Methods

Materials

Acetonitrile (CAS# 75-05-8) and 12-N hydrochloric acid (CAS# 7647-01-0) were purchased from Fisher Scientific (Pittsburgh, PA). Citral (CAS# 5392-40-5), PG (CAS# 57-55-6), GLY (CAS# 56-81-5), hexane (CAS# 110-54-3), heptadecane (CAS# 629-78-7), methanol (CAS# 67-56-1), phenyl-*N*-*tert*-butylnitrone (PBN) (CAS# 3376-24-7), 2,2,6,6-tetramethyl-1-piperidinyloxyl (TEMPO) (CAS# 2564-83-2), *tert*-butylbenzene (CAS# 98-06-6), and diglyme (CAS# 111-96-6) and dinitrophenylhydrazones of formaldehyde (CAS# 1081-15-8), acetaldehyde (CAS# 1019-57-4), acetone (CAS# 1567-89-1), and propionaldehyde (CAS# 725-00-8) were purchased from Sigma–Aldrich (St. Louis, MO). 2,4-Dinitrophenylhydrazine (DNPH) (CAS# 119-26-6) was purchased from BOC Sciences (Shirley, NY), recrystallized in acetonitrile to remove water.[18]

Aerosol Generation

Aerosols were generated using a Human Puff Profile Cigarette Smoking Machine (CSM-HPP; CH Technologies, NJ) using a custom-built mouthpiece. Each e-cig puff had a puff volume of 75 mL, puff duration of 2.5 s, and interpuff interval of 30 s. This puff profile is based on the CORESTA method[19] with modifications (increased volume and shortened puff duration) made in order to achieve an adequate flow rate to activate this device. Ten puffs and a minimum of three replicates were performed for all conditions. Cartomizers were weighed before and after each session, and the loss in mass was used to calculate the mass of aerosol generated.

Nicotine and Solvent Analysis

E-cig aerosols were passed through a Cambridge filter pad. Nicotine and e-liquid solvent (PG and GLY) were then analyzed by gas chromatography with flame-ionization detection using instrumentation and method described in detail previously.[20]

E-Liquid Replacement

Unused Juul pods were emptied of e-liquid, washed with water and methanol, and then allowed to dry overnight. The pods were refilled with different mixtures of PG and GLY (30:70 or 60:40) or 4 mg/mL citral in 60:40.

Free Radicals Analysis

Similar to previous work done by our lab,[8] e-cig aerosol was pumped into an impinger containing 0.05-M nitrone spin trap, PBN in hexane, evaporated, and reconstituted in 500 µL of *tert*-benzene. Samples were added to high purity quartz electron paramagnetic resonance tubes and deoxygenated using a freeze-pump-thaw technique with a Schlenk line.[8]

Electron Paramagnetic Resonance Measurements

PBN radical adduct-derived spectra were measured with a Bruker eScan R spectrometer (Bruker BioSpin, Billerica, MA) operating in X-band using the following parameters: microwave frequency, 9.7 GHz; modulation frequency, 86.0 kHz; microwave power, 2.89 mW; scan range, 60 G; modulation amplitude, 1.15 G; sweep time, 10.49 s; time constant, 20.48 ms; and conversion time, 20.48 ms. All measurements were conducted at room temperature (22 ± 1°C). As previously reported, quantitation of the free radicals was done using the second integral, and the values were compared against known concentrations of a stable radical standard, TEMPO.[8]

Carbonyl Analysis

Similar to previous work with cigarettes, the e-cig aerosol was pumped into 10-mL DNPH solution.[21] After vaping, 500 µL of pyridine was added, and the solution was stored at 4°C until HPLC-UV analyses were performed also as described previously.[21]

Statistics

All measurements were done at least in triplicate, and significant differences ($p < .05$) between groups were determined using a one-way ANOVA and Tukey's multiple comparison or *t* test where applicable via GraphPad Prism (San Diego, CA).

Results

E-Liquid and Aerosol Analysis of Commercial Flavors

The percentage of GLY in the e-liquid (Table 1) was significantly higher ($p < .05$) in the tobacco (71%) and menthol (70%) flavors than the fruit punch (69%) and crème brûlée (69%) flavors. Nicotine delivery in the aerosol did not differ significantly between the flavors on either a per puff or a per gram e-liquid consumed basis (Table 1). Free radicals produced by the Juul flavors did not differ significantly from each other. Among the commercial flavors (Tobacco, Crème Brûlée, Fruit Punch, Mint), no significant differences were seen for formaldehyde, acetone, acetaldehyde, or propionaldehyde on either a per puff or a per gram e-liquid consumed basis.

Aerosol Analysis of Modified E-Liquid

When the commercial e-liquid was replaced with a 30:70 (PG:GLY) mixture that mimicked the PG:GLY ratio, no differences in free radicals and carbonyl yields were seen when compared with the commercial liquids. When the e-liquid was replaced with a 60:40 mixture with or without citral, the free-radical production rose significantly compared with the commercial flavors (Table 1). There were no significant differences between any of the modified e-liquids on a per puff basis. On a per gram e-liquid consumed basis, the 30:70 mixture was not significantly different than the commercial flavors but was significantly lower than the other modified e-liquids. Levels of formaldehyde were significantly higher with the addition of citral in the 60:40 mixture on a per puff basis. A similar trend was noticed on a per gram e-liquid consumed basis; however, the citral, blank 60:40 and 30:70, and Fruit Punch samples were not significantly different from each other. Acetone production was significantly higher with both of the 60:40 modified e-liquids as compared with the commercial samples. The e-liquid containing citral produced significantly higher levels of acetone than all other e-liquids. This trend was observed on both a per puff and per gram e-liquid consumed basis. While no acetaldehyde was observed in the commercial flavors, all of the modified e-liquids showed some acetaldehyde formation. On a per puff, the e-liquid containing citral produced significantly higher levels of acetaldehyde compared with the other modified e-liquid. On a per gram e-liquid consumed basis, the citral sample was only significantly higher than the 30:70 sample. Propionaldehyde production was not seen with the commercial flavors or the 30:70 sample, but both 60:40 e-liquids showed some production with the citral sample producing the most on a per puff basis; however, this increase was not significantly different from the 60:40 e-liquid. When viewed on a per gram e-liquid consumed basis, significant differences were not observed.

Discussion

Our results show that Juul devices produce harmful oxidants and thus could cause potential harm. The levels of oxidants delivered from these devices are much lower than those reported from cigarettes[22] and from other e-cig devices,[8,9,23] while the levels of nicotine delivered per puff are much higher.[16] These differences are of importance when considering the potential use of Juul-type devices as a reduced harm product for smokers,[22] especially when considered on a per milligram nicotine basis. However, the high amounts of nicotine delivered from the device suggest that nicotine-naive users could potentially develop a nicotine addiction more easily than from other e-cigarette devices as the levels delivered from Juul are higher than many breath activated, commercial e-cigs.[24,25] High levels of nicotine (83 µg/puff) in the Juul aerosols have been reported by others.[26] These levels are slightly less than what we report, but this is likely because of a different puffing regiment (puff volume: 70 mL, duration: 2 s, puff interval: 10 s) and their use of liquid-based nicotine capturing method as compared with our Cambridge filter pad nicotine trapping and extraction method. Based on pharmacodynamic and pharmacokinetic data, abuse liability for e-cigs has been demonstrated to correlate well with e-cig nicotine content.[25] The nicotine levels delivered by the Juul are similar to or even higher than those delivered by cigarettes (range: 14–189 µg/puff).[27]

As previously reported, the production of free radicals and carbonyls is heavily influenced by both the solvents (PG and GLY)[9–11] as well as the flavorants used.[8] This trend appears to hold true for the Juul as well. When the PG content in the e-liquid was increased, we saw an increase in both free-radical and carbonyl production. While carbonyls increase with PG, a finding opposite than predicted by the literature, it is possible that the temperature the device reaches plays a substantial role as the amount of carbonyls delivered by each solvent type is strongly related to coil temperature.[11] In addition, we found previously[8] that the addition of citral resulted in a significant increase in radical production. When we added citral to 60:40 PG:GLY in the Juul device, we did observe an increase in radical production; however, that increase was not significant. The change in carbonyl delivery with citral after correcting for aerosol delivery was not significantly different from 60:40 alone with the exception of acetone, which could be an effect of the chemical itself. These findings suggest that the low oxidant delivery is caused at least in part by the e-liquid's unique composition. When mimicking the PG:GLY ratio of the commercial samples at 30:70, we saw no significant differences in oxidant production when compared with the commercial flavors suggesting that the presence of nicotine appears to have little to no effect on oxidant production. Nicotine content has been shown to have no effect on carbonyl production in previous studies.[28] Other factors influencing these yields could be from the unique design of the device itself (including, but not limited to, the silica wick used, the temperature controlled coil, and the flow rate required for activation) that need to be tested in detail in future studies.

This work is limited as the comparisons with other e-cig devices are through literature comparisons. Thus, to better compare with the literature despite differences in puffing regimes and devices, we corrected for aerosol delivery. We also performed these tests under one puffing regime, limiting generalizability; however, the results are a starting point to address the potential for harm of these products. Future work will need to be done to address how the products perform under other conditions.

In conclusion, this brief report demonstrates the relative oxidant and nicotine levels produced by the Juul product as well as characterizes the PG:GLY and nicotine content in the e-liquid itself. These findings suggest that Juul might be a useful e-cig for oxidant reduction in smokers looking to quit. However, these findings do

Table 1. Nicotine, Free Radicals, and Carbonyls in Juul Aerosols and PG:GLY Levels in Juul E-Liquids by Flavor

		Flavors						
		Tobacco	Creme brulee	Fruit punch	Mint	30:70	60:40	Citral
E-liquid	PG:GLY	29:71[a] (n = 3)	31:69[b] (n = 3)	31:69[b] (n = 3)	30:70[a] (n = 3)	30:70	60:40	60:40
Per puff	Nicotine (µg/puff)	156.66 ± 47.65 (n = 3)	169.91 ± 14.46 (n = 3)	154.41 ± 48.84 (n = 3)	188.42 ± 24.69 (n = 3)	n/a	n/a	n/a
	Free radicals (pmol/puff)	5.90 ± 1.62[a] (n = 3)	6.13 ± 1.12[a] (n = 3)	5.47 ± 1.79[a] (n = 3)	5.90 ± 0.63[a] (n = 3)	7.92 ± 1.09[a,b] (n = 3)	9.37 ± 1.16[b] (n = 3)	10.87 ± 0.83[b] (n = 3)
	Formaldehyde (µg/puff)	0.23 ± 0.10[a] (n = 4)	0.12 ± 0.06[a] (n = 3)	0.26 ± 0.08[a] (n = 3)	0.19 ± 0.13[a] (n = 3)	0.34 ± 0.04[a] (n = 3)	0.31 ± 0.07[a] (n = 3)	0.69 ± 0.21[b] (n = 3)
	Acetone (µg/puff)	0.19 ± 0.08[a] (n = 4)	0.17 ± 0.02[a] (n = 3)	0.20 ± 0.05[a] (n = 3)	0.22 ± 0.06[a] (n = 3)	0.32 ± 0.12[a,b] (n = 3)	0.57 ± 0.15[b] (n = 3)	1.19 ± 0.16[c] (n = 3)
	Acetaldehyde (µg/puff)	n/d (n = 4)	n/d (n = 3)	n/d (n = 3)	n/d (n = 3)	0.00 ± 0.01[a] (n = 3)	0.05 ± 0.05[a] (n = 3)	0.13 ± 0.03[b] (n = 3)
	Propionaldehyde (µg/puff)	n/d (n = 4)	n/d (n = 3)	n/d (n = 3)	n/d (n = 3)	n/d (n = 3)	0.03 ± 0.03 (n = 3)	0.05 ± 0.04 (n = 3)
Per gram e-liquid consumed	Nicotine (mg/g)	78.33 ± 23.82 (n = 3)	63.72 ± 5.42 (n = 3)	66.17 ± 20.93 (n = 3)	94.21 ± 12.34 (n = 3)	n/a	n/a	n/a
	Free radicals (nmol/g)	2.95 ± 0.81[a] (n = 3)	2.56 ± 0.34[a] (n = 3)	2.32 ± 0.18[a] (n = 3)	2.95 ± 0.32[a] (n = 3)	3.01 ± 0.28[a] (n = 3)	4.68 ± 0.58[b] (n = 3)	4.78 ± 0.73[b] (n = 3)
	Formaldehyde (µg/g)	72.61 ± 35.88[a] (n = 4)	42.88 ± 15.07[a] (n = 3)	98.91 ± 34.24[a,b] (n = 3)	67.12 ± 41.81[a] (n = 3)	103.65 ± 14.84[a,b] (n = 3)	97.39 ± 34.18[a,b] (n = 3)	197.07 ± 83.48[b] (n = 3)
	Acetone (µg/g)	59.66 ± 22.45[a] (n = 4)	67.76 ± 24.94[a] (n = 3)	75.16 ± 6.21[a] (n = 3)	80.45 ± 38.25[a] (n = 3)	95.23 ± 23.91[a,b] (n = 3)	171.56 ± 39.32[b] (n = 3)	327.48 ± 37.47[c] (n = 3)
	Acetaldehyde (µg/g)	n/d (n = 4)	n/d (n = 3)	n/d (n = 3)	n/d (n = 3)	0.82 ± 1.44[a] (n = 3)	14.92 ± 15.30[a,b] (n = 3)	36.70 ± 14.24[b] (n = 3)
	Propionaldehyde (µg/g)	n/d (n = 4)	n/d (n = 3)	n/d (n = 3)	n/d (n = 3)	n/d (n = 3)	8.07 ± 8.99 (n = 3)	14.09 ± 14.22 (n = 3)

Values are means ± SD. Different letters indicate significant differences ($p < .05$) between flavors. n/d represents that no quantifiable amounts were observed with our setup.

not suggest the product is harmless. In particular, the high nicotine delivery and content of the device suggests that it has a much higher addictive potential than previous e-cigs, which is very important considering the alarming uptake of the product by youth.

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Declaration of Interests

None declared.

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