

## Flavorant–Solvent Reaction Products and Menthol in JUUL E-Cigarettes and Aerosol



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### INTRODUCTION

The “JUUL” e-cigarette is the best-selling e-cigarette on the U.S. market.<sup>1,2</sup> JUUL refill “pods” contain nicotine benzoate salt and flavorants dissolved in a 30:70 ratio of propylene glycol (PG) and glycerol (VG for vegetable glycerin). Nicotine benzoate is perceived as more satisfactory and less harsh, enabling the delivery of higher amounts of nicotine to users. As such, nicotine concentrations in JUUL e-liquids are higher (5%; 3% since August 2018) than in non-JUUL e-liquids (typically 0.3%–2.4%). JUUL e-liquids are available in several fruity flavors, known to be particularly appealing to youth.<sup>3</sup> Common e-cigarette (including JUUL) flavorants include menthol and various aldehydes (e.g., vanillin); aldehydes are known to react with alcohols (e.g., PG and VG) to form acetals (structural and optical isomers).<sup>4</sup> The inhalational safety of flavor aldehyde PG/VG acetals is unknown; however, a recent study found that several acetals, including vanillin PG acetal, activate pro-inflammatory irritant receptors more strongly than their parent compounds (e.g., vanillin).<sup>4,5</sup>

Despite the popularity of JUUL, little is known about the composition of JUUL aerosol. The aim of this study was to evaluate the carryover of vanillin and its reaction products with PG and VG, menthol, and nicotine benzoate from JUUL e-liquid to aerosol to understand potential human exposures.

### METHODS

A JUUL device and pods of all eight flavors (Figure 1) were purchased online in 2018. For aerosol capture (both gas phase and microdroplets<sup>6</sup>), a custom-built vaping machine with liquid nitrogen–chilled traps was used as described previously.<sup>7</sup> The puffing regime was 20 puffs of 2.8-second length, 79-mL volume, and a 30-second cooldown between puffs. Neat e-liquids and captured aerosol were diluted and analyzed by gas chromatography mass spectroscopy.<sup>4</sup> Commercially available standards were used for quantification except for vanillin VG acetals, which were synthesized in house. Aerosol concentrations and

percentage carryover were calculated per experiment by dividing the amount of compound trapped by the pod mass change, and as aerosol concentration over neat e-liquid concentration, respectively (Figure 1).

### RESULTS

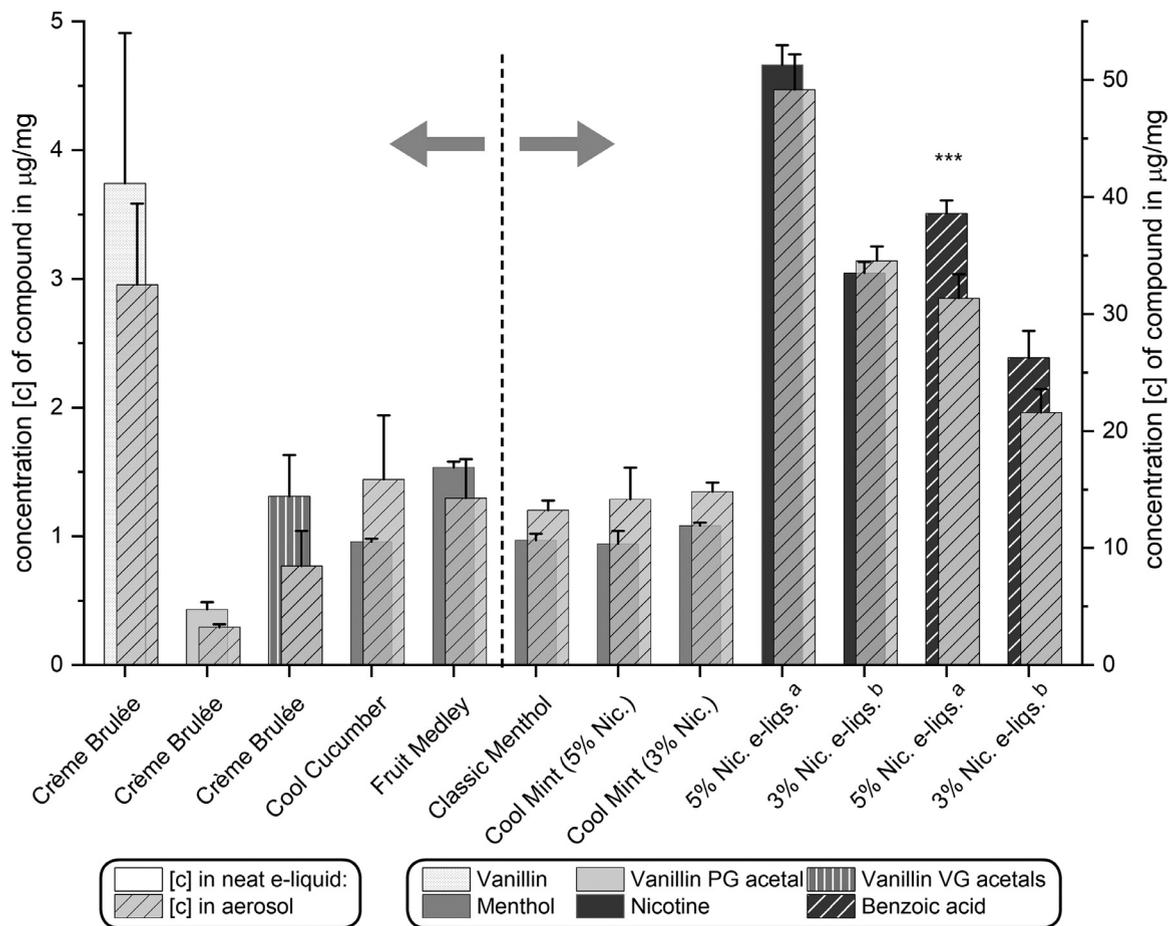
The reaction products vanillin PG acetal and vanillin VG acetals were detected in JUUL “Crème Brûlée” e-liquid and carried over to aerosol at 68±4% (mean±95% CI, all *n*=3) and 59±20%, or 0.8±0.04 µg/puff and 2.0±0.5 µg/puff, respectively (Figure 1). Vanillin was carried over at 79±17%, resulting in the delivery of 7.9±0.8 µg/puff. Menthol was found in four of the eight tested flavors, and the menthol aerosol concentration of “Classic Menthol” and “Cool Mint” was 34±3 µg/puff and 38±12 µg/puff, respectively, which is comparable to mentholated cigarettes (29–392 µg/puff<sup>8</sup> for ten puffs/cigarette; 10%–20% carryover to cigarette smoke<sup>9</sup>). Nicotine and benzoic acid carryover were 98±6% and 82±5% (5%-pods, *n*=21), and 102±4% and 80±14% (3%-pods, *n*=5), respectively. However, a statistical significance between e-liquid and aerosol concentrations was found only for benzoic acid (Figure 1). Absolute nicotine aerosol content (114±13 µg/puff, 5%-pods, 65±15 µg/puff, 3%-pods) was comparable to previous reports analyzing JUUL or combustible cigarettes (50–180 µg/puff; ten puffs/cigarette).<sup>10–12</sup>

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**Figure 1.** Comparison of the concentrations of six compounds in neat e-liquid (background bars, varying shading) and captured aerosol (foreground bars, striped) for different JUUL flavors.

Note: Error bars represent 95% CI. Two-way ANOVAs with Bonferroni post-test results to compare neat e-liquids versus aerosol concentrations per compound were carried out using GraphPad Prism 8 software. A  $p$ -value of  $<0.05$  was interpreted as significant;  $***p<0.001$ .

<sup>a</sup>5%-nicotine flavors: Crème Brûlée, Fruit Medley, Mango, Cool Cucumber, Cool Mint, Classic Menthol, Classic Tobacco, and Virginia Tobacco.

<sup>b</sup>3%-nicotine flavors: Cool Mint, and Virginia Tobacco.

PG, propylene glycol; VG, glycerol.

## DISCUSSION

This study is the first to report the presence of flavor aldehyde VG acetals in e-liquids and aerosols and expands the authors' prior finding of flavor aldehyde PG acetals in commercial e-liquids.<sup>4</sup> JUUL e-liquids contain higher levels of vanillin VG acetals compared with vanillin PG acetal because of the higher VG:PG ratio. Flavor aldehyde–solvent acetal formation can be expected in any e-liquid–containing flavor aldehydes, including JUUL, at room temperature (e.g., without heating in the e-cigarette).<sup>4</sup> Furthermore, the possibility of other unintended chemical reactions between e-liquid constituents should be considered in future research.

Compounds present in JUUL e-liquids are delivered efficiently to the aerosol, exposing users to similar quantities of nicotine as cigarettes, to menthol in four of eight flavors, and to the PG and VG acetals of vanillin

(“Crème Brûlée”). Although vanillin PG/VG acetal aerosol carryover is slightly lower than nicotine, indicating possible acetal hydrolysis, appreciable amounts of acetals are present in the aerosol, which, if inhaled, may cause irritation and contribute to inflammatory responses.<sup>4,5</sup> The average vanillin puff concentration was  $101 \text{ mg/m}^3$ . In comparison, chronic inhalational exposure to vanillin in occupational environments is limited to  $10 \text{ mg/m}^3$ ,<sup>13</sup> raising the question of what long-term effects regular inhalation of vanillin at such doses and frequency (200 puffs/pod) might have. Aerosol menthol levels from “Fruit Medley” (5.3 ppm), which is not labeled as mentholated, and the other mentholated JUUL e-liquids (“Cool Cucumber”: 7.5 ppm, “Classic Menthol”: 63 ppm, and “Cool Mint”: 70 ppm) are sufficient to suppress respiratory irritation responses to aldehydes and tobacco smoke and increase nicotine intake.<sup>14,15</sup>

Future e-cigarette regulatory policy should address (1) the formation of new compounds with potential toxicologic properties within e-liquids, (2) JUUL menthol levels that may increase nicotine intake, and (3) flavorant exposure effects in e-cigarette users as also recently highlighted by the U.S. Food and Drug Administration.<sup>16</sup>

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