Comparative Health Risk Assessment of JUUL System and Combustible Cigarette

Roxana Weil, Charlene Liu, Perla Valencia Landestoy, Vincent Cheah, Christina Sulaiman, Bryant Hiraki, Clarissa Yang, Mike Oldham, Jie Zheng, and Felix Ayala-Fierro Juul Labs, Inc.

Introduction

Tobacco smoke is a highly complex mixture containing over 5000 constituents, 93 of which have been identified in tobacco products and tobacco smoke or aerosol by the U.S. Food and Drug Administration (USFDA) as harmful and potentially harmful constituents (HPHCs) linked to the most serious health effects of tobacco use (cancer, cardiovascular and respiratory diseases, and reproductive effects) (USFDA 2012). The JUUL System heats a nicotine-containing liquid within a pre-defined temperature range designed to minimize HPHCs formed as heat degradation by-products of the e-liquid ingredients. With the premarket tobacco product application (PMTA) as the pathway to market for electronic nicotine delivery systems (ENDS) in the US, there is a need to determine the potential health risks of ENDS products not only in relation to combustible cigarettes, but also as an independent product as an alternative to smoking. The objective of this study was to assess the relative noncancer hazards and cancer risk from use of the JUUL System (Virginia Tobacco 5.0% and Menthol 5.0%) compared to combustible cigarettes.

Methodology

Established and proposed HPHCs recommended by USFDA in the draft and final PMTA guidance for ENDS products (USFDA 2016 and 2019) were analyzed in aerosols for JUUL Virginia Tobacco 5.0% and Menthol 5.0% under both non-intense and intense puffing regimes, respectively. Non-intense puffing conditions were defined as puff volume 55 milliliter (mL), puff duration 3 seconds, and puff interval 30 seconds as per the CORESTA Recommended Method (CRM) No. 81 (55:3:30 CORESTA 2015). JUUL product-specific intense puffing condition was defined as 110 mL per puff, 6 second puffs with a 30 second interval (110:6:30). Aerosol generation, collection and chemical analysis were performed by an International Organization for Standardization (ISO) 17025 certified contract research organization (Labstat International Inc., Ontario, Canada and Enthalpy Analytical, Durham, NC) and all analytical methods were validated and included in their scope of accreditation when the analyses were performed.

For mainstream cigarette smoke, machine-generated HPHC yields in reference cigarette 3R4F smoke were obtained from the literature (Jaccard et al 2019) under ISO (35:2:60, ISO 2010) and ISO intense (55:2:30 ISO 2018) smoking conditions (formerly the Health Canada intense smoking regimen).

Average constituent levels normalized to per milligram (mg) nicotine from the non-intense puffing regimen for JUUL System were compared to those of 3R4F using ISO smoking regimen for cigarettes, and results using the intense puffing regimen for JUUL products were compared with results using the HCI smoking regimen for cigarettes. For the purpose of comparison with 3R4F, when a constituent in JUUL System aerosol is below limit of detection (LOD), its level is computed as half of reported LOD; when the constituent is below limit of quantification (LOQ), the level is considered as the average of reported LOD and LOQ. Comparisons could not be calculated for constituents when a yield value in the 3R4F cigarette was not available or the constituent yields were below LOD/LOQ in both the JUUL System and the 3R4F cigarette smoke.

Results

The aerosol produced from heating the JUUL System showed a marked reduction in the overall number and levels of HPHC and target constituents relative to cigarette smoke. The majority (41 out of 52) of the measured constituents, including HPHCs (established and proposed) were either below LOD or below the LOQ in the JUUL System aerosols. Of the 26 constituents measured in both JUUL System and 3R4F, all constituents in the JUUL System aerosols were present at lower levels relative to the yields in 3R4F cigarette smoke, resulting in a 94% or greater reduction in aerosol levels of chemicals or HPHCs (**Figures 1** and **2**). The only exceptions were propylene glycol, glycerin, and nicotine, which form the base formulation for JUUL System with benzoic acid.

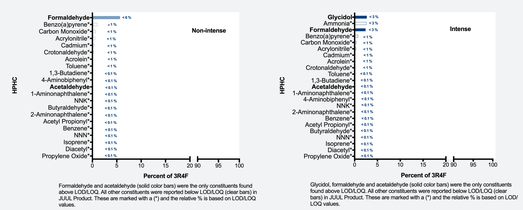
Table 1. Cancer classification and toxicological endpoints of the most hazardous constituents in cigarette smoke

HPHC	Cancer Classification			Toxicological Endpoints (USFDA 2012)		
	USEPA (2020)	US NTP (2016)	IARC (2020)	Respiratory Toxicant	Cardiovascular Toxicant	Reproductive or Developmental Toxicant
Acetaldehyde	Group B2	Reasonably anticipated to be a human carcinogen	Group 2B	√	-	-
Acrolein	-	-	-	√	√	-
Benzene	Group A	Known to be a human carcinogen	Group 1	-	√	√
Benzo(a)pyrene	Carcinogenic to Humans	Reasonably anticipated to be a human carcinogen	Group 1	-	-	-
1,3-Butadiene	Group B2	Known to be a human carcinogen	Group 1	√	-	√
Carbon Monoxide	-	-	-	-	-	√
Formaldehyde	Group B1	Known to be a human carcinogen	Group 1	√	-	-
NNK	-	Reasonably anticipated to be a human carcinogen	Group 1	-	-	-
NNN	-	Reasonably anticipated to be a human carcinogen	Group 1	-	-	-

HPHC=harmful or potentially harmful constituent; NNK= 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN=N'-nitrosonornicotine;
USFDA=United States Food and Drug Administration; US NTP= United States National Toxicology Program.
IARC=International Agency for Research on Cancer USEPA=United States Environmental Protection Agency
Group 1: Carcinogenic to humans Group A: Known human carcinogen
Group 2B: Possibly carcinogenic to humans Group B1 and B2: Probable human carcinogen

Nine HPHCs are identified by the World Health Organization (WHO) Study Group on Tobacco Product Regulation (Burns et al. 2008) as playing a major role in combustible cigarette smoke toxicity and mandated for reduction in cigarette smoke, including 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK), N'-nitrosonornicotine (NNN), acetaldehyde, acrolein, benzene, benzo[a]pyrene, 1,3-butadiene, carbon monoxide, and formaldehyde. Among the nine constituents, seven are classified as known or probable human carcinogens by the International Agency for Research on Cancer (IARC) and six are identified as respiratory, cardiovascular, and/or reproductive or developmental toxicants by the USFDA (2012) (**Table 1**). As shown **Figures 3** and **4**, seven of these most potent toxicants and carcinogens were absent in JUUL System aerosols and two were substantially reduced, resulting in greater than 94 to 99% reduction compared to those found in cigarette smoke. The marked decreases in the numbers and levels of these most hazardous constituents in JUUL System aerosols compared to cigarette smoke support substantial reductions in subsequent exposures and associated cancer risks and noncancer hazards from use of the JUUL System relative to cigarette smoking.

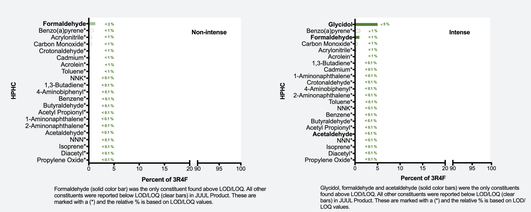
Figure 1. Comparison of HPHC levels in JUUL Virginia Tobacco 5.0% aerosol to levels in reference cigarette smoke 3R4F under non-intense and intense puffing/smoking conditions



Formaldehyde and acetaldehyde (solid color bars) were the only constituents found above LOD/LOQ. All other constituents were reported below LOD/LOQ in JUUL Product. These are marked with a (*) and the percent reduction is based on LOD/LOQ values.

Glycidol, formaldehyde and acetaldehyde (solid color bars) were the only constituents found above LOD/LOQ. All other constituents were reported below LOD/LOQ (clear bars) in JUUL Product. These are marked with a (*) and the relative % is based on LOD/LOQ values.

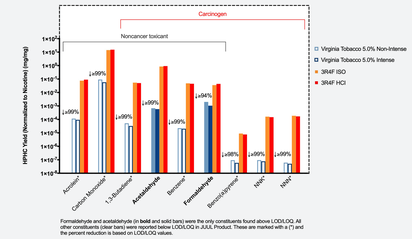
Figure 2. Comparison of HPHC levels in JUUL Menthol 5.0% aerosol to levels in reference cigarette smoke 3R4F under non-intense and intense puffing/smoking conditions



Glycidol, formaldehyde and acetaldehyde (solid color bars) were the only constituents found above LOD/LOQ. All other constituents were reported below LOD/LOQ (clear bars) in JUUL Product. These are marked with a (*) and the relative % is based on LOD/LOQ values.

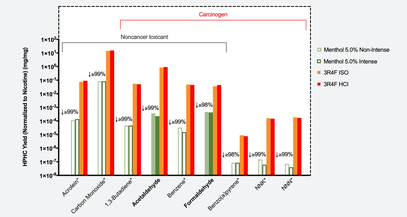
Glycidol, formaldehyde and acetaldehyde (solid color bars) were the only constituents found above LOD/LOQ. All other constituents were reported below LOD/LOQ (clear bars) in JUUL Product. These are marked with a (*) and the relative % is based on LOD/LOQ values.

Figure 3. Comparison of HPHC levels and percent reduction for the most hazardous HPHCs in JUUL Virginia Tobacco 5.0% aerosol to levels in 3R4F reference cigarette smoke under non-intense and intense puffing/smoking conditions



Formaldehyde and acetaldehyde (in **bold** and solid bars) were the only constituents found above LOD/LOQ. All other constituents (clear bars) were reported below LOD/LOQ in JUUL Product. These are marked with a (*) and the percent reduction is based on LOD/LOQ values.

Figure 4. Comparison of HPHC levels and percent reduction for the most hazardous HPHCs in JUUL Menthol 5.0% aerosol to levels in 3R4F reference cigarette smoke under non-intense and intense puffing/smoking conditions



Formaldehyde and acetaldehyde (in **bold** and solid bars) were the only constituents found above LOD/LOQ. All other constituents (clear bars) were reported below LOD/LOQ in JUUL Product. These are marked with a (*) and the percent reduction is based on LOD/LOQ values.

Conclusions

JUUL System aerosol targeted chemical characterization data demonstrate that although some thermal degradation products are present, these are far fewer in number and present in the aerosols at substantially lower levels in comparison to cigarette smoke. The decrease in the number and levels of HPHCs in JUUL System aerosols demonstrate likely substantial reductions in toxicant exposures and the overall associated health hazards (i.e., cancer risks and noncancer hazards) compared to cigarette smoking.

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