Targeted Characterization of the Chemical Composition of Novel JUUL Product Aerosol and Comparison with 3R4F Reference Cigarette Smoke

David K. Cook, Devon C. O'Regan, Adam O. Ozvald, Clarissa Yang, Gene I. Gillman

JUUL Labs Inc., Washington, D.C., U.S.A.

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 prototype study product consists of a closed pod and device which 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, 2019) and European Tobacco Product Directive (EUTPD, 2014) as the primary pathways to market for electronic nicotine delivery systems (ENDS) in the EU and 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 HPHC levels measured in aerosol generated from a prototype study product with four novel e-liquid formulations in 18 mg/mL nicotine concentration and compare to the 3R4F reference cigarette.

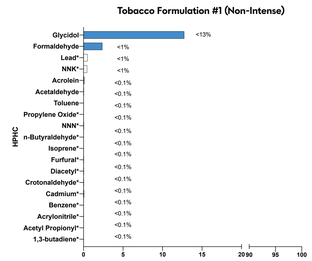
Methods

Established and proposed HPHCs recommended by global regulatory agencies (USFDA PMTA ENDS Guidance, 2019, and EUTPD, 2014) were analyzed in aerosols on four prototype formulations with an 18 mg/mL nicotine concentration 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). product-specific intense puffing condition was defined as 110 mL per puff, 6 second puff duration, and puff interval 30 seconds (110:6:30). Aerosol constituent levels were determined as a function of number of puffs based upon device mass loss (whole pod yield). Generation, collection, and chemical analysis were performed by an International Organization for Standardization (ISO) 17025 accredited contract research organization (Enthalpy Analytical, Durham, NC) and all analytical methods were validated and included in their scope of accreditation when the analyses were performed.

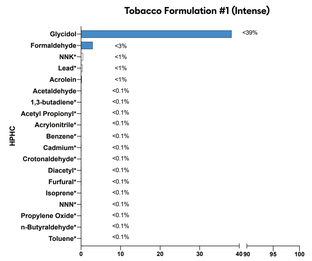
For mainstream cigarette smoke, machine generated HPHC yields in reference cigarette smoke were obtained from the literature (Jaccard et al 2019, Moldovenau et al 2017) under ISO (35:2:60, ISO 2010) and ISO intense (55:2:30 ISO 2018) smoking conditions (formerly the Health Canada Intense (HCI) smoking regimen) with one exception. Under ISO (35:2:60, ISO 2010), literature data for Glycidol was unavailable and a study was performed externally (Enthalpy Analytical, Richmond, VA) to obtain values for comparison.

Average constituent levels normalized to per milligram (mg) nicotine from the non-intense puffing regimen for the prototype study product were compared to those of 3R4F using ISO smoking regimen for cigarettes, and results using the intense puffing regimen for the prototype products were compared with results using the HCI smoking regimen for cigarettes. For the purpose of comparison with 3R4F, when a constituent in the prototype study product aerosol is below the limit of detection (LOD), its level is computed as half of the 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 prototype and the 3R4F cigarette smoke.

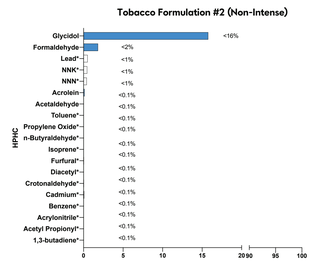
Figure 1. Comparison of HPHC levels in novel tobacco formulation (18 mg/mL) aerosol levels to 3R4F reference cigarette smoke under non-intense and intense puffing/smoking conditions



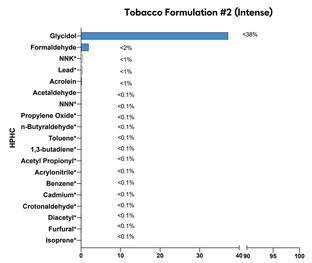
Formaldehyde, acrolein, acetaldehyde and toluene (solid color bars) were the only comparable constituents found above LOD/LOQ. All other constituents were reported below LOD/LOQ (clear bars) in JUUL product. These are marked with a (*) and the relative % is based on LOD/LOQ values.



Glycidol, formaldehyde, acrolein, and acetaldehyde (solid color bars) were the only comparable 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.

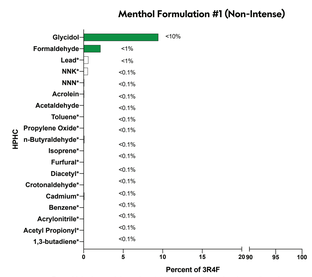


Formaldehyde, acrolein, and acetaldehyde (solid color bars) were the only comparable constituents found above LOD/LOQ. All other constituents were reported below LOD/LOQ (clear bars) in JUUL product. These are marked with a (*) and the relative % is based on LOD/LOQ values.

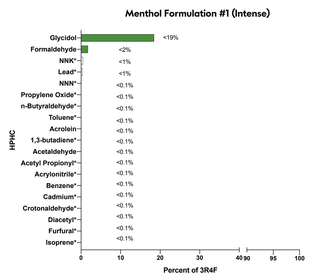


Glycidol, formaldehyde, acrolein, and acetaldehyde (solid color bars) were the only comparable constituents found above LOD/LOQ. All other constituents were reported below LOD/LOQ (clear bars) in JUUL product. These are marked with a (*) and the relative % is based on LOD/LOQ values.

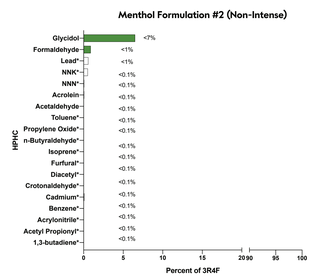
Figure 2. Comparison of HPHC levels in novel menthol formulation (18 mg/mL) aerosol levels to 3R4F reference cigarette smoke under non-intense and intense puffing/smoking conditions



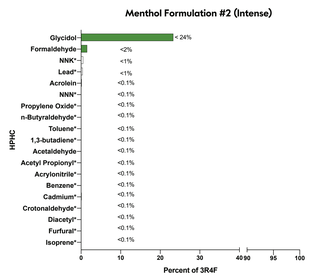
Formaldehyde, acrolein, and acetaldehyde (solid color bars) were the only comparable constituents found above LOD/LOQ. All other constituents were reported below LOD/LOQ (clear bars) in JUUL product. These are marked with a (*) and the relative % is based on LOD/LOQ values.



Glycidol, formaldehyde, acrolein, and acetaldehyde (solid color bars) were the only comparable 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.



Formaldehyde, acrolein, and acetaldehyde (solid color bars) were the only comparable 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.

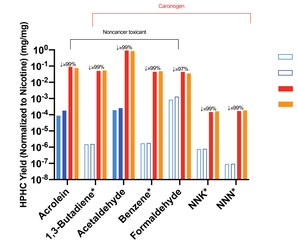


Glycidol, formaldehyde, acrolein, and acetaldehyde (solid color bars) were the only comparable constituents found above LOD/LOQ. All other constituents were reported below LOD/LOQ (clear bars) in JUUL product. These are marked with a (*) and the relative % is based on LOD/LOQ values.

Results

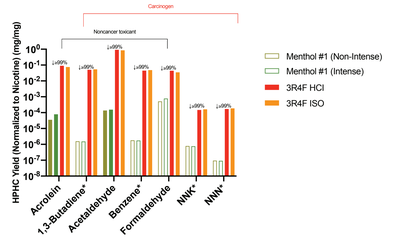
The aerosol produced from heating the prototype study product showed a marked reduction in the overall number and levels of HPHC and target constituents relative to cigarette smoke. The majority (38 out of 54) of the measured constituents, including HPHCs (established and proposed) were either below LOD or below the LOQ in the prototype study product aerosols. Six HPHCs (β-Nicotyrine, Ethyl Acetate, Iron, Mysomine, Nicotine-N-Oxide, and Nornicotine) were above the LOQ in one or more of the prototype study product aerosols but comparisons could not be calculated due to unavailable 3R4F cigarette yields. Of the 19 constituents measured in both the prototype study product and 3R4F, all constituents in the prototype aerosols were present at lower levels relative to the yields in 3R4F cigarette smoke, resulting in a 96% or greater reduction in aerosol levels of chemicals or HPHCs, on average (**Figures 1 and 2**). The only exceptions were propylene glycol, glycerin, and nicotine, which form the base formulation for the prototype study product with benzoic acid.

Figure 3. Comparison of HPHC levels and percent reduction for the most hazardous HPHCs in novel tobacco formulation (18 mg/mL) aerosol levels to 3R4F reference cigarette smoke under non-intense and intense puffing/smoking conditions



Formaldehyde and acetaldehyde (solid bars) were the only comparable 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 4. Comparison of HPHC levels and percent reduction for the most hazardous HPHCs in novel menthol formulation (18 mg/mL) aerosol levels to 3R4F reference cigarette smoke under non-intense and intense puffing/smoking conditions



Formaldehyde and acetaldehyde (in solid bars) were the only comparable 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.

Among the constituents tested, six are known or probable human carcinogens by the International Agency for Research on Cancer (IARC) and five are identified as respiratory, cardiovascular, and/or reproductive or developmental toxicants by the USFDA (2012). As shown **Figures 3 and 4**, five of the most potent toxicants and carcinogens were absent in the prototype study product aerosols and two were substantially reduced, resulting in greater than 99% reduction compared to those found in cigarette smoke. The marked decreases in the numbers and levels of these most hazardous constituents in the prototype study product aerosols compared to cigarette smoke support substantial reductions in subsequent exposures and associated cancer risks and noncancer hazards from use of the prototype study product relative to cigarette smoking.

Conclusions

The prototype study product aerosol targeted chemical characterization data demonstrate that although some thermal degradation products are present, these are far fewer in number at substantially lower levels in comparison to cigarette smoke. The decrease in the number and levels of HPHCs in 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.

References

CORESTA. Routine Analytical Machine For E-Cigarette Aerosol Generation And Collection - Definitions And Standard Conditions. Coresta 2015. No. 81;2015

International Agency for Research on Cancer. Agents Classified by the IARC Monographs, Volumes 1–127. https://monographs.iarc.fr/agents-classified-by-the-iarc/. Updated 26 June 2020, Accessed September 2020. International Standard Organization (ISO), ISO-3308, Routine Analytical Cigarette-Smoking Machine-Definitions and Standard Conditions, 2000.

Jaccard G, Djoko D, Korneliou A, Stabbert R, Belushkin M, Esposito M. Mainstream smoke constituents and in vitro toxicity comparative analysis of 3R4F and 1R6F reference cigarettes. Toxicology Reports. 2019;6:222-231.

MOLDOVEANU S.; HUDSON A.G.; HARRISON A. The determination of diacetyl and acetylpropionyl in aerosols from electronic smoking devices using gas chromatography triple quad mass spectrometry. Beiträge zur Tabakforschung International. Contributions to Tobacco Research Volume 27 @ No. 7 @ August 2017 DOI:10.1515/cttr-2017-0015

USFDA. Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems. Guidance for Industry. In: Silver Spring, MD: Food and Drug Administration, Center for Tobacco Products,; 2019: https://www.fda.gov/media/127853/download.

This study was funded by JUUL Labs, Inc.