Comparative Harmful and Potentially Harmful Constituent Assessment of NJOY® ACE and Marketed Electronic Nicotine Delivery Systems Products

Abstract

Background and purpose: As part of the US Food and Drug Administration's (FDA's) assessment of the risks and benefits of marketing a new tobacco product to the population, those seeking Premarket Tobacco Product Application (PMTA) approval must demonstrate that the new products are protective of public health compared to combustible cigarettes and to products within the same category.

Methods: Harmful and Potentially Harmful Constituent (HPHC) emissions data from 74 peer-reviewed studies were examined for Electronic Nicotine Delivery Systems (ENDS) across a range of product categories (including cig-a-like, heat-not-burn, pod, fixed power tank, and variable power tank products) and for combustible cigarettes. Aerosol concentration data were converted to µg/puff from the range of reported concentrations and normalized to nicotine to enable consistent comparisons across studies. The average HPHC:nicotine ratios of carbonyls, volatile organic compounds (VOCs), tobacco-specific nitrosamines (TSNAs), metals, and humectants in cigarettes or comparator ENDS from the literature were compared to measured 95th percentile values of constituents in the aerosol of NJOY ACE products.

Results: NJOY ACE products produced markedly lower levels of carbonyls (98%-100% less), VOCs (99.5%-100% less), TSNAs (86.6%-99.9% less), and major constituents or associated HPHCs (68.7%-100% less) compared to cigarette smoke when normalized to an equivalent dose of nicotine. Carbonyls, VOCs, TSNAs, and major constituents or associated HPHCs from NJOY ACE products were less than the average of these constituents from other comparator ENDS products. Chromium and nickel emissions produced by NJOY ACE products exceeded levels observed in combustible cigarette smoke (these metals are generally nondetectable in cigarettes); however, these levels were lower or comparable to other comparator ENDS products.

Conclusions: The exposures to most HPHCs from NJOY ACE products are significantly less than those from combustible cigarettes. NJOY ACE product HPHC exposures which exceed those from combustible cigarettes, are lower than or comparable to those from other ENDS products. NJOY ACE products resulted in lower cumulative exposure to HPHCs when compared to combustible cigarettes and lower or comparable exposures when compared to other ENDS products.

Introduction

The assessment of HPHCs in ENDS is a critical component of regulatory evaluation, particularly in the context of a PMTA. The FDA requires manufacturers to demonstrate that a new tobacco product is appropriate for the protection of public health (APPH) by evaluating its potential risks to adult smokers relative to existing products on the market. NJOY ACE, a closed-system pod-based ENDS, has been evaluated alongside combustible cigarettes and other marketed ENDS to compare HPHC profiles, providing insight into product specific exposure risks. This comparative assessment is essential for understanding variations in aerosol-delivered toxicants, informing regulatory decision-making, and ensuring consumers have access to potentially lower-risk alternatives to combustible

Methods



HPHC emissions data from 74 published peer-review studies were examined for combustible cigarettes and ENDS across a range of product categories (including cig-a-likes, pods, tanks, and heated tobacco). 36 HPHCs were the target of this search. This data was used to determine whether the NJOY ACE product delivers more or less HPHCs per unit of nicotine compared to e-cigarettes, as well as combustible cigarettes. Of the HPHCs (not including nicotine) listed in the FDA PMTA final guidance, approximately 24 HPHCs were measured and described in the available combustible cigarette smoke literature. Databases searched: PubMed, Scopus, Web of Science, PsycINFO (ProQuest), MEDLINE (Ovid), and Embase (Ovid).

Where studies reported individual concentrations, weighted averages were calculated and included in the analysis for each HPHC where available. Values reported as below or equal to the limit of detection (LOD), limit of quantification (LOQ), or non-detect (ND), were calculated as one half the reported LOD or LOQ for that study (e.g., LOD/2). Inconvertible data were excluded from our analysis. Aerosol concentration data were converted to µg/puff and µg/L from the range of reported concentrations (e.g., mg/m3, ppm/puff, µg/15 puffs) to allow for consistent comparison across studies.

Consumer use and topography are driven by self-titration to a desired level of nicotine; normalizing HPHCs to nicotine allows for a "side-by-side" comparison of NJOY ACE to other tobacco products. HPHC mean concentration data (ug/puff) were normalized to reported mean nicotine concentrations (ug/puff) for all ENDS device types by calculating the ratio of HPHC concentrations to nicotine concentrations when possible. For combustible cigarettes, 15 cigarettes/day at 2 mg nicotine/cigarette were considered for an average adult smoker. HPHC to nicotine ratios for each device type were compared to those for combustible cigarettes and expressed as percent change:

> ENDS HPHC: nicotine ratio – Combustible HPHC: nicotine ratio $-x \, 100$ Combustible HPHC: nicotine ratio

Evaluation **ENDS** Literature



*NJOY ACE HPHC concentrations (mg/puff) were measured in the aerosol from both standard (non-intense-puff) duration and volume of 3 seconds and 55 mL, 30 sec. interval) and intense (puff duration and volume of 5 seconds and 71 mL, 60 sec. interval) puffing regimens. T0 stability data from 10 formulations (5 flavors in 2 nicotine strengths) were assessed. The 95th percentile values of the measured aerosol concentrations from NJOY ACE products were used in the comparative assessment as a conservative approach representing the upper-bound consumer exposures associated with NJOY ACE products.

Results

The majority of HPHCs in NJOY ACE are substantially reduced compared to **Combustible Cigarettes when normalized to nicotine content**



Select HPHCs (chromium, nickel, glycidol, propylene glycol, and glycerol), are elevated in NJOY ACE products relative to combustible cigarettes



Percent reductions presented are based on NJOY ACE product non-intense T0 data and are representative of all conditions and timepoin assessed per stability study data; the lowest value in the range is reported in charts as a ercent reduction from reference cigarette 1R6F. HPHC:nicotine ratios reported ranges: 98.2-100% lower for carbonyls; 90.1 - 99.9% ower for VOCs; 99.5- 100.0% lower for TSNAs; 86.6 – 99.9% lower for cadmium and lead; VOCs - volatile organic compounds; TSNAs tobacco-specific nitrosamines

 <Limit Of Detection (LOD) or <Limit Of Quantification (LOQ).

- Glycidol and chromium concentrations were not detected or quantified.
- Exposure estimates in this risk assessment are driven by detection limits and exposures are likely overestimated due to nondetectable measurements in cigarette smoke.

Results





The red dashed line represents the combustible cigarette value. Box plots are presented, such that the median, upper and lower quartiles (75th and 25th percentiles) and upper and lower extremes (90th and 10th percentiles) of the reported mean ENDS concentrations (gray bars) and measured 95th percentiles of NJOY ACE concentrations are presented (green bars); Statistical differences are indicated with capital letters, such that boxes that share the same letter are not statistically significant (p<0.05). Additional analytes not shown: Carbonyls: Acetyl propionyl, acrolein, butyraldehyde, diacetyl, furfural; VOCs: Benzene, Propylene oxide; TSNAs: NNK, NNN: Metals: Cadmium, Lead.

- products.

Conclusion

- to combustible cigarettes or other ENDS products

References

Counts et al., 2005; Jaccard et al., 2019; Margham et al., 2016; Pierce et al., 2014; St Helen et al., 2018

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NJOY ACE exposures are less than or comparable to marketed ENDS products

HPHCs from NJOY ACE were significantly lower than combustible cigarettes for majority of HPHCs Select HPHCs were higher than combustible cigarettes, including chromium, nickel, glycidol (glycidol) measurements were non-detectable), propylene glycol, and glycerol, HPHC:nicotine ratios • NJOY ACE HPHC exposures that exceed CC levels are lower than or comparable to those from other ENDS

The total cumulative exposure to HPHCs measured in NJOY ACE was markedly reduced compared to CC

• The use of the NJOY ACE product results in overall lower exposure to HPHCs when compared

• The reduced exposure to HPHCs relative to CC and comparable exposures to other ENDS products contributed to the FDA CTP APPH determination of tobacco and menthol products.



