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# E-CIGARETTES COMPOSITION: NICOTINE CONCENTRATION AND NICOTINE SALTS

April 2020

Public Health England;[1] the National Academies of Science, Engineering and Medicine;[2] and the FDA have recognized that nicotine products exist on a continuum of risk,[3] with e-cigarettes at the lower end near traditional nicotine replacement therapies and combustible cigarettes at the highest end of the risk spectrum.

Importantly, in its comprehensive report, Public Health England stated that e-cigarettes are unlikely to exceed 5 percent of the risk associated with combustible cigarettes.[4] These products are recognized as presenting a reduced risk because they don't employ the traditional cigarette combustion process that releases around 7,000 chemicals, some of which are highly carcinogenic. Former FDA Commissioner Scott Gottlieb also made reduced-risk products like e-cigarettes central to the FDA's roadmap:

> While it's the addiction to nicotine that keeps people smoking, it's primarily the combustion, which releases thousands of harmful constituents into the body at dangerous levels, that kills people. This fact represents both the biggest challenge to curtailing cigarette addiction—and also holds the seeds of an opportunity that's a central construct for our actions. E-cigarettes may present an important opportunity for adult smokers to transition off combustible tobacco products.[5]

## NICOTINE CONCENTRATION

### Nicotine concentration in combustible use

It is vital that products intended to replace combustible cigarettes are able to achieve a nicotine delivery profile similar to that of combustible cigarettes.[6] During daily smoking, typical peak blood nicotine concentrations range from 19 to 50 ng/ml, while typical trough concentrations range from 10 to 37 ng/ml; depending on how the cigarette is smoked, each cigarette increases blood nicotine concentrations by 5 to 30 ng/ml.[7] By contrast, unrestricted use of nicotine replacement therapy products generally achieves only one- to two-thirds the blood nicotine concentration achieved from combustible cigarettes.[8] For an individual with high nicotine dependence, the ability to more accurately duplicate the nicotine delivery profile of combustible cigarettes with e-cigarettes may be what makes complete switching successful.

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1. RCP policy: public health, *Nicotine without smoke: Tobacco harm reduction*, Royal College of Physicians, April 28, 2016. https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction-0. Ann McNeill, et al., "Vaping in England: an evidence update including mental health and pregnancy, March 2020 A report commissioned by Public Health England," Public Health England. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/869401/Vaping_in_England_evidence_update_March_2020.pdf

2. "The Public Health Consequences of E-cigarettes," National Academies of Science, Engineering and Medicine, January 2018. http://nationalacademies.org/hmd/reports/2018/public-health-consequences-of-e-cigarettes.aspx. "Across a range of studies and outcomes, e-cigarettes appear to pose less risk to an individual than combustible tobacco cigarettes."

3. Scott Gottlieb, M.D., on new steps to address epidemic of youth e-cigarette use, "Statement from FDA Commissioner," U.S. Food and Drug Administration, 2018. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm620185.htm.

4. Tobacco Advisory Group, "Nicotine without smoke: tobacco harm reduction," Royal College of Physicians, 2016. p. 87. https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction-0.

5. Scott Gottlieb, M.D., on comprehensive regulatory plan to shift trajectory of tobacco-related disease, death, "Statement from FDA Commissioner," U.S. Food and Drug Administration, 2018. https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm568923.htm. "A key piece of the FDA's approach is demonstrating a greater awareness that nicotine – while highly addictive – is delivered through products that represent a continuum of risk and is most harmful when delivered through smoke particles in combustible cigarettes."

6. Konstantinos Farsalinos et al. "Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices." *Scientific Reports* 4:4133 (2014). https://www.ncbi.nlm.nih.gov/pubmed/24569565/.

7. Neal L. Benowitz et al. "Nicotine Chemistry, Metabolism, Kinetics and Biomarkers." Handbook of Experimental Pharmacology 192 (2009), pp. 29-60. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2953858/.

8. Ibid.

### E-cigarettes and nicotine concentration

If e-cigarettes are to be a viable substitute for combustible cigarettes, the nicotine concentration in e-cigarettes must mimic that of combustible cigarettes.

In their article assessing nicotine absorption from e-cigarettes, Dr. Konstantinos Farsalinos et al. state that "Nicotine delivery to the bloodstream is important in determining the addictiveness of ECs, but also their efficacy as smoking substitutes."[9] They also find that e-liquids with a nicotine concentration of approximately 50 mg/ml are necessary to deliver nicotine in a similar profile to combustible cigarettes.

Farsalinos et al. found that 20 percent of e-cigarette users initiated use with e-liquids that contained nicotine concentrations greater than 20 mg/ml and nearly a quarter used nicotine concentrations greater than 20 mg/ml at the time they stopped using combustible cigarettes.[10] These results suggest that increasing the availability of e-liquids with nicotine concentrations greater than 20 mg/ml may assist smokers who have not quit successfully with the products currently available.[11]

## E-CIGARETTE ADDITIVES AND "SALTS"

### Defining "salts"

"Salts" refers to inactive ionized compounds that attach to a biologically active compound. Salts are used to alter the pH of a compound to maximize solubility and absorption.

Salts are important in drug formulation because they maximize efficient delivery of active compounds to their intended biological target and stability of the active compound.[12] Salts do not change the biological effects of the active compound, but they can change the factors that enable bodies to absorb, deliver and metabolize the active compounds. Linking an appropriate salt to an active compound can improve factors such as solubility, stability, toxicity and poor absorption. More than half of commonly used drugs consist of pharmaceutical salts.

### Salts in e-cigarettes

Due to the higher pH of freebase nicotine (i.e., molecularly unaltered nicotine) that is poorly absorbed, nicotine salts are used to achieve a pH closer to neutral. This allows e-liquids to contain higher nicotine concentrations without becoming intolerable, allowing them to more closely replicate the nicotine delivery of combustible cigarettes.

One key aspect of the utility of e-cigarettes in transitioning away from combustible products is their ability to closely match nicotine distribution in the body. Nicotine exists at a pH that makes this process inefficient. However, when combined with combustion, nicotine becomes more acidic and thus better able to distribute itself throughout the body. In an e-cigarette, a similar concentration of nicotine results in approximately 70 percent less exposure than that of combustible cigarettes.[13] Interestingly, as the concentration of nicotine—and thus the pH of the solution—in e-cigarettes increases, this distribution becomes less effective.

Combined with a salt formulation, such as benzoic acid or nicotine lactate, the nicotine solution can be lowered to a pH that allows for better distribution at lower concentrations. Although there is no evidence that nicotine in any currently marketed e-cigarette can reach the plasma concentrations of combustible products,

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9. Konstantinos Farsalinos et al. (2014) https://www.ncbi.nlm.nih.gov/pubmed/24569565/.

10. Konstantinos Farsalinos et al., "Evaluating Nicotine Levels Selection and Patterns of Electronic Cigarette Use in a Group of "Vapers" Who Had Achieved Complete Substitution of Smoking," *Substance Abuse* 7 (2013), pp. 139-146. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3772898/

11. Ibid

12. Deepak Gupta et al., Salts of Therapeutic Agents: Chemical, Physicochemical, and Biological Considerations, Molecules 23:7 (2018) https://www.ncbi.nlm.nih.gov/pubmed/30011904

13. Grant O'Connell et al., "A randomised, open-label, cross-over clinical study to evaluate the pharmacokinetic profles of cigarettes and e-cigarettes with nicotine salt formulations in US adult smokers," *Internal and Emergency Medicine*. 14 (2019) pp. 853-861. https://link.springer.com/article/10.1007/s11739-019-02025-3.

distribution does increase to approximately 77 percent of that of combustible cigarettes at the highest concentrations available (5mg).[14]

Using nicotine salts to manufacture e-liquids also decreases the volume of e-liquid a user must inhale in order to achieve a similar blood concentration and facilitates aerosolization at a lower temperature compared to e-liquids made with freebase nicotine.[15] The use of salts to facilitate delivery of more highly concentrated substances is common in pharmacology, because the process often makes substances more stable, improves absorption and allows greater purity, often making a drug compound more effective and more easily manufactured.[16]

### Nicotine concentration after switching.

Research indicates that higher nicotine concentrations help smokers make the initial switch from combustible cigarettes. They can achieve nicotine delivery similar to combustible cigarettes, and the concentration can be decreased gradually based on the user's needs and desires.[17] It has been shown that nicotine concentrations used after complete switching from combustible cigarettes decreased compared to what was used at initiation or complete transition.[18]

## USING HARM REDUCTION POLICY TO REDUCE THE DISEASE BURDEN FROM SMOKING

When considering regulations aimed at reducing the burden of smoking, we strongly urge policymakers to consider the utility of harm reduction and reduced-risk products alongside prevention measures. It is imperative that access to e-cigarettes and vapor products remains at a level that encourages, rather than discourages, people to choose these less harmful products over combustible cigarettes. Doing so will reduce the incidence and cost of tobacco-related disease.

## CONTACT US

For more information on this subject, contact the R Street Institute, 1212 New York Ave. N.W., Washington, D.C. 20005, 202-525-5717.

Chelsea Boyd
Research Associate, Harm Reduction
cboyd@rstreet.org

14. Peter Hajek et al., "Nicotine delivery to users from cigarettes and from different types of e-cigarettes," *Psychopharmacology* 234 (2017) pp. 773–779. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5306435/.

15. Ann McNeill, et al. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/869401/Vaping_in_England_evidence_update_March_2020.pdf

16. Timothy Scott Wiedmann and Amir Naqwi, "Pharmaceutical salts: Theory, use in solid dosage forms and in situ preparation in an aerosol," *Asian Journal of Pharmaceutical Sciences* 11:6 (2016) pp. 722-734. sciencedirect.com/science/article/pii/S1818087616300514

17. Konstantinos Farsalinos et al., 2013. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3772898/.

18. Ibid.