Why nicotine salts make vaping products more addictive

Pass the salt

What is a nicotine salt?

Chemically speaking, a salt is a substance that is produced by the reaction of an acid with a base.

Nicotine, as extracted from tobacco or created synthetically, is a base (pH greater than 7). In this form, it is sometimes called **freebase nicotine**. Freebase nicotine is harsh to the taste and hard to inhale.

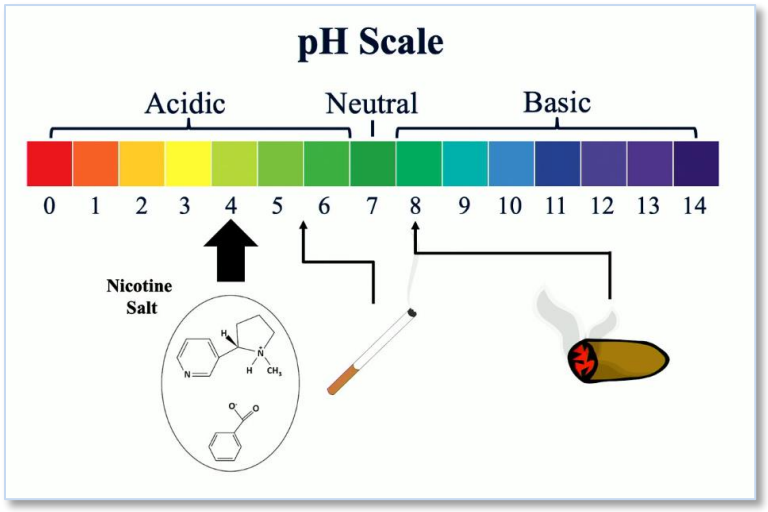

Figure 1 courtesy of Dr. Arit Harvanko, UCSF

Exposing freebase nicotine to an acid converts the nicotine to a salted form. The nicotine molecule picks up a hydrogen proton, making it similar to the **protonated nicotine** found in cigarettes. This form has lower pH and produces a smoother sensation when being inhaled.

E-cigarette companies treat nicotine with organic acid to produce nicotine salts. JUUL uses benzoic acid; Vype uses lactic acid. Other brands use levulinic acid, or a combination of organic acids.

E-cigarettes that are not treated with organic acids to create nicotine salts would have a pH of about 7.5-8.0. Like cigars, they would be harsh to the taste and hard to inhale. Canadian cigarettes, which are smoother to the taste than American-blend cigarettes, have a slightly lower pH in the range of 5 to 6.[1] [2]

Tobacco companies studied nicotine salts but used other ways to control pH in cigarette smoke.

The tobacco industry has long known that organic acids could be used to create nicotine salts and that this would reduce harshness and make cigarettes more inhalable, and their studies of these methods began in the 1950s and continued until the 1990s.[3]

Cigarette manufacturers, however, chose other methods to produce smooth-tasting cigarettes with low pH. American-blend cigarettes are made with both flue-cured and air-cured tobaccos, the latter being higher in pH and harsh to the taste. To reduce the pH, the air-cured tobaccos are treated with sugar, licorice and other additives. These additives are not necessary in flue-cured tobaccos because the sugars are created during the curing process, when leaf starches are converted into sugars. Canadian cigarettes, which are made entirely from flue-cured tobacco have very high sugar content (about 20%), are smooth to the taste and have low pH.

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Sugars are neither acidic nor basic but are precursors of tobacco organic acids. Whether added or created in the curing process, when these sugars are combined with freebase nicotine and undergo a chain of chemical reactions, monoprotonated nicotine is formed. As a result, the nicotine in cigarettes is mostly easily inhalable monoprotonated nicotine, but this acidic form of nicotine is derived indirectly from sugars, not directly from organic acids.[4]

E-cigarette makers used tobacco company science to make their products deliver more nicotine.

Our awareness of tobacco industry science is made possible by the Truth Tobacco Library, a public resource of formerly secret industry documents that was created mainly so that public health researchers could better understand what went on behind closed doors in the tobacco industry in the past.[5]

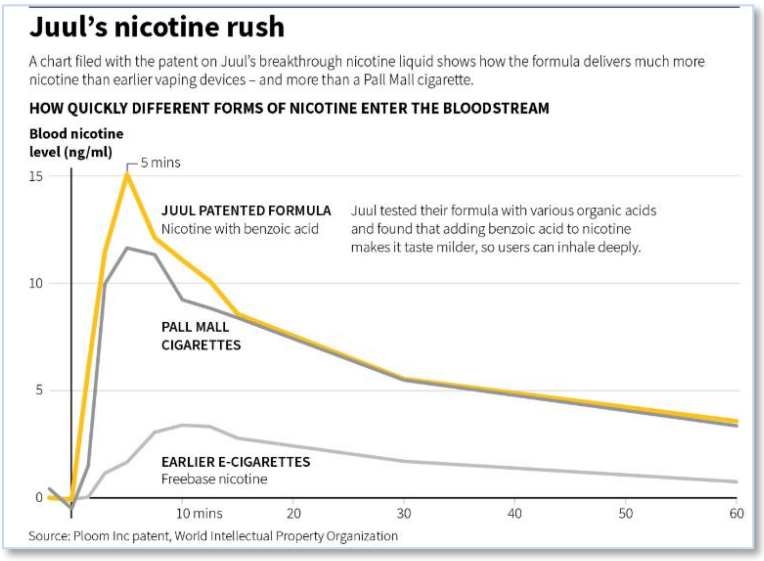

Figure 2: Data from JUUL inventors' patent application

A public record, like the Truth Tobacco Library is open to all, even those more interested in private gain than the public good. JUUL Lab's founders, James Monsees and Adam Bowen took advantage of the Truth Tobacco Library to thoroughly study tobacco industry research into organic acids. This led them to try adding organic acids to their e-cigarette products.

By converting freebase nicotine to nicotine salts, they found they could change a harsh-feeling product into a more inhalable one. They also found they could greatly increase the concentration of nicotine and still maintain a smooth taste.[6] They patented their methods, noting that the "formulation facilitates administration of nicotine to an organism (e.g. lungs)" and measuring the speed of absorption in the blood.[7] They applied the technology to JUUL, which they started marketing in 2015.

This patented formulation quickly delivered nicotine to the blood and in larger quantity than a Pall Mall cigarette, as shown in the figure above[8]. This nicotine "kick" was achieved using a nicotine concentration of 4%, less than the 5% concentration most commonly sold.

JUUL was the first e-cigarette brand to use nicotine salts, but other manufacturers have quickly copied JUUL, and achieved similar results. Imperial Tobacco Canada, a subsidiary of British-American Tobacco (BAT) sells Vype ePen 3 and ePod. These products are similarly designed to JUUL but use lactic acid instead of benzoic acid to generate nicotine salts.

BAT found that it could almost exactly mimic a cigarette for delivery of blood nicotine by using 30 mg of nicotine salts in its ePen 3.[9] It is reasonable to assume that a 57 mg/ml product (5%), which they sell in Canada as the ePod, delivers even more nicotine to the blood.

Freebase nicotine and nicotine salts can be used together to produce an optimized nicotine hit.

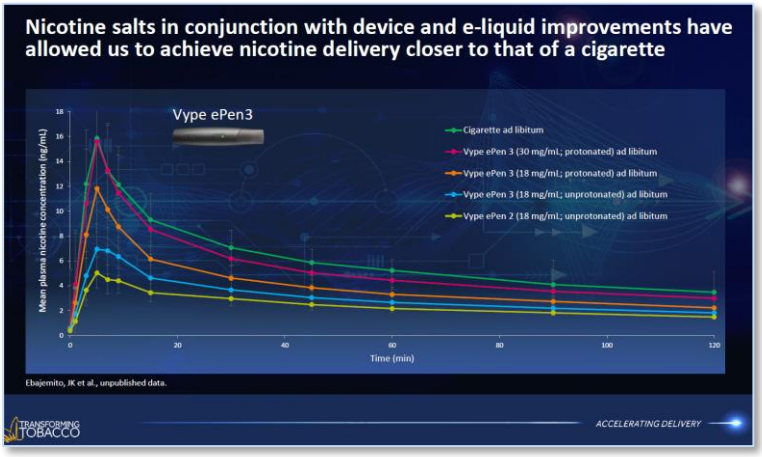

Figure 3: The green line shows how much and how quickly nicotine is in the blood stream from a 30 mg/ml protonated e-cigarette; the red line gives values for a combustible cigarette.

If one is looking for nicotine to reach the brain quickly, the freebase version of nicotine has one desirable property. Because it is volatile, it is very quickly and readily absorbed through the semi-permeable membranes that line the mouth and tiny air sacs in the lungs. But the drug delivery designer also faces problems with this version of nicotine. Because of its harshness, it is impossible to inhale large quantities deeply into the lungs.

Nicotine that is absorbed through the lining of the mouth instead of being inhaled into the lungs will pass into venous blood. This takes longer to reach the brain. Venous blood has to pass from capillaries to larger veins, through the liver where the nicotine will be partly metabolized into cotinine, then to the heart, then through the pulmonary artery to the lungs where the blood will be re-oxygenated, then back to the heart through the pulmonary vein, then through the aorta and then through arteries, arterioles and capillaries, all before it reaches the brain. This whole cycle takes about 30 seconds to a minute. This form of drug administration delivers gentle rise and a gentle fall in blood nicotine (like the grey line in Figure 2).

The more acidic, smoother version of nicotine also presents its own advantages and disadvantages to the drug delivery device designer. Without the irritation of a “throat hit”, it is easier to inhale. But with an extra proton on each molecule, it is slower to be absorbed into the bloodstream. Little if any will pass into the bloodstream through the lining of the mouth. When it reaches the alveoli in the lungs it will be absorbed a few seconds slower than any freebase nicotine that could get inhaled.

Once across the semi-permeable membranes in the lungs and into the bloodstream, however, the nicotine is delivered quickly to the brain. Inhalation short-circuits de-toxification in the liver. The blood in the lungs is being re-oxygenated. Now blood bearing nicotine and oxygen is sent back to the heart through the pulmonary vein and is immediately pumped through the aorta and throughout the body, including the brain. Inhaled nicotine will reach the brain in about 7-10 seconds. It will only begin to be metabolized to cotinine on its second circuit through the circulatory system when it will pass through the liver. Repeated puffs will keep short-circuiting the liver and delivering large doses of nicotine to the brain every 7-10 seconds.

By following the path of tobacco companies, e-cigarette companies have also made their products more addictive.

A nicotine delivery system which maximizes addiction will be looking to optimize nicotine delivery by using both the advantages of rapid absorption of freebase nicotine and the smooth taste and deep inhalation of monoprotonated nicotine, the nicotine salt. The solution is to make an inhalable product that is mostly smooth-tasting acidic nicotine but that nevertheless has a small proportion of harsh but rapidly absorbed harsh higher pH nicotine.

American blend cigarettes offer this optimized solution. The most widely sold of these is Marlboro Red, which delivers 90% smoother lower pH nicotine and 10% faster-acting but harsh higher pH nicotine. The harsh taste of the latter is somewhat masked by the smooth taste of the former.[10] Canadian cigarettes, made entirely from flue-cured tobacco achieve this solution too, but with a smoother, milder inhalation experience. They deliver about 99% smooth-tasting nicotine and 1% harsh freebase nicotine.[11]

Some e-cigarettes have also optimized nicotine delivery to the lungs. The most successful is JUUL, which has 40% of the U.S. e-cigarette market.[12] JUUL, like Marlboro Red, delivers nicotine to the lungs that is about 10% harsh, freebase nicotine and 90% smoother nicotine salt.

> "De-freebasing has undoubtedly made e-cigarettes more effective as substitutes to get smokers off combustibles. However, as with smoked tobacco, it is likely that e-cigarettes have also been made vastly more addictive for never-smokers. The full public health implications of widely prevalent e-cigarette use will only become fully apparent perhaps a decade hence." – Duell, AK et al, 2019

Researchers have recently examined proportion of freebase nicotine and nicotine salt in the aerosol of several brands of American e-cigarettes.[13] Most of the JUUL brand variants stood out from other brands as offering the highest total nicotine delivery (50-60 mg/ml) while also containing about 10% fast-acting freebase nicotine. This study also found a way to compare the amount of nicotine in cigarettes with that in e-cigarettes, observing that JUUL at 57 mg/ml was roughly equivalent to a cigarette. In short, JUUL not only found a way to encourage the inhalation of large concentrations of nicotine, equivalent to that in cigarettes, it also optimized the way nicotine was delivered to produce an impact similar to that of many cigarette brands.

The researchers concluded that e-cigarette manufacturers were following the same trajectory that had been established by cigarette companies. Just as additives had made air-cured tobacco less harsh so that cigarette smokers could inhale more nicotine, the same is now happening with e-cigarettes. "It's déjà vu all over again," they conclude: "The evolution of e-cigarettes has followed a similar overall trajectory… exactly as occurred with smoked tobacco, this evolution has made e-cigarette products vastly more addictive for never-smokers."[14]

Health regulators have been slow to respond.

For more than two decades, regulators have recognized the need to address the use of additives in tobacco products, including those which increase the attractiveness and addictiveness of the products. The 2005 guidelines that were developed to assist parties to the Framework Convention on Tobacco Control in controlling the contents of tobacco products, for example, recommend that "Parties should regulate, by prohibiting or restricting, ingredients that may be used to increase palatability in tobacco products" and set reducing addictiveness as a regulatory objective.[15]

The European Union appointed a panel of experts to report on the "Addictiveness and Attractiveness of Tobacco Additives." Their 2010 report predated e-cigarettes, but concluded that "additives that facilitate deeper inhalation… may enhance the addictiveness of nicotine indirectly," and that additives that increased attractiveness could result in "decreasing the harshness of the smoke, and inducing a pleasant experience of smoking.".[16]

When the European Union Directive on tobacco was revised in 2014 to include e-cigarettes, it required Member States to ban the use in tobacco products of "additives that facilitate inhalation or nicotine uptake."[17] Some governments have also banned the use of such additives in e-cigarettes: France bans "des additifs qui facilitent l'inhalation ou l'absorption de nicotine" in vaping products,[18] as does Iceland.[19] Despite this, e-liquids made with nicotine salts are for sale in France.

ENDNOTES

1 Hood J. Smoke pH. Quebec Class Actions. January 17, 1979, Exhibit 676A. https://www.industrydocuments.ucsf.edu/tobacco/docs/#id=mlnv0223.

2 Harvanko A and Kozlovich S. Nicotine salts: What are they and what are they doing in e-cigarettes. Presentation at UCSF Seminar "Its about a billion lives." January 31, 2020. https://lecture.ucsf.edu/ets/Play/491aa488c1d74cb08cb3ae73d84bc87e1d.

3 RJ Reynolds Tobacco. Review of the use of organic acids and nicotine salts in tobacco burning cigarettes. April 6, 1990. https://www.industrydocuments.ucsf.edu/docs/#id=lmmn0097

4 See: Hood J. Smoke pH. Quebec Class Actions. January 17, 1979. https://www.industrydocuments.ucsf.edu/tobacco/docs/#id=mlnv0223 and Flue-cured tobacco variety data: 1989 tests and summaries. Agriculture Research Station. Delhi, Ontario, Canada. https://www.industrydocuments.ucsf.edu/tobacco/docs/#id=pjfh0223

5 University of California at San Francisco. Industry Documents Library: Overview. https://www.industrydocuments.ucsf.edu/about/overview/.

6 Kirkham C. Special Report: Juul disregarded early evidence it was hooking teens. Reuters. November 5, 2019. https://www.reuters.com/article/us-juul-ecigarettes-special-report/special-report-juul-disregarded-early-evidence-it-was-hooking-teens-idUSKBN1XF1JG

7 Bowen et al. Nicotine salt formulations for aerosol devices and methods thereof. US Patent US 2015/0020824 https://patentimages.storage.googleapis.com/57/f8/7e/2db69f396801d5/US20150020824A1.pdf

8 Ploom Inc. patent. World Intellectual Property Organization. As reported by Reuters. https://www.reuters.com/article/us-juul-ecigarettes-special-report/special-report-juul-disregarded-early-evidence-it-was-hooking-teens-idUSKBN1XF1JG

9 BAT Investor Day. 14 May 2019. Science supporting accelerated delivery. Slide 21.

10 Duell AK, Pankow JF, Peyton DH. Nicotine in tobacco product aerosols: 'It's déjà vu all over again'. Tob Control 2019;**0**:1–7. doi:10.1136/tobaccocontrol-2019-055275. https://tobaccocontrol.bmj.com/content/tobaccocontrol/early/2019/12/16/tobaccocontrol-2019-055275.full.pdf

11 Hood J. Smoke pH. Quebec Class Actions. January 17, 1979. https://www.industrydocuments.ucsf.edu/tobacco/docs/#id=mlnv0223

12 Altria. Fourth Quarter 2019 Earnings Conference Call. January 2020. http://investor.altria.com/Cache/1001260222.PDF?O=PDF&T=&Y=&D=&FID=1001260222&iid=4087349

13 Duell AK, Pankow JF, Peyton DH. Nicotine in tobacco product aerosols: 'It's déjà vu all over again'. Tob Control 2019;**0**:1–7. doi:10.1136/tobaccocontrol-2019-055275. https://tobaccocontrol.bmj.com/content/tobaccocontrol/early/2019/12/16/tobaccocontrol-2019-055275.full.pdf

14 Duell AK, Pankow JF, Peyton DH. Nicotine in tobacco product aerosols: 'It's déjà vu all over again'. Tob Control 2019;**0**:1–7. doi:10.1136/tobaccocontrol-2019-055275. https://tobaccocontrol.bmj.com/content/tobaccocontrol/early/2019/12/16/tobaccocontrol-2019-055275.full.pdf

15 Framework Convention on Tobacco Control. Partial guidelines for implementation of Articles 9 and 10. https://www.who.int/fctc/treaty_instruments/guidelines_articles_9_10_2017_english.pdf?ua=1

16 European Union. Scientific Committee on Emerging and Newly Identified Health Risks. Addictiveness and Attractiveness of Tobacco Additives, 2010. https://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_031.pdf

17 European Union. Directive 2014/40/EU of the European Parliament and of the Council of 3 April 2014. https://ec.europa.eu/health//sites/health/files/tobacco/docs/dir_201440_en.pdf

18 Government of France. Ordonnance n° 2016-623 du 19 mai 2016 portant transposition de la directive 2014/40/UE sur la fabrication, la présentation et la vente des produits du tabac et des produits connexes. Art. L. 3513-7 https://www.legifrance.gouv.fr/jo_pdf.do?id=JORFTEXT000032547462

19 Government of Iceland. Act on electronic cigarettes and refill containers for electronic cigarettes, No. 87/2018. Article 9. https://www.tobaccocontrollaws.org/files/live/Iceland/Iceland%20-%20E-Cigs%20Act%20%28No.%2087_2018%29.pdf

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