

Tobacco Product Standard for Nicotine Level:

The FDA Should Set a Nicotine Level to be Achieved in a Single Step for All Combusted Tobacco Products

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The scientific evidence supports a specific standard for all combusted tobacco products, with a nicotine level for the standard implemented in a single step. The tobacco companies have already shown that it is technically possible to implement such a standard. In implementing this standard there are substantial risks of adversely affecting risk perceptions, especially among youth, that could lead to increased use of nicotine products not covered by the new standard. Effectively countering these adverse effects needs to be part of the standard and associated public education from the beginning to prevent the tobacco industry from taking advantage of this standard to expand its market resulting in net population harm. *Lowering the nicotine delivery of all combusted tobacco products – not just cigarettes – if written and enforced vigorously in a way that anticipates tobacco industry efforts to thwart the intent of the standard, holds promise for improving public health.*¹

1. SCOPE

(1) If FDA were to propose a product standard setting a maximum nicotine level, should such a standard cover other combusted tobacco products in addition to cigarettes? If so, which other products? If FDA were to propose to include additional categories of combusted tobacco products in a nicotine tobacco product standard, should the standard be tailored to reflect differences in these products? What criteria should be used to determine whether, and which, products should be covered?

The product standard should, at a minimum, include all combusted products. Cigarette smokers can smoke branded cigarettes and roll-your-own tobacco, as well as little cigars and cigarillos. Pipe tobacco has been used as a roll-your-own tobacco product. *Because of the interchangeability of tobacco products, any national nicotine reduction should apply to all combustible tobacco products.*

The original Benowitz and Henningfield proposal

¹ This conclusion should not be read as an endorsement of the hypothesis that other forms of recreational tobacco use are safer or more desirable than combusted products. Assessment of that question is beyond the scope of this comment.

The original proposal to reduce the nicotine content and cigarettes was published by Benowitz and Henningfield in 1994.² The rationale for that proposal was primarily to prevent youth who experimented with cigarette smoking from becoming addicted adult smokers. While most youth who try cigarettes begin for social reasons and indicate that they do not intend to remain smokers as adults, when surveyed 5 years later most have become addicted smokers and are unable to quit. A non-addicted person cannot truly appreciate what drug addiction is like, and therefore cannot make a reasonably informed consent to take that risk. Cigarettes are manufactured with nicotine content and delivery levels that will sustain addiction, based on tobacco company research. Thus, a young person who begins smoking for social reasons may transition to smoking for the pharmacologic effects of nicotine and ultimately become an addicted adult smoker. Cigarettes that deliver nicotine in levels that produce addiction are unreasonably dangerous in part because consent to their use by youth is impossible. Thus, reducing nicotine levels will likely significantly reduce the probability likelihood that a youth experimenting with cigarettes or other combustible tobacco products would become addicted.

Another beneficial effect of reducing nicotine would be to promote quitting in addicted adult smokers. Most smokers want to quit smoking, and wish they had never started. Reducing the nicotine content of cigarettes to non-addicting levels would result in smokers finding their cigarettes to be much less satisfying and likely quitting smoking. For smokers with a high degree of nicotine dependence, it was proposed that non-combustible forms of nicotine would be readily available so that smokers would not have to suffer severe withdrawal symptoms or lose any perceived benefits of nicotine for mood modulation or other self-medication for psychiatric reasons. The original proposal was to gradually reduce the nicotine content of cigarettes over time, to simulate a tapering process that is commonly used to detoxify people from other drugs of abuse. However, as discussed below, a rapid reduction of nicotine levels might provide better overall public health benefit.

Clinical studies of feasibility and safety

Most of the initial studies on the feasibility and safety of nicotine reduction came from the Benowitz research group at UCSF. The researchers obtained cigarettes that contained different levels of nicotine, ranging from 10 mg to 0.6 mg.³ These cigarettes were supplied by Philip Morris, who mixed regular tobacco with tobacco from which nicotine had been extracted with liquid carbon dioxide and made into a Marlboro-like cigarette. These research cigarettes differ from commercial low yield cigarettes, which contain high levels of nicotine, and are low yield due to engineering features, including filter ventilation.

One of the major concerns about reducing nicotine in cigarettes was that smokers would smoke more cigarettes or smoke cigarettes more intensively to maintain desired levels of nicotine intake. In a UCSF laboratory study, smokers were asked to smoke on separate days cigarettes with various levels of nicotine, with measurement of plasma nicotine levels, cigarette

² Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction. The implications for tobacco regulation. N Engl J Med. 1994 Jul 14;331(2):123-5.

³ Benowitz NL, Jacob P 3rd, Herrera B. Nicotine intake and dose response when smoking reduced-nicotine content cigarettes. Clin Pharmacol Ther. 2006 Dec;80(6):703-14.

satisfaction ratings, and various nicotine-related pharmacologic effects.⁴ Exposure to nicotine, based on the area under the plasma nicotine concentration curve, was highly correlated with the nicotine content of the cigarettes. There was some evidence of compensation at intermediate nicotine levels, but little compensation at low levels of nicotine. As expected, smokers found very low nicotine cigarettes to be less satisfying than cigarettes with higher nicotine levels. Compensation did not occur because the nicotine content in the lowest nicotine cigarette was just too low – approximately 5% of the nicotine of conventional cigarettes – and also because the smoke was too harsh to inhale extremely large amounts.

Following this study, two clinical trials with gradual nicotine reduction were conducted at UCSF. One was a pilot study of 20 smokers who reduced their nicotine content of their cigarettes weekly for 6 weeks, and then had a 4-week follow up.⁵ At the higher nicotine levels, there was a small increase in number of cigarettes smoked per day, but at the end of 6 weeks, smokers smoked fewer cigarettes compared to baseline. Nicotine intake decreased by 70%, and a lower level of nicotine dependence was reported. Extensive biomarker measurement found no evidence of compensation. Withdrawal symptoms were minimal, although participants did gain weight. In the four weeks following the end of the study, smokers smoked fewer cigarettes per day and had lower intake of nicotine compared to baseline, suggesting a resetting of their internal nicotine seeking set point.

A second UCSF study involved a larger number of smokers (N = 135) who reduced their nicotine levels monthly over 6 months, and then remained on the lowest nicotine cigarette for 6 months.⁶ A control group included smokers smoking their usual brand of normal nicotine content cigarettes. The findings were similar to the pilot study, in that smokers decreased their nicotine intake by on average 70%, withdrawal symptoms were minimal, and there was no evidence of compensation, either by cigarettes per day or biomarkers of exposure. Smokers of very low nicotine cigarettes for 6 months continued to have reduced nicotine exposure, but nicotine exposure did increase over time. In both studies, nicotine intake was higher than expected from the nicotine content of cigarettes, consistent with some non-compliance with research cigarettes.

After these studies, other researchers published studies on reduced nicotine, and generally replicated the findings of our earlier studies.⁷

⁴ Benowitz NL, Jacob P 3rd, Herrera B. Nicotine intake and dose response when smoking reduced-nicotine content cigarettes. *Clin Pharmacol Ther.* 2006 Dec;80(6):703-14.

⁵ Benowitz NL, Hall SM, Stewart S, Wilson M, Dempsey D, Jacob P 3rd. Nicotine and carcinogen exposure with smoking of progressively reduced nicotine content cigarette. *Cancer Epidemiol Biomarkers Prev.* 2007 Nov;16(11):2479-85.

⁶ Benowitz NL, Dains KM, Hall SM, Stewart S, Wilson M, Dempsey D, Jacob P 3rd. Smoking behavior and exposure to tobacco toxicants during 6 months of smoking progressively reduced nicotine content cigarettes. *Cancer Epidemiol Biomarkers Prev.* 2012 May;21(5):761-9. doi: 10.1158/1055-9965.EPI-11-0644. Epub 2012 Feb 21. Benowitz NL, Nardone N, Dains KM, Hall SM, Stewart S, Dempsey D, Jacob P 3rd. Effect of reducing the nicotine content of cigarettes on cigarette smoking behavior and tobacco smoke toxicant exposure: 2-year follow up. *Addiction.* 2015 Oct;110(10):1667-75. doi: 10.1111/add.12978. Epub 2015 Jul 21.

⁷ Hatsukami DK, Kotlyar M, Hertsgaard LA, Zhang Y, Carmella SG, Jensen JA, Allen SS, Shields PG, Murphy SE, Stepanov I, Hecht SS. Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation. *Addiction.* 2010 Feb;105(2):343-55. doi: 10.1111/j.1360-0443.2009.02780.x.

(2) Some suggest that large cigars and those cigars typically referred to as “premium” cigars should be regulated differently from other cigars, asserting that they are used primarily by adults and their patterns of use are different from those of regular cigars (81 FR 28973 (/citation/81-FR-28973) at 29024). FDA requests information and data on whether large and/or so-called premium cigars should be excluded from a possible nicotine tobacco product standard based on asserted different patterns of use, and whether large and/or so-called premium cigars would be migration (or dual use) candidates if FDA were to issue a nicotine tobacco product standard that excluded premium cigars from its scope. FDA also requests data and information on whether and how there is a way that, if FDA were to exclude premium cigars from the scope of a nicotine tobacco product standard, FDA could define “premium cigar” to include only unlikely migration or dual use products and thereby minimize such consequences.

The FDA should include *all* combusted products in this standard. Use patterns of “premium” cigars are currently different from cigarettes, in part because the pH of the smoke is more alkaline than cigarette smoke, which allows nicotine to be absorbed through the oral cavity without inhalation, but renders the smoke difficult to inhale. Exempting them would create a loophole that tobacco companies could exploit by lowering the pH of large cigars, making the smoke easier to inhale without discomfort, and making cigars more addictive than they currently are. An exemption for premium cigars would leave the door open for tobacco companies to turn premium cigars into large cigarettes.

(3) Should waterpipe tobacco products, which are different from regular pipe tobacco, be included in such a standard? Are there data showing different use topographies or that they are not likely to be migration substitutes or dual use candidates? If FDA were to issue a nicotine tobacco product standard that did not include waterpipe tobacco products within the scope, what would be the likelihood that former smokers would switch to waterpipe tobacco to maintain their nicotine addiction? What are the relative risk consequences of switching to waterpipe tobacco?

Waterpipes are not safer alternatives to combustible cigarettes. Several studies have measured tobacco-related toxicants in waterpipe smoke, including polycyclic aromatic hydrocarbons (PAHs), volatile organic compounds (VOCs) such as formaldehyde, acetone, and acrolein, and carcinogenic tobacco-specific nitrosamines (TSNAs).⁸ Waterpipe smoking machine studies indicated that the amount of waterpipe tobacco used in a single smoking session

Hatsukami DK, Donny EC, Koopmeiners JS, Benowitz NL. Compensatory smoking from gradual and immediate reduction in cigarette nicotine content. *Cancer Epidemiol Biomarkers Prev.* 2015 Feb;24(2):472-6. doi: 10.1158/1055-9965.EPI-14-0739. Epub 2014 Dec 16.

⁸ Schubert J, Heinke V, Bewersdorff J, Luch A, Schulz TG. Waterpipe smoking: the role of humectants in the release of toxic carbonyls. *Arch Toxicol.* 2012;86(8):1309-16.

Shihadeh A, Saleh R. Polycyclic aromatic hydrocarbons, carbon monoxide, "tar", and nicotine in the mainstream smoke aerosol of the narghile water pipe. *Food Chem Toxicol.* 2005;43(5):655-61.

Schubert J, Hahn J, Dettbarn G, Seidel A, Luch A, Schulz TG. Mainstream smoke of the waterpipe: does this environmental matrix reveal as significant source of toxic compounds? *Toxicol Lett.* 2011;205(3):279-84.

produced 100-fold more tar, 4-fold more nicotine, 11-fold more CO, and 2- to 5-fold more polycyclic aromatic hydrocarbons than did a single cigarette.⁹

Tobacco used in waterpipe is often a sweetened flavored tobacco mixture and contains nicotine at various concentrations on the label, such as 0.05% or 0.5% nicotine. Waterpipe tobacco in the US is usually composed of a moist fruit preparation containing varying amounts of tobacco, which explains the varying nicotine concentrations. The nicotine level advertised on the label does not predict nicotine exposure even when users' smoking topography is standardized.¹⁰ This is because the nicotine on the labels may not be accurate. For this reason, and because the manufacturers could easily increase the amount of tobacco in the fruit preparation, waterpipe tobacco should be included in the standard.

The health risks associated with waterpipe use are determined to a great extent by the use patterns and intensity of use. Although the prevalence and/or frequency of waterpipe use in the U.S. may be lower than that of combustible cigarettes, a single waterpipe session typically lasts for 45 minutes and may produce 50 to 100 times the smoke volume inhaled from a single cigarette.¹¹ An hour-long session of smoking waterpipes gives users a dose of nicotine similar to smoking two to three cigarettes, and delivers qualitatively the same toxicants, albeit at different concentrations, to the body.¹²

To date, UCSF has conducted three comprehensive studies of systemic intake of tobacco-related toxicants from waterpipe use.

In the first study, involving a single use of waterpipe in a hospital research ward, we measured plasma nicotine levels that were comparable to levels attained after smoking cigarettes; carbon monoxide levels were much higher than in cigarette smokers; and we measured significant increases in urine NNAL, a breakdown product of NNK (a nicotine-derived nitrosamine and known pulmonary carcinogen), as well as breakdown products of PAHs.¹³

We then conducted a crossover study to compare nicotine intake and carcinogen exposure from waterpipe and cigarette smoking. This study was also conducted in a hospital research ward. Compared to cigarette smoking, we reported lower nicotine intake, greater carbon monoxide exposure, and a different pattern of carcinogen exposure, with greater exposure to

⁹ Shihadeh A, Saleh R. Polycyclic aromatic hydrocarbons, carbon monoxide, "tar", and nicotine in the mainstream smoke aerosol of the narghile water pipe. *Food Chem Toxicol* 2005;43:655–61.

¹⁰ Vansickel AR, Shihadeh A, Eissenberg T. Waterpipe tobacco products: nicotine labelling versus nicotine delivery. *Tob Control* 2011;tc. 2010.042416.

¹¹ Haddad L, El-Shahawy O, Ghadban R, et al. Waterpipe Smoking and Regulation in the United States: A Comprehensive Review of the Literature. *Int J Environ Res Public Health* 2015;12(6):6115–6135. doi:10.3390/ijerph120606115.

¹² Jacob P 3rd, Abu Raddaha AH, Dempsey D, Havel C, Peng M, Yu L, Benowitz NL. Nicotine, carbon monoxide, and carcinogen exposure after a single use of a water pipe. *Cancer Epidemiol Biomarkers Prev*. 2011 Nov;20(11):2345-53. doi: 10.1158/1055-9965.EPI-11-0545. Epub 2011 Sep 9.

Jacob P 3rd, Abu Raddaha AH, Dempsey D, Havel C, Peng M, Yu L, Benowitz NL. Comparison of nicotine and carcinogen exposure with water pipe and cigarette smoking. *Cancer Epidemiol Biomarkers Prev*. 2013 May;22(5):765-72. doi: 10.1158/1055-9965.EPI-12-1422. Epub 2013 Mar 5.

Everts S. What's Hookah, And Is It Healthier Than Smoking A Cigarette? *Chemical & Engineering News*, Vol. 93, Issue 25, p. 41, June 22, 2015.

¹³ Jacob P, Raddaha AHA, Dempsey D, Havel C, Peng M, Yu L, et al. Nicotine, carbon monoxide, and carcinogen exposure after a single use of a water pipe. *Cancer Epidemiology Biomarkers & Prevention*. 2011;20(11):2345-53.

benzene and high molecular weight PAHs, and less exposure to tobacco-specific nitrosamines, 1,3-butadiene and acrolein, acrylonitrile, propylene oxide, ethylene oxide, and low molecular weight PAHs following waterpipe smoking.¹⁴ This study showed that exposure to tobacco smoke toxicants in waterpipe smoke is similar qualitatively but quantitatively delivers higher levels of several toxicants than cigarette smoke. Importantly, exposure to benzene, a chemical known to cause leukemia in humans, and high molecular weight PAHs, which are known to be more potent carcinogens than the lighter weight PAHs, were higher while smoking waterpipe than tobacco cigarettes.

The third study entailed assessing nicotine intake and exposure to tobacco-specific nitrosamines and volatile organic compounds from waterpipe smoking in a natural setting (i.e., hookah bars or lounges) as opposed to a hospital research ward. In the natural setting, waterpipe users shared waterpipes with multiple users. Again, this study showed substantial nicotine intake comparable to at least one cigarette as well as significant exposure to NNK (measured using urine NNAL) and breakdown products of carcinogenic VOCs such as benzene, 1,3-butadiene, acrylonitrile, and ethylene oxide.¹⁵

Carbon monoxide (CO) is a toxicant that is a risk for all users,⁹ with some studies showing extremely high CO levels for users.¹⁶ Case reports have even indicated CO poisoning among young adult waterpipe users.^{17 18 19}

A study published in March 2016 assessing the effects of waterpipe smoking on the human lung in young, light-use waterpipe smokers found that young, light-use waterpipe-only smokers have a variety of abnormalities in multiple lung-related biologic and clinical parameters including more cough and sputum, lower lung diffusing capacity, abnormal epithelial lining fluid metabolome profile, increased proportions of small airway epithelial (SAE) secretory and intermediate cells, reduced proportions of SAE ciliated and basal cells, markedly abnormal SAE and alveolar macrophage transcriptomes, and elevated levels of apoptotic endothelial cell microparticles.²⁰ These results suggest that even limited waterpipe use has broad consequences on human lung biology and health.

The charcoal used to heat the tobacco-fruit preparation is a significant source of toxicants in the waterpipe smoke that users inhale. Charcoal is produced by incomplete combustion of wood. As in incomplete combustion of other organic materials, polycyclic aromatic hydrocarbons (PAHs) are produced. It is well known that burning charcoal produces large amounts of CO.

¹⁴ Jacob P, Raddaha AHA, Dempsey D, Havel C, Peng M, Yu L, et al. Comparison of Nicotine and Carcinogen Exposure with Water pipe and Cigarette Smoking. *Cancer Epidemiology Biomarkers & Prevention*. 2013;22(5):765-72.

¹⁵ St.Helen G, Benowitz NL, Dains KM, Havel C, Peng M, Jacob P, 3rd. Nicotine and carcinogen exposure after water pipe smoking in hookah bars. *Cancer Epidemiol Biomarkers Prev*. 2014;23(6):1055-66.

¹⁶ Barnett TE, Curbow BA, Weitz JR, et al. (2009) Water pipe tobacco smoking among middle and high school students. *AJPH*, 99, 2014-2019. doi:10.2105/AJPH.2008.151225.

¹⁷ Ashurst JV, Urquhart M., Cook MD (2012). Carbon monoxide poisoning secondary to hookah smoking. *Journal American Osteopathic Association*, 112,686–688.

¹⁸ Cavus UY, Rehber ZH, Ozeke O (2010). Carbon monoxide poisoning associated with Narghile use. *Emergency Medicine Journal*, 27, 406. doi:10.1136/emj.2009.077214

¹⁹ Lim BL, Lim GH, Seow E (2010). Case of carbon monoxide poisoning after smoking shisha. *International Journal of Emergency Medicine*, 11, 121–122. doi:10.1007/s12245-009-0097-8

²⁰ Strulovici-Barel Y, Shaykhiev R, Salit J, et al. Pulmonary Abnormalities in Young, Light-use Waterpipe (Hookah) Smokers. *AJRCCM Articles in Press*. Published on 23-March-2016 as 10.1164/rccm.201512-2470OC.

Burning charcoal produces benzene,²¹ a carcinogen associated with increased incidence of leukemia. Charcoal emissions were the primary source of CO and carcinogenic PAHs; 90% of CO and 75-92% of 4- and 5-ring PAHs (the heavy molecular PAHs) originated from the charcoal.²²

Waterpipe smoking presents health risks that in some ways are higher than cigarette smoking. One session of waterpipe use can lead to inhalation of 40 to 80 liters of smoke versus approximately 1 liter of smoke from a cigarette.²³ Many of the toxicants found in cigarette smoke are found in waterpipe smoke, which includes polycyclic aromatic hydrocarbons, volatile aldehydes, carbon monoxide, and heavy metals. Given the higher volume of smoke inhalation, a waterpipe user can be exposed to greater levels of these toxicants than from smoking a cigarette.²⁴

It is not known to what extent former cigarette smokers would switch to waterpipe smoking under a Very Low Nicotine Content (VLNC) cigarette policy, but to the extent that people do so, it would be bad for public health. Waterpipe smoking has increased over the past decade in the United States, most notably among adolescents and young adults.²⁵ Young adults who engage in waterpipe smoking are most often dual- or poly-users with other tobacco or nicotine products: among young-adult waterpipe smokers in the FDA/NIH Population Assessment of Tobacco and Health (PATH) study, only 29% were exclusive users of waterpipe.²⁶ The high prevalence of dual-use suggests that waterpipe smoking would be viewed as an acceptable alternative to cigarettes for at least some adult cigarette smokers. On the other hand, relatively few waterpipe smokers presently use waterpipe on a daily (4%) or weekly (23%) basis.²⁷ At a low frequency of use, waterpipe smoking may not serve as a satisfactory replacement for cigarettes. However, if VLNC cigarette policy drives an increase in waterpipe smoking frequency, the subsequent increase in toxicant exposure would be significant.

Finally, presenting waterpipe as a “safer” alternative to conventional cigarettes could increase youth use, something harmful in its own right, and that may have additional consequences because waterpipe use is a gateway to conventional cigarette use. Waterpipe use among never cigarette smoking youth is associated with about a doubling (OR, 1.92; 95% CI,

²¹ Olsson M; Petersson G. Benzene emitted from glowing charcoal. *Science of the Total Environment* 2003; 303: 215-220.

²² Monzer B, Sepetdjian E, Saliba N, Shihadeh A. Charcoal emissions as a source of CO and carcinogenic PAH in mainstream narghile waterpipe smoke. *Food Chem Toxicol.* 2008;46(9):2991-5.

²³ Pepper JK, Eissenberg T. Waterpipes and electronic cigarettes: increasing prevalence and expanding science. *Chem Res Toxicol.* 2014 Aug 18;27(8):1336-43.

²⁴ Shihadeh AL, Eissenberg TE. Significance of smoking machine toxicant yields to blood-level exposure in water pipe tobacco smokers. *Cancer Epidemiol Biomarkers Prev.* 2011 Nov;20(11):2457-60; Pepper JK, Eissenberg T. Waterpipes and electronic cigarettes: increasing prevalence and expanding science. *Chem Res Toxicol.* 2014 Aug 18;27(8):1336-43.

²⁵ Soule EK, Lipato T, Eissenberg T. Waterpipe tobacco smoking: A new smoking epidemic among the young? *Curr Pulmonol Rep.* 2015 Dec 1;4(4):163-172.

²⁶ Salloum RG, Thrasher JF, Getz KR, Barnett TE, Asfar T, Maziak W. Patterns of Waterpipe Tobacco Smoking Among U.S. Young Adults, 2013-2014. *Am J Prev Med.* 2017 Apr;52(4):507-512.

²⁷ Salloum RG, Thrasher JF, Getz KR, Barnett TE, Asfar T, Maziak W. Patterns of Waterpipe Tobacco Smoking Among U.S. Young Adults, 2013-2014. *Am J Prev Med.* 2017 Apr;52(4):507-512.

1.17-3.17) of the odds of subsequent cigarette initiation in PATH.²⁸

To the extent that smokers switch to waterpipe, they could increase their levels of toxicant exposure, so this effect needs to be considered as part of developing any nicotine standard.

2. MAXIMUM NICOTINE LEVEL

A. Very low nicotine content (VLNC) cigarettes

(1) FDA specifically requests comment on the conclusions of the 2013 Benowitz paper (<https://www.ncbi.nlm.nih.gov/pubmed/23591498>) and the possible impact of higher or lower maximum nicotine levels.

In the original Benowitz and Henningfield proposal,²⁹ a threshold nicotine content for a minimally-addictive cigarette was estimated to be 0.5 mg, as compared to 10 to 15 mg for typical commercial cigarettes. The basis for this estimate was that a person smoking 5 cigarettes per day, a level associated with low levels of addiction, would consume a maximum of 5 mg nicotine per day from a typical 10 mg cigarettes. Assuming an average absolute bioavailability of nicotine from a cigarette of 10%, and assuming an attempt at compensation to increase inhalation up to four-fold, it would require smoking 30 cigarettes or more per day to take in 5 mg from 0.5 mg cigarettes. For an addicted smoker who normally takes in 20 mg nicotine per day, reaching that level would take more than 100 cigarettes per day. Thus, it was reasoned that smokers would not be able, and would not try, to compensate to reach addicting levels of nicotine from a cigarette that contained 0.5 mg nicotine.

Subsequently a large study by Donny et al., in which UCSF was a participating site, compared smoking behavior over 6 weeks in smokers provided with cigarettes of differing nicotine content, ranging from 15.8 to 0.4 mg nicotine/gram tobacco.³⁰ In smokers who switched to cigarettes containing 2.4, 1.3, or 0.4 mg nicotine/gram tobacco, the number of cigarettes and intake of nicotine decreased significantly compared to controls smoking higher nicotine content cigarettes. Withdrawal symptoms were minimal, dependence scores decreased, and there was no biochemical evidence of compensation. The study concluded that a 0.4 mg nicotine content cigarette would be the best target for nicotine reduction to make cigarettes minimally addictive.

The research on nicotine thresholds and effects on consumption and cessation has focused on adult established cigarette smokers. It is possible that lower nicotine cigarettes may appeal to youth. On one hand, if the nicotine level in cigarette tobacco was reduced to non-addicting levels, then youth who wanted to experiment with cigarettes or smoke for social reasons might

²⁸ Watkins SL, Glantz SA, Chaffee BW. Association of Noncigarette Tobacco Product Use With Future Cigarette Smoking Among Youth in the Population Assessment of Tobacco and Health (PATH) Study, 2013-2015. *JAMA Pediatr.* 2018 Feb 1;172(2):181-187. doi: 10.1001/jamapediatrics.2017.4173.

²⁹ Benowitz NL, Henningfield JE. Reducing the nicotine content to make cigarettes less addictive. *Tob Control.* 2013 May;22 Suppl 1:i14-7. doi: 10.1136/tobaccocontrol-2012-050860. <https://www.ncbi.nlm.nih.gov/pubmed/23591498>

³⁰ Donny EC, Denlinger RL, Tidey JW, Koopmeiners JS, Benowitz NL, Vandrey RG, al'Absi M, Carmella SG, Cinciripini PM, Dermody SS, Drobos DJ, Hecht SS, Jensen J, Lane T, Le CT, McClernon FJ, Montoya ID, Murphy SE, Robinson JD, Stitzer ML, Strasser AA, Tindle H, Hatsukami DK. Randomized Trial of Reduced-Nicotine Standards for Cigarettes. *N Engl J Med.* 2015 Oct;373(14):1340-9. doi: 10.1056/NEJMsa1502403.

be able to do so and then quit without difficulty. On the other hand, these very low nicotine cigarettes could become a gateway to other higher nicotine products, just as smokeless tobacco manufacturers developed a range of commonly branded products that begin with low nicotine levels to attract youth, who graduate to “full flavor” high nicotine products.³¹

It is impossible to study the threshold for acquisition of nicotine addiction in youth non-smokers. It is possible that the threshold for cigarette reward is lower in never-smokers. An important aspect of a national nicotine reduction program would have to be surveillance, and if there was any evidence of youth becoming dependent on cigarette smoking, a further modification of the threshold nicotine level would be necessary. In the meantime, however, FDA would be responsible for increasing youth addiction to nicotine.

(2) FDA requests data and information regarding the risks to smokers from inhalation of VLNC cigarette smoke.

The nicotine reduction policy does not reduce the risk of smoking. All of the toxicants are likely the same in VLNC cigarette smoke as in smoke from conventional cigarettes. The hope for nicotine reduction is that by making smoked products less addictive, smokers will smoke less or quit and youth would not become addicted in the first place. The smoke of VLNCs and conventional cigarettes are not expected to be drastically different except VLNCs will have much lower levels of nicotine and nicotine-derived toxicants. Smoking of VLNCs will lead to exposure to toxicants such as volatile organic compounds and polycyclic aromatic hydrocarbons. Smoke of VLNCs may have lower levels of some tobacco-specific nitrosamines which are produced during the curing process from reactions with nicotine. Risk assessment models attribute the majority of cancer and non-cancer risk of smoking tobacco cigarettes to volatile organic compounds.³² Thus, continued smoking of VLNCs is not expected to result in a significant reduction in disease risk.

FDA should not assume any health benefits of requiring VLNCs beyond any direct effect on consumption of regulated products together with possible offsetting increases in the use of other tobacco products.

B. Estimate of addiction threshold levels

(1) The Tobacco Control Act prohibits FDA from reducing nicotine yields in any combusted tobacco product to zero (section 907(d)(3) of the FD&C Act). If FDA were to propose a maximum nicotine level for cigarettes, what should be the maximum level to ensure that the product is minimally addictive or nonaddictive, using the best available science to determine a level that is appropriate for the protection of the public health? Rather than establishing a nicotine target to make products “minimally addictive” or

³¹ Connolly GN. The marketing of nicotine addiction by one oral snuff manufacturer. *Tob Control* 1995;4(1):73; Mejia AB, Ling PM. Tobacco industry consumer research on smokeless tobacco users and product development. *Am J Public Health* 2010;100(1):78-87

³² Fowles J, Dybing E. Application of toxicological risk assessment principles to the chemical constituents of cigarette smoke. *Tob Control* 2003;12(4):424-430.
Haussmann H-J. Use of hazard indices for a theoretical evaluation of cigarette smoke composition. *Chem Res Toxicol* 2012;25(4):794-810.

“nonaddictive,” should FDA consider a different threshold (e.g., less addictive than current products on the market)? How should the maximum level be measured (e.g., nicotine yield, nicotine in cigarette filler, something else)? What would be the potential health impacts of requiring a maximum nicotine level such as 0.4 mg nicotine/g of tobacco filler? FDA is interested in public health impacts of requiring different maximum nicotine levels, such as 0.3, 0.4, and 0.5 mg nicotine/gram of tobacco filler, as well as other maximum nicotine levels and solicits comments about the potential health impacts of different maximum levels.

As detailed below, the safest approach is a single step reduction, and that good first estimate for a target nicotine level is 0.4 mg/gm tobacco.

(2) FDA lists four types of studies to estimate the threshold of nicotine addiction (i.e., indirect estimates; findings of increased cessation for VLNC cigarettes; subjective effects, craving, and withdrawal associated with VLNC cigarettes; and lower nAChR occupancy and cerebral response from the use of VLNC cigarettes). Should FDA rely on some or all of these types of studies? Why or why not? Is there a different method that FDA should investigate or use to determine the threshold for nicotine addiction?

In a cross-over study of smokers smoking cigarettes with different nicotine contents conducted at UCSF, smokers obtained reasonable satisfaction and acceptability from smoking cigarettes containing 1.5 mg nicotine or more per cigarette, but substantially lower acceptability while smoking cigarettes containing 0.6 mg nicotine per cigarette.³³ Since each cigarette contains about 0.7 gm tobacco, the 0.6 mg nicotine cigarette is equivalent to the 0.4 mg nicotine/gm tobacco cigarette selected as a target in the Donny study.³⁴

(3) In addition to nicotine, minor tobacco alkaloids (including nornicotine, cotinine, anabasine, anatabine, and myosamine) and tobacco smoke aldehydes (such as acetaldehyde) are pharmacologically active and may contribute to addiction (see, e.g., Refs. 98 and 99). Researchers have investigated the abuse potential of nornicotine, cotinine, anabasine, and acetaldehyde in animals (Ref. 100). However, many of these compounds are only present in tobacco smoke at low levels and are likely less potent than nicotine in mediating pharmacological response and, therefore, reinforcement (Refs. 101 and 102). In addition to setting a maximum nicotine level, should the product standard also set maximum levels of other constituents (e.g., nornicotine, acetaldehyde, anabasine) that may have the potential to produce dependence and be addictive? If so, at what levels?

These minor alkaloids, such as nornicotine and anabasine, have pharmacologic activity. A nicotine reduction plan should include analysis of reduced nicotine products to be sure that levels of minor alkaloids are not increased, and that other nicotine-like chemicals are not added to

³³ Benowitz NL, Jacob P 3rd, Herrera B. Nicotine intake and dose response when smoking reduced-nicotine content cigarettes. *Clin Pharmacol Ther.* 2006 Dec;80(6):703-14.

³⁴ Donny EC, Denlinger RL, Tidey JW, Koopmeiners JS, Benowitz NL, Vandrey RG, al'Absi M, Carmella SG, Cinciripini PM, Dermody SS, Drobes DJ, Hecht SS, Jensen J, Lane T, Le CT, McClernon FJ, Montoya ID, Murphy SE, Robinson JD, Stitzer ML, Strasser AA, Tindle H, Hatsukami DK. Randomized Trial of Reduced-Nicotine Standards for Cigarettes. *N Engl J Med.* 2015 Oct;373(14):1340-9. doi: 10.1056/NEJMsa1502403.

tobacco.

Addiction to nicotine is thought to be enhanced by inhibition of the enzyme monoamine oxidase (MAO) in the brain. This enzyme breaks down dopamine, which mediates much of the addictive action of nicotine. MAO inhibitors block the effect of monoamine oxidase, so that the dopamine that is released by nicotine is present in higher concentrations and for longer periods of time. Blocking MAO with drugs in rats increases self-administration of nicotine, indicating a greater nicotine abuse potential. Cigarette smoke contains chemicals that inhibit MAO. The FDA should assess MAO inhibition activity in cigarette tobacco to ensure that activity is not higher than in usual cigarettes, to avoid the possibility that greater MAO inhibition will allow lower levels of nicotine to be more addicting.

(4) If FDA were to finalize a nicotine tobacco product standard, what is the potential that adults and adolescents would perceive these VLNC cigarettes as “safe”—and how could youth and adult risk perceptions of these cigarettes impact initiation, use, and cessation habits of combusted tobacco products?

Industry efforts to minimize the health risks of nicotine

Since the 1988 Surgeon General’s Report on Nicotine Addiction, the tobacco industry has worked to undermine public perceptions of the addictiveness of nicotine, and to normalize its use. These efforts included coordinated programs, such as the 1980s-1990s promotion of the “Associates for Research in the Science of Enjoyment” (ARISE) whose members included prominent social scientists, physiologists and philosophers who toured the world promoting the health benefits of the use of legal substances, including tobacco, for stress relief and relaxation.³⁵ In addition, the cigarette companies worked for decades to shift the debate on tobacco from the addictive qualities of nicotine and the adverse health effects of smoking to smokers’ perceptions of the physiological benefits from nicotine, in order to counter declining cigarette sales and improve the tobacco industry’s image using carefully crafted research programs and promotion of their findings to the scientific community, the other tobacco companies, and to the public. Communication strategies promoted messages that undermined perceptions of nicotine’s potential health risks by comparing it with socially accepted substances such as caffeine and coffee. Tobacco industry documents describe a consistent and long-running effort by tobacco companies and their industry-funded scientific collaborators to promote nicotine while minimizing its health risks.³⁶

With the growing popularity of alternative nicotine products, including but not limited to electronic cigarettes, many of the messages normalizing nicotine, trivializing addiction, or even promoting nicotine as a cognitive enhancer have been reflected in the public dialogue about nicotine. For example, authors in the popular press (such as newspaper, magazine articles, blogs,

³⁵ Landman A, Cortese DK, Glantz S. Tobacco industry sociological programs to influence public beliefs about smoking. *Soc Sci Med.* 2008 Feb;66(4):970-81. doi: 10.1016/j.socscimed.2007.11.007. PubMed PMID: 18164524; PubMed Central PMCID: PMC2267871.

³⁶ England L, Glantz SA, Ling PM. Tobacco company strategies to identify and promote the benefits of nicotine. *Tobacco Control.* In press.

and books³⁷) make assertions that nicotine has health benefits such as improved concentration and memory, relaxation, alertness, and use as a treatment for neurological disorders.

Adolescents' and Young Adults' Perceptions of Nicotine, and effects of perceptions of risk on using other tobacco products

Recent studies show that youth and young adults hold perceptions about nicotine that differ from those for other tobacco constituents. Wiseman et al. conducted a study of adolescents (age 13-17) and young adults (ages 18-25), utilizing focus groups to elicit participants' knowledge and beliefs related to the chemical constituents in novel (non-cigarette) tobacco products.³⁸ Nearly all participants were familiar with nicotine, arsenic, carbon monoxide, and formaldehyde. Whereas participants near universally raised health concerns and expressed negative views about arsenic, carbon monoxide, formaldehyde, and other less-familiar constituents (such as benzene and N-nitrosonornicotine), there was less agreement and some confusion related to the properties and health risks of nicotine. Participants agreed that nicotine was addictive and could cause illness at high doses but were uncertain about how nicotine influences the body. The study relayed a quote from a young adult tobacco non-user:

"I know what nicotine is, but I don't honestly know that much about it."³⁹

Nicotine-related beliefs differed between tobacco users and non-users, with nicotine users generally concerned about addiction. However, tobacco users typically shared positive views of nicotine. Wiseman, et al. quoted one young adult: "...I feel like nicotine, I don't know, it helps me concentrate a lot. Like if I'm stressed out, it's a good de-stresser...."⁴⁰

Other research has shown that youth and young adults misperceive nicotine addiction, and that addiction is a particularly challenging for public health messaging. Adolescents may report that cigarettes are addictive, but they remain uncertain regarding the definition of addiction, and may fail to recognize that addiction means experiencing difficulty quitting and continuing to smoke longer than expected.⁴¹ A qualitative study of young female adolescent smokers found

³⁷ Alban, D. Nicotine: an unlikely brain enhancing drug. Be Brain Fit. Better Mind. Better Life.

<https://bebrainfit.com/nicotine-brain-enhancing-drug/> Accessed June 12, 2018.

Sutherland, R. The Wiki Man: So it might really be true – nicotine is good for your brain. The Spectator. 27 April 2013. <https://www.spectator.co.uk/2013/04/so-maybe-its-true-smoking-does-make-you-smarter/>

Accessed June 12, 2018.

Tri. Nicotine as a smart drug. Examined Existence. <https://examinedexistence.com/nicotine-as-a-smart-drug/> Accessed June 12, 2018.

Hurley, D. Smarter: The new science of building brain power. Penguin Random House. December 2014.

³⁸ Wiseman KD, Cornacchione J, Wagoner KG, Noar SM, Moracco KE, Teal R, Wolfson M, Sutfin EL.

Adolescents' and Young Adults' Knowledge and Beliefs About Constituents in Novel Tobacco Products. Nicotine Tob Res. 2016 Jul;18(7):1581-7.

³⁹ Wiseman KD, Cornacchione J, Wagoner KG, Noar SM, Moracco KE, Teal R, Wolfson M, Sutfin EL.

Adolescents' and Young Adults' Knowledge and Beliefs About Constituents in Novel Tobacco Products. Nicotine Tob Res. 2016 Jul;18(7):1581-7.

⁴⁰ Wiseman KD, Cornacchione J, Wagoner KG, Noar SM, Moracco KE, Teal R, Wolfson M, Sutfin EL.

Adolescents' and Young Adults' Knowledge and Beliefs About Constituents in Novel Tobacco Products. Nicotine Tob Res. 2016 Jul;18(7):1581-7.

⁴¹ Roditis M, Lee J, Halpern-Felsher BL. Adolescent (Mis)Perceptions About Nicotine Addiction: Results From a Mixed-Methods Study. Health Education & Behavior. Vol 43, Issue 2, pp. 156 – 164. Aug 2015.

that nicotine addiction was an unintended consequence of their smoking,⁴² and children have reported perceptions that they may avoid addiction by avoiding enjoying the experience of smoking.⁴³ Elsewhere, adolescents have described addiction to tobacco as personally and easily avoidable, as long as tobacco products were not used at an intensity or duration that they did not intend to reach.⁴⁴

Conversely, while some young people may seek nicotine in alternative tobacco products, the absence of nicotine from cigarettes may decrease perceptions of the harm of smoking. Similar to light, low tar, low additive, or low smoke cigarettes,^{45,46,47} low nicotine cigarettes may be perceived as safer, which is likely to encourage use among young people. Youth who report using electronic cigarettes without nicotine perceive lower health risks from e-cigarettes and were more likely to have answer knowledge items about nicotine incorrectly.⁴⁸

It is important to consider youth and adult risk perceptions in the context of recent experience with e-cigarettes and other novel tobacco products. The available evidence on currently marketed novel tobacco products (including e-cigarettes) conducted independent of the tobacco industry consistently shows that the introduction of novel nicotine products will attract adolescent non-users into initiating tobacco use. Adolescents' decisions to adopt use of any tobacco product are based on several considerations, including whether the product appeals to them, the product's flavors, smell and taste, the product's perceived harm, and the ease and location of use.⁴⁹ The marketing of new nicotine products with harm reduction claims makes it likely that these products will appeal to youth.

The experience with e-cigarettes, a nicotine product that has been promoted with harm reduction and "smokeless" messages, is directly relevant. Since e-cigarettes were first introduced in the U.S. less than a decade ago, there has been a rapid rise in their use.⁵⁰ E-cigarette use is especially common among adolescents and young adults. On the U.S. market since 2007, in 2016 past 30-day use of e-cigarettes has surpassed use of conventional cigarettes, with use prevalence

⁴² Moffat, B.M. and Johnson, J.L. (2001) Through the haze of cigarettes: teenagers girls' stories about cigarette addiction. *Qualitative Health Research*, 11, 668–681.

⁴³ C. Wang, N. Henley, R. J. Donovan; Exploring children's conceptions of smoking addiction, *Health Education Research*, Volume 19, Issue 6, 1 December 2004, Pages 626–634, <https://doi.org/10.1093/her/cyg087>

⁴⁴ Couch ET, Darius E, Walsh MM, Chaffee BW. Smokeless Tobacco Decision-Making Among Rural Adolescent Males in California. *J Community Health*. 2017 Jun;42(3):544-550.

⁴⁵ Kropp RY, Halpern-Felsher BL. Adolescents' beliefs about the risks involved in smoking "light" cigarettes. *Pediatrics*. 2004 Oct;114(4):e445-51.

⁴⁶ Tindle HA, Shiffman S, Hartman AM, Bost JE. Switching to "lighter" cigarettes and quitting smoking. *Tob Control*. 2009 Dec;18(6):485-90.

⁴⁷ Shiffman S, Pillitteri JL, Burton SL, Rohay JM, Gitchell JG. Smokers' beliefs about "Light" and "Ultra Light" cigarettes. *Tob Control*. 2001;10 Suppl 1:i17-23.

⁴⁸ Pepper JK, Farrelly MC, Watson KA. Adolescents' understanding and use of nicotine in e-cigarettes. *Addict Behav*. 2018 Jul;82:109-113.

⁴⁹ McKelvey, K., Ramos, M., Roditis, M., Ramamurthi, D., Halpern-Felsher, B. A Qualitative Analysis of Adolescents' Appeal of Various Tobacco Products. In preparation.

⁵⁰ McMillen RC, Gottlieb MA, Schaefer RM et al., Trends in Electronic Cigarette Use Among U.S. Adults: Use is increasing in both smokers and non-smokers. *Nicotine Tob Res*. 2015 Oct;17(10):1195-202.

of 11.3% among high school students (8.0% for cigarettes).⁵¹ 2017 Monitoring the Future data show a growing divide between cigarette and e-cigarette use in 8th-12th graders (12% had used e-cigarettes in the past month, 5.4% had smoked cigarettes).⁵² Among young adults 18-24 years old, 23.5% have ever used an e-cigarette.⁵³ Youth are also most likely to use flavored e-cigarette and other tobacco products.⁵⁴ Flavors increase teens' intentions to use e-cigarettes and decrease their risk perceptions associated with e-cigarette use.⁵⁵

Many adolescents at low risk of initiating nicotine use with conventional cigarettes initiate with e-cigarettes.⁵⁶ Adolescents who initiate nicotine use with e-cigarettes are more susceptible

⁵¹ Jamal A, Gentzke A, Hu SS, et al. Tobacco Use Among Middle and High School Students — United States, 2011–2016. *MMWR Morb Mortal Weekly Rep* 2017; 66:597–603. DOI: <http://dx.doi.org/10.15585/mmwr.mm6623a1>.

Syamlal G, King BA, Mazurek JM. Tobacco Use Among Working Adults — United States, 2014–2016. *MMWR Morb Mortal Weekly Rep* 2017;66:1130–1135. DOI: <http://dx.doi.org/10.15585/mmwr.mm6642a2>. Centers for Disease Control and Prevention. "National Youth Tobacco Survey (NYTS)." 2015. Web. 22 Aug. 2016; Centers for Disease Control and Prevention "Youth and Tobacco Use." 2016. Web. 22 Aug. 2016.

Barrington-Trimis JL, Urman R, Leventhal AM, et al. E-cigarettes, cigarettes, and the prevalence of adolescent tobacco use. *Pediatrics*. 2016;138(2):10.1542/peds.2015-3983. Epub 2016 Jul 11.

Gilreath TD, Leventhal A, Barrington-Trimis JL, et al. Patterns of alternative tobacco product use: Emergence of hookah and E-cigarettes as preferred products amongst youth. *Journal of Adolescent Health*. 2016;58(2):181-185. NIDA. Tobacco/nicotine and E-cigs. <https://www.drugabuse.gov/drugs-abuse/tobacconicotine-e-cigs>. Updated 2017.

⁵² Johnston, L.D., O'Malley, P.M., Miech, R.A., Bachman, J.G., Schulenberg, J.E., 2018.

Monitoring the Future National Results on Adolescent Drug Use: Overview of Key Findings, 2017. University of Michigan Institute for Social Research, Ann Arbor, MI.

⁵³ QuickStats: Percentage of adults who ever used an e-cigarette and percentage who currently use e-cigarettes, by age group. National Health Interview Survey, United States, 2016. *MMWR Morb Mortal Weekly Report*, 2017;66:892. DOI: <http://dx.doi.org/10.15585/mmwr.mm6633a6>

⁵⁴ Ambrose BK, Day HR, Rostron B, et al. Flavored tobacco product use among us youth aged 12-17 years, 2013-2014. *JAMA*. 2015;314(17):1871-1873; Brown JE, Luo W, Isabelle LM, Pankow JF. Candy flavorings in tobacco. *N Engl J Med*. 2014;370(23):2250-2252; Feirman SP, Lock D, Cohen JE, Holtgrave DR, Li T. Flavored tobacco products in the united states: A systematic review assessing use and attitudes. *Nicotine Tob Res*. 2016;18(5):739-749; Wagoner KG, Cornacchione J, Wiseman KD, Teal R, Moracco KE, Sutfin EL. E-cigarettes, hookah pens and vapes: Adolescent and young adult perceptions of electronic nicotine delivery systems. *Nicotine Tob Res*. 2016.

⁵⁵ Pepper JK, Ribisl KM, Brewer NT. Adolescents' interest in trying flavoured e-cigarettes. *Tob Control* 2016; 25:ii62-ii66. Doi: 10.1136/tobaccocontrol-2016-053174.

Shang C, Huang J, Chaloupka FJ, Emery SL. The impact of flavour, device type and warning messages on youth preferences for electronic nicotine delivery systems: evidence from an online discrete choice experiment. *Tob Control*. Published online first: 2 Nov 2017. Doi: 10.1136/tobaccocontrol-2017-053754

⁵⁶ Dutra, LM, Glantz, SA. E-cigarettes and national adolescent cigarette use: 2004-2014. *Pediatrics*. 1239(2), 2017. Wills TA, Sargent JD, Knight R, Pagano I, Gibbons FX. E-cigarette use and willingness to smoke: a sample of adolescent non-smokers. *Tob Control*. 2016 Apr;25(e1):e52-9.

Barrington-Trimis JL, Urman R, Leventhal AM, et al. E-cigarettes, cigarettes, and the prevalence of adolescent tobacco use. *Pediatrics*. 2016;138(2):10.1542/peds.2015-3983. Epub 2016 Jul 11

Best, C., Haseen, F., Currie, D., Ozakinci, G., MacKintosh, A.M., Stead, M., Eadie, D., MacGregor, A., Pearce, J., Amos, A., Frank, J., Haw, S., 2017. Relationship between trying an electronic cigarette and subsequent cigarette experimentation in Scottish adolescents: a cohort study. *Tob. Control*. <http://dx.doi.org/10.1136/tobaccocontrol-2017-053691>. Epub ahead of print.

Conner, M., Grogan, S., Simms-Ellis, R., Flett, K., Sykes-Muskett, B., Cowap, L., Lawton, R., Armitage, C.J., Meads, D., Togerson, C., West, R., Siddiqi, K., 2017. Do electronic cigarettes increase cigarette smoking in UK adolescents? evidence from a 12-month prospective study. *Tob. Control*. <http://dx.doi.org/10.1136/tobaccocontrol-2016-053539>. Epub ahead of print.

to smoking combustible cigarettes.⁵⁷ This experience with e-cigarettes raises the concern that more adolescents will become dual and poly-users of e-cigarettes along with other tobacco products.⁵⁸ Adolescent and young adult smokers who use novel tobacco products often use two or more kinds of tobacco products concurrently.⁵⁹ Dual and poly-use of tobacco products is more common among youth than adults.⁶⁰

Newer e-cigarette devices appear to deliver nicotine more effectively than early “cigalikes”;⁶¹ these products include larger tank systems and, most recently, the pod devices like the new JUUL device, which has rapidly come to dominate the e-cigarette market.⁶² The FDA recently took several enforcement actions stop youth access and use of JUUL due to its rapid uptake among youth.⁶³ Young adults participating in research have described JUUL’s standardized pods as “ridiculously strong,” and have reported that the major benefit of the JUUL

Wills, T.A., Sargent, J.D., Gibbons, F.X., Pagano, I., Schweitzer, R., 2017. E-cigarette use is differentially related to smoking onset among lower risk adolescents. *Tob. Control* 26, 534–539.

⁵⁷ Barrington-Trimis JL, Urman R, Leventhal AM, et al. E-cigarettes, cigarettes, and the prevalence of adolescent tobacco use. *Pediatrics*. 2016;138(2):10.1542/peds.2015-3983. Epub 2016 Jul 11

Soneji S, Barrington-Trimis JL, Wills TA, Leventhal AM, Unger JB, Gibson LA, Yang J, Primack BA, Andrews JA, Miech RA, Spindle TR, Dick DM, Eissenberg T, Hornik RC, Dang R, Sargent JD. Association Between Initial Use of e-Cigarettes and Subsequent Cigarette Smoking Among Adolescents and Young Adults: A Systematic Review and Meta-analysis. *JAMA Pediatr*. 2017 Aug 01;171(8):788-797.

Barnett TE, Soule EK, Forrest JR, Porter L, Tomar SL. Adolescent electronic cigarette use: Associations with conventional cigarette and hookah smoking. *Am J Prev Med*. 2015;49(2):199-206.

Miech RA, O'Malley PM, Johnston LD, Patrick ME. E-cigarettes and the drug use patterns of adolescents. *Nicotine Tob Res*. 2016;18(5):654-659.

Leventhal AM, Strong DR, Kirkpatrick MG, et al. Association of electronic cigarette use with initiation of combustible tobacco product smoking in early adolescence. *JAMA*. 2015;314(7):700-707.

Wills TA, Sargent JD, Knight R, Pagano I, Gibbons FX. E-cigarette use and willingness to smoke: a sample of adolescent non-smokers. *Tob Control*. 2016 Apr;25(e1):e52-9.

⁵⁸ Barnett TE, Soule EK, Forrest JR, Porter L, Tomar SL. Adolescent electronic cigarette use. *Nicotine Tob Res*. 2016;18(5):654-659; Barrington-Trimis JL, Urman R, Leventhal AM, et al. E- cigarettes, cigarettes, and the prevalence of adolescent tobacco use. *Pediatrics*. 2016;138(2):10.1542/peds.2015-3983. Epub 2016 Jul 11

⁵⁹ Jamal A, Gentzke A, Hu SS, Cullen KA, Apelberg BJ, Homa DM, et al. Tobacco use among middle and high school students - United States, 2011-2016. *MMWR Morb Mortal Wkly Rep*. 2017;66(23):597-603.

⁶⁰ Kowitz, SD, Patel, T., Ranney, LM, Huang, LL, Sutfin, EL, Goldstein, AO. Poly-tobacco use among high school students. *Int J Environ Res Public Health*. 2015 Nov; 12(11): 14477–14489. Published online 2015 Nov 13. doi: 10.3390/ijerph121114477. PMID: PMC4661661; Soneji, S., Sargent, J, Tanski, S Multiple tobacco product use among US adolescents and young adults. *Tobacco control*, 25(2), 2016.

⁶¹ Williams RS, Derrick J, Liebman AK, LaFleur K. Content analysis of e-cigarette products, promotions, prices and claims on Internet tobacco vendor websites, 2013-2014. *Tob Control*. 2017 Nov 3. pii: tobaccocontrol-2017-053762. doi: 10.1136/tobaccocontrol-2017-053762. [Epub ahead of print] PubMed PMID: 29101294.

⁶² Ramakanth Kavuluru, S.H., Ellen J. Hahn, *On the popularity of the USB flash drive-shaped electronic cigarette JUUL*. *Tob Control*, 2018.

Huang J, Duan Z, Kwok J, et al Vaping versus JUULing: how the extraordinary growth and marketing of JUUL transformed the US retail e-cigarette market *Tobacco Control* Published Online First: 31 May 2018. doi: 10.1136/tobaccocontrol-2018-054382

⁶³ Statement from FDA Commissioner Scott Gottlieb, M.D., on new enforcement actions and a Youth Tobacco Prevention Plan to stop youth use of, and access to, JUUL and other e-cigarettes. April 24, 2018. FDA. <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm605432.htm>

device was, “It’s like a lot of nicotine, from what I understand.”⁶⁴ At the same time, while seeking high levels of nicotine in JUUL, young adult users failed to recognize potential signs of nicotine addiction in their experiences using the devices, such as a propensity to use the device shortly after waking in the morning, or having environmental cues trigger cravings, such as meals or following exercise. Young adults have also reported increasing use of nicotine facilitated by e-cigarettes due to the ability to use the devices in places and times when smoking is prohibited.⁶⁵

In its rulemaking FDA needs to be cognizant of the fact that while some young people may seek nicotine in alternative tobacco products, the absence of nicotine from cigarettes may decrease perceptions of the harm of smoking. Adolescents’ risk perceptions and smoking behavior have a bidirectional relationship, such that decreased risk perceptions influence smoking and experience with smoking predicts changes in risk perceptions.⁶⁶ Moreover, youth using electronic cigarettes without nicotine, particularly those with “only flavors,” perceive these products are safer and without risk of addiction. Similar to low tar, low additive, or low smoke cigarettes, low nicotine cigarettes could well be perceived as safer, which is likely to encourage use among young people.

3. IMPLEMENTATION (SINGLE TARGET VS. STEPPED-DOWN APPROACH)

(1) What data are available to demonstrate that a single target approach to reach a maximum nicotine level would or would not result in any unintended consequences?

The FDA should not take a step-down approach.

As noted above, the original Benowitz and Henningfield proposal⁶⁷ suggested stepping down nicotine content of cigarettes over several years. The reason for that was to gradually reduce the level of dependence in smokers, and minimize withdrawal discomfort. However, the studies conducted to date with much shorter periods of nicotine reduction indicate that nicotine withdrawal is not a major problem.

Moreover, when switched to cigarettes containing 0.4 mg nicotine/gram tobacco, smokers smoke fewer cigarettes per day compared to smokers smoking their own brand or high nicotine research cigarettes.⁶⁸ However, with gradual reduction there is a small increase in cigarettes per

⁶⁴ Keamy-Minor E, McQuoid J, Ling PM. Young adult perceptions of JUUL and other electronic cigarette pod devices. Tobacco Control. Submitted.

⁶⁵ McDonald EA, Ling PM One of several ‘toys’ for smoking: young adult experiences with electronic cigarettes in New York City Tobacco Control 2015;24:588-593.

⁶⁶ Gerrard M, Gibbons FX, Benthin AC, Hessling RM. A longitudinal study of the reciprocal nature of risk behaviors and cognitions in adolescents: What you do shapes what you think, and vice versa. Health Psychology. 1996;15(5):344–354.

Morrell HER, Song AV, Halpern-Felsher BL. Predicting adolescent perceptions of the risks and benefits of cigarette smoking: a longitudinal investigation. Health Psychology. 2010;29(6):610-617

⁶⁷ Benowitz NL, Henningfield JE. Establishing a nicotine threshold for addiction. The implications for tobacco regulation. N Engl J Med. 1994 Jul 14;331(2):123-5.

⁶⁸ Donny EC, Denlinger RL, Tidey JW, Koopmeiners JS, Benowitz NL, Vandrey RG, al'Absi M, Carmella SG, Cinciripini PM, Dermody SS, Drobes DJ, Hecht SS, Jensen J, Lane T, Le CT, McClernon FJ, Montoya ID, Murphy

day when nicotine content is moderately reduced.⁶⁹

Rapid reduction is advantageous in that there would be much less concern with compensation, which might occur in earlier phases of nicotine reduction, and smokers would avoid many years of ongoing exposure to tobacco smoke toxins during the course of nicotine reduction. A small study by Hatsukami⁷⁰ and the larger study by Donny⁷¹ support the idea that rapid nicotine reduction is generally well tolerated, reduces the level of tobacco dependence, and results in a rapid decrease in exposure to tobacco smoke toxicants without evidence of compensation. The body of evidence indicates that rapid reduction of nicotine in cigarettes would be most beneficial to public health, particularly if an acceptable alternative source of nicotine were available to deal with needs for nicotine to manage withdrawal.

Another reason for not taking a step-down approach is that a step-down approach would give the cigarette companies more opportunities to adapt to and manipulate their products and marketing, similar to how they have used color coding of packages to nullify the legal requirement to stop promoting “light” and “mild” products.⁷²

A multiple target approach would also create a situation in which smokers could mix products with different nicotine delivery levels, effectively nullifying the goal of the policy. It

SE, Robinson JD, Stitzer ML, Strasser AA, Tindle H, Hatsukami DK. Randomized Trial of Reduced-Nicotine Standards for Cigarettes. *N Engl J Med.* 2015 Oct;373(14):1340-9. doi: 10.1056/NEJMsa1502403.

⁶⁹ Benowitz NL, Hall SM, Stewart S, Wilson M, Dempsey D, Jacob P 3rd. Nicotine and carcinogen exposure with smoking of progressively reduced nicotine content cigarette. *Cancer Epidemiol Biomarkers Prev.* 2007 Nov;16(11):2479-85.

Benowitz NL, Dains KM, Hall SM, Stewart S, Wilson M, Dempsey D, Jacob P 3rd. Smoking behavior and exposure to tobacco toxicants during 6 months of smoking progressively reduced nicotine content cigarettes. *Cancer Epidemiol Biomarkers Prev.* 2012 May;21(5):761-9. doi: 10.1158/1055-9965.EPI-11-0644. Epub 2012 Feb 21.

⁷⁰ Hatsukami DK, Kotlyar M, Hertsgaard LA, Zhang Y, Carmella SG, Jensen JA, Allen SS, Shields PG, Murphy SE, Stepanov I, Hecht SS. Reduced nicotine content cigarettes: effects on toxicant exposure, dependence and cessation. *Addiction.* 2010 Feb;105(2):343-55. doi: 10.1111/j.1360-0443.2009.02780.x.

⁷¹ Donny EC, Denlinger RL, Tidey JW, Koopmeiners JS, Benowitz NL, Vandrey RG, al'Absi M, Carmella SG, Cinciripini PM, Dermody SS, Drobles DJ, Hecht SS, Jensen J, Lane T, Le CT, McClernon FJ, Montoya ID, Murphy SE, Robinson JD, Stitzer ML, Strasser AA, Tindle H, Hatsukami DK. Randomized Trial of Reduced-Nicotine Standards for Cigarettes. *N Engl J Med.* 2015 Oct;373(14):1340-9. doi: 10.1056/NEJMsa1502403.

⁷² Connolly GN, Alpert HR. Has the tobacco industry evaded the FDA's ban on 'Light' cigarette descriptors? *Tob Control.* 2014;23:140-5.

Altria Sales & Distribution. Retailer brochure: introducing new packaging on many Philip Morris USA (PM USA) brands. Philip Morris; 2010. <https://industrydocuments-library.ucsf.edu.ucsf.idm.oclc.org/tobacco/docs/fgmf0217>. New packaging guide. Philip Morris; 2010. [Author unknown]

<http://legacy.library.ucsf.edu.ucsf.idm.oclc.org/tid/xjn30i00>

Sarmiento J. FW: Packaging changes. Philip Morris; Jun 17, 2010.

<http://legacy.library.ucsf.edu.ucsf.idm.oclc.org/tid/xwr30i00>.

Pugh K. FDA pack identifiers. Philip Morris; Jan 28, 2010.

<http://legacy.library.ucsf.edu.ucsf.idm.oclc.org/tid/cjl30i00>.

Wilson D. Coded to obey law, Lights become Marlboro

Gold. 2010 http://www.nytimes.com/2010/02/19/business/19smoke.html?_r=0.

Wilson D. FDA seeks explanation of Marlboro

Marketing. 2010 http://www.nytimes.com/2010/06/18/health/18tobacco.html?_r=0.

⁷² Lempert LK, Glantz S. Packaging colour research by tobacco companies: the pack as a product characteristic *Tobacco Control* 2017;26:307-315.

would also create complexity, which would complicate policy implementation and create many opportunities for the tobacco companies to manipulate the market. See also response to question 2B(1).

The safest approach is a single step reduction, and that good first estimate for a target nicotine level is 0.4 mg/gm tobacco

- (2) In the alternative, what data are available to demonstrate that a stepped-down approach involving a sequence of incremental levels and implementation dates to reach a proposed nicotine level would or would not result in any unintended consequences?**

See response to question 2B(1).

- (3) If FDA were to select a stepped-down approach for a nicotine tobacco product standard, what scientific evidence exists to support particular interim nicotine levels and the appropriate number of steps that would be needed to reach the target level?**

As discussed above, FDA should not take a step down approach.

- (4) Would a single target and a stepped-down approach for implementation result in comparable quit rates or reduced initiation rates?**

As discussed above, FDA should use a single target, not a step-down approach.

- (5) What would be the likely implementation differences, including implementation timelines and transition costs, between a single target approach or a stepped-down approach involving a sequence of incremental levels and implementation dates?**

As discussed above, FDA should use a single target, not a step-down approach.

4. ANALYTICAL TESTING METHOD

- (1) If FDA were to issue a product standard, should the Agency require a standard method of product testing to analyze the nicotine levels in products subject to the standard? If so, what method or methods should FDA use?**

Yes. FDA should require a standard method of testing nicotine in products and for testing nicotine delivery from the product. The Health Canada intense (HCI) machine-smoking protocol, which includes 55 mL puff volume, 30 seconds puff interval, 2 seconds puff, and 100% vent blocking should be used for testing nicotine delivery.

- (2) Should the Agency require manufacturers to sample their products in a specific manner to ensure that products do not contain excess levels of nicotine? Should manufacturers be required to test each manufactured batch to ensure compliance with a product standard limiting nicotine levels? What criteria should be used to determine if a batch passes or fails testing?**

The FDA should require random testing of products to ensure that the companies cannot manipulate the testing process. The criteria should be that all products in the sample meet the standard.

5. TECHNICAL ACHIEVABILITY

- (1) What methods are tobacco product manufacturers currently using to maintain consistency of the nicotine in their products, given the variability of nicotine levels over growing seasons and crop type? How could these methods be adapted to ensure that certain combusted tobacco products meet a potential nicotine tobacco product standard?**

This is not an issue. Cigarette companies have refined their product design and manufacturing processes to maintain remarkable consistency on puff-by-puff nicotine delivery over time despite changes in growing seasons and tobacco products over time.

The FDA needs to monitor the products to ensure that the companies do not use changes in raw tobacco as an excuse to sidestep any FDA nicotine delivery standard.

- (2) What is the feasibility of using the techniques discussed in this section, or other nicotine reduction techniques, to reduce the nicotine in cigarettes?**

The cigarette companies have already designed and marketed nicotine-free cigarettes. Philip Morris marketed the nicotine-free Next cigarette in 1989 and 1990 and Vector marketed the very low nicotine Quest in 2003.

- (3) What is the feasibility of using the techniques discussed in this section, or other nicotine reduction techniques, for non-cigarette combusted tobacco products (e.g., cigarette tobacco, RYO tobacco, little cigars, large cigars, cigarillos, pipe tobacco, and waterpipe tobacco) that FDA is considering covering under a nicotine tobacco product standard?**

They are feasible for the same reasons that they are feasible for conventional cigarettes. These manufacturers would use the same process as for conventional cigarettes.

- (4) If FDA were to propose a tobacco product standard setting a maximum nicotine level, how, if at all, would such a product standard impact tobacco farmers' growing and/or curing practices? If FDA were to finalize a nicotine tobacco product standard, what would be the costs and benefits for tobacco farmers and tobacco processors, particularly regarding how any such rulemaking might affect them in light of new technologies and business opportunities that are foreseeable, but not now in place? In addition, if FDA were to finalize a nicotine tobacco product standard, what would be the costs for farmers in light of such a standard?**

Other than noting that farmers have adapted their growing practices over the years to meet evolving requirements specified by the cigarette manufacturers, we do not see this as a

substantive issue. Any changes in costs of production would be reflected in the price of tobacco that the manufactures negotiate with farmers, which is beyond FDA jurisdiction.

(5) Section 907(d)(2) of the FD&C Act provides that a tobacco product standard must set forth the effective date of the standard, which may not be less than 1 year after publication of a final rule unless FDA determines that an earlier effective date is necessary for the protection of the public health (and that such effective date be established “to minimize, consistent with the public health, economic loss to, and disruption or dislocation of, domestic and international trade”). This section also provides that the effective date be a minimum of 2 years after publication of a final rule if the tobacco standard can be met only by requiring “substantial changes to the methods of farming the domestically grown tobacco used by the manufacturer.” Therefore, if FDA were to propose a product standard setting a maximum nicotine level, when should this standard become effective? What implementation timeframe would allow adequate time for industry to comply? Should the same timeframe be required for all tobacco product manufacturers, regardless of their number of employees and/or annual revenues? [11] Given the currently available processes to reduce the nicotine in tobacco products (e.g., chemical processes, genetic engineering), what do manufacturers and others with relevant expertise consider an appropriate timeframe to implement a product standard to reduce nicotine? Would a 2-year, 4-year, or 6-year timeframe be appropriate?

The FDA should set a 2 year time limit, the minimum required by law. As discussed in the response to question 5(2), the cigarette companies already have the technology needed to manufacture low nicotine cigarettes, including completely nicotine-free cigarettes. Continued delay will delay the benefits of the proposed very low nicotine policy and give the cigarette companies more time to design marketing campaigns and products designed to thwart the purpose of the standard.

The same timeframe should be required for all manufacturers regardless of their number of employees and/or annual revenues to avoid the likelihood of simply shifting people between different addictive products. The long time that developing this regulation will take together with the 2 year transition period is enough warning for all companies.

(6) Should the standard include provisions that would allow manufacturers, distributors, or retailers to sell off existing nonconforming inventory of manufactured combusted tobacco products? If so, what would be a reasonable sell-off period?

No. The extensive period of the development of the standard combined with the 2 year phase-in period gives the companies and retailers more than enough time to sell-off existing stocks.

(7) What are the potential outcomes of implementing methods to reduce nicotine content in cigarettes in terms of impact on characteristics of cigarettes (flavor, taste, aroma, etc.) and user experience?

These are issues for the manufacturers, who can reasonably be expected to design and market products designed to be as attractive to their customers as possible. Indeed, to the extent that the very low nicotine standard makes tobacco products less attractive, the policy will be a success.

CONCLUSION

A product standard to reduce nicotine delivery in all combustible recreational tobacco products could have unintended negative consequences, such as increasing the demand for and innovation of other inhaled nicotine products, such as e-cigarettes. The likelihood of increased youth and young adult initiation is of particular concern. ***A reduced nicotine product standard could bring substantial public health benefits if it is done in a way that does not open the door to the tobacco companies to deter cessation and expand their customer base.***