Final Summary Report

External Letter Peer Review of FDA's

The Science of a Nicotine Standard for Combusted Tobacco Products

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I. INTRODUCTION

Versar, Inc. (Versar), an independent Food and Drug Administration (FDA) contractor, coordinated an external letter peer review of "The Science of a Nicotine Standard for Combusted Tobacco Products" document. The peer review was conducted for FDA's Center for Tobacco Products.

The death and disease caused by use of cigarettes and other combusted tobacco products (e.g., cigars, roll-your-own tobacco, pipe tobacco) contributes to a tremendous public health burden. Nicotine, the primary addictive constituent of tobacco products, results in repeated use and, therefore, continuously exposes users and non-users to toxicants in the smoke (U.S. Department of Health and Human Services, 1988, 2010). The majority of adult cigarette smokers want to quit but are unable to do so because of the addictive nature of these products (National Center for Health Statistics). Research indicates that reduction of nicotine in cigarettes to levels that are minimally addictive would make it more likely for smokers to quit smoking (e.g., Benowitz et al., 2012; Benowitz et al., 2007; Fiore & Baker, 2015; Hatsukami et al., 2010). In addition, reduction of nicotine levels in cigarettes could prevent experimenters (mainly youth and young adults) from progressing to regular smoking.

The Tobacco Control Act, enacted on June 22, 2009, amended the Federal Food, Drug, & Cosmetic Act (FD&C Act) and provided FDA with the authority to regulate tobacco products (Pub. L. 111-31). Section 907 of the FD&C Act establishes certain product standards for tobacco products, in order to protect public health. The FD&C Act also gives FDA the authority to establish additional product standards through rulemaking as appropriate for the protection of public health (§ 907(c) and (d)), including a tobacco product standard on nicotine (§ 907(a)(4)), as long as levels are not reduced to zero (§ 907(d)(3)). FDA hypothesizes that making combusted tobacco products minimally addictive could increase the number of successful quit attempts by smokers seeking to quit and could potentially prevent experimenters from developing addiction and becoming regular smokers. To inform potential rulemaking, FDA evaluated the available scientific evidence relevant to a proposed nicotine tobacco product standard including its technical achievability and implementation, applicability of a reduced nicotine tobacco standard to all combusted products, possible individual and public health effects from enactment of a reduced nicotine tobacco product standard, as well as consumer knowledge, attitudes, perceptions, beliefs, and planned behavior regarding reduced nicotine tobacco products.

For this peer review, six experts with expertise in at least one of the following fields/disciplines: 1) behavioral science (e.g., addiction, pharmacology), 2) social science (e.g., health communication, harm perception); and 3) chemistry, agriculture, or genetics were selected as peer reviewers to answer five charge questions and to evaluate and provide written comments on FDA's "The Science of a Nicotine Standard for Combusted Tobacco Products" document.

Peer Reviewers:

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II. CHARGE TO REVIEWERS

FDA has conducted a review of the available scientific evidence relevant to a proposed reduced nicotine tobacco product standard, "The Science of a Nicotine Standard for Combusted Tobacco Products". This review includes scientific evidence regarding:

- applicability of the reduced nicotine tobacco standard to all combusted products
- technical achievability of a proposed reduced nicotine tobacco product standard
- potential individual and public health effects from enactment of a reduced nicotine tobacco product standard
- consumer knowledge, attitudes, perceptions, beliefs, and planned behavior regarding reduced nicotine tobacco products

Charge Questions
Please provide written responses to the following questions:

1. Is the report clearly written and does it follow a logical structure? If not, provide suggestions for how to improve the document.

2. Does the executive summary accurately reflect the content of the overall document and provide sufficient information to capture the critical components?

3. For each section that you reviewed, were the conclusions appropriate given the available evidence? If not, provide specific examples as to where conclusions are not appropriate.

4. Are you aware of additional publicly available information which should have been included? If so, please specify.

5. Provide any additional comments including limitations and outcomes not discussed, or editorial suggestions not addressed in the previous questions.

III. SUMMARY OF PEER REVIEWER COMMENTS

I. Response to Charge Questions

1. ***Is the report clearly written and does it follow a logical structure? If not, provide suggestions for how to improve the document.***

   The reviewers generally found the report to be thorough, clearly written, and for the most part, logical in structure. However, some suggestions to improve structure included starting each section with a paragraph that outlines the focus and rationale for that section and ending each section with a conclusions subsection. Other suggestions included specific ordering of topics within a given section, i.e., section III. Scope where the jump from policy implementation approach to analytic testing did not feel logical to one reviewer; and re-ordering of the existing sections, i.e., section iv. Choice where the reviewer felt it could be moved after section i. Drug Liking, since it would follow logically that smokers would be less likely to choose very low nicotine content (VLNC) products if they are rated as less satisfying and less pleasant. Another reviewer thought section V.C. Potential for Non-Cigarette Combusted Tobacco Product Switching could be absorbed as part of the Unintended Consequences, section IV.C.

   For the reviewers, flow was interrupted when too much time was spent on a given topic that was not deemed necessary, as on the section on cigarette price increases, where one reviewer felt covering behavioral economics adds little and it could be eliminated. Additionally, another reviewer notes that given the many non-cigarette combustible products available, the extensive discussion in the background section focusing on cigars distracts from the flow of the document and it should either be shortened or a discussion of other products integrated into that section.

   The lack of excessive use of jargon was appreciated, but more than one reviewer noted the disjointed nature of the introduction of "nicotine content" and "nicotine yield" and commented that it would be helpful to describe the differences between them. Another reviewer noted keeping the terminology consistent for other words and phrases would be helpful, i.e., "continued tobacco use" vs. "maintenance of tobacco use behavior"; "single target" vs. "immediate reduction"; "nicotine delivery" vs. "nicotine yield". Along the same lines of consistency, one reviewer noted when first introducing the background, only combustible cigarettes are presented at the end of the continuum of risk. To keep this consistent with the subsequent argument about the need to cover all combusted tobacco products, maybe change this to "combustible cigarettes, and other combusted tobacco products, at the most harmful end of this continuum" (bottom of p. 6).

2. ***Does the executive summary accurately reflect the content of the overall document and provide sufficient information to capture the critical components?***

   Overall, the reviewers found the executive summary easy to read and accurately summarized the main points in the report. However, more than one reviewer thought the report contained substantial evidence on the technical achievability of producing VLNC and that a statement reflecting that should be in the executive summary. One reviewer also felt it was evident from the report the importance of combusted tobacco other than cigarettes, but that the executive summary should contain a clear statement regarding FDA's belief that regulation of nicotine content in those products is necessary. One reviewer indicated that it is unclear

what level of nicotine reduction is being considered because the executive summary gives two numbers: a range of 0.2-0.7 mg nicotine content per cigarette is mentioned in the beginning (p. 5) and then a single number is given (0.4 mg of nicotine per gram of tobacco filler) toward the end. For the executive summary, the reviewer argues it would be better to give a single number as the target to avoid potential confusion. Finally, only some of the supporting science in the executive summary has citations while other research topics did not, which the reviewer found confusing.

3. For each section that you reviewed, were the conclusions appropriate given the available evidence? If not, provide specific examples as to where conclusions are not appropriate.

Overall, the reviewers felt the conclusions were logically determined based on the evidence. However, as mentioned previously in the report structure comments, reviewers felt that explicit conclusion subsections would help the reader. In addition, one reviewer commented that the report seems to end abruptly and the overall conclusion summarizing the total weight of evidence in support of the nicotine standard is missing.

Regarding specific sections of the report, one reviewer cited issues with section IV.B.b.i. Smoking Cessation. The reviewer stated that an argument can be made that current data present a conservative estimate of the probability of abstinence due to VLNC, because abstinence would be substantially more likely if VLNC cigarettes were the only cigarettes available. Under those circumstances, there would be little or no chance of relapse to the more attractive NNC cigarettes. However, the reviewer did not see that argument presented in the report. Another reviewer had some section comments along with several suggestions on additional papers to include. In section IV.B.b.ii. Cigarettes Per Day (CPD), the reviewer believes Hatsukami et al., 2018 *JAMA* should be added, which reported significant decreases in CPD in the immediate vs. gradual and immediate vs. control, but where there were no significant differences between gradual vs. control conditions. The reviewer's other suggested papers include: IV.B.b.iii.: Denlinger-Apte et al., 2019d that reports smoking topography from a VLNC trial of smokers with serious mental illness; IV.B.b.iv.: Cassidy et al., 2019a which reports Cigarette Purchase Task data among adolescent daily smokers; IV.B.b.v. and all the sections under IV.B.c.: Hatsukami et al., 2018 *JAMA*; IV.C.d.i.: Apelberg et al., 2018 *NEJM*; IV.C.D.ii.: Tidey et al., 2019 and Denlinger-Apte et al., 2019d; and finally, all the individual product sections under V. should be updated to reflect the most recent use data, especially among middle and high school students. Lastly, this same reviewer did not follow the content in section IV.B.d., or what the conclusions were related to VLNC cigarettes.

Another reviewer thought in section II.A., Levin et al., 2007 better supports the report's statement that the adolescent brain is more vulnerable to developing nicotine dependence than the adult brain but cautions against confusing addiction and dependence in this section. This reviewer also cautions against suggesting a specific product, such as ENDS, as a safer alternative to combustible tobacco here and throughout the document. The reviewer found very few human-subject studies to support the report's hypothesis that lowering nicotine levels will reduce the risk of progression from experimentation to regular use. Regarding section III.C., the reviewer felt it misleading to write that VLNCs resulted in significantly fewer cigarettes per day, as not all of the references cited support this statement. This reviewer also thought that section IV.B.d is poorly supported and does not contribute much

to the overall document and recommends either removing it or making a major revision with more supporting references.

4. Are you aware of additional publicly available information which should have been included? If so, please specify.

All reviewers agreed that there were additional sources of published information that could be included in the report. One reviewer noted that in December, *Nicotine and Tobacco Research* published a supplement devoted to VLNC (Nicotine & Tobacco Research, 21, Supplement 1, December 2019). The supplement included 21 articles focused on this topic and the majority of those appear to support the conclusions reached in this report. All reviewers also agreed that some of the topics covered in the report have more recent research published than what is cited. For example, in section III.A., the reviewer notes a change in mean nicotine yields in more recent literature compared to the cited literature. A separate reviewer also goes on to list several recent articles from 2019 and 2020 that address gaps in the report's reviewed literature. This same reviewer also lists a few publications from 2004, 2011, and 2018, based more on the article's contribution to the report's content than being a more updated source. One reviewer noted that for section VII., while there have been additional studies published since the scoping review was conducted in September 2017, the overall conclusions are still valid: people still overwhelmingly believe nicotine is the main (or one of the main) harmful chemicals in tobacco and that it causes cancer. However, it might be worthwhile to update the review if resources permit.

5. Provide any additional comments including limitations and outcomes not discussed, or editorial suggestions not addressed in the previous questions.

More than one reviewer noted the report did not acknowledge the many other chemicals in tobacco smoke and how they would fit in with this proposal to reduce nicotine. Two reviewers also noted that the report does not mention heated tobacco products, such as IQOS. One reviewer suggested giving more emphasis to how most current dependent smokers regret having started, which is more supporting evidence for a policy to reduce nicotine content of tobacco and help those people permanently quit. Another reviewer recommended adding a brief description to section II.A. on addiction/substance use disorder, specifically tobacco use disorder, for the lay-reader to understand the serious nature of nicotine addiction. The same reviewer suggested a comparison of the rates of smoking cessation with VLNCs with rates of cessation during unassisted quit attempts would underscore the point that VLNCs make quitting easier. Additionally, this reviewer believes there is a lack of research on the effects of VLNCs on light (using 5 CPD or less) and non-daily smokers. These smokers might be much more likely to reduce or quit cigarettes than heavy smokers (using at least 10 CPD) and the reviewer believes this would be an important area for more research.

Another reviewer considered the audience and that a reader versed in biochemistry may easily be able to generalize this to other tobacco combustible products, but for the general scientist, the document would be more convincing if there were some mention of how the lower nicotine levels would be achieved in these products. This reviewer also noted the lack of discussion on the potential harms of ENDS, especially since FDA seems to anticipate that reduction of nicotine content in cigarettes will increase use of ENDS among all age groups and the effects are unknown.

IV. INDIVIDUAL REVIEWER COMMENTS

I. Reviewer #1

External Letter Peer Review of "The Science of a Nicotine Standard for Combusted Tobacco Products"

Reviewer #1

I. RESPONSE TO CHARGE QUESTIONS

1. ***Is the report clearly written and does it follow a logical structure? If not, provide suggestions for how to improve the document.***

   The report is thorough, clearly written, and follows a logical structure.

2. ***Does the executive summary accurately reflect the content of the overall document and provide sufficient information to capture the critical components?***

   The executive summary accurately reflects the content of the overall document and provides sufficient information to capture the critical components.

3. ***For each section that you reviewed, were the conclusions appropriate given the available evidence? If not, provide specific examples as to where conclusions are not appropriate.***

   The conclusions were appropriate given the available evidence. When published data apparently supported different conclusions in a few cases, results from opposing points of view were included in an unbiased manner. However, if the weight of evidence provided greater support for one conclusion more than for another when opposing points of view had been published on a given topic, the thought logic that was used to arrive at the supported conclusion was clearly stated. The logic in each case was very defensible.

4. ***Are you aware of additional publicly available information which should have been included? If so, please specify.***

   Perkins and Karelitz (Perkins, K.A., Karelitz, J.L. Differences in acute reinforcement across reduced nicotine content cigarettes. Psychopharmacology, 2020, https://doi.org/10.1007/s00213-020-05509-9) recently reported a study with a small number of subjects in which the evidence showed a higher nicotine threshold relative to VLNC cigarettes below which participants did not show preference vs. VLNC cigarettes. It is not compulsory, but this information could be useful to include in section IV B, possibly others.

5. ***Provide any additional comments including limitations and outcomes not discussed, or editorial suggestions not addressed in the previous questions.***

   No additional comments.

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"

Page	Paragraph/Line	Comment
39-40		As stated in response to section I, question 4 above, the 2020 Perkins and Karelitz paper could contribute information to the discussion on levels of nicotine relative to "Choice" in section IV. B. b. iv.

II. Reviewer #2

External Letter Peer Review of "The Science of a Nicotine Standard for Combusted Tobacco Products"

Reviewer #2

I. RESPONSE TO CHARGE QUESTIONS

1. ***Is the report clearly written and does it follow a logical structure? If not, provide suggestions for how to improve the document.***

   The report is written fairly clearly. The structure is somewhat logical, but each section (after the executive summary) likely should start with a paragraph that outlines the focus and rationale for the subsequent text in that section, to aid the reader's full understanding of the purpose behind this possible policy. Similarly, each section should finish with an explicit "conclusions" subsection, as noted below in #3.

   Some text in the footnotes is repeated elsewhere in text and vice versa. Example: footnote 5 on p. 12 is repeated in p. 13 text near bottom; Footnote 1 on p. 5 is repeated in footnote 7 on p. 22 and then in text on pp. 31-32. Seems repetitive but not too distracting; pp. 71-74: The focus on Apelberg et al., 2018 is appropriate, given its results on expected effects of regulating nicotine to levels insufficient to support addiction, but extensive preliminary details in the first two pages, before any findings are outlined, seems unnecessary and interrupts text flow.

2. ***Does the executive summary accurately reflect the content of the overall document and provide sufficient information to capture the critical components?***

   The executive summary of 1.5 pages is accurate in briefly outlining the rationale for proposing a reduced nicotine standard for all combustible tobacco products.

3. ***For each section that you reviewed, were the conclusions appropriate given the available evidence? If not, provide specific examples as to where conclusions are not appropriate.***

   The apparent conclusions were appropriate. However, section "conclusions" are not obviously organized, at the ends of the major (or minor) sections, such as II. Background, III. Scope, IV. VLNC literature review, V, VI, etc. Occasional text near the end of some minor sections start with "In sum,…" (or "In all…" for the Behavioral Economic subsection of V., or "All together" at the end of section VII.), which indicates conclusions for the prior paragraphs, but that text is not set apart or differentiated from the other text. More explicit "Conclusion" subsections, with headings labeled "Conclusions" at the end of these major sections (and listed in the table of Contents on p. 1), might help the reader comprehend the summary and implications of that prior section for the proposed policy.

4. ***Are you aware of additional publicly available information which should have been included? If so, please specify.***

   Around pp. 16-17, more text supporting the notion that non-nicotine smoked products are not dependence producing would help justify why reducing nicotine content to very low levels,

minimally above zero, should be sufficient to minimize risk of dependence onset.

From p. 20, some estimates appear out of date, e.g. text there states "…and conventional cigarettes generally have nicotine smoke yields in the 1.1 mg to 1.7 mg range (*National Cancer Institute*, 1998a)." Mean nicotine "yields" now are closer to 0.9 mg (see Carmines & Gillman 2019; https://content.sciendo.com/view/journals/cttr/28/6/article-p253.xml)

p.31: Only one sentence mentioning Quest brand cigarettes? Seems to be an inadequate mention, similar to brief comments on "Next" and Ultratech VLNC cigarettes, which attracted much less research attention than Quest. Separate studies with Quest are occasionally noted later on, but these were the best-controlled low and very low nicotine content cigarettes for research (0.6, 0.3, and 0.05 mg nicotine yields) in the first decade of 2000s, prior to Spectrum.

p. 34, On "History of Addiction threshold": More recent studies on choice between Spectrum cigs differing in nicotine content seem very relevant, although these are acute lab studies and extremely recent (Perkins 2019 NTR; Perkins & Karelitz 2020 NTR; 2020 *Psychopharmacology*, each cited below), rather than clinical trials of long-term switching to lower nicotine cigarettes. Given the organization of the text, this likely needs to be provided in the "Choice" section on p. 39. These controlled for non-nicotine aspects of smoking behavior, so that only the differences in nicotine content per se influenced choice responses. The 2019 NTR paper shows that threshold for nicotine discrimination directly relates to threshold for choice (i.e. preference, or reinforcement), and Shoaib & Perkins (2020) review paper outlines broader research on relevance of nicotine discrimination to reinforcement. The Perkins & Karelitz 2020 NTR paper indicates Spectrum cigs above 2.4 mg/g nicotine content are chosen more than the 0.4 mg/g VLNC. Perkins & Karelitz 2020 *Psychopharmacology* paper confirms that finding in a better controlled test; it also indicates cigs at or below 2.4 mg/g are chosen LESS than the 18 mg/g "regular nic cig" (similar to commercial brands). This is potentially important, as these results are consistent with the decline in cigs/day seen in the switching study of Donny et al. (2015), later described in detail on p. 37, when groups were randomized to the lower nic content Spectrum cigs from their initial brands.

pp. 44-45, on Drug Liking and other Subjective effects: Our most recent research shows that immediate pleasurable perceptions of smoking Spectrum cigarettes varying in nicotine content actually mediate the acute reinforcing effects of those cigarettes. This result indicates self-administration of the higher nicotine cigarettes (in a choice procedure, comparing vs. the 0.4 mg/g VLNC) is caused by those rated perceptions upon smoking them. Although often assumed, this was the first time causation for reinforcement by acute subjective responses has been shown in humans, to our knowledge. This is Karelitz & Perkins (2020), but it is not yet in press.

Papers cited above:

Karelitz JL, Perkins KA (2020). Acute pleasurable perceptions mediate cigarette reinforcement efficacy. Under review.

Perkins KA (2019) Research on behavioral discrimination of nicotine may inform FDA policy on setting a maximum nicotine content in cigarettes. *Nicotine Tob Res* 21(suppl 1):S5–S12. https://doi.org/10. 1093/ntr/ntz136

Perkins KA, Karelitz JL (2020) A forced choice procedure to assess the acute relative

reinforcing effects of nicotine dose per se in humans. *Nicotine Tob Res*; in press. https://doi.org/10.1093/ntr/ntz224Perkins KA, Karelitz JL (2020) Differences in acute reinforcement across reduced nicotine content cigarettes. *Psychopharmacology*; in press. https://doi.org/10.1007/s00213-020-05509-9

Shoaib M, Perkins KA. (2020) Preclinical and clinical research on the discriminative stimulus effects of nicotine. *Neuropharmacology*, in press.

5. Provide any additional comments including limitations and outcomes not discussed, or editorial suggestions not addressed in the previous questions.

On p.10, more emphasis should be given to the (now brief) mention (one sentence) that most current dependent smokers regret having started, as that is a very strong indication of loss of control over drug use (i.e. "autonomy"), or dependence on the drug. A policy to reduce nicotine content of tobacco would thus be expected to help restore some of that control, to allow users to succeed in dealing effectively with that regret by permanently quitting, which is also briefly noted in the next sentence, but seems to warrant more attention in supporting policy rationale.

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"

Page	Paragraph/Line	Comment
p. 8	first full paragraph	Update for new minimum age of cig purchase? Text says 18 but new law is 21 (as has been the case in several states in recent years). So, perhaps "Despite recent increase in age for purchase from 18 to 21 nationwide, surreptitious access to tobacco is likely to continue among adolescents and older teens." Later text in that paragraph, on very high rates of youth underestimating risks of dependence onset within a few years, is effective and could even be given more emphasis.
p.216 in refs:		Perkins et al., 2017 and 2018, each with 2 papers by same authors (marked "a" and "b" are actually the same paper, as one includes doi and the other does not).

III. Reviewer #3

External Letter Peer Review of "The Science of a Nicotine Standard for Combusted Tobacco Products"

Reviewer #3

I. RESPONSE TO CHARGE QUESTIONS

1. ***Is the report clearly written and does it follow a logical structure? If not, provide suggestions for how to improve the document.***

   The report is written very clearly and stays away from jargon. I thought it followed a logical structure. Some minor suggested revisions are as follows:

   Page 20, nicotine yield is described on this page before the explanation of the difference between yield and content, which is explained on page 31. It would help the reader if the future paragraph on page 31 is referenced, or if a brief explanation of yield vs. content is described on page 20.

   Page 24, the biomarker outcomes are described, but it is not written here why this is important (i.e., biomarkers of tobacco smoke exposure could reveal whether there was compensatory smoking).

   Section iv. Choice (page 39), this section could be moved after section i. Drug Liking (page 44), since it would follow logically that smokers would be less likely to choose VLNCs if they are rated as less satisfying and less pleasant.

2. ***Does the executive summary accurately reflect the content of the overall document and provide sufficient information to capture the critical components?***

   The executive summary is concise, easy to read, and summarizes the main points of the document.

3. ***For each section that you reviewed, were the conclusions appropriate given the available evidence? If not, provide specific examples as to where conclusions are not appropriate.***

   Section II. A. (page 8, 3rd paragraph) ("The adolescent brain is more vulnerable to developing nicotine dependence than the adult brain") this statement isn't supported by Apelberg et al., 2014, who did not compare adolescents to adults. The Levin et al., 2007 citation supports this statement better: adolescent rats self-administer more nicotine than adults, and there are age-related differences in nicotine's action in the brain (e.g., Levin et al., 2007 https://doi.org/10.1016/j.ntt.2007.02.002). Also, be careful to not confuse addiction with dependence. A more accurate sentence would be "The adolescent brain may be more vulnerable to the reinforcing effects of nicotine, which increases adolescents' likelihood of becoming addicted."

   Section II. A. (page 10) "Decreasing the nicotine content…switch to potentially less harmful tobacco products such as e-cigs". It is really controversial right now if e-cigs/ENDS are less harmful. I would recommend not suggesting a specific product, such as ENDS, as a safer

alternative to combustible tobacco here and throughout the document.

Throughout the document: Evidence that lowering nicotine levels will reduce the risk of progression from experimentation to regular use (especially among adolescents and young adults). This is certainly a reasonable hypothesis, but of the literature reviewed and summarized in the appendices, I see very few human-subject studies to support this hypothesis. This lack of research is noted on page 56. There have been preclinical studies in rodents and primates that might be cited to bolster this claim (e.g., https://doi.org/10.1007/s00213-016-4293-y, https://doi.org/10.1016/j.neuropharm.2016.06.026). Some other relevant literature is summarized in this editorial regarding the FDA's proposed nicotine-reduction regulation https://doi.org/10.1093/ntr/ntz101.
See also: Shiffman et al., 2019 Very-low-nicotine-content cigarettes and dependence among non-daily smokers https://doi.org/10.1016/j.drugalcdep.2018.12.021. Cassidy et al., 2019 Age moderates smokers' subjective response to very-low nicotine content cigarettes: evidence from a randomized controlled trial. doi: 10.1093/ntr/nty079. Davis et al., 2019 Examining age as a potential moderator of Response to Reduced Nicotine Content Cigarettes in Vulnerable Populations https://doi.org/10.1093/ntr/ntz134.

Page 34. Similar to above, there appear to be only 2 cited papers (Benowitz and Henningfield 1994, and Sofuoglu and LeSage 2012) that support the hypothesis that nicotine can be reduced to a non-reinforcing level. This would be a stronger argument if there were more citations, especially of studies using nicotine-naïve animals (e.g., Donny 1995 Nicotine self-administration in rats Psychopharm 122:390-394). A recent paper by Perkins 2019 https://doi.org/10.1093/ntr/ntz136 shows that smokers could not detect nicotine in the 0.4 mg nicotine cigarette. Also see Shoaib and Perkins 2020 https://doi.org/10.1016/j.neuropharm.2020.108063

Page 23, it is a little misleading to write that VLNCs resulted in significantly fewer cigarettes per day. Likewise, Page 36 reads "switching to LNC or VLNC cigarettes may produce modest decreases in CPD." Not all of the references cited on page 37 support this statement. In Donny et al., 2015, the average CPD did not change from baseline among people given VLNCs (CPD stayed around 15 per day), even though at the end of 6 weeks, smokers given free NNCs increased their cigarette consumption (there was a between-group difference, not a within-group difference in the VLNC group). I think Dermody 2016 and Hatsukami 2015 just re-analyze this same data. (However, Donny 2007 showed an average within-subject decrease of 3.5 cigarettes per day among smokers using 12 cigs/day at baseline in support of this claim). It should be noted that for established smokers, switching to VLNCs does not stop their smoking, or even diminish it by all that much. More accurately, VLNCs do appear to prevent escalation of use (also very important).

See also Smith et al., 2019 Randomized trial of low-nicotine cigarettes and transdermal nicotine. https://doi.org/10.1016/j.amepre.2019.05.010. Shiffman et al., 2019 Very-low-nicotine-content cigarettes and dependence among non-daily smokers https://doi.org/10.1016/j.drugalcdep.2018.12.021.

Section d. Lower nAChR occupancy (page 50). "Although there is enough nicotine in VLNC cigarettes to bind to acetylcholine receptors in the brain and to release dopamine, there is not

enough to consistently produce the full range of subjective or physiological responses." While this statement is most likely true, it is not supported by the citations (Addicott 2014, Rose 2003). Addicott 2014 shows there is a cerebral response to VLNCs, which appears to contradict the section title. I disagree that the withdrawal-relieving effects of VLNCs are exclusively due to conditioned learning, and not due to some of the other 7000 chemicals in tobacco smoke. Overall, this entire section (section d.) is poorly supported and does not contribute much to the overall document. I would recommend either removing it or making a major revision with more supporting references.

4. ***Are you aware of additional publicly available information which should have been included? If so, please specify.***

Section II. B. (page 11): I like the reference Lopez-Quintero et al., 2011 (https://doi.org/10.1016/j.drugalcdep.2010.11.004) that shows the probability of transitioning from first use to dependence is 67% for nicotine/tobacco – but less than 25% for alcohol, cocaine and cannabis. This suggests a relatively stronger addiction liability for nicotine/tobacco than other drugs of abuse (some of which are also legal and easily obtained, i.e., alcohol).

Section II. B. (page 12): I also like the reference Hackshaw et al., 2018 (https://doi.org/10.1136/bmj.j5855) that shows there is no "safe" level of smoking, just smoking one cigarette per day increases the risk of stroke and coronary artery disease.

Page 16. Hughes, Keely, and Naud (2004) reported that the majority of smokers who attempt to quit relapse within eight days. https://doi.org/10.1111/j.1360-0443.2004.00540.x

Here are several recent articles that address gaps in the document's reviewed literature…

Shiffman et al., 2019 Very-low-nicotine-content cigarettes and dependence among non-daily smokers https://doi.org/10.1016/j.drugalcdep.2018.12.021. Non-daily smokers were experimentally switched to very-low-nicotine cigarettes. Tobacco dependence decreased, along with cigarette consumption.

Smith et al., 2019 Randomized trial of low-nicotine cigarettes and transdermal nicotine. https://doi.org/10.1016/j.amepre.2019.05.010. Assignment to very low nicotine content cigarettes and assignment to wear a nicotine patch both reduced the number of cigarettes smoked per day during Week 6 ($p=0.001$ and 0.04, respectively).

Cassidy et al., 2019 Age moderates smokers' subjective response to very-low nicotine content cigarettes: evidence from a randomized controlled trial. doi: 10.1093/ntr/nty079. Results indicated that younger adults (age 18–24) who smoked cigarettes with 2.4–0.4 mg/g nicotine reported significantly less smoking satisfaction and psychological reward, and smoked fewer cigarettes per day, than older adults (25+ years) after two weeks of use. No differences in topography were observed at either time point. After six weeks of use, differences had diminished on all measures.

Pacek et al., 2019 Young adult dual combusted cigarette and e-cigarette users' anticipated responses to a nicotine reduction policy and menthol ban in combusted cigarettes

https://doi.org/10.1016/j.drugalcdep.2018.10.005. Hypothetical nicotine reduction led to intentions to quit/reduce cigarette use. Hypothetical nicotine reduction led to intentions to increase e-cigarette use.

Benowitz et al., 2019 The role of compensation in nicotine reduction https://doi.org/10.1093/ntr/ntz120. Assuming that a 10 CPD smoker is trying to maintain an intake of 10 mg nicotine per day, and assuming the most intensive compensation, it would require that the smoker smoke 100 CPD to achieve full compensation.

Davis et al., 2019 Examining age as a potential moderator of Response to Reduced Nicotine Content Cigarettes in Vulnerable Populations https://doi.org/10.1093/ntr/ntz134. Young adults exhibited lower demand for reduced nicotine content cigarettes than older adults across three of five CPT indices (ps < .05). No differences by age were observed on other measures of reinforcing efficacy, subjective effects, craving/withdrawal, or smoking topography where effects generally decreased as an orderly function of decreasing nicotine content (ps <.05).

Perkins and Karelitz 2020 Differences in acute reinforcement across reduced nicotine content cigarettes. doi: 10.1007/s00213-020-05509-9. Results indicate that nicotine reduction to ≤ 2.3 mg/g in cigarettes would attenuate reinforcement.

Gaalema et al., 2019. Potential Moderating Effects of Psychiatric Diagnosis and Symptom Severity on Subjective and Behavioral Responses to Reduced Nicotine Content Cigarettes. doi: 10.1093/ntr/ntz139. Reducing nicotine dose reduced measures of cigarette addiction potential, with little evidence of moderation by either psychiatric diagnosis or symptom severity, providing evidence that those with comorbid psychiatric disorders would respond to a nicotine reduction policy similarly to other smokers.

Tidey et al., 2019 Effects of 6-Week Use of Very Low Nicotine Content Cigarettes in Smokers With Serious Mental Illness doi: 10.1093/ntr/ntz133. These results suggest that a reduced-nicotine standard for cigarettes would reduce smoking among smokers with SMI

5. ***Provide any additional comments including limitations and outcomes not discussed, or editorial suggestions not addressed in the previous questions.***

There are more than 7000 chemicals in tobacco smoke – some of these are the products of combustion, some are added by tobacco companies (Rodgman A, Perfetti TA. The Chemical Components of Tobacco and Tobacco Smoke. New York, NY: CRC Press; 2013). Some of these ingredients may be primary reinforcers, conditioned reinforcers, or contribute to physical dependence/withdrawal symptoms. Tobacco companies know which additives make cigarettes/tobacco products more satisfying, easier to smoke, and more reinforcing (e.g., menthol). If they are forced to remove nicotine, why wouldn't they just add more of the other ingredients to keep smokers hooked? I know there are other regulations and proposed regulations concerning added ingredients (e.g., flavor), but how does that fit in with this proposal to reduce nicotine?

Page 36, perhaps a comparison of the rates of smoking cessation with VLNCs with rates of cessation during unassisted quit attempts would underscore the point that VLNCs make

quitting easier.

Several times it is mentioned that this product standard would apply to all combusted tobacco products, but there is no mention of IQOS, the 'heated not burned' tobacco product.

Section II. A. (page 10). It might be useful for a lay-reader to have a brief description of addiction/substance use disorder, specifically tobacco use disorder (i.e., persistent use of tobacco despite negative consequences, characterized by craving, compulsive use, physical tolerance, dependence, and withdrawal). I think many people do not consider tobacco use disorder a serious addiction (compared to – say- alcohol use disorder, which causes intoxication, problems with the law, etc). I think many people still perceive tobacco use as a "choice" people make. This document needs to drive home the point that tobacco is strongly addictive, and most people smoke because they have to – in response to powerful cravings and in order to avoid withdrawal symptoms – rather than just because they want to.

In addition to earlier comments I made about VLNCs not reducing cigarettes per day among established smokers…I think many businesses, farmers, and states who profit or receive tax dollars are going to resist this proposed reduction in nicotine, and here is an opportunity to allay some fears that people will stop smoking altogether if nicotine is reduced in cigarettes. It appears that established smokers will continue to smoke cigarettes. Reducing nicotine would ensure that people choose to smoke because they want to, not because they have to due to their nicotine addiction. I think this 'free will' argument has been used by the tobacco companies to help keep tobacco legal.

Page 30. Some of the ways in which VLNC tobacco can be grown/harvested/processed is described, but I'm curious about some of the barriers for these changes. Would farmers have to change their practices, or get new equipment? Would nicotine extraction increase the price of VLNC cigarettes? Are those costs absorbed by the tobacco companies or by the farmers? Additionally, much tobacco grown in America is exported, and will continue to be exported at full nicotine concentrations if this regulation is passed. Would the domestic implementation of low nicotine content cigarettes conflict with exports?

There is apparently a lack of research on the effects of VLNCs on light (using 5 CPD or less) and non-daily smokers. These smokers might be much more likely to reduce or quit cigarettes than heavy smokers (using at least 10 CPD). It appears that most of the research to date has been on smokers who use at least 10 cigarettes per day, who continue to use VLNCs at about the same rate. I think it would be important to put out a call for research in this area.

Section a. Illicit tobacco products (page 51), will there be any special considerations for enforcing laws against illicit tobacco given that vulnerable populations have the highest smoking prevalence rates and are most likely to be affected?

II. Specific Observations on *"The Science of a Nicotine Standard for Combusted Tobacco Products"*

None provided.

IV. Reviewer #4

External Letter Peer Review of "The Science of a Nicotine Standard for Combusted Tobacco Products"

Reviewer #4

I. RESPONSE TO CHARGE QUESTIONS

1. ***Is the report clearly written and does it follow a logical structure? If not, provide suggestions for how to improve the document.***

   The report is clearly written, and much of the presentation is logical and flows well. I have three comments.

   First, there are sections where the evidence presented is confusing, or leaves the reader wondering whether the conclusion reached in the document is correct. In both cases, the insertion of one or two sentences that would integrate the evidence or explain the conclusion would strengthen the presentation.

   Second, the section on cigarette price increases is of marginal relevance. The section on behavioral economics adds little, distracts from the flow of the paper, and could be eliminated.

   Third, given the many non-cigarette combustible products available, the extensive discussion in the background section focusing on cigars distracts from the flow of the document. It should either be shortened or a discussion of other products integrated into that section.

2. ***Does the Executive Summary accurately reflect the content of the overall document and provide sufficient information to capture the critical components?***

   For the most part, the Executive Summary does reflect the content of the document. However, there were two missing sections that are important.

   First, there is nothing in the summary on technical achievability. There is considerable evidence in the document itself that producing VLNC is technically achievable. A statement to this effect should be included in the Executive Summary.

   Second, the importance of combusted tobacco other than cigarettes is well summarized. However, the report itself states that FDA believes it necessary to also regulate nicotine content in these products for meaningful public health impact. This is implied in the Executive Summary, but not clearly stated. A clear statement should be inserted.

3. ***For each section that you reviewed, were the conclusions appropriate given the available evidence? If not, provide specific examples as to where conclusions are not appropriate.***

   I reviewed the entire report and agree with the conclusions based on the available evidence in each section, with one exception. That is Section IV B. b.i. , Smoking Cessation; (pages 35-36).

The report concludes that "Taken together, results from these studies suggest that, regardless of interest in quitting, smokers who are given VLNC cigarettes may be more likely to quit compared to those who continue to smoke usual brand or NNC cigarettes. In addition, provision of NRT may further increase smoking cessation among individuals interested in quitting". I am not in total disagreement with the statement, but given the relatively weak evidence, the statement should be modified throughout the document to take into account the strength of the evidence.

The issues are: (1) When compared to the plethora of well-controlled studies that address smoking rate, topography, cigarette choice, biomarkers, subjective effects, dependence, and withdrawal symptoms, there are relatively few studies on the relationship of VLNC to abstinence.

(2) Of those studies addressing VLNC and abstinence, few meet all or most of the criteria one would expect from a convincing clinical trial that had abstinence as an endpoint. That is, no study includes all, or even most, of the optimal methodologies, including an RCT design, biochemical verification; attention or placebo controls, adequate follow-up rate, and both short and long-term follow-up assessments. Often, abstinence is assessed as a secondary endpoint in a study focused on another issue, and in these studies, there may not be a useful control condition.

(3) The narrative seems biased towards reporting positive outcomes. Findings that indicate no differences between or among conditions are not clearly spelled out. Admittedly, when outcome data are combined with laboratory data on cigarettes per day, biomarkers, and subjective effects, there is a signal here that VLNC cigarettes may help smokers quit, but the studies are sufficiently weak in design with respect to abstinence that it would be best throughout the report to qualify the statement that VLNC cigarettes increase likelihood of quitting, especially long term abstinence.

The argument can be made that current data present a conservative estimate of the probability of abstinence due to VLNC, because abstinence would be substantially more likely if VLNC cigarettes were the only cigarettes available. Under those circumstances, there would be little or no chance of relapse to the more attractive NNC cigarettes. However, I did not see that argument presented.

4. Are you aware of additional publicly available information which should have been included? If so, please specify.

In December, Nicotine and Tobacco Research published a supplement devoted to VLNC (Nicotine & Tobacco Research, 21, Supplement 1, December 2019). The supplement included 21 articles focused on this topic. The majority of those appear to support the conclusions reached in this document, with the possible exception of Klemperer, et al.'s paper (Increasing quit attempts by transitioning to very low nicotine content cigarettes versus reducing number of cigarettes per day: A secondary analysis of an exploratory randomized trial, s81-s86); this paper found that reducing CPD resulted in more 24 hour quit attempts than VLNC cigarettes, but that there were no differences for quit attempts >24 hours. However, as the authors note, there were methodological issues with the study that suggest additional research is needed to address the soundness of this conclusion. The papers

addressing menthol cigarettes (Delinger-Apte et al. pages S63-S72 and S73-S80) add to the information in the current document. The papers by Piper et al (Behavioral and Subjective Effects of Reducing Nicotine in Cigarettes: A Cessation commentary S19-21 and Smith et al. Behavioral outcomes of nicotine reduction in current adult smokers, S125-127) conclude that VLNC increases quit attempts and when used with NRT, increases quit rates. The former is supportable; in my estimation, the conclusion that the implementation of VLNC cigarettes will result in an increase in actual quit rates is not as strong, especially with respect to prolonged abstinence.

5. Provide any additional comments including limitations and outcomes not discussed, or editorial suggestions not addressed in previous questions.

The technical information (included in the report under Analytical Testing Method and Technical Achievability) makes a strong case that FDA will in fact be able to produce a cigarette of an appropriate nicotine level. Most of the material, however, refers to cigarettes. The reader who is versed in biochemistry may easily be able to generalize this to other tobacco combustible products. But for the general scientist, the document would be more convincing if there were at least some mention of how the lower nicotine levels would be achieved in these products.

Second, the issue of the potential harms of ENDS is not discussed, particularly increased levels of nicotine addiction of youth and young adults. FDA seems to clearly anticipate that reduction of nicotine content in cigarettes will increase use of ENDS among all age groups; therefore, it seems dismissive to not consider the implications of this addiction, or at the very least, acknowledge it, and note that the effects are unknown.

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"

Page	Paragraph/Line	Comment
5	1/9	Insert comment that producing lowered nicotine content in VLNC is technically achievable.
5	1/14	Insert 'possibly' before 'increased quit rates among current smokers'.
5	1/16	Omit 'also' in the sentence beginning "There is ~~also~~
5	1/21-22	The phrase 'substantial portion' is used twice in the same sentence. The sentence should be rewritten.
6	1/7	After line 7, insert comment that FDA proposes to limit nicotine content in non-cigarette products.
10	1/last line	Given the recent concern with Juul and other e-cigarettes, it seems rather incomplete that there is little discussion at any point in the manuscript about the possible addiction to nicotine via e-cigarettes, especially in terms of youth and young adults.

Page	Paragraph/Line	Comment
11	2/5	As described below the evidence concerning the facilitation of quitting via VLNC is suggestive, but not so strong as that supporting the minimal addictiveness of VLNC. Therefore, I suggest that line 5 of paragraph 2 be slightly modified so that (2) reads as follows enhance the possibility that addicted users will be able to quit, or will switch to other products which are possibly less harmful
13	2	FDA proposes to limit nicotine levels in 'all forms of combustible tobacco', as I understand it, not just cigarettes and cigars. Given this, the detailed description of the harms of cigars alone seems unbalanced. Suggest it be condensed, and some information on, or at least more detailed reference to, non-cigarette combustible products.
13	2/3 and 4	Extensive discussion of cigars, in light of the many non-cigarette combustible products available, distracts from the flow of the document. Should be shortened, and at least passing reference made to other non-cigarette combustible products.
17	1/5	Eliminate part of the sentence that begins with "potentially easier…. Rewrite this section to read, "potentially easier for smokers to make more successful quit attempts. Studies on the effects of reduced nicotine tobacco products on relapse have not been done. However, it is plausible that, under such a standard when more attractive and addictive nicotine products are not available, that relapse rates would also be impacted favorably". The next sentence would begin, "Former smokers who chose…:
18	4/6	Replace "would" with "may well"
24	2/all	In discussing Hatsukami et al (2018), reports a significantly lower completion rate for immediate reduction than gradual reduction and control conditions. Concludes that immediate reduction is associated with positive outcomes (e. g, less toxicant exposure, less nicotine dependence, increased abstinence). Fails to discuss the possible effects of differential drop-out on the dependent variables or offer evidence that differential drop-out did not influence the outcome.
24	2/7	Completion rates in the immediate reduction group were markedly lower than in the gradual reduction group. The report does not indicate whether these differences were statistically significant, nor does it discuss the possibility that they should be considered in interpreting differences between the two conditions. If neither of these concerns affects the results and the conclusions that can be drawn from them, there should be a statement to that effect.

Page	Paragraph/Line	Comment
35	1/7	Insert the following paragraph after the sentence ending…and those uninterested in quitting. "of those studies addressing VLNC and abstinence, few meet most of the criteria that define major clinical trials that have abstinence as an endpoint, and results are sometimes inconsistent, especially with respect to long-term follow-up. Often, abstinence is assessed as a secondary endpoint in a study addressing another issue, and subsequently there is no control condition. Nevertheless, the preponderance of the evidence suggests that, when taken together, results from these studies…..
35	2/1-6	At the end of the paragraph, insert "it should be noted that although significant differences were found at week 6, differences did not reach traditional levels of significance at weeks 1, 7 and 8'.
35	3/9	After the sentence ending, "promoting continuous abstinence than VLNC cigarettes alone, insert, "However, as the authors note, abstinence at 3- and 6-month follow-up) could not adequately assessed due to attrition at those time points".
35	3/16	After the sentence ending, ….received usual care (15%)", Insert, "Abstinence rates were based on self-report alone; further, the study lacked a placebo or other control for VLNC. Thus, abstinence rates may have been inflated, and it is unclear whether the results reported were biased due to the effects of receiving an novel intervention ".
36	2/13	Remove sentence beginning with "Although 7%.... Insert sentence " Quit rates were low in both groups and did not reach traditional levels of statistical significance at any point up to 24 months.
45	1/13-16	In discussing the results of several studies, reports somewhat contradictory ratings on items designed to measure subjective effects of VLNC without any attempt to integrate or explain the contradiction (e. g. VLNC both rated lower on aversiveness and sickness and higher on dislike and unpleasant.
60	2/2	Consider updating data on use rates of e-cigarettes in high school students if they have changed substantially since the report was written.
65	3/to end of page	Consider eliminating or summarizing
66	1&2/all	Consider eliminating or summarizing.
66	3/to end of page	eliminate
67	Whole page	eliminate

V. Reviewer #5

External Letter Peer Review of "The Science of a Nicotine Standard for Combusted Tobacco Products"

Reviewer #5

I. RESPONSE TO CHARGE QUESTIONS

1. Is the document clearly written and does it follow a logical structure? If not, provide suggestions for how to improve the document.

Overall, the report is clearly written and has a logical flow. However, I have highlighted a few sections that could be reorganized to improve the document.

Section III. Scope
This section felt a little disjointed as I read it. It might be helpful to describe the differences between 'nicotine content' and 'nicotine yield' earlier in the review. The jump from policy implementation approach to analytic testing did not feel logical to me. Perhaps Section III could be revised as follows:
A. Analytic Testing (how do we test for nicotine levels)
B. Technical Achievability (how would manufacturers achieve the maximum nicotine level)
C. Maximum Nicotine Level (what is the desired outcome)
D. Inclusion of Combusted Products (what products have to meet that maximum nicotine level)
E. Implementation (how do we move combusted products to the maximum nicotine level)

Section IV.C. Unintended Consequences
a. **Illicit Tobacco Products**: I would make this the last topic in the section. It has the least amount of empirical data specifically related to VLNC cigarettes.
b. **Noncompliance**: I'm not sure that it makes sense to frame noncompliance as an unintended consequence of low nicotine product standard. Noncompliance highlights that smokers are motivated to use conventional cigarettes or other nicotine products for various reasons during a trial (i.e., craving, stopping withdrawal symptoms, tastes better). This information might be better if combined with Section V.C. - Potential for Non-Cigarette Combusted Tobacco Product Switching. Smokers are dissatisfied with VLNC cigarettes and switch to other combusted products or seek out illicit NNC cigarettes.
c. **Compensatory Smoking**: This should be the first topic in the section. It's the most important health-related concern of a nicotine reduction policy and provides the most compelling data that nicotine reduction likely won't lead to increased smoking. Smith et al., 2020a and Smith et al., 2020b are two recent publications that should be incorporated into this section fairly extensively since they both are studies specifically to address compensation.
d. **Impact on Vulnerable Populations**: I definitely understand the need for this section; however, at times, I felt like information on vulnerable populations should have also been included in the overall narrative and not relegated to a separate section after the primary points have already been made.

Sections V.A. and V.B. These two sections, Who Uses Combusted Tobacco Products? and Abuse Potential of Non-Cigarette Combusted Tobacco Products, could have come before the

VLNC cigarette literature review section. The very first sentence of the executive summary mentions all combusted tobacco products but the review does not mention other combusted tobacco products until page 59.

Section V.C. Potential for Non-Cigarette Combusted Tobacco Product Switching could be absorbed as part of the Unintended Consequences, Section IV.C.

2. ***Does the executive summary accurately reflect the content of the overall document and provide sufficient information to capture the critical components?***

The executive summary accurately reflects the content of the overall document and provides sufficient information. However, it does not include information about cigarette manufacturing practices for creating VLNC cigarettes. This section could be important to mention in the executive summary because it establishes the feasibility of implementing the product standard. When I read the manufacturing section, it struck me as a very useful section for building the argument of why the FDA can and should implement a product standard. Having 1-2 sentences in the executive summary highlighting the industry-driven feasibility of cigarette nicotine reduction could be an added strength, as well as prepare the reader for the upcoming content.

Minor comment: Only some of the supporting science in the executive summary had citations (e.g., the policy simulation by Apelberg et al., 2018) while other research topics did not. This was a little confusing.

3. ***For each section that you reviewed, were the conclusions appropriate given the available evidence? If not, provide specific examples as to where conclusions are not appropriate.***

Section I. Executive Summary
One issue that stood out to me in the executive summary was that the authors write "… without evidence of… compensatory smoking" and "… no evidence of differential effects of VLNC cigarettes in vulnerable populations". This definitive language surprised me. Most clinical trials and lab studies included in this review report the average treatment effects and do not necessarily include individual differences analyses or treatment effect heterogeneity. I do agree that, on average, use of VLNC cigarettes does not result in compensation or differential effects among priority smoking populations. I'm not necessarily suggesting this wording needs to be changed but wanted to bring caution that we do not know how nicotine reduction will impact all groups of smokers.

Section II. Background
The background information is justified to include. The conclusions regarding the harms associated with cigarette smoking are appropriate given the data available. The assessment of the contribution of nicotine in cigarettes to establishing and maintaining smoking behavior is also accurate.

Section III. Scope
No additional comments on this section.

Section IV. VLNC Cigarette Literature Review

B. Estimate of Addiction Threshold Levels

b. Findings Related to Cessation, Use Behaviors, Biomarkers of Exposure, and Physiological Effects of VLNC Cigarettes

i. Smoking Cessation: The conclusion that VLNC in combination with NRT and standard of care increased smoking cessation outcomes is appropriate given the data available. Additionally, the evidence suggests that use of VLNC cigarettes increases smoking cessation interest, attempts or success among smokers who previously reported no interest in quitting.

ii. Cigarettes Per Day (CPD): The authors conclude there is no evidence of increased CPD when using VLNC for extended periods and some studies found modest decreases in CPD. These conclusions are appropriate given the data available. One study that should be added to this section is Hatsukami et al., 2018 *JAMA*, which reported significant decreases in CPD in the immediate vs gradual and immediate vs control. No significant differences between gradual vs control conditions. One limitation is noted that many studies did not account for use of non-study CPD. If accurate, then the review should reference the studies that do not account for non-study CPD.

iii. Smoking Topography: The Strasser et al., 2007 citation is supporting the statement of fewer puffs per cigarette but the study also reported higher CO boost and total puff volume for 0.05 vs 0.30 mg Quest cigarettes (according to the abstract). I would suggest reviewing the article to determine if those results should also be included in this sentence "one brief exposure study showed higher puff volume and puff duration when participants smoked VLNC cigarettes, but these effects diminished within a single laboratory session (MacQueen et al., 2012)". One study that could be added is Denlinger-Apte et al., 2019d that reports smoking topography from a VLNC trial of smokers with serious mental illness.

iv. Choice: The conclusion that NNC cigarettes are preferred over VLNC cigarettes is appropriate given the data available. One study that should be added is Cassidy et al., 2019a. It reports Cigarette Purchase Task data among adolescent daily smokers.

v. Biomarkers of Exposure: The conclusions that CO does not differ between VLNC and NNC and there is minimal evidence of increased CO exposure are appropriate given the data available. The conclusion that TNEs/cotinine are decreased is appropriate given the data available. The conclusion that HPHCs are mixed results when smoking VLNC cigarettes is appropriate given the data available. The Hatsukami et. al., 2018 *JAMA* manuscript should be added to each section (CO, TNE, HPHCs).

vi. Physiological Effects: The conclusions that VLNC cigarettes produce inconsistent physiological effects is appropriate given the data available.

c. Subjective Effects, Dependence, and Relief of Withdrawal Symptoms Associated with VLNC Cigarettes.

i. Drug Liking and Other Subjective Effects: The conclusion that VLNC cigarettes are rated lower in subjective effects is appropriate given the data available. Smith et al.,

2019b reports lower subjective ratings in the immediate reduction condition (secondary analysis of Hatsukami et al., 2018 *JAMA*).

ii. Dependence: The conclusion that use of VLNC cigarettes reduces cigarette dependence is appropriate given the data available. The Hatsukami et. al., 2018 *JAMA* manuscript should be added.

iii. Relief from Withdrawal Symptoms: The conclusion that use of VLNC cigarettes suppresses withdrawal symptoms is appropriate given the data available. The Hatsukami et. al., 2018 *JAMA* manuscript should be added.

d. Lower nAChR Occupancy and Cerebral Response from the Use of VLNC Cigarettes: I did not follow this section or what the conclusions were related to VLNC cigarettes.

C. Unintended Consequences

a. Illicit Tobacco Products: It is appropriate to include this section as an unintended consequence.

b. Noncompliance: The conclusion that noncompliance is common with VLNC cigarettes is appropriate given the data available. As I mentioned previously, I don't know that I view noncompliance as an unintended consequence of a nicotine reduction policy.

c. Compensatory Smoking: The conclusion that extended use of VLNC cigarettes does not result in compensatory smoking is appropriate given the data available.

d. Impact on Vulnerable populations:

i. Adolescents: The conclusion that adolescents like VLNC cigarettes less is appropriate given the data available. The review acknowledges the very limited data regarding adolescent VLNC use. With respect to adolescent initiation with VLNC cigarettes there is no data available and this could be acknowledged too. The following quote should have a citation: "However, it is expected that significantly fewer individuals would become established combusted tobacco product users; thereby, dramatically reducing the long-term health impact of chronic combusted tobacco product use." I assume this is based on Apelberg et al., 2018 *NEJM* but it would be good to support this assertion.

ii. Individuals with Symptoms of Mental Health and Substance Use Disorders: The conclusion that VLNC cigarettes do not increase harm in smokers with mental health conditions is appropriate given the data available, but acknowledging the limited data are important. Tidey et al., 2019 and Denlinger-Apte et al., 2019d should be added to this section.

V. Justification for the Inclusion of all Combusted Products in a Nicotine Tobacco Product Standard

The conclusions that non-cigarette combusted tobacco products (cigars, waterpipes, loose tobacco) have abuse potential and thus are a threat to public health are appropriate given the data. However, the individual product sections should be updated to reflect the most recent

use data, especially among middle and high school students.

VI. Potential Public Health Benefits of Preventing Initiation to Regular Use and Increasing Cessation

The conclusion that quitting smoking at any age is beneficial to health is appropriate given the data.

VII. The Impact Perceptions Around Nicotine and Reduced Nicotine May Have on a Proposed Nicotine Standard

The conclusions that many smokers incorrectly perceive nicotine as the harmful constituent in cigarettes and that VLNC are perceived by some as less harmful are appropriate given the data available.

4. Are you aware of additional publicly available information which should have been included? If so, please specify.

Several VLNC studies have been published since the last PubMed search for this review was conducted in 2018. I acknowledge these studies in the Comments table below with suggestions of where in the review they could be included.

Byron, JM., Jeong, M., Abrams, D.B. & Brewer, N.T. (2018). Public misperception that very low nicotine content cigarettes are less carcinogenic. *Tobacco Control*. 27(6), 712-714. doi: 10.1136/tobaccocontrol-2017-054124.

Byron, JM., Hall, M.G., King, J.L., Ribisl, K.M., & Brewer, N.T. (2019). Reducing nicotine without misleading the public: Description of cigarette nicotine level and accuracy of perceptions about nicotine content, addictiveness, and risk. *Nicotine & Tobacco Research*, 21(Suppl_1), S101-S107. doi: 10.1093/ntr/ntz161

Cassidy, R.N., Miller, M.E., Tidey, J.W., DiGiuseppi, G., Denlinger-Apte, R.L., & Colby, S.M. (2019a). The impact of nicotine dose on the reinforcing value of cigarettes in adolescents. *Tobacco Regulatory Science*, 5(2), 105-114. doi:10.18001/TRS.5.2.2

Cassidy, R.N., Tidey, J.W., Cao, Q., Colby, S.M., McClernon, F.J., Koopmeiners, J.S., Hatsukami, D.K., & Donny, E.C. (2019b). Age moderates smokers' subjective response to very-low nicotine content cigarettes: Evidence from a randomized controlled trial. *Nicotine & Tobacco Research*, 21(7), 962-969. doi:10.1093/ntr/nty079

Davis, D.R., Miller, M.E., Streck, J.M., Bergeria, C.L., Sigmon, S.C., Tidey, J.W., Heil, S.H., Gaaleema, D.E., Villanti, A.C., Stitzer, M.L., Priest, J.S., Bunn, J.Y., Skelly, J.M., Diaz, V., Arger, C.A., & Higgins, S.T. (2019). Response to reduced nicotine content in vulnerable populations: Effect of menthol status. *Tobacco Regulatory Science*, 5(2), 135-142. doi: 10.18001/TRS.5.2.5

Denlinger-Apte, R.L., Tidey, J.W., Koopmeiners, J.S., Hatsukami, D.K., Smith, T.T., Pacek, L.R., McClernon, F.J., & Donny, E.C. (2019a). Correlates of support for a nicotine reduction policy in smokers with 6-Week exposure to very low nicotine cigarettes. *Tobacco Control,* 28(3), 352-355. doi:10.1136/tobaccocontrol-2018-054622

Denlinger-Apte, R.L., Cassidy, R.N., Colby, S.M., Sokolovsky, A., & Tidey, J.W. (2019b). Effects of cigarette nicotine content and menthol preference on perceived health risks, subjective ratings, and carbon monoxide exposure among adolescent smokers. *Nicotine & Tobacco Research*, 21(Suppl_1), S56-S62. doi: 10.1093/ntr/ntz127

Denlinger-Apte, R.L., Kotlyar, M., Koopmeiners, J.S., Tidey, J.W., Luo, X., Jensen, J.A., Vandrey, R.G., Pacek, L.R., Smith, T.T., Donny, E.C., & Hatsukami, D.K. (2019c). Effects of very low nicotine content cigarettes on smoking behavior and biomarkers of exposure in menthol and non-menthol smokers. *Nicotine & Tobacco Research*, 21(Suppl_1), S63-S72. doi: 10.1093/ntr/ntz160

Denlinger-Apte, R.L., Donny, E.C., Lindgren, B., Rubin, N., Moulding, C., DeAtley, T., Colby, S.M., Cioe, P., Hatsukami, D.K., & Tidey, J.W. (2019d). Smoking topography characteristics during a six-week trial of very low nicotine content cigarettes in smokers with serious mental illness. *Nicotine & Tobacco Research*. E-pub ahead of print

Hall, M.G., Brewer, N.T., Noar, S.M., & Ribisl, K.M. (2019). Interest in illicit purchase of cigarettes under a very low nicotine content product standard. *Nicotine & Tobacco Research*, 21(Suppl_1), S128-S132. doi: 10.1093/ntr/ntz159

Nardone, N., Benowitz, N.B., Smith, T.T., Denlinger-Apte, R.L., Hatsukami, D.K., Koopmeiners, J.S., Ren, Y., Donny, E.C. (2019). Reasons for non-compliance in a cigarette nicotine reduction trial. *Tobacco Regulatory Science*, 5(1), 87-93. doi:10.18001/TRS.5.1.8

Robinson, J.D., Kypriotakis, G., al'Absi, M., Denlinger-Apte, R.L., Drobes, D.J., Leischow S., McClernon F.J., Pacek L.R., Severson H., Smith T.T., Donny E.C., Luo X., Jensen, J.A., Strayer, L.G., Cinciripini, P.M., Hatsukami, D.K. (2019) Very low nicotine content cigarettes disrupt the feedback loop of affective states and smoking behavior. *Nicotine & Tobacco Research*. E-pub ahead of print

Ribisl, K.M., Hatsukami D.K., Huang, J., Williams, R.S., & Donny, E.C. (2019). Strategies to reduce illicit trade of regular nicotine tobacco products after introduction of a low-nicotine tobacco product standard. *American Journal of Public Health*, 109(7), 1007-1014. doi10.2105/AJPH.2019.305067

Smith, T.T., Koopmeiners, J.S., Tessier, K., Davis, E., Conklin, C.A., Denlinger-Apte, R.L., Lane, T., Murphy, S.S., Tidey, J.W., Hatsukami, D.K., & Donny, E.C. (2019a). A randomized clinical trial investigating the impact of very low nicotine content cigarettes and transdermal nicotine in smokers not trying to quit. *American Journal of Preventive Medicine*, 57(4), 515-524. doi: 10.1016/j.amepre.2019.05.010

Smith, T.T., Donny, E.C., Luo, X., Koopmeiners, J.S., Allen, A., Denlinger-Apte, R.L., Pacek, L.R., McClernon, F.J., Vandrey, R. & Hatsukami, D.K. (2019b). The impact of gradual and immediate nicotine reduction on subjective cigarette ratings. *Nicotine & Tobacco Research*, 21(Suppl_1), S73-S80. doi: 10.1093/ntr/ntz158

Smith, T.T., Koopmeiners, J.S., White, C.M., Denlinger-Apte, R.L., Pacek, L.R., DeJesus, V.R., Wang, L., Watson, C.H., Blout, B.C., Hatsukami, D.K., Benowitz, N.L., Donny, E.C.,

& Carpenter, M.J. (2020a). The impact of exclusive use of very low nicotine cigarettes on compensatory smoking: An inpatient crossover clinical trial. *Cancer, Epidemiology, Biomarkers & Prevention*, 29(4), 880-886. doi: 10.1158/1055-9965.EPI-19-0963

Smith, T.T., Koopmeiners, J.S., Hatsukami, D.K., Tessier, K.M., Benowitz, N.L., Murphy, S.E., Strasser, A.A., Tidey, J.W., Blout, B.C., Valentin, L,. Bravo Cardenas, R., Watson, C.H., Pirkle, J.L. &, Donny, E.C. (2020b). Mouth-level nicotine intake estimates from discarded filter butts to examine compensatory smoking in low nicotine cigarettes. *Cancer, Epidemiology, Biomarkers & Prevention*, 29(3), 643-649. doi: 10.1158/1055-9965.EPI-19-0905

Tidey, J.W., Colby, S.M., Denlinger-Apte, R.L., Cioe, P., Goodwin, C., Lindgren, B.R., Rubin, N., Hatsukami, D.K., & Donny, E.C. (2019). Effects of 6-week use of very low nicotine content cigarettes in smokers with serious mental illness. *Nicotine & Tobacco Research*, 21(Suppl_1), S38-S45. doi: 10.1093/ntr/ntz133.

5. Provide any additional comments including limitations and outcomes not discussed, or editorial suggestions not addressed in the previous questions.

Nicotine content reporting:
In III.E. Technical Achievability (and throughout the document), cigarette nicotine contents are described in both percent of nicotine and mg of nicotine. As a reader, it was slightly difficult for me to compare across different VLNC products within the text or to know what was considered LNC vs VLNC. Table 1 on page 32 was really helpful to review. Perhaps this table could be moved to earlier in the section. You may also want to add a column to Table 1 that includes nicotine % reduction since sometimes this is how products were described in the text. That would make it easy to compare across generations of products and different projects.

Section IV.C. Unintended Consequences:
Another section of potential unintended consequences to consider adding is how a nicotine reduction policy may affect use of other drugs. Dermody et al., 2016 *ACER* and Pacek et al., 2016 *DAD* are both secondary analyses from Donny et al., 2015 *NEJM*. They did not report increased use of alcohol or cannabis among smokers assigned to VLNC cigarettes which are encouraging initial findings.

Additionally, a paragraph on the impact of nicotine reduction by menthol smoking status could also contribute positively to the review since currently menthol cigarettes are commercially available and a product standard would apply to them. Perkins et al., 2017 *Psychopharmacology* reported nicotine dose discrimination by menthol smoking status and Perkins et al., *Journal of Psychopharmacology* reported VLNC perceptions by menthol smoking status. Davis et al., 2019 is a secondary analysis of Higgins et al., 2017 *JAMA* Psychiatry and reported no differences by menthol status. Denlinger-Apte et al., 2019c is a secondary analysis of Hatsukami et al., 2018 *JAMA* that reported outcomes by menthol smoking status and found that a nicotine reduction policy was likely to benefit both menthol and non-menthol smokers; but VLNC treatment effects were significantly smaller among menthol smokers.

Adolescent Smoking Prevention:
Adolescent and young adult smoking prevention is clearly an important policy outcome. Obtaining clinical data on adolescent initiation is clearly unethical; however, this results in a substantial gap in the literature. In this review, Apelberg et al., 2018 *NEJM* provides the most compelling information about how a nicotine reduction policy would affect initiation. However, it is simulated data. Given the lack of human subjects data, I wondered about adding in preclinical research that addresses this initiation outcome. Certainly, animal models have their limitations but they do provide complementary data. For example, Shassberger et al., 2016 *NTR* and Smith et al., 2014 *ECP* examined nicotine self-administration in adolescent and adult nicotine naive rats to assess the impact of low dose nicotine (i.e., VLNC cigarettes) on initiation. They found that the same low nicotine doses that reduced self-administration in nicotine-using rats was also sufficient for preventing nicotine self-administration acquisition in nicotine-naive rats. I do understand that preclinical studies were excluded as part of this review, so perhaps this is not possible. It may be worthwhile to include a couple sentences explicitly acknowledging this limitation.

In addition, some of the citations throughout the II.C.a.Youth Cigarette Smoking Initiation and Dependence section feel out of date. Over the past five years, significant declines in middle and high school smoking have occurred. Wang et al., 2019 reports past 30 day use of cigarettes at 5.7% for high school and 2.3% for middle school students. A nicotine reduction product standard will likely continue reducing adolescent smoking but substantial achievements, including surpassing the *Healthy People 2020* goal of 16% past 30-day smoking, have already occurred.

IV.C.d. Impact on Vulnerable Populations:
Having a separate section specifically highlighting vulnerable populations is a strength of this review. However, throughout the document, references to vulnerable populations were inconsistently cited. I would suggest including the citations in both locations, when discussing the overall topic (e.g., subjective effects) and in the vulnerable populations section.

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"

Page	Paragraph/Line	Comment
7	Paragraph 2	"In 2014, the Surgeon General estimated that, unless the current trajectory is changed dramatically, 5.6 million youth aged 0 to 17 years alive today will die prematurely from a smoking-related disease." This quote feels slightly outdated given the significant decline in middle and high school student smoking over the past 5 years. I recognize this is probably the most recent data available but perhaps somehow acknowledging that declines in smoking are occurring but a nicotine reduction policy could further render cigarettes unappealing to adolescents. Perhaps there are also differences in adolescent smoking by priority populations (e.g., LGBTQ+, those with mental health conditions) that could be included in this section and how a nicotine reduction policy could help reduce smoking in these populations. It feels a little

Page	Paragraph/Line	Comment
		disingenuous to reference an adolescent smoking epidemic that has changed substantially since this publication. Also, consider Wang et al., 2019 which reports that cigar use is the second most popular tobacco product, ahead of cigarettes, among high school students. This highlights the need for the product standard to apply to all combusted products and not just cigarettes.
8	Line 8	The legal age to purchase tobacco is now 21
10	Paragraph 2	Consider adding the 2020 Surgeon General's Report on Cessation
10	Paragraph 3	First sentence consider dropping the 'escape and'; redundant with 'to avoid nicotine withdrawal.
10	Paragraph 3	Minor comment: throughout the document your citation manager seems to include J.E. initials for Rose et al., 2004; 2006; 2010 citations. This occurs for a few repeated citations.
17	Paragraph 1	"Smokers would be unable to obtain enough nicotine from cigarettes to sustain addiction no matter how they smoked them and eventually would stop trying to do so." I don't understand why the proceeding references were included to support that statement (vs other nicotine reduction references that were excluded). The majority of smokers using VLNC cigarettes for extended periods, including these citations, continue to smoke cigarettes.
19	Paragraph 1	The rationale for references included vs excluded is not clear to me. Are the Benowitz et al., 2012; 2007 and Hatsukami et al., 2010 not included within the scope of the review and are instead background information?
19	Paragraph 1	"FDA hypothesizes that a tobacco product standard limiting the nicotine level in combusted tobacco products could significantly increase the number of successful quit attempts by the majority of smokers seeking to quit smoking every year and potentially prevent experimenters from developing addiction to combusted cigarettes and becoming regular smokers." The hypothesis that the majority of smokers would be successful at quitting must be based on the Apelberg at al., 2018 *NEJM* policy simulation. If so, I would acknowledge the policy simulation data as the foundation. To my knowledge, most clinical trials have enrolled non-treatment-seeking smokers that continue to smoke so the cessation outcomes are potentially underestimated.
23	Paragraph 2	Donny et al., 2015 *NEJM* reported increases in spontaneous quit attempts during the 30-day follow-up period for those in the VLNC conditions relative to NNC condition. This information is on page 15 of the online supplemental materials associated with the manuscript.
24	Paragraph 2	Hatsukami et al., 2018 *JAMA* reported abstinence and cigarette-free days during the trial. This information is on page 13 of the second online supplemental materials associated with the

Page	Paragraph/Line	Comment
		manuscript.
26	Paragraph 4	Consider adding one sentence about the commercial availability of Quest brand cigarettes.
28	Paragraph 4	The Philip Morris citation does not include a date or any other identifiable information.
29	Paragraph 4	Delete this last sentence about patents for genes since this information is also included on page 31, paragraph 2.
31	Paragraph 2	Move the first and last sentences of Paragraph 2 to the previous paragraph and then focus only on 22nd Century products in Paragraph 2.
31	Paragraph 3	This paragraph explains the differences between nicotine 'yield' vs 'content'. It would be better located much earlier in this section so unfamiliar readers can follow along with the different terms describing the different VLNC products.
34	Paragraph 1	The quote from Benowitz & Henningfield 1994 includes "provide enough nicotine for taste and sensory stimulation." Is this something the FDA must consider with respect to nicotine reduction? If not, I would exclude this part of the quote. Studies indicated lower subjective ratings after smoking VLNCs.
35	Paragraph 1	Additional studies of smokers not interested in quitting that report quit attempts or abstinence at the end of the trial: Donny et al., 2015 *NEJM* reported increases in spontaneous quit attempts during the 30-day follow-up period for those in the VLNC condition relative to NNC condition. This information is on page 15 of the online supplemental materials associated with the manuscript. Hatsukami et al., 2018 *JAMA* reported abstinence and cigarette-free days during the trial. This information is on page 13 of the second online supplemental materials associated with the manuscript. Smith et al., 2019a is a trial of VLNC+patch that included a 7-day abstinence assessment after 6-weeks of VLNC exposure. Denlinger-Apte et al,. 2019c is a secondary analysis of Hatsukami et al., 2018 - reported odds of Week 20 abstinence in the immediate reduction condition by menthol smoking status. n.
35	Paragraph 1	The last sentence of the paragraph needs a citation (possibly Hatsukami, Heertsgard et al., 2013).
35	Paragraph 3	Smith et al., 2019a is a trial of VLNC+patch that included a 7-day abstinence assessment after 6-weeks of VLNC exposure. The study did not report significant differences for VLNC+patch vs VLNC alone.

Page	Paragraph/Line	Comment
36	Paragraph 2	Donny et al., 2015 *NEJM* reported increases in spontaneous quit attempts during the 30-day follow-up period for those in the VLNC condition relative to NNC condition. This information is on page 15 of the online supplemental materials associated with the manuscript.
37	Paragraph 1	Tidey et al., 2019 is a VLNC trial among smokers with serious mental illness. It could be included in this section and/or the vulnerable populations section.
37	Paragraph 1	The last sentence of the paragraph should cite Hatsukami et al., 2018 not 2015.
37	Paragraph 2	Donny et al., 2015 *NEJM* reported increases in spontaneous quit attempts during the 30-day follow-up period for those in the VLNC condition relative to NNC condition. This information is on page 15 of the online supplemental materials associated with the manuscript.
37	Paragraph 3	Cite the studies that did not account for non-study CPD.
38	Paragraph 2	Add Smith et al., 2020a - In-patient study examining VLNC compensation.
39	Paragraph 1	Denlinger-Apte et al., 2019d is a secondary analysis of Tidey et al., 2019 reporting VLNC smoking topography in smokers with serious mental illness. It could be included in this section and/or the vulnerable populations section.
40	Paragraph 2	Cassidy et al., 2019a is a secondary analysis of Cassidy et al., 2018 *DAD* that reports Cigarette Purchase Task data among adolescent daily smokers. It could be included in this section and/or the vulnerable populations section.
41		Since this section is about choice you might consider adding another paragraph about the Hatsukami et al., 2016 exploratory trial. Smokers could buy VLNC or alternative products.
42	Paragraph 1	Hatsukami et al., 2018 *JAMA* reported significant reductions in CO between the immediate vs gradual and immediate vs control.
42	Paragraph 1	Add CO outcomes for following studies: Smith et al., 2019a Smith et al., 2020a
43	Paragraph 1	Add TNE outcomes for the following studies: Hatsukami et al., 2018 *JAMA* Denlinger, Smith et al., 2016 *Tob Reg Sci* Smith et al., 2019a Smith et al., 2020a
43	Paragraph 2	Hatsukami et al., 2018 *JAMA* reported NNAL, 3-HPMA, and CEMA and many other biomarkers of exposure.
44	Paragraph 4	Cassidy et al., 2018 *DAD* reported VLNC subjective effects. It could be included in this section and/or the vulnerable populations section.
45	Paragraph 1	Higgins et al., 2017 *JAMA Psychiatry* reported VLNC subjective effects.

Page	Paragraph/Line	Comment
45	Paragraph 3	Cassidy et al., 2019b is an age moderation manuscript of Donny et al., 2015 *NEJM*; reported VLNC subjective effects. It could be included in this section and/or the vulnerable populations section. Smith et al., 2019b is a secondary analysis of Hatsukami et al., 2018 *JAMA* that reports VLNC subjective effects. Tidey et al 2019 reports VLNC subjective effects. It could be included in this section and/or the vulnerable populations section.
46	Paragraph 2	Streck et al., 2019 secondary analysis of Higgins et al., 2017 *JAMA Psychiatry*; gender moderation of VLNC subjective effects
47	Paragraph 2	Hatsukami et al., 2018 *JAMA* reports FTCD and WISMD scores with reductions in immediate vs gradual and immediate vs control. No differences in gradual vs control. Tidey et al., 2019 reports FTCD scores but not significant differences between VLNC and NNC conditions.
49	Paragraph 2	Hatsukami et al., 2018 *JAMA* reports MNWS and QSU scores
49	Paragraph 4	Smith et al., 2019a reports MNWS and QSU outcomes
52	Paragraph 2	Ribisl et al., 2019 reports strategies to mitigate illicit NNC market if a low nicotine product standard is implemented. It could be an informative addition to this section. Hall et al., 2019 reports interest is purchasing illicit cigarettes after a VLNC product standard. It could be an informative addition to this section.
53	Paragraph 2	The last sentence of the paragraph about NTR needs a citation.
54	Paragraph 3	Add Smith et al., 2019a - did not report differences in compliance based on NTR use.
55	Paragraph 2	Citations for compensation are incomplete. Donny et al., 2015 *NEJM* - reductions in CPD, no differences in CO, reductions in total puff volume. Hatsukami et al., 2018 *JAMA* - reductions CPD and CO New citations to include: Denlinger-Apte et al., 2019d is a secondary analysis of Tidey et al., 2019 reporting VLNC smoking topography in smokers with serious mental illness. It could be included in this section and/or the vulnerable populations section. Smith et al., 2020b - Solanesol paper. Secondary analysis from Donny et al 2015 *NEJM*. CDC examined cigarette butt filters for solanesol to assess compensation. No evidence of increased compensation in VLNC groups.
56	Paragraph 3	Denlinger-Apte et al,. 2019b is a secondary analysis of Cassidy et al., 2018 *DAD* that reports the Perceived Health Risk Scale by

Page	Paragraph/Line	Comment
		menthol smoking status. It could be included here and/or on pages 78-79 that report other risk perception studies.
58	Paragraph 2	Add Tidey et al., 2019
58	Paragraph 2	Tidey et al., 2019 reports MNWS, Craving and CES
59	Paragraph 1	Denlinger-Apte et al., 2019d is a secondary analysis of Tidey et al., 2019 reporting VLNC smoking topography in smokers with serious mental illness.
59	Paragraph 1	Other manuscripts to consider including as vulnerable populations: Dermody et al., 2016 *ACER*; Secondary analysis of Donny et al., 2015 *NEJM* examining alcohol outcomes. Pacek et al., 2016 *DAD*; Secondary analysis of Donny et al., 2015 *NEJM* examining cannabis use.
60	Paragraph 1	This section should be revised to reflect the most recent data from December 2019. E-cigarettes and cigars were more commonly used than cigarettes among high school students. Update citation to Wang et al., 2019 *MMWR*
60	Paragraph 2	This section should be revised to reflect the most recent data from December 2019. E-cigarettes and cigars were more commonly used than cigarettes among high school students. Update citation to Wang et al., 2019 *MMWR*
61	Paragraphs 1-2	Update use percentages and citation to Wang et al., 2019 *MMWR*
78	Paragraph 1	Add Byron et al., 2018 and Byron et al., 2019
80	Paragraph 2	Add Denlinger-Apte et al,. 2019b which is a secondary analysis of Cassidy et al., 2018 *DAD.* Reports the Perceived Health Risk Scale by menthol smoking status.
81	Paragraph 4	Add Denlinger-Apte et al., 2019a is a secondary analysis of Donny et al., 2015 *NEJM.* Reports support for a nicotine reduction policy did not different by treatment condition after 6-weeks.
86	Paragraph 1	Poster abstracts were ineligible for review. On page 80, Joel, Hatsukami, Hertsgaard, Dermody & Donny, 2014 was referenced. It says the results were only published in abstract form so I'm not sure if this would be ineligible for inclusion.
106	Paragraph 2	Arger et al., 2017 is only referenced in Table A.2: Reduced Nicotine Content Cigarettes. The findings are not reported anywhere in the review text.
113	Paragraph 4	Perkins et al., 2018 - effects by menthol smoking status - Were these findings reported anywhere in the review?
127	Paragraph 3	Dermody et al., 2018 - secondary analysis of Donny et al., 2015 *NEJM*. Should this be added to the withdrawal and craving section?
129	Paragraph 3	Robinson et al., 2017 - secondary analysis of Donny et al., 2015 *NEJM.* Should this be added to sections about mental health or subjective effects?

VI. Reviewer #6

External Letter Peer Review of "The Science of a Nicotine Standard for Combusted Tobacco Products"

Reviewer #6

I. RESPONSE TO CHARGE QUESTIONS

1. Is the report clearly written and does it follow a logical structure? If not, provide suggestions for how to improve the document.

The report is mostly clearly written, but there are some sections that can be improved. I provide specific editing recommendations in II. Specific Observations. A couple of general comments here that relate to consistency of terminology, order of presentation, and referring to cigarettes only vs. all combusted tobacco products:

"Combusted cigarettes" and "combustible cigarettes" are technically the same thing, but it might be better to just use one of the terms consistently.

Similarly, keeping the terminology consistent for other words and phrases would be helpful. For example, "continued tobacco use" vs. "maintenance of tobacco use behavior"; "single target" vs. "immediate reduction"; "nicotine delivery" vs. "nicotine yield".

In some sections (detailed in the II. Specific Observations), it would be helpful to keep the presentation of results parallel. For example, when talking about rates of use, always present youth first, followed by adults, and keeping the order of products consistent.

As I comment on p. 12 (detailed in II. Specific Observations), sentences on different topics are mixed in in different paragraphs. For clarity, it would be good to have each paragraph deal with only one issue.

This issue with multiple topics being mixed in in paragraphs is present throughout the report. I did not detail each occurrence, but it would helpful to read through the report with an eye on sentences that better fit with another paragraph (usually it's the one immediately following the current paragraph).

When first introducing the background, only combustible cigarettes are presented at the end of the continuum of risk. To keep this consistent with the subsequent argument about the need to cover all combusted tobacco products, maybe change to "combustible cigarettes, and other combusted tobacco products, at the most harmful end of this continuum" (bottom of p. 6).

Throughout the report, it would be helpful to consistently use "combusted tobacco products" instead of "cigarettes", for example "FDA expects that making cigarettes minimally addictive by reducing the nicotine content may have significant benefits for youth by reducing the risk that youth experimenters progress to regular use of cigarettes as a result of nicotine dependence." (p. 8).

2. Does the executive summary accurately reflect the content of the overall document and provide sufficient information to capture the critical components?

The executive summary (ES) accurately reflects the content of the overall document and captures the critical components. Its writing and structure can be improved slightly:

The front part of the ES is very dense, and the first paragraph is very long. It would be helpful, if possible, to summarize the main point of the document in 1-2 sentences and to break down the first paragraph into shorter ones.

The flow of the ES seems to be different from the presentation of the studies in the review – the ES has perceptions and communications (end of paragraph 1 on p. 5) before the modeling study (middle of p. 6). The report presents the modeling study before the perceptions and communications.

It is unclear what level of nicotine reduction is being considered. The ES gives two numbers: a range of 0.2-0.7 is mentioned in the beginning (p. 5) and then a single number is given (0.4) on p. 6. For the ES, it would be better to give a single number as the target to avoid potential confusion.

3. For each section that you reviewed, were the conclusions appropriate given the available evidence? If not, provide specific examples as to where conclusions are not appropriate.

Overall, the conclusions are appropriate, although their wording can be improved (see II. Specific Observations). In addition, it seems that the report ends abruptly and the overall conclusion summarizing the total weight of evidence in support of the nicotine standard is missing.

4. Are you aware of additional publicly available information which should have been included? If so, please specify.

Section VII. The Impact Perceptions Around Nicotine and Reduced Nicotine May Have on a Proposed Nicotine Standard reports on the results of a scoping review conducted in September 2017. While there have been additional studies published since the scoping review was conducted in September 2017, the overall conclusions are still valid: people still overwhelmingly believe nicotine is the main (or one of the main) harmful chemicals in tobacco and that it causes cancer. Similarly, reduced nicotine cigarettes are believed to be less harmful (although this can be mitigated through different communication messages). In general, the beliefs about addictiveness and harm of nicotine are connected and people have a hard time separating the two (nicotine is addictive, but not the main cause of harm from tobacco). It might be worthwhile to update the review if resources permit.

Below are some of the additional studies (although the list is not exhaustive since this is not a thorough scoping review) that appeared in the last 2-3 years that are relevant to the issues around nicotine perceptions.

Additional studies for A. Consumer Knowledge, Attitudes, Beliefs, or Perceptions About Nicotine (these don't include studies with participants outside the US and are all quantitative):

Villanti, A. C., Naud, S., West, J. C., Pearson, J. L., Wackowski, O. A., Niaura, R. S., ... & Rath, J. M. (2019). Prevalence and correlates of nicotine and nicotine product perceptions in US young adults, 2016. *Addictive behaviors*, 98, 106020.

Overall, 55% of young adults believed that nicotine is a cause of cancer, with an additional 24% reporting that they did not know. More than 60% of respondents believed that a relatively or very large part of the health risks (66%) or cancer (60%) caused by smoking come from the nicotine.

Patel, D., Peiper, N., & Rodu, B. (2013). Perceptions of the health risks related to cigarettes and nicotine among university faculty. *Addiction Research & Theory*, 21(2), 154-159.

The majority of respondents (faculty at the University of Louisville) perceived nicotine as either high or moderate risk.

Kemp, C. B., Spears, C. A., Pechacek, T. F., & Eriksen, M. P. (2018). Adults' Perceptions of Nicotine Harm to Children. *Pediatrics*, 142(2).

The majority (83.2%; 95% CI: 82.3%–84.1%) of adults characterized nicotine as definitely harmful to children, 6.2% (95% CI: 5.7%–6.8%) as maybe harmful, 1.7% (95% CI: 1.3%–2.0%) as unlikely harmful, 0.6% (95% CI: 0.4%–0.8%) as not harmful, and 8.3% (95% CI: 7.6%–9.0%) responded that they don't know how harmful nicotine is when used by children." ("The following question elicited perceptions of nicotine harm to children regarding children <13 years old: 'Tobacco products, including electronic vapor products, contain nicotine. When used by the following groups, how harmful is nicotine in amounts usually found in tobacco products?' Response options were not harmful, unlikely harmful, maybe harmful, definitely harmful, or don't know.")

Additional studies for B. Consumer Knowledge, Attitudes, Beliefs, or Perceptions Regarding Reduced Nicotine Tobacco Products:

a. Studies not Employing Study Cigarettes or Advertising Stimuli

Popova, L., Owusu, D., Nyman, A. L., Weaver, S. R., Yang, B., Huang, J., & Ashley, D. L. (2019). Effects of framing nicotine reduction in cigarettes on anticipated tobacco product use intentions and risk perceptions among US adult smokers. *Nicotine and Tobacco Research*, 21(Supplement_1), S108-S116.

Data from 2018 nationally representative sample of US adult smokers showed that framing the nicotine tobacco product standard as cigarettes no longer relieved cravings resulted in the highest proportion of smokers reporting they intend to quit in response to this standard (43.9%), lowest proportions reporting anticipated intentions to continue using combusted tobacco products (45.3%), and lowest proportion believing that VLNCs are less harmful than regular cigarettes (26%).

Patel, M., Cuccia, A. F., Zhou, Y., Czaplicki, L., Pitzer, L., Hair, E. C., ... & Vallone, D. M. (2019). Nicotine Perceptions and Response to Proposed Low-Nicotine Cigarette Policy. *Tobacco Regulatory Science*, 5(6), 480-490.

Results from 2018 nationally representative sample of US adult smokers: 63% of survey participants accurately identified nicotine alone as the addiction cause, 49% incorrectly indicated that a relatively large or a very large/all of the cancer caused by cigarette smoking comes from the nicotine itself and 56% indicated that increased health risk caused by cigarette smoking comes from nicotine.

Mercincavage, M., Lochbuehler, K., Villanti, A. C., Wileyto, E. P., Audrain-McGovern, J., & Strasser, A. A. (2019). Examining risk perceptions among daily smokers naïve to reduced nicotine content cigarettes. *Nicotine and Tobacco Research*, 21(7), 985-990.

Baseline data from two experiments with non-treatment seeking daily smokers (2014-2017 data). Although the majority of participants did not misperceive RNC cigarettes as less harmful than regular nicotine cigarettes, 63.4% did not think RNC cigarettes were less addictive and 51% did not think they make it easier to quit. More than 20% of the sample reported being unsure about RNC-related risks, especially tar content (51.8%). Non-White smokers were 2.5 to 3 times more likely to be incorrect about multiple RNC cigarette risks ($p = .002–.006$).

Byron, M. J., Jeong, M., Abrams, D. B., & Brewer, N. T. (2018). Public misperception that very low nicotine cigarettes are less carcinogenic. *Tobacco control*, 27(6), 712-714.

Data from 2015-16 nationally representative sample of adult smokers. Overall, 47.1% of smokers believed that smoking VLNC cigarettes for 30 years would be less likely to cause cancer than smoking current cigarettes. This misperception was more common among smokers who were aged above 55 (56.6%) and black (57.4%). Additionally, 23.9% of smokers reported they would be less likely to quit if the USA adopted a VLNC standard. Thinking that VLNC cigarettes would be less carcinogenic was associated with smokers reporting they would be less likely to quit ($P<0.01$).

Byron, M. J., Hall, M. G., King, J. L., Ribisl, K. M., & Brewer, N. T. (2019). Reducing nicotine without misleading the public: Descriptions of cigarette nicotine level and accuracy of perceptions about nicotine content, addictiveness, and risk. *Nicotine and Tobacco Research*, 21(Supplement_1), S101-S107.

Online experiment with convenience sample of US adults (22% smokers). Randomized to view different VLNC cigarettes descriptions. Compared to control, the percentage description resulted in more accurate perceptions about nicotine content (76% vs. 49% accuracy) and addictiveness (44% vs. 34%), but less accurate perceptions about cancer risk (56% vs. 68%; all $ps < .05$). Adding interpretation or pictographs to the percentage description did not increase accuracy. The concise language description reduced accuracy of perceived nicotine content and addictiveness but increased accuracy of cancer risk (all $p < .05$).

Nguyen, A. B., Zhao, X., Hoffman, L., Morse, A. L., & Delahanty, J. (2018). Nicotine and addiction beliefs and perceptions among the US-born and foreign-born populations. *Preventive Medicine*, 114, 107-114.

Secondary analysis of data from 2015 and 2017 HINTS survey. Compared to US-born respondents, foreign-born respondents were more likely to believe that low nicotine cigarettes would have much lower lung cancer risk than a typical cigarette. Among the foreign-born, NH-Black and Hispanic respondents were more likely to see low nicotine cigarettes as harmful and addictive compared to NH-White respondents.

c. Studies Employing the Use of Packaging or Advertising Stimuli:

Johnson, A. C., Mays, D., Villanti, A. C., Niaura, R. S., Rehberg, K., Phan, L., ... & Strasser, A. A. (2019). Marketing influences on perceptions of reduced nicotine content cigarettes. *Nicotine and Tobacco Research*, 21(Supplement_1), S117-S124.

Online experiment with convenience sample of young adult smokers (18-30). Participants were randomized in a 2 (implicit: red package vs. blue package) × 2 (explicit: corrective message vs. no corrective message) design to view an advertisement for Quest VLNC cigarettes. There was no main or interaction effects of package color or the corrective message on product beliefs or use intentions.

Yang, B., Owusu, D., & Popova, L. (2020). Effects of a Nicotine Fact Sheet on Perceived Risk of Nicotine and E-Cigarettes and Intentions to Seek Information About and Use E-Cigarettes. *International Journal of Environmental Research and Public Health*, 17(1), 131.

Online experiment with convenience sample of US adult smokers, randomized to view a nicotine fact sheet or bottle water ad (control). Compared to control, the nicotine fact sheet doubled the probability of disagreeing that nicotine is the main cause of smoking-related disease (26.2% vs. 12.7%, RR = 2.06, 95% CI = 1.51, 2.82, $p < 0.001$). However, nearly three quarters of participants viewing the nicotine fact sheet still thought that nicotine is the main cause of smoking-related disease.

Additional studies for C. Consumer Knowledge, Attitudes, Beliefs, Perceptions, or Planned Behavior Regarding FDA Regulation of Tobacco:

Patel, M., Cuccia, A. F., Zhou, Y., Czaplicki, L., Pitzer, L., Hair, E. C., ... & Vallone, D. M. (2019). Nicotine Perceptions and Response to Proposed Low-Nicotine Cigarette Policy. *Tobacco Regulatory Science*, 5(6), 480-490.

Smokers showed high support (72%) for a proposed low-nicotine policy. Greater misperception about nicotine harm was associated with greater odds (aOR = 1.66, $p < .05$) of policy support. Shorter time to first cigarette was associated with greater intent to smoke low-nicotine cigarettes but was not associated with policy support.

5. Provide any additional comments including limitations and outcomes not discussed, or editorial suggestios not addressed in the previous questions.

Throughout the report, little cigars and cigarillos are either absent or incorporated under "cigars". Given their superior suitability as substitutes for combusted cigarettes, they need to be brought up early in the report and singled out or more explicitly acknowledged as the subset of cigars.

Is there evidence of technical achievability of a nicotine standard for other tobacco products? It would be helpful to add something along those lines (even though other tobacco products with reduced nicotine have not been produced, the methods for reducing nicotine that work for cigarettes would be applicable to all other tobacco products).

We are currently conducting focus groups about the tobacco nicotine standard, and we keep hearing this question from participants in our focus groups: "Why reduce nicotine, but not

the other bad chemicals?" It might be worthwhile to acknowledge this question and provide the answer to it – maybe something about technical achievability of reduced nicotine, but that it's impossible to reduce other harmful chemicals to the levels that would have meaningful impact on health outcomes.

The report does not mention heated tobacco products, such as IQOS. The FDA has referred to them as "non-combusted cigarettes." Given that they are on the US market now, the FDA needs to consider (and probably include in the report) the implications of either including heated tobacco products with combusted tobacco under the nicotine standard or treating them as non-combusted tobacco products (like smokeless tobacco and ENDS). In either case, the report might need to discuss the potential of heated tobacco products to serve as a substitute for combusted cigarettes and the resultant health implications, or at least acknowledge the existing lack of science on these topics.

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"

Page	Paragraph/Line	Comment
7-9		Pp. 7-8 present the arguments for why nicotine reduction would be beneficial for youth. The arguments are laid out and then a conclusion is made, "For these reasons, FDA is considering mitigating the addictiveness of combusted tobacco products by setting a product standard…" (middle of p. 9). Yet the next paragraph lists another reason for the standard "because age restrictions on the sale of tobacco products by themselves are not entirely effective"), and the end of this paragraph has another conclusion ("FDA is considering taking this additional step to ensure that even if youth do obtain access to cigarettes, they will be less likely to: (1) become addicted to these products; (2) progress to regular use; and (3) increase their risk of the many diseases caused by combusted tobacco product use (Grucza et al., 2013)."). It might be better to move the paragraph about ineffectiveness of age restrictions one paragraph up, and then have a single conclusion to the argument for the effects on youth.
10	Line 4	Can add more recent citation to "In high-income countries, about 7 of 10 adult smokers say they regret initiating smoking and would like to stop (Prabhat & Chaloupka, 1999)": Nayak P, Pechacek TF, Slovic P, Eriksen MP. Regretting ever starting to smoke: results from a 2014 national survey. International journal of environmental research and public health. 2017 Apr;14(4):390. (Data from 2014 showing that among US smokers, 71.5% regretted starting smoking).
11		Section **B. (Negative Health Effects of Combusted Tobacco Product Use)** starts with describing the effects of nicotine in facilitating addiction. This is not what I expected to see first in a section titled "**B. Negative Health Effects of Combusted Tobacco Product Use".** Given that there is a section on p. 14

Page	Paragraph/Line	Comment
		titled "**C. Nicotine in Combusted Tobacco Products and Its Influence on Addiction"** it would be more appropriate to place the information on nicotine there.
12		The two first paragraphs on p. 12 talk about deaths from three leading smoking-related causes, but the same information is repeated twice. It would be better to combine them to streamline. For example, instead of starting with the generic "Cigarettes are responsible for hundreds of thousands of premature deaths every year from many diseases" and then in the second paragraph explain the total death toll and the top three diseases, just start: "Cigarettes are responsible for at least 480,000 premature deaths each year (U.S. Department of Health and Human Services, 2014 at p.659)." Then continue with describing the specific causes and numbers (the rest of the first paragraph and a weave in the mention of the top three diseases ("The three leading causes of smoking-attributable death for current and former smokers were lung cancer, heart disease, and COPD" but make sure it is in line with the numbers ("163,700 deaths from cancer, 160,600 deaths from cardiovascular and metabolic diseases, and 131,100 deaths from pulmonary diseases" – are these all cancer deaths or just lung cancer?). Finish the paragraph with "163,700 deaths from cancer, 160,600 deaths from cardiovascular and metabolic diseases, and 131,100 deaths from pulmonary diseases".
12	Paragraph 2	The sentence about other combusted products seem out of place ("However, this estimate does not include deaths caused by other combusted forms of tobacco…"). I would recommend moving it to the first full paragraph on p. 13.
12	Bottom of page	Another example of sentences mixed into wrong paragraphs: paragraph on the bottom of p. 12 starts with the effects of secondhand smoke, but then jumps to the Surgeon General's Report that talks about general effects of smoking. It would be better to reorganize the paragraphs that are currently suffering from these issues (pretty much all paragraphs on p. 12) so each one only deals with a single topic: first one with the harms of smoking; second with the harms of secondhand smoke. If you want to close on the impressive note from the SG's report, put it in the separate paragraph that would be the conclusion to this section.
13	First full paragraph	Recommend starting the first full paragraph on p. 13 with describing what "other combusted tobacco products" are (just briefly mention that they are "cigars, cigarillos, pipes, roll your own tobacco," etc.) This paragraph (on other combusted tobacco products) only focuses on cigars. It would be better to also briefly describe the evidence on the health effects of other combusted tobacco

Page	Paragraph/Line	Comment
		products, particularly cigarillos and roll your own tobacco. To make space for that, the research on cigars that is currently presented in a lot of detail, can be shortened and summarized.
14		The section "**C. Nicotine in Combusted Tobacco Products and Its Influence on Addiction"** should start with describing the nicotine effects (2 last paragraphs from p. 11 mentioned earlier). It would also be helpful to then include the argument that these effects are the same for the other combusted tobacco products.
14	Last paragraph	"meaning that they have tried smoking at least one puff of a cigarette (but smoked no more than 25 cigarettes in their lifetime)" – the parentheses should be removed since the second part is an integral part of the definition of the "early experimenters".
14	Last paragraph	"The Centers for Disease Control and Prevention (CDC) and other researchers have estimated that 30 percent or more of experimenters become established smokers (Centers for Disease Control and Prevention, 1998; Choi, Pierce, Gilpin, Farkas, & Berry, 1997; Mowery et al., 2004)." – is it 30% of "early experimenters"? It would be good to keep the language consistent. If the "early experimenters" and "experimenters" are not the same, then need to define both.
16	Second paragraph	The way the research is summarized in some sections makes it a bit hard for the reader to draw a single conclusion. For example, 2nd paragraph on p. 16 talks about success of quit attempts. It goes through the list of studies showing their results, but it does not synthesize the findings. This laundry list is confusing because it reports data not in chronological order and in different formats, for example: Babb et al: 2015 data - 55.4% of smokers tried to quit - 7.4% of former smokers recently quit Fiore et al: 2005 data - 19 million smokers tried to quit - 4-7% successfully quit IOM: 2004 data - -40.5% of smokers tried to quit - 3-5% were successful It would be better to summarize these data: "each year, about 40-55% of adults smokers try to quit, but only 3-7% succeed." (Then you can present the results of individual studies in chronological order brought to the common denominator – percent instead of numbers of smokers).

Page	Paragraph/Line	Comment
16	Second paragraph	"Approximately 40.5 percent" – this number is pretty precise, so would recommend dropping "approximately".
16	Last paragraph	The definition of relapse is a bit unclear: "Relapse refers to the point after an attempt to stop smoking when tobacco use becomes ongoing and persistent" – I think the part about restarting smoking is missing.
17		Section "**c. Impact of a Nicotine Product Standard on Combusted Product Users"** does not mention youth (preventing progression to regular use). There might not be direct empirical evidence on that, but it is reasonable to hypothesize based on the evidence listed earlier on the progression to regular smoking among youth.
19-20		Section **A. Maximum Nicotine Level** nicely describes the history on reduced nicotine products and what is possible technically. But it seems like this section should actually list the final target (in mg?) and succinctly describe the reason for it.
20	Bottom of page	Cigarillos are not listed along other products when the "other combusted tobacco products" are introduced (here and in other places) (although they are discussed in specific studies).
22		So, does gradual reduction lead to compensatory smoking or not? This section states both: "neither gradual nor immediate reduction of nicotine in cigarettes leads to compensatory smoking after individuals switch to VLNC cigarettes […]. Limited evidence also suggests that gradual reduction may lead to compensatory smoking during the intermediate steps of a gradual reduction approach when participants are smoking products with low to moderate nicotine content."
23-24		"Studies have also shown that gradually reducing the nicotine content of cigarettes is associated with high levels of noncompliance when participants reach the VLNC cigarette phase of the intervention" (p. 23) – but noncompliance was lower under immediate reduction? This does not seem to be the case: "much like the gradual reduction studies, a secondary analysis showed that noncompliance was high in participants randomized to the VLNC cigarette group (Nardone et al., 2016)." (p. 23) and also "The immediate reduction group had higher rates of noncompliance with non-study cigarette use" (p. 24).
25-26		Section "D. Analytical Testing Method" starts with describing the criteria FDA is considering for the analytical testing method for the nicotine content in combusted tobacco. Then, it lists several methods, but there is no conclusion. Also, the first two methods are described in great detail, the third briefly, and then a bunch are just mentioned. (And it is unclear if "CORESTA Method No. 62" is the same as one of the previous two CORESTA methods). What should the reader take away from

Page	Paragraph/Line	Comment
		this section? It needs to be clearly stated at the end if the FDA is still choosing the method or if one should be selected.
27	Last paragraph	"manufacturers could replace more commonly used nicotine-rich varieties like *Nicotiana rustica* with lower nicotine varieties (Tengs, Ahmad, Savage, Moore, & Gage, 2005)" - would be helpful to provide an example of the variety with lower nicotine.
27	Last paragraph	"Oriental Turkish-type cigarettes also deliver substantially less nicotine than cigarettes that contain air-cured Burley tobacco (Shelar, Bernasek, & Furin, 1992; Wayne & Carpenter, 2009)" - is it because they use different variety of nicotine or because they are cured differently? (If the former, how is it different from a previous sentence? If it's the curing process, then it would be helpful to be more specific about that.)
30	Third paragraph	It was very interesting to learn about the effects of caterpillars on nicotine level, but it was not clear to me what happens to nicotine (I imagined that harvested leaves are treated with the salivatory extracts.) It might be worth slightly changing the explanation to mention "growing tobacco leaves" or something like that (as opposed to harvested leaves).
33	Last paragraph	First paragraph in section "a. History of the Estimation of an Addiction Threshold" starts by talking about "chippers", but then does not mention how specifically studying this group led to the estimation of the threshold level of nicotine. I expected some sort of argument that because chippers smoked a certain number of cigarettes and were not dependent, this translates to xxx.
51	First full paragraph	An introduction to section "C. Unintended Consequences" lists some unintended consequences (continued use of combusted VLNC products, switch or co-use of noncombustible products), but the subsequent sections detail completely other consequences (illicit products, noncompliance). It would be good to bring the introduction in line with the rest of the section. Related to the previous point, I am not sure that continued use of VLNC products or switch/dual use with noncombusted tobacco products are unintended consequences – complete switch to noncombusted tobacco products might be a benefit. Also, on p. 64 it is listed as an expected outcome: "It is FDA's expectation that once a nicotine product standard for combusted tobacco products is in place, a significant portion of combusted tobacco product smokers would choose to switch completely to a potentially less harmful nicotine delivery product (e.g., ENDS) (National Academies of Sciences, 2018) to maintain their nicotine dose."

Page	Paragraph/Line	Comment
53	First full paragraph	"alternative combusted nicotine-containing products if a nicotine standard were implemented (e.g., full nicotine little cigars or cigarettes available through illicit trade, legally marketed non-combusted tobacco products)" (p. 53) - the first part of the sentence talks about "combusted" products, but the example in parentheses includes "non-combusted".
59		Section "ii. Individuals with Symptoms of Mental Health and Substance Use Disorders" discusses lots of different effects and outcomes for VLNC cigarettes in populations with mental health symptoms, but concludes with a summary of only one effect: "In sum, results of studies reviewed in this document provide little to no evidence that VLNC cigarettes increase risk of adverse effects (e.g., exacerbations of psychiatric symptomatology) in smokers with symptoms of mental health disorders." (p. 59). It would be better to also summarize the rest of the section here.
60	Top of the page	"Cigarette smoking prevalence rates among adults have also declined in recent years (from 20.9% in 2005 to 15.1% in 2015); however, in 2015 there were increased smoking prevalence rates among males, young adults,…" - does "increased" implies that the rates increased from 2005 to 2015 among males and young adults? Or that the smoking rates were higher among "males, young adults, …"?
59-62		It would be helpful to make reporting in different sections under "A. Who Uses Combusted Tobacco Products?" more parallel. For example, the beginning of these sections currently flips the order of presentation for middle and high school students, the section on cigars lists other products, waterpipe section starts with the international use and adults, etc. Using the same structure for each section (middle and high school youth, followed by adults, followed by disparities in use) would make it easier. (If you want to keep some extraneous information, such as the information about different tobacco product use in the cigar section: "Among high school students, the most commonly used forms of tobacco other than cigarettes are e-cigarettes (11.7%), cigars (7.7%), smokeless tobacco (5.5%), hookah (3.3%), pipe tobacco (0.8%), and bidis (0.7%)(T. W. Wang et al., 2018)" reword it so the focus is on cigars: "Among high school students, cigars were as popular as cigarettes (7.7% vs. 7.6%) and second only to e-cigarettes (11.7%).")
61		Is "Loose tobacco" roll-your-own and pipe tobacco? Would be helpful to specify from the outset.
82		The conclusion to section VII that starts with "All together, these studies indicate that there is strong and consistent evidence to suggest that a substantial proportion of American adults falsely believe …" summarizes the findings in different

Page	Paragraph/Line	Comment
		order than the previous sections, and it would be better to start with the summary of the perceptions of nicotine followed by the perceptions of reduced nicotine cigarettes. (In addition, it is likely that the perceptions of nicotine drive perceptions of reduced nicotine cigarettes and not vice versa, so that order is justified for that reason as well.)
82		What is "substantial proportion"? The conclusions paragraph to section VII uses this phrase to describe the proportion of American adults who a) falsely believe that nicotine is the main cause of harm from tobacco, b) falsely believe that reduced nicotine cigarettes are less harmful, and c) accurately believe that reduced nicotine cigarettes are less addictive. However, the proportions for these three beliefs are very different with a lot more people supporting a and b and fewer supporting c. It might be helpful to changes this to "majority" and "substantial minority" or something like that.
82		"Regarding the belief held by some Americans that reduced nicotine cigarettes are less addictive, whether they held this belief seems to depend on the nicotine content of the cigarette." (p. 82) - this sentence is not very clear. Did it depend on the level of nicotine about which they were asked or on the level of nicotine in the cigarette they tried, as in some in-person studies?
82	Second to last paragraph	"To ensure a positive net impact on population health, it will be important to ensure that consumers understand that nicotine is not a carcinogen nor a primary cause of smoking-related disease." - Rather than emphasizing this understanding, I think it is more important to directly address its derivative – the belief that VLNC cigarettes are less harmful, so I would emphasize this (or make sure it is mentioned in addition to the need to change perceptions of nicotine).
208		Some of the references need to be updated, for example, Hatsukami et al., 2016 should be 2017 and include the journal volume and page numbers (Hatsukami, D. K., Luo, X., Dick, L., Kangkum, M., Allen, S. S., Murphy, S. E., ... & al'Absi, M. (2017). Reduced nicotine content cigarettes and use of alternative nicotine products: exploratory trial. *Addiction*, *112*(1), 156-167.)
212-213		Some references are listed twice, for example: Mercincavage, M., Saddleson, M. L., Gup, E., Halstead, A., Mays, D., & Strasser, A. A. (2017a). Reduced nicotine content cigarette advertising: How false beliefs and subjective ratings affect smoking behavior. *Drug and Alcohol Dependence, 173*, 99-106. doi:10.1016/j.drugalcdep.2016.12.022

Page	Paragraph/Line	Comment
		Mercincavage, M., Saddleson, M. L., Gup, E., Halstead, A., Mays, D., & Strasser, A. A. (2017b). Reduced nicotine content cigarette advertising: How false beliefs and subjective ratings affect smoking behavior. *Drug Alcohol Depend, 173*, 99-106. Perkins, K. A., Karelitz, J. L., & Kunkle, N. (2017a). Sex differences in subjective responses to moderate versus very low nicotine content cigarettes. *Nicotine & Tobacco Research*. Perkins, K. A., Karelitz, J. L., & Kunkle, N. (2017b). Sex differences in subjective responses to moderate versus very low nicotine content cigarettes. *Nicotine Tob Res*. doi:10.1093/ntr/ntx205

V. PEER REVIEWER COMMENT TABLE

I. Response to Charge Questions

CHARGE QUESTION 1. Is the report clearly written and does it follow a logical structure? If not, provide suggestions for how to improve the document.		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #1	The report is thorough, clearly written, and follows a logical structure.	
Reviewer #2	The report is written fairly clearly. The structure is somewhat logical, but each section (after the executive summary) likely should start with a paragraph that outlines the focus and rationale for the subsequent text in that section, to aid the reader's full understanding of the purpose behind this possible policy. Similarly, each section should finish with an explicit "conclusions" subsection, as noted below in #3.	
Reviewer #2	Some text in the footnotes is repeated elsewhere in text and vice versa. Example: footnote 5 on p. 12 is repeated in p. 13 text near the bottom; Footnote 1 on p. 5 is repeated in footnote 7 on p. 22 and then in text on pp. 31-32. Seems repetitive but not too distracting;	
Reviewer #2	pp. 71-74: The focus on Apelberg et al. 2018 is appropriate, given its results on expected effects of regulating nicotine to levels insufficient to support addiction, but extensive preliminary details in the first two pages, before any findings are outlined, seems unnecessary and interrupts text flow.	
Reviewer #3	The report is written very clearly and stays away from jargon. I thought it followed a logical structure. Some minor suggested revisions are as follows: Page 20, nicotine yield is described on this page before the explanation of the difference between yield and content, which is explained on page 31. It would help the reader if the future paragraph on page 31 is referenced, or if a brief explanation of yield vs content is described on page 20.	
Reviewer #3	Page 24, the biomarker outcomes are described, but it is not written here why this is important (i.e., biomarkers of tobacco smoke exposure could reveal whether there was compensatory smoking).	
Reviewer #3	Section iv. Choice (page 39), this section could be moved after Section i. Drug Liking (page 44), since it would follow logically that smokers would be less likely to choose VLNCs if they are rated as less satisfying and less pleasant.	
Reviewer #4	The report is clearly written, and much of the presentation is logical and flows well. I have three comments. First, there are sections where the evidence presented is confusing, or leaves the reader wondering whether the conclusion reached in the document is correct. In both cases, the	

CHARGE QUESTION 1. Is the report clearly written and does it follow a logical structure? If not, provide suggestions for how to improve the document.		
REVIEWER	**COMMENT**	**RESPONSE**
	insertion of one or two sentences that would integrate the evidence or explain the conclusion would strengthen the presentation.	
Reviewer #4	Second, the section on cigarette price increases is of marginal relevance. The section on behavioral economics adds little, distracts from the flow of the paper, and could be eliminated.	
Reviewer #4	Third, given the many non-cigarette combustible products available, the extensive discussion in the background section focusing on cigars distracts from the flow of the document. It should either be shortened or a discussion of other products integrated into that section.	
Reviewer #5	Overall, the report is clearly written and has a logical flow. However, I have highlighted a few sections that could be reorganized to improve the document. Section III. Scope This section felt a little disjointed as I read it. It might be helpful to describe the differences between 'nicotine content' and 'nicotine yield' earlier in the review. The jump from policy implementation approach to analytic testing did not feel logical to me. Perhaps Section III could be revised as follows: A. Analytic Testing (how do we test for nicotine levels) B. Technical Achievability (how would manufacturers achieve the maximum nicotine level) C. Maximum Nicotine Level (what is the desired outcome) D. Inclusion of Combusted Products (what products have to meet that maximum nicotine level) E. Implementation (how do we move combusted products to the maximum nicotine level)	
Reviewer #5	Section IV.C. Unintended Consequences **a. Illicit Tobacco Products**: I would make this the last topic in the section. It has the least amount of empirical data specifically related to VLNC cigarettes. **b. Noncompliance:** I'm not sure that it makes sense to frame noncompliance as an unintended consequence of low nicotine product standard. Noncompliance highlights that smokers are motivated to use conventional cigarettes or other nicotine products for various reasons during a trial (i.e., craving, stopping withdrawal symptoms, tastes better). This information might be better if combined with Section V.C. - Potential for Non-Cigarette Combusted Tobacco Product Switching. Smokers are dissatisfied with VLNC cigarettes and switch to other combusted products or seek out illicit NNC cigarettes.	

CHARGE QUESTION 1. Is the report clearly written and does it follow a logical structure? If not, provide suggestions for how to improve the document.		
REVIEWER	**COMMENT**	**RESPONSE**
	c. Compensatory Smoking: This should be the first topic in the section. It's the most important health-related concern of a nicotine reduction policy and provides the most compelling data that nicotine reduction likely won't lead to increased smoking. Smith et al., 2020a and Smith et al., 2020b are two recent publications that should be incorporated into this section fairly extensively since they both are studies specifically to address compensation. **d. Impact on Vulnerable Populations**: I definitely understand the need for this section; however, at times, I felt like information on vulnerable populations should have also been included in the overall narrative and not relegated to a separate section after the primary points have already been made.	
Reviewer #5	Sections V.A. and V.B. These two sections, Who Uses Combusted Tobacco Products? and Abuse Potential of Non-Cigarette Combusted Tobacco Products, could have come before the VLNC cigarette literature review section. The very first sentence of the executive summary mentions all combusted tobacco products but the review does not mention other combusted tobacco products until page 59.	
Reviewer #5	Section V.C. Potential for Non-Cigarette Combusted Tobacco Product Switching could be absorbed as part of the Unintended Consequences, Section IV.C.	
Reviewer #6	The report is mostly clearly written, but there are some sections that can be improved. I provide specific editing recommendations in II. Specific Observations. A couple of general comments here that relate to consistency of terminology, order of presentation, and referring to cigarettes only vs. all combusted tobacco products: "Combusted cigarettes" and "combustible cigarettes" are technically the same thing, but it might be better to just use one of the terms consistently.	
Reviewer #6	Similarly, keeping the terminology consistent for other words and phrases would be helpful. For example, "continued tobacco use" vs. "maintenance of tobacco use behavior"; "single target" vs. "immediate reduction"; "nicotine delivery" vs. "nicotine yield".	
Reviewer #6	In some sections (detailed in the II. Specific Observations), it would be helpful to keep the presentation of results parallel. For example, when talking about rates of use, always present youth first, followed by adults, and keeping the order of products consistent.	

CHARGE QUESTION 1. Is the report clearly written and does it follow a logical structure? If not, provide suggestions for how to improve the document.		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #6	As I comment on p. 12 (detailed in II. Specific Observations), sentences on different topics are mixed in in different paragraphs. For clarity, it would be good to have each paragraph deal with only one issue. This issue with multiple topics being mixed in in paragraphs is present throughout the report. I did not detail each occurrence, but it would be helpful to read through the report with an eye on sentences that better fit with another paragraph (usually it's the one immediately following the current paragraph).	
Reviewer #6	When first introducing the background, only combustible cigarettes are presented at the end of the continuum of risk. To keep this consistent with the subsequent argument about the need to cover all combusted tobacco products, maybe change to "combustible cigarettes, and other combusted tobacco products, at the most harmful end of this continuum" (bottom of p. 6).	
Reviewer #6	Throughout the report, it would be helpful to consistently use "combusted tobacco products" instead of "cigarettes", for example "FDA expects that making cigarettes minimally addictive by reducing the nicotine content may have significant benefits for youth by reducing the risk that youth experimenters progress to regular use of cigarettes as a result of nicotine dependence." (p. 8).	

CHARGE QUESTION 2. Does the executive summary accurately reflect the content of the overall document and provide sufficient information to capture the critical components?		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #1	The executive summary accurately reflects the content of the overall document and provides sufficient information to capture the critical components.	
Reviewer #2	The executive summary of 1.5 pages is accurate in briefly outlining the rationale for proposing a reduced nicotine standard for all combustible tobacco products.	
Reviewer #3	The executive summary is concise, easy to read, and summarizes the main points of the document.	
Reviewer #4	For the most part, the Executive Summary does reflect the content of the document. However, there were two missing sections that are important.	

CHARGE QUESTION 2. Does the executive summary accurately reflect the content of the overall document and provide sufficient information to capture the critical components?		
REVIEWER	**COMMENT**	**RESPONSE**
	First, there is nothing in the summary on technical achievability. There is considerable evidence in the document itself that producing VLNC is technically achievable. A statement to this effect should be included in the Executive Summary.	
Reviewer #4	Second, the importance of combusted tobacco other than cigarettes is well summarized. However, the report itself states that FDA believes it necessary to also regulate nicotine content in these products for meaningful public health impact. This is implied in the Executive Summary, but not clearly stated. A clear statement should be inserted.	
Reviewer #5	The executive summary accurately reflects the content of the overall document and provides sufficient information. However, it does not include information about cigarette manufacturing practices for creating VLNC cigarettes. This section could be important to mention in the executive summary because it establishes the feasibility of implementing the product standard. When I read the manufacturing section, it struck me as a very useful section for building the argument of why the FDA can and should implement a product standard. Having 1-2 sentences in the executive summary highlighting the industry-driven feasibility of cigarette nicotine reduction could be an added strength, as well as prepare the reader for the upcoming content.	
Reviewer #5	Minor comment: Only some of the supporting science in the executive summary had citations (e.g., the policy simulation by Apelberg et al., 2018) while other research topics did not. This was a little confusing.	
Reviewer #6	The executive summary (ES) accurately reflects the content of the overall document and captures the critical components. Its writing and structure can be improved slightly: The front part of the ES is very dense, and the first paragraph is very long. It would be helpful, if possible, to summarize the main point of the document in 1-2 sentences and to break down the first paragraph into shorter ones.	
Reviewer #6	The flow of the ES seems to be different from the presentation of the studies in the review – the ES has perceptions and communications (end of paragraph 1 on p. 5) before the modeling study (middle of p. 6). The report presents the modeling study before the perceptions and communications.	
Reviewer #6	It is unclear what level of nicotine reduction is being considered. The ES gives two numbers: a range of 0.2-0.7 is mentioned in the beginning (p. 5) and then a single number is given (0.4) on p. 6. For the ES, it would be better to give a single number as the target to avoid potential confusion	

CHARGE QUESTION 3. For each section that you reviewed, were the conclusions appropriate given the available evidence? If not, provide specific examples as to where conclusions are not appropriate.		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #1	The conclusions were appropriate given the available evidence. When published data apparently supported different conclusions in a few cases, results from opposing points of view were included in an unbiased manner. However, if the weight of evidence provided greater support for one conclusion more than for another when opposing points of view had been published on a given topic, the thought logic that was used to arrive at the supported conclusion was clearly stated. The logic in each case was very defensible.	
Reviewer #2	The apparent conclusions were appropriate. However, Section "conclusions" are not obviously organized, at the ends of the major (or minor) sections, such as II. Background, III. Scope, IV. VLNC literature review, V, VI, etc. Occasional text near the end of some minor sections start with "In sum,…" (or "In all…" for the Behavioral Economic subsection of V., or "All together" at the end of section VII.), which indicates conclusions for the prior paragraphs, but that text is not set apart or differentiated from the other text. More explicit "Conclusion" subsections, with headings labeled "Conclusions" at the end of these major sections (and listed in the table of Contents on p. 1), might help the reader comprehend the summary and implications of that prior section for the proposed policy.	
Reviewer #3	Section II. A. (page 8, 3rd paragraph) ("The adolescent brain is more vulnerable to developing nicotine dependence than the adult brain") this statement isn't supported by Apelberg et al., 2014, who did not compare adolescents to adults. The Levin 2007 citation supports this statement better: adolescent rats self-administer more nicotine than adults, and there are age-related differences in nicotine's action in the brain (e.g., Levin et al., 2007 https://doi.org/10.1016/j.ntt.2007.02.002). Also, be careful to not confuse addiction with dependence. A more accurate sentence would be "The adolescent brain may be more vulnerable to the reinforcing effects of nicotine, which increases adolescents' likelihood of becoming addicted."	
Reviewer #3	Section II. A. (page 10) "Decreasing the nicotine content…switch to potentially less harmful tobacco products such as e-cigs". It is really controversial right now if e-cigs/ENDS are less harmful. I would recommend not suggesting a specific product, such as ENDS, as a safer alternative to combustible tobacco here and throughout the document.	
Reviewer #3	Throughout the document: Evidence that lowering nicotine levels will reduce the risk of progression from experimentation to regular use (especially among adolescents and young	

CHARGE QUESTION 3. For each section that you reviewed, were the conclusions appropriate given the available evidence? If not, provide specific examples as to where conclusions are not appropriate.		
REVIEWER	**COMMENT**	**RESPONSE**
	adults). This is certainly a reasonable hypothesis, but of the literature reviewed and summarized in the appendices, I see very few human-subject studies to support this hypothesis. This lack of research is noted on page 56. There have been preclinical studies in rodents and primates that might be cited to bolster this claim (e.g., https://doi.org/10.1007/s00213-016-4293-y, https://doi.org/10.1016/j.neuropharm.2016.06.026). Some other relevant literature is summarized in this editorial regarding the FDA's proposed nicotine-reduction regulation https://doi.org/10.1093/ntr/ntz101. See also: Shiffman et al., 2019 Very-low-nicotine-content cigarettes and dependence among non-daily smokers https://doi.org/10.1016/j.drugalcdep.2018.12.021. Cassidy et al., 2019 Age moderates smokers' subjective response to very-low nicotine content cigarettes: evidence from a randomized controlled trial. doi: 10.1093/ntr/nty079. Davis et al., 2019 Examining age as a potential moderator of Response to Reduced Nicotine Content Cigarettes in Vulnerable Populations https://doi.org/10.1093/ntr/ntz134.	
Reviewer #3	Page 34. Similar to above, there appear to be only 2 cited papers (Benowitz and Henningfield 1994, and Sofuoglu and LeSage 2012) that support the hypothesis that nicotine can be reduced to a non-reinforcing level. This would be a stronger argument if there were more citations, especially of studies using nicotine-naïve animals (e.g., Donny 1995 Nicotine self-administration in rats Psychopharm 122:390-394). A recent paper by Perkins 2019 https://doi.org/10.1093/ntr/ntz136 shows that smokers could not detect nicotine in the 0.4 mg nicotine cigarette. Also see Shoaib and Perkins 2020 https://doi.org/10.1016/j.neuropharm.2020.108063	
Reviewer #3	Page 23, it is a little misleading to write that VLNCs resulted in significantly fewer cigarettes per day. Likewise, Page 36 reads "switching to LNC or VLNC cigarettes may produce modest decreases in CPD." Not all of the references cited on page 37 support this statement. In Donny et al., 2015, the average CPD did not change from baseline among people given VLNCs (CPD stayed around 15 per day), even though at the end of 6 weeks, smokers given free NNCs increased their cigarette consumption (there was a between-group difference, not a within-group difference in the VLNC group). I think Dermody 2016 and Hatsukami 2015 just re-analyze this same data. (However, Donny 2007 showed an average within-subject decrease of 3.5 cigarettes per day among smokers using 12 cigs/day at baseline in support of this claim). It should be noted that for established smokers, switching to VLNCs does not stop their smoking, or even diminish	

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	it by all that much. More accurately, VLNCs do appear to prevent escalation of use (also very important). See also Smith et al., 2019 Randomized trial of low-nicotine cigarettes and transdermal nicotine. https://doi.org/10.1016/j.amepre.2019.05.010. Shiffman et al., 2019 Very-low-nicotine-content cigarettes and dependence among non-daily smokers https://doi.org/10.1016/j.drugalcdep.2018.12.021.	
Reviewer #3	Section d. Lower nAChR occupancy (page 50). "Although there is enough nicotine in VLNC cigarettes to bind to acetylcholine receptors in the brain and to release dopamine, there is not enough to consistently produce the full range of subjective or physiological responses." While this statement is most likely true, it is not supported by the citations (Addicott 2014, Rose 2003). Addicott 2014 shows there is a cerebral response to VLNCs, which appears to contradict the section title. I disagree that the withdrawal-relieving effects of VLNCs are exclusively due to conditioned learning, and not due to some of the other 7000 chemicals in tobacco smoke. Overall, this entire section (section d. is poorly supported and does not contribute much to the overall document. I would recommend either removing it or making a major revision with more supporting references.	
Reviewer #4	I reviewed the entire report and agree with the conclusions based on the available evidence in each section, with one exception. That is Section IV. B. b.i. Smoking Cessation; (pages 35-36). The report concludes that "Taken together, results from these studies suggest that, regardless of interest in quitting, smokers who are given VLNC cigarettes may be more likely to quit compared to those who continue to smoke usual brand or NNC cigarettes. In addition, provision of NRT may further increase smoking cessation among individuals interested in quitting". I am not in total disagreement with the statement, but given the relatively weak evidence, the statement should be modified throughout the document to take into account the strength of the evidence. The issues are: (1) When compared to the plethora of well-controlled studies that address smoking rate, topography, cigarette choice, biomarkers, subjective effects, dependence, and withdrawal symptoms, there are relatively few studies on the relationship of VLNC to abstinence.	
Reviewer #4	(2) Of those studies addressing VLNC and abstinence, few meet all or most of the criteria one would expect from a convincing clinical trial that had abstinence as an endpoint. That is, no study includes all, or even most, of the optimal methodologies, including an RCT design, biochemical verification; attention or placebo controls, adequate follow-up rate, and both short	

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	and long-term follow-up assessments. Often, abstinence is assessed as a secondary endpoint in a study focused on another issue, and in these studies, there may not be a useful control condition.	
Reviewer #4	(3) The narrative seems biased towards reporting positive outcomes. Findings that indicate no differences between or among conditions are not clearly spelled out. Admittedly, when outcome data are combined with laboratory data on cigarettes per day, biomarkers, and subjective effects, there is a signal here that VLNC cigarettes may help smokers quit, but the studies are sufficiently weak in design with respect to abstinence that it would be best throughout the report to qualify the statement that VLNC cigarettes increase likelihood of quitting, especially long term abstinence.	
Reviewer #4	The argument can be made that current data present a conservative estimate of the probability of abstinence due to VLNC, because abstinence would be substantially more likely if VLNC cigarettes were the only cigarettes available. Under those circumstances, there would be little or no chance of relapse to the more attractive NNC cigarettes. However, I did not see that argument presented.	
Reviewer #5	Section I. Executive Summary One issue that stood out to me in the executive summary was that the authors write "… without evidence of… compensatory smoking" and "… no evidence of differential effects of VLNC cigarettes in vulnerable populations". This definitive language surprised me. Most clinical trials and lab studies included in this review report the average treatment effects and do not necessarily include individual differences analyses or treatment effect heterogeneity. I do agree that, on average, use of VLNC cigarettes does not result in compensation or differential effects among priority smoking populations. I'm not necessarily suggesting this wording needs to be changed but wanted to bring caution that we do not know how nicotine reduction will impact all groups of smokers.	
Reviewer #5	Section II. Background The background information is justified to include. The conclusions regarding the harms associated with cigarette smoking are appropriate given the data available. The assessment of the contribution of nicotine in cigarettes to establishing and maintaining smoking behavior is also accurate.	
Reviewer #5	Section III. Scope No additional comments on this section.	

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REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #5	Section IV. VLNC Cigarette Literature Review B. Estimate of Addiction Threshold Levels b. Findings Related to Cessation, Use Behaviors, Biomarkers of Exposure, and Physiological Effects of VLNC Cigarettes i. Smoking Cessation: The conclusion that VLNC in combination with NRT and standard of care increased smoking cessation outcomes is appropriate given the data available. Additionally, the evidence suggests that use of VLNC cigarettes increases smoking cessation interest, attempts or success among smokers who previously reported no interest in quitting.	
Reviewer #5	ii. Cigarettes Per Day (CPD): The authors conclude there is no evidence of increased CPD when using VLNC for extended periods and some studies found modest decreases in CPD. These conclusions are appropriate given the data available. One study that should be added to this section is Hatsukami et al., 2018 *JAMA*, which reported significant decreases in CPD in the immediate vs gradual and immediate vs control. No significant differences between gradual vs control conditions. One limitation is noted that many studies did not account for use of non-study CPD. If accurate, then the review should reference the studies that do not account for non-study CPD.	
Reviewer #5	iii. Smoking Topography: The Strasser et al., 2007 citation is supporting the statement of fewer puffs per cigarette but the study also reported higher CO boost and total puff volume for 0.05 vs 0.30 mg Quest cigarettes (according to the abstract). I would suggest reviewing the article to determine if those results should also be included in this sentence "one brief exposure study showed higher puff volume and puff duration when participants smoked VLNC cigarettes, but these effects diminished within a single laboratory session (MacQueen et al., 2012)". One study that could be added is Denlinger-Apte et al., 2019d that reports smoking topography from a VLNC trial of smokers with serious mental illness.	
Reviewer #5	iv. Choice: The conclusion that NNC cigarettes are preferred over VLNC cigarettes is appropriate given the data available. One study that should be added is Cassidy et al., 2019a. It reports Cigarette Purchase Task data among adolescent daily smokers.	
Reviewer #5	v. Biomarkers of Exposure: The conclusions that CO does not differ between VLNC and NNC and there is minimal evidence of increased CO exposure are appropriate given the data available. The conclusion that TNEs/cotinine are decreased is appropriate given the data available. The	

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	conclusion that HPHCs are mixed results when smoking VLNC cigarettes is appropriate given the data available. The Hatsukami et. al., 2018 *JAMA* manuscript should be added to each section (CO, TNE, HPHCs).	
Reviewer #5	vi. Physiological Effects: The conclusions that VLNC cigarettes produce inconsistent physiological effects is appropriate given the data available.	
Reviewer #5	c. Subjective Effects, Dependence, and Relief of Withdrawal Symptoms Associated with VLNC Cigarettes. i. Drug Liking and Other Subjective Effects: The conclusion that VLNC cigarettes are rated lower in subjective effects is appropriate given the data available. Smith et al., 2019b reports lower subjective ratings in the immediate reduction condition (secondary analysis of Hatsukami et al., 2018 *JAMA*).	
Reviewer #5	ii. Dependence: The conclusion that use of VLNC cigarettes reduces cigarette dependence is appropriate given the data available. The Hatsukami et. al., 2018 *JAMA* manuscript should be added.	
Reviewer #5	iii. Relief from Withdrawal Symptoms: The conclusion that use of VLNC cigarettes suppresses withdrawal symptoms is appropriate given the data available. The Hatsukami et. al., 2018 *JAMA* manuscript should be added.	
Reviewer #5	d. Lower nAChR Occupancy and Cerebral Response from the Use of VLNC Cigarettes: I did not follow this section or what the conclusions were related to VLNC cigarettes.	
Reviewer #5	C. Unintended Consequences a. Illicit Tobacco Products: It is appropriate to include this section as an unintended consequence.	
Reviewer #5	b. Noncompliance: The conclusion that noncompliance is common with VLNC cigarettes is appropriate given the data available. As I mentioned previously, I don't know that I view noncompliance as an unintended consequence of a nicotine reduction policy.	
Reviewer #5	c. Compensatory Smoking: The conclusion that extended use of VLNC cigarettes does not result in compensatory smoking is appropriate given the data available.	
Reviewer #5	d. Impact on Vulnerable populations:	

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	i. Adolescents: The conclusion that adolescents like VLNC cigarettes less is appropriate given the data available. The review acknowledges the very limited data regarding adolescent VLNC use. With respect to adolescent initiation with VLNC cigarettes there is no data available and this could be acknowledged too. The following quote should have a citation: "However, it is expected that significantly fewer individuals would become established combusted tobacco product users; thereby, dramatically reducing the long-term health impact of chronic combusted tobacco product use." I assume this is based on Apelberg et al., 2018 *NEJM* but it would be good to support this assertion.	
Reviewer #5	ii. Individuals with Symptoms of Mental Health and Substance Use Disorders: The conclusion that VLNC cigarettes do not increase harm in smokers with mental health conditions is appropriate given the data available, but acknowledging the limited data are important. Tidey et al., 2019 and Denlinger-Apte et al., 2019d should be added to this section.	
Reviewer #5	V. Justification for the Inclusion of all Combusted Products in a Nicotine Tobacco Product Standard The conclusions that non-cigarette combusted tobacco products (cigars, waterpipes, loose tobacco) have abuse potential and thus are a threat to public health are appropriate given the data. However, the individual product sections should be updated to reflect the most recent use data, especially among middle and high school students.	
Reviewer #5	VI. Potential Public Health Benefits of Preventing Initiation to Regular Use and Increasing Cessation The conclusion that quitting smoking at any age is beneficial to health is appropriate given the data.	
Reviewer #5	VII. The Impact Perceptions Around Nicotine and Reduced Nicotine May Have on a Proposed Nicotine Standard The conclusions that many smokers incorrectly perceive nicotine as the harmful constituent in cigarettes and that VLNC are perceived by some as less harmful are appropriate given the data available.	
Reviewer #6	Overall, the conclusions are appropriate, although their wording can be improved (see II. Specific Observations). In addition, it seems that the report ends abruptly and the overall conclusion summarizing the total weight of evidence in support of the nicotine standard is missing.	

CHARGE QUESTION 4. Are you aware of additional publicly available information which should have been included? If so, please specify.		
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Reviewer #1	Perkins and Karelitz (Perkins, K.A., Karelitz, J.L. Differences in acute reinforcement across reduced nicotine content cigarettes. *Psychopharmacology*, 2020, https://doi.org/10.1007/s00213-020-05509-9) recently reported a study with a small number of subjects in which the evidence showed a higher nicotine threshold relative to VLNC cigarettes below which participants did not show preference vs. VLNC cigarettes. It is not compulsory, but this information could be useful to include in section IV B, possibly others.	
Reviewer #2	Around pp. 16-17, more text supporting the notion that non-nicotine smoked products are not dependence producing would help justify why reducing nicotine content to very low levels, minimally above zero, should be sufficient to minimize risk of dependence onset.	
Reviewer #2	From p. 20, some estimates appear out of date, e.g. text there states "…and conventional cigarettes generally have nicotine smoke yields in the 1.1 mg to 1.7 mg range (*National Cancer Institute*, 1998a)." Mean nicotine "yields" now are closer to 0.9 mg (see Carmines & Gillman 2019; https://content.sciendo.com/view/journals/cttr/28/6/article-p253.xml)	
Reviewer #2	p.31: Only one sentence mentioning Quest brand cigarettes? Seems to be an inadequate mention, similar to brief comments on "Next" and Ultratech VLNC cigarettes, which attracted much less research attention than Quest. Separate studies with Quest are occasionally noted later on, but these were the best-controlled low and very low nicotine content cigarettes for research (0.6, 0.3, and 0.05 mg nicotine yields) in the first decade of 2000s, prior to Spectrum.	
Reviewer #2	p. 34, On "History of Addiction threshold": More recent studies on choice between Spectrum cigs differing in nicotine content seem very relevant, although these are acute lab studies and extremely recent (Perkins 2019 NTR; Perkins & Karelitz 2020 NTR; 2020 *Psychopharmacology*, each cited below), rather than clinical trials of long-term switching to lower nicotine cigarettes. Given the organization of the text, this likely needs to be provided in the "Choice" section on p. 39. These controlled for non-nicotine aspects of smoking behavior, so that only the differences in nicotine content per se influenced choice responses. The 2019 NTR paper shows that threshold for nicotine discrimination directly relates to threshold for choice (i.e. preference, or reinforcement), and Shoaib & Perkins (2020) review paper outlines broader research on relevance of nicotine discrimination to reinforcement. The Perkins & Karelitz 2020 NTR paper indicates Spectrum cigs above 2.4 mg/g nicotine content are chosen more than the 0.4 mg/g VLNC. Perkins & Karelitz 2020 *Psychopharmacology* paper confirms that finding in a better controlled test; it also indicates cigs at or below 2.4 mg/g are chosen LESS than the 18 mg/g "regular nic	

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	cig" (similar to commercial brands). This is potentially important, as these results are consistent with the decline in cigs/day seen in the switching study of Donny et al. (2015), later described in detail on p. 37, when groups were randomized to the lower nic content Spectrum cigs from their initial brands.	
Reviewer #2	pp. 44-45, on Drug Liking and other Subjective effects: Our most recent research shows that immediate pleasurable perceptions of smoking Spectrum cigarettes varying in nicotine content actually mediate the acute reinforcing effects of those cigarettes. This result indicates self-administration of the higher nicotine cigarettes (in a choice procedure, comparing vs. the 0.4 mg/g VLNC) is caused by those rated perceptions upon smoking them. Although often assumed, this was the first time causation for reinforcement by acute subjective responses has been shown in humans, to our knowledge. This is Karelitz & Perkins (2020), but it is not yet in press.	
Reviewer #2	Papers cited above: Karelitz JL, Perkins KA (2020). Acute pleasurable perceptions mediate cigarette reinforcement efficacy. Under review. Perkins KA (2019) Research on behavioral discrimination of nicotine may inform FDA policy on setting a maximum nicotine content in cigarettes. *Nicotine Tob Res* 21(suppl 1):S5–S12. https://doi.org/10. 1093/ntr/ntz136 Perkins KA, Karelitz JL (2020) A forced choice procedure to assess the acute relative reinforcing effects of nicotine dose per se in humans. *Nicotine Tob Res*; in press. https://doi.org/10.1093/ntr/ntz224 Perkins KA, Karelitz JL (2020) Differences in acute reinforcement across reduced nicotine content cigarettes. *Psychopharmacology*; in press. https://doi.org/10.1007/s00213-020-05509-9 Shoaib M, Perkins KA. (2020) Preclinical and clinical research on the discriminative stimulus effects of nicotine. *Neuropharmacology*, in press.	
Reviewer #3	Section II. B. (page 11): I like the reference Lopez-Quintero et al., 2011 (https://doi.org/10.1016/j.drugalcdep.2010.11.004) that shows the probability of transitioning from first use to dependence is 67% for nicotine/tobacco – but less than 25% for alcohol, cocaine and cannabis. This suggests a relatively stronger addiction liability for nicotine/tobacco than other drugs of abuse (some of which are also legal and easily obtained, i.e., alcohol).	

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Reviewer #3	Section II. B (page 12): I also like the reference Hackshaw et al. 2018 (doi: https://doi.org/10.1136/bmj.j5855) that shows there is no "safe" level of smoking, just smoking one cigarette per day increases the risk of stroke and coronary artery disease.	
Reviewer #3	Page 16. Hughes, Keely, and Naud (2004) reported that the majority of smokers who attempt to quit relapse within eight days. https://doi.org/10.1111/j.1360-0443.2004.00540.x	
Reviewer #3	Here are several recent articles that address gaps in the document's reviewed literature… Shiffman et al., 2019 Very-low-nicotine-content cigarettes and dependence among non-daily smokers https://doi.org/10.1016/j.drugalcdep.2018.12.021. Non-daily smokers were experimentally switched to very-low-nicotine cigarettes. Tobacco dependence decreased, along with cigarette consumption. Smith et al., 2019 Randomized trial of low-nicotine cigarettes and transdermal nicotine. https://doi.org/10.1016/j.amepre.2019.05.010. Assignment to very low nicotine content cigarettes and assignment to wear a nicotine patch both reduced the number of cigarettes smoked per day during Week 6 (p=0.001 and 0.04, respectively). Cassidy et al., 2019 Age moderates smokers' subjective response to very-low nicotine content cigarettes: evidence from a randomized controlled trial. doi: 10.1093/ntr/nty079. Results indicated that younger adults (age 18–24) who smoked cigarettes with 2.4–0.4 mg/g nicotine reported significantly less smoking satisfaction and psychological reward, and smoked fewer cigarettes per day, than older adults (25+ years) after two weeks of use. No differences in topography were observed at either time point. After six weeks of use, differences had diminished on all measures. Pacek et al., 2019 Young adult dual combusted cigarette and e-cigarette users' anticipated responses to a nicotine reduction policy and menthol ban in combusted cigarettes https://doi.org/10.1016/j.drugalcdep.2018.10.005. Hypothetical nicotine reduction led to intentions to quit/reduce cigarette use. Hypothetical nicotine reduction led to intentions to increase e-cigarette use.	

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	Benowitz et al., 2019 The role of compensation in nicotine reduction https://doi.org/10.1093/ntr/ntz120. Assuming that a 10 CPD smoker is trying to maintain an intake of 10 mg nicotine per day, and assuming the most intensive compensation, it would require that the smoker smoke 100 CPD to achieve full compensation. Davis et al., 2019 Examining age as a potential moderator of Response to Reduced Nicotine Content Cigarettes in Vulnerable Populations https://doi.org/10.1093/ntr/ntz134. Young adults exhibited lower demand for reduced nicotine content cigarettes than older adults across three of five CPT indices (ps < .05). No differences by age were observed on other measures of reinforcing efficacy, subjective effects, craving/withdrawal, or smoking topography where effects generally decreased as an orderly function of decreasing nicotine content (ps <.05). Perkins and Karelitz 2020 Differences in acute reinforcement across reduced nicotine content cigarettes. doi: 10.1007/s00213-020-05509-9. Results indicate that nicotine reduction to ≤ 2.3 mg/g in cigarettes would attenuate reinforcement. Gaalema et al., 2019. Potential Moderating Effects of Psychiatric Diagnosis and Symptom Severity on Subjective and Behavioral Responses to Reduced Nicotine Content Cigarettes. doi: 10.1093/ntr/ntz139. Reducing nicotine dose reduced measures of cigarette addiction potential, with little evidence of moderation by either psychiatric diagnosis or symptom severity, providing evidence that those with comorbid psychiatric disorders would respond to a nicotine reduction policy similarly to other smokers. Tidey et al., 2019 Effects of 6-Week Use of Very Low Nicotine Content Cigarettes in Smokers With Serious Mental Illness doi: 10.1093/ntr/ntz133. These results suggest that a reduced-nicotine standard for cigarettes would reduce smoking among smokers with SMI.	
Reviewer #4	In December, *Nicotine and Tobacco Research* published a supplement devoted to VLNC (*Nicotine & Tobacco Research*, 21, Supplement 1, December 2019). The supplement included 21 articles focused on this topic. The majority of those appear to support the conclusions reached in this document, with the possible exception of Klemperer, et al.'s paper (Increasing quit attempts by transitioning to very low nicotine content cigarettes versus reducing number of cigarettes per day: A secondary analysis of an exploratory randomized trial, s81-s86); this paper	

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	found that reducing CPD resulted in more 24 hour quit attempts than VLNC cigarettes, but that there were no differences for quit attempts >24 hours. However, as the authors note, there were methodological issues with the study that suggest additional research is needed to address the soundness of this conclusion. The papers addressing menthol cigarettes (Delinger-Apte et al. pages S63-S72 and S73-S80) add to the information in the current document. The papers by Piper et al. (Behavioral and Subjective Effects of Reducing Nicotine in Cigarettes: A Cessation commentary S19-21 and Smith et al. Behavioral outcomes of nicotine reduction in current adult smokers, S125-127) conclude that VLNC increases quit attempts and when used with NRT, increases quit rates. The former is supportable; in my estimation, the conclusion that the implementation of VLNC cigarettes will result in an increase in actual quit rates is not as strong, especially with respect to prolonged abstinence.	
Reviewer #5	Several VLNC studies have been published since the last PubMed search for this review was conducted in 2018. I acknowledge these studies in the II. Specific Observations table with suggestions of where in the review they could be included. Byron, JM., Jeong, M., Abrams, D.B. & Brewer, N.T. (2018). Public misperception that very low nicotine content cigarettes are less carcinogenic. *Tobacco Control*. 27(6), 712-714. doi: 10.1136/tobaccocontrol-2017-054124. Byron, JM., Hall, M.G., King, J.L., Ribisl, K.M., & Brewer, N.T. (2019). Reducing nicotine without misleading the public: Description of cigarette nicotine level and accuracy of perceptions about nicotine content, addictiveness, and risk. *Nicotine & Tobacco Research*, 21(Suppl_1), S101-S107. doi: 10.1093/ntr/ntz161 Cassidy, R.N., Miller, M.E., Tidey, J.W., DiGiuseppi, G., Denlinger-Apte, R.L., & Colby, S.M. (2019a). The impact of nicotine dose on the reinforcing value of cigarettes in adolescents. *Tobacco Regulatory Science*, 5(2), 105-114. doi:10.18001/TRS.5.2.2 Cassidy, R.N., Tidey, J.W., Cao, Q., Colby, S.M., McClernon, F.J., Koopmeiners, J.S., Hatsukami, D.K., & Donny, E.C. (2019b). Age moderates smokers' subjective response to very-low nicotine content cigarettes: Evidence from a randomized controlled trial. *Nicotine & Tobacco Research*, 21(7), 962-969. doi:10.1093/ntr/nty079	

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REVIEWER	**COMMENT**	**RESPONSE**
	Davis, D.R., Miller, M.E., Streck, J.M., Bergeria, C.L., Sigmon, S.C., Tidey, J.W., Heil, S.H., Gaaleema, D.E., Villanti, A.C., Stitzer, M.L., Priest, J.S., Bunn, J.Y., Skelly, J.M., Diaz, V., Arger, C.A., & Higgins, S.T. (2019). Response to reduced nicotine content in vulnerable populations: Effect of menthol status. *Tobacco Regulatory Science*, 5(2), 135-142. doi: 10.18001/TRS.5.2.5 Denlinger-Apte, R.L., Tidey, J.W., Koopmeiners, J.S., Hatsukami, D.K., Smith, T.T., Pacek, L.R., McClernon, F.J., & Donny, E.C. (2019a). Correlates of support for a nicotine reduction policy in smokers with 6-Week exposure to very low nicotine cigarettes. *Tobacco Control,* 28(3), 352-355. doi:10.1136/tobaccocontrol-2018-054622 Denlinger-Apte, R.L., Cassidy, R.N., Colby, S.M., Sokolovsky, A., & Tidey, J.W. (2019b). Effects of cigarette nicotine content and menthol preference on perceived health risks, subjective ratings, and carbon monoxide exposure among adolescent smokers. *Nicotine & Tobacco Research*, 21(Suppl_1), S56-S62. doi: 10.1093/ntr/ntz127 Denlinger-Apte, R.L., Kotlyar, M., Koopmeiners, J.S., Tidey, J.W., Luo, X., Jensen, J.A., Vandrey, R.G., Pacek, L.R., Smith, T.T., Donny, E.C., & Hatsukami, D.K. (2019c). Effects of very low nicotine content cigarettes on smoking behavior and biomarkers of exposure in menthol and non-menthol smokers. *Nicotine & Tobacco Research*, 21(Suppl_1), S63-S72. doi: 10.1093/ntr/ntz160 Denlinger-Apte, R.L., Donny, E.C., Lindgren, B., Rubin, N., Moulding, C., DeAtley, T., Colby, S.M., Cioe, P., Hatsukami, D.K., & Tidey, J.W. (2019d). Smoking topography characteristics during a six-week trial of very low nicotine content cigarettes in smokers with serious mental illness. *Nicotine & Tobacco Research*. E-pub ahead of print Hall, M.G., Brewer, N.T., Noar, S.M., & Ribisl, K.M. (2019). Interest in illicit purchase of cigarettes under a very low nicotine content product standard. *Nicotine & Tobacco Research*, 21(Suppl_1), S128-S132. doi: 10.1093/ntr/ntz159	

CHARGE QUESTION 4. Are you aware of additional publicly available information which should have been included? If so, please specify.		
REVIEWER	**COMMENT**	**RESPONSE**
	Nardone, N., Benowitz, N.B., Smith, T.T., Denlinger-Apte, R.L., Hatsukami, D.K., Koopmeiners, J.S., Ren, Y., Donny, E.C. (2019). Reasons for non-compliance in a cigarette nicotine reduction trial. *Tobacco Regulatory Science*, 5(1), 87-93. doi:10.18001/TRS.5.1.8 Robinson, J.D., Kypriotakis, G., al'Absi, M., Denlinger-Apte, R.L., Drobes, D.J., Leischow S., McClernon F.J., Pacek L.R., Severson H., Smith T.T., Donny E.C., Luo X., Jensen, J.A., Strayer, L.G., Cinciripini, P.M., Hatsukami, D.K. (2019) Very low nicotine content cigarettes disrupt the feedback loop of affective states and smoking behavior. *Nicotine & Tobacco Research*. E-pub ahead of print Ribisl, K.M., Hatsukami D.K., Huang, J., Williams, R.S., & Donny, E.C. (2019). Strategies to reduce illicit trade of regular nicotine tobacco products after introduction of a low-nicotine tobacco product standard. *American Journal of Public Health*, 109(7), 1007-1014. doi10.2105/AJPH.2019.305067 Smith, T.T., Koopmeiners, J.S., Tessier, K., Davis, E., Conklin, C.A., Denlinger-Apte, R.L., Lane, T., Murphy, S.S., Tidey, J.W., Hatsukami, D.K., & Donny, E.C. (2019a). A randomized clinical trial investigating the impact of very low nicotine content cigarettes and transdermal nicotine in smokers not trying to quit. *American Journal of Preventive Medicine*, 57(4), 515-524. doi: 10.1016/j.amepre.2019.05.010 Smith, T.T., Donny, E.C., Luo, X., Koopmeiners, J.S., Allen, A., Denlinger-Apte, R.L., Pacek, L.R., McClernon, F.J., Vandrey, R. & Hatsukami, D.K. (2019b). The impact of gradual and immediate nicotine reduction on subjective cigarette ratings. *Nicotine & Tobacco Research*, 21(Suppl_1), S73-S80. doi: 10.1093/ntr/ntz158 Smith, T.T., Koopmeiners, J.S., White, C.M., Denlinger-Apte, R.L., Pacek, L.R., DeJesus, V.R., Wang, L., Watson, C.H., Blout, B.C., Hatsukami, D.K., Benowitz, N.L., Donny, E.C., & Carpenter, M.J. (2020a). The impact of exclusive use of very low nicotine cigarettes on compensatory smoking: An inpatient crossover clinical trial. *Cancer, Epidemiology, Biomarkers & Prevention*, 29(4), 880-886. doi: 10.1158/1055-9965.EPI-19-0963	

CHARGE QUESTION 4. Are you aware of additional publicly available information which should have been included? If so, please specify.		
REVIEWER	**COMMENT**	**RESPONSE**
	Smith, T.T., Koopmeiners, J.S., Hatsukami, D.K., Tessier, K.M., Benowitz, N.L., Murphy, S.E., Strasser, A.A., Tidey, J.W., Blout, B.C., Valentin, L,. Bravo Cardenas, R., Watson, C.H., Pirkle, J.L. &, Donny, E.C. (2020b). Mouth-level nicotine intake estimates from discarded filter butts to examine compensatory smoking in low nicotine cigarettes. *Cancer, Epidemiology, Biomarkers & Prevention*, 29(3), 643-649. doi: 10.1158/1055-9965.EPI-19-0905 Tidey, J.W., Colby, S.M., Denlinger-Apte, R.L., Cioe, P., Goodwin, C., Lindgren, B.R., Rubin, N., Hatsukami, D.K., & Donny, E.C. (2019). Effects of 6-week use of very low nicotine content cigarettes in smokers with serious mental illness. *Nicotine & Tobacco Research*, 21(Suppl_1), S38-S45. doi: 10.1093/ntr/ntz133.	
Reviewer #6	Section VII. The Impact Perceptions Around Nicotine and Reduced Nicotine May Have on a Proposed Nicotine Standard reports on the results of a scoping review conducted in September 2017. While there have been additional studies published since the scoping review was conducted in September 2017, the overall conclusions are still valid: people still overwhelmingly believe nicotine is the main (or one of the main) harmful chemicals in tobacco and that it causes cancer. Similarly, reduced nicotine cigarettes are believed to be less harmful (although this can be mitigated through different communication messages). In general, the beliefs about addictiveness and harm of nicotine are connected and people have a hard time separating the two (nicotine is addictive, but not the main cause of harm from tobacco). It might be worthwhile to update the review if resources permit.	
Reviewer #6	Below are some of the additional studies (although the list is not exhaustive since this is not a thorough scoping review) that appeared in the last 2-3 years that are relevant to the issues around nicotine perceptions. **Additional studies for A. Consumer Knowledge, Attitudes, Beliefs, or Perceptions About Nicotine (these don't include studies with participants outside the US and are all quantitative):** Villanti, A. C., Naud, S., West, J. C., Pearson, J. L., Wackowski, O. A., Niaura, R. S., ... & Rath, J. M. (2019). Prevalence and correlates of nicotine and nicotine product perceptions in US young adults, 2016. *Addictive behaviors*, 98, 106020.	

CHARGE QUESTION 4. Are you aware of additional publicly available information which should have been included? If so, please specify.		
REVIEWER	**COMMENT**	**RESPONSE**
	Overall, 55% of young adults believed that nicotine is a cause of cancer, with an additional 24% reporting that they did not know. More than 60% of respondents believed that a relatively or very large part of the health risks (66%) or cancer (60%) caused by smoking come from the nicotine. Patel, D., Peiper, N., & Rodu, B. (2013). Perceptions of the health risks related to cigarettes and nicotine among university faculty. *Addiction Research & Theory*, 21(2), 154-159. The majority of respondents (faculty at the University of Louisville) perceived nicotine as either high or moderate risk. Kemp, C. B., Spears, C. A., Pechacek, T. F., & Eriksen, M. P. (2018). Adults' Perceptions of Nicotine Harm to Children. *Pediatrics*, 142(2). The majority (83.2%; 95% CI: 82.3%–84.1%) of adults characterized nicotine as definitely harmful to children, 6.2% (95% CI: 5.7%–6.8%) as maybe harmful, 1.7% (95% CI: 1.3%–2.0%) as unlikely harmful, 0.6% (95% CI: 0.4%–0.8%) as not harmful, and 8.3% (95% CI: 7.6%–9.0%) responded that they don't know how harmful nicotine is when used by children." ("The following question elicited perceptions of nicotine harm to children regarding children <13 years old: 'Tobacco products, including electronic vapor products, contain nicotine. When used by the following groups, how harmful is nicotine in amounts usually found in tobacco products?' Response options were not harmful, unlikely harmful, maybe harmful, definitely harmful, or don't know.")	
Reviewer #6	**Additional studies for B. Consumer Knowledge, Attitudes, Beliefs, or Perceptions Regarding Reduced Nicotine Tobacco Products:** <u>a. Studies not Employing Study Cigarettes or Advertising Stimuli</u> Popova, L., Owusu, D., Nyman, A. L., Weaver, S. R., Yang, B., Huang, J., & Ashley, D. L. (2019). Effects of framing nicotine reduction in cigarettes on anticipated tobacco product use intentions and risk perceptions among US adult smokers. *Nicotine and Tobacco Research*, 21(Supplement_1), S108-S116. Data from 2018 nationally representative sample of US adult smokers showed that framing the nicotine tobacco product standard as cigarettes no longer relieved cravings resulted in the highest	

CHARGE QUESTION 4. Are you aware of additional publicly available information which should have been included? If so, please specify.		
REVIEWER	**COMMENT**	**RESPONSE**
	proportion of smokers reporting they intend to quit in response to this standard (43.9%), lowest proportions reporting anticipated intentions to continue using combusted tobacco products (45.3%), and lowest proportion believing that VLNCs are less harmful than regular cigarettes (26%). Patel, M., Cuccia, A. F., Zhou, Y., Czaplicki, L., Pitzer, L., Hair, E. C., ... & Vallone, D. M. (2019). Nicotine Perceptions and Response to Proposed Low-Nicotine Cigarette Policy. *Tobacco Regulatory Science*, 5(6), 480-490. Results from 2018 nationally representative sample of US adult smokers: 63% of survey participants accurately identified nicotine alone as the addiction cause, 49% incorrectly indicated that a relatively large or a very large/all of the cancer caused by cigarette smoking comes from the nicotine itself and 56% indicated that increased health risk caused by cigarette smoking comes from nicotine. Mercincavage, M., Lochbuehler, K., Villanti, A. C., Wileyto, E. P., Audrain-McGovern, J., & Strasser, A. A. (2019). Examining risk perceptions among daily smokers naïve to reduced nicotine content cigarettes. *Nicotine and Tobacco Research*, 21(7), 985-990. Baseline data from two experiments with non-treatment seeking daily smokers (2014-2017 data). Although the majority of participants did not misperceive RNC cigarettes as less harmful than regular nicotine cigarettes, 63.4% did not think RNC cigarettes were less addictive and 51% did not think they make it easier to quit. More than 20% of the sample reported being unsure about RNC-related risks, especially tar content (51.8%). Non-White smokers were 2.5 to 3 times more likely to be incorrect about multiple RNC cigarette risks ($p = .002–.006$). Byron, M. J., Jeong, M., Abrams, D. B., & Brewer, N. T. (2018). Public misperception that very low nicotine cigarettes are less carcinogenic. *Tobacco control*, 27(6), 712-714. Data from 2015-16 nationally representative sample of adult smokers. Overall, 47.1% of smokers believed that smoking VLNC cigarettes for 30 years would be less likely to cause cancer than smoking current cigarettes. This misperception was more common among smokers who were aged above 55 (56.6%) and black (57.4%). Additionally, 23.9% of smokers reported they would be less likely to quit if the USA adopted a VLNC standard. Thinking that VLNC cigarettes	

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REVIEWER	**COMMENT**	**RESPONSE**
	would be less carcinogenic was associated with smokers reporting they would be less likely to quit (P<0.01). Byron, M. J., Hall, M. G., King, J. L., Ribisl, K. M., & Brewer, N. T. (2019). Reducing nicotine without misleading the public: Descriptions of cigarette nicotine level and accuracy of perceptions about nicotine content, addictiveness, and risk. *Nicotine and Tobacco Research*, 21(Supplement_1), S101-S107. Online experiment with convenience sample of US adults (22% smokers). Randomized to view different VLNC cigarettes descriptions. Compared to control, the percentage description resulted in more accurate perceptions about nicotine content (76% vs. 49% accuracy) and addictiveness (44% vs. 34%), but less accurate perceptions about cancer risk (56% vs. 68%; all ps < .05). Adding interpretation or pictographs to the percentage description did not increase accuracy. The concise language description reduced accuracy of perceived nicotine content and addictiveness but increased accuracy of cancer risk (all p < .05). Nguyen, A. B., Zhao, X., Hoffman, L., Morse, A. L., & Delahanty, J. (2018). Nicotine and addiction beliefs and perceptions among the US-born and foreign-born populations. *Preventive Medicine*, 114, 107-114. Secondary analysis of data from 2015 and 2017 HINTS survey. Compared to US-born respondents, foreign-born respondents were more likely to believe that low nicotine cigarettes would have much lower lung cancer risk than a typical cigarette. Among the foreign-born, NH-Black and Hispanic respondents were more likely to see low nicotine cigarettes as harmful and addictive compared to NH-White respondents.	
Reviewer #6	<u>c. Studies Employing the Use of Packaging or Advertising Stimuli:</u> Johnson, A. C., Mays, D., Villanti, A. C., Niaura, R. S., Rehberg, K., Phan, L., ... & Strasser, A. A. (2019). Marketing influences on perceptions of reduced nicotine content cigarettes. *Nicotine and Tobacco Research*, 21(Supplement_1), S117-S124. Online experiment with convenience sample of young adult smokers (18-30). Participants were randomized in a 2 (implicit: red package vs. blue package) × 2 (explicit: corrective message vs. no corrective message) design to view an advertisement for Quest VLNC cigarettes. There	

CHARGE QUESTION 4. Are you aware of additional publicly available information which should have been included? If so, please specify.		
REVIEWER	**COMMENT**	**RESPONSE**
	was no main or interaction effects of package color or the corrective message on product beliefs or use intentions. Yang, B., Owusu, D., & Popova, L. (2020). Effects of a Nicotine Fact Sheet on Perceived Risk of Nicotine and E-Cigarettes and Intentions to Seek Information About and Use E-Cigarettes. *International Journal of Environmental Research and Public Health*, 17(1), 131. Online experiment with convenience sample of US adult smokers, randomized to view a nicotine fact sheet or bottle water ad (control). Compared to control, the nicotine fact sheet doubled the probability of disagreeing that nicotine is the main cause of smoking-related disease (26.2% vs. 12.7%, RR = 2.06, 95% CI = 1.51, 2.82, $p < 0.001$). However, nearly three quarters of participants viewing the nicotine fact sheet still thought that nicotine is the main cause of smoking-related disease.	
Reviewer #6	**Additional studies for C. Consumer Knowledge, Attitudes, Beliefs, Perceptions, or Planned Behavior Regarding FDA Regulation of Tobacco:** Patel, M., Cuccia, A. F., Zhou, Y., Czaplicki, L., Pitzer, L., Hair, E. C., ... & Vallone, D. M. (2019). Nicotine Perceptions and Response to Proposed Low-Nicotine Cigarette Policy. *Tobacco Regulatory Science*, 5(6), 480-490. Smokers showed high support (72%) for a proposed low-nicotine policy. Greater misperception about nicotine harm was associated with greater odds (aOR = 1.66, $p < .05$) of policy support. Shorter time to first cigarette was associated with greater intent to smoke low-nicotine cigarettes but was not associated with policy support.	

CHARGE QUESTION 5. Provide any additional comments including limitations and outcomes not discussed, or editorial suggestions not addressed in the previous questions.		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #1	No additional comments.	
Reviewer #2	On p.10, more emphasis should be given to the (now brief) mention (one sentence) that most current dependent smokers regret having started, as that is a very strong indication of loss of control over drug use (i.e. “autonomy”), or dependence on the drug. A policy to reduce nicotine content of tobacco would thus be expected to help restore some of that control, to allow users to	

CHARGE QUESTION 5. Provide any additional comments including limitations and outcomes not discussed, or editorial suggestions not addressed in the previous questions.		
REVIEWER	**COMMENT**	**RESPONSE**
	succeed in dealing effectively with that regret by permanently quitting, which is also briefly noted in the next sentence, but seems to warrant more attention in supporting policy rationale.	
Reviewer #3	There are more than 7000 chemicals in tobacco smoke – some of these are the products of combustion, some are added by tobacco companies (Rodgman A, Perfetti TA. The Chemical Components of Tobacco and Tobacco Smoke. New York, NY: CRC Press; 2013). Some of these ingredients may be primary reinforcers, conditioned reinforcers, or contribute to physical dependence/withdrawal symptoms. Tobacco companies know which additives make cigarettes/tobacco products more satisfying, easier to smoke, and more reinforcing (e.g., menthol). If they are forced to remove nicotine, why wouldn't they just add more of the other ingredients to keep smokers hooked? I know there are other regulations and proposed regulations concerning added ingredients (e.g., flavor), but how does that fit in with this proposal to reduce nicotine?	
Reviewer #3	Page 36, perhaps a comparison of the rates of smoking cessation with VLNCs with rates of cessation during unassisted quit attempts would underscore the point that VLNCs make quitting easier.	
Reviewer #3	Several times it is mentioned that this product standard would apply to all combusted tobacco products, but there is no mention of IQOS, the 'heated not burned' tobacco product.	
Reviewer #3	Section II. A. (page 10). It might be useful for a lay-reader to have a brief description of addiction/substance use disorder, specifically tobacco use disorder (i.e., persistent use of tobacco despite negative consequences, characterized by craving, compulsive use, physical tolerance, dependence, and withdrawal). I think many people do not consider tobacco use disorder a serious addiction (compared to – say- alcohol use disorder, which causes intoxication, problems with the law, etc). I think many people still perceive tobacco use as a "choice" people make. This document needs to drive home the point that tobacco is strongly addictive, and most people smoke because they have to – in response to powerful cravings and in order to avoid withdrawal symptoms – rather than just because they want to.	
Reviewer #3	In addition to earlier comments I made about VLNCs not reducing cigarettes per day among established smokers…I think many businesses, farmers, and states who profit or receive tax dollars are going to resist this proposed reduction in nicotine, and here is an opportunity to allay some fears that people will stop smoking altogether if nicotine is reduced in cigarettes. It appears that established smokers will continue to smoke cigarettes. Reducing nicotine would ensure that	

CHARGE QUESTION 5. Provide any additional comments including limitations and outcomes not discussed, or editorial suggestions not addressed in the previous questions.		
REVIEWER	**COMMENT**	**RESPONSE**
	people choose to smoke because they want to, not because they have to due to their nicotine addiction. I think this 'free will' argument has been used by the tobacco companies to help keep tobacco legal.	
Reviewer #3	Page 30. Some of the ways in which VLNC tobacco can be grown/harvested/processed is described, but I'm curious about some of the barriers for these changes. Would farmers have to change their practices, or get new equipment? Would nicotine extraction increase the price of VLNC cigarettes? Are those costs absorbed by the tobacco companies or by the farmers? Additionally, much tobacco grown in America is exported, and will continue to be exported at full nicotine concentrations if this regulation is passed. Would the domestic implementation of low nicotine content cigarettes conflict with exports?	
Reviewer #3	There is apparently a lack of research on the effects of VLNCs on light (using 5 CPD or less) and non-daily smokers. These smokers might be much more likely to reduce or quit cigarettes than heavy smokers (using at least 10 CPD). It appears that most of the research to date has been on smokers who use at least 10 cigarettes per day, who continue to use VLNCs at about the same rate. I think it would be important to put out a call for research in this area.	
Reviewer #3	Section a. Illicit tobacco products (page 51), will there be any special considerations for enforcing laws against illicit tobacco given that vulnerable populations have the highest smoking prevalence rates and are most likely to be affected?	
Reviewer #4	The technical information (included in the report under Analytical Testing Method and Technical Achievability) makes a strong case that FDA will in fact be able to produce a cigarette of an appropriate nicotine level. Most of the material, however, refers to cigarettes. The reader who is versed in biochemistry may easily be able to generalize this to other tobacco combustible products. But for the general scientist, the document would be more convincing if there were at least some mention of how the lower nicotine levels would be achieved in these products.	
Reviewer #4	Second, the issue of the potential harms of ENDS is not discussed, particularly increased levels of nicotine addiction of youth and young adults. FDA seems to clearly anticipate that reduction of nicotine content in cigarettes will increase use of ENDS among all age groups; therefore, it seems dismissive to not consider the implications of this addiction, or at the very least, acknowledge it, and note that the effects are unknown.	
Reviewer #5	Nicotine content reporting:	

CHARGE QUESTION 5. Provide any additional comments including limitations and outcomes not discussed, or editorial suggestions not addressed in the previous questions.		
REVIEWER	**COMMENT**	**RESPONSE**
	In III.E. Technical Achievability (and throughout the document), cigarette nicotine contents are described in both percent of nicotine and mg of nicotine. As a reader, it was slightly difficult for me to compare across different VLNC products within the text or to know what was considered LNC vs VLNC. Table 1 on page 32 was really helpful to review. Perhaps this table could be moved to earlier in the section. You may also want to add a column to Table 1 that includes nicotine % reduction since sometimes this is how products were described in the text. That would make it easy to compare across generations of products and different projects.	
Reviewer #5	Section IV.C. Unintended Consequences: Another section of potential unintended consequences to consider adding is how a nicotine reduction policy may affect use of other drugs. Dermody et al., 2016 *ACER* and Pacek et al., 2016 *DAD* are both secondary analyses from Donny et al., 2015 *NEJM*. They did not report increased use of alcohol or cannabis among smokers assigned to VLNC cigarettes which are encouraging initial findings.	
Reviewer #5	Additionally, a paragraph on the impact of nicotine reduction by menthol smoking status could also contribute positively to the review since currently menthol cigarettes are commercially available and a product standard would apply to them. Perkins et al., 2017 *Psychopharmacology* reported nicotine dose discrimination by menthol smoking status and Perkins et al., *Journal of Psychopharmacology* reported VLNC perceptions by menthol smoking status. Davis et al., 2019 is a secondary analysis of Higgins et al., 2017 *JAMA* Psychiatry and reported no differences by menthol status. Denlinger-Apte et al., 2019c is a secondary analysis of Hatsukami et al., 2018 *JAMA* that reported outcomes by menthol smoking status and found that a nicotine reduction policy was likely to benefit both menthol and non-menthol smokers; but VLNC treatment effects were significantly smaller among menthol smokers.	
Reviewer #5	Adolescent Smoking Prevention: Adolescent and young adult smoking prevention is clearly an important policy outcome. Obtaining clinical data on adolescent initiation is clearly unethical; however, this results in a substantial gap in the literature. In this review, Apelberg et al., 2018 *NEJM* provides the most compelling information about how a nicotine reduction policy would affect initiation. However, it is simulated data. Given the lack of human subjects data, I wondered about adding in preclinical research that addresses this initiation outcome. Certainly, animal models have their limitations but they do provide complementary data. For example, Shassberger et al., 2016 *NTR* and Smith et	

CHARGE QUESTION 5. Provide any additional comments including limitations and outcomes not discussed, or editorial suggestions not addressed in the previous questions.		
REVIEWER	**COMMENT**	**RESPONSE**
	al., 2014 *ECP* examined nicotine self-administration in adolescent and adult nicotine naive rats to assess the impact of low dose nicotine (i.e., VLNC cigarettes) on initiation. They found that the same low nicotine doses that reduced self-administration in nicotine-using rats was also sufficient for preventing nicotine self-administration acquisition in nicotine-naive rats. I do understand that preclinical studies were excluded as part of this review, so perhaps this is not possible. It may be worthwhile to include a couple sentences explicitly acknowledging this limitation.	
Reviewer #5	In addition, some of the citations throughout the II.C.a.Youth Cigarette Smoking Initiation and Dependence section feel out of date. Over the past five years, significant declines in middle and high school smoking have occurred. Wang et al., 2019 reports past 30 day use of cigarettes at 5.7% for high school and 2.3% for middle school students. A nicotine reduction product standard will likely continue reducing adolescent smoking but substantial achievements, including surpassing the *Healthy People 2020* goal of 16% past 30-day smoking, have already occurred.	
Reviewer #5	IV.C.d. Impact on Vulnerable Populations: Having a separate section specifically highlighting vulnerable populations is a strength of this review. However, throughout the document, references to vulnerable populations were inconsistently cited. I would suggest including the citations in both locations, when discussing the overall topic (e.g., subjective effects) and in the vulnerable populations section.	
Reviewer #6	Throughout the report, little cigars and cigarillos are either absent or incorporated under “cigars”. Given their superior suitability as substitutes for combusted cigarettes, they need to be brought up early in the report and singled out or more explicitly acknowledged as the subset of cigars.	
Reviewer #6	Is there evidence of technical achievability of a nicotine standard for other tobacco products? It would be helpful to add something along those lines (even though other tobacco products with reduced nicotine have not been produced, the methods for reducing nicotine that work for cigarettes would be applicable to all other tobacco products).	
Reviewer #6	We are currently conducting focus groups about the tobacco nicotine standard, and we keep hearing this question from participants in our focus groups: “Why reduce nicotine, but not the other bad chemicals?” It might be worthwhile to acknowledge this question and provide the answer to it – maybe something about technical achievability of reduced nicotine, but that it’s impossible to reduce other harmful chemicals to the levels that would have meaningful impact on health outcomes.	

CHARGE QUESTION 5. Provide any additional comments including limitations and outcomes not discussed, or editorial suggestions not addressed in the previous questions.		
REVIEWER	**COMMENT**	**RESPONSE**
Reviewer #6	The report does not mention heated tobacco products, such as IQOS. The FDA has referred to them as "non-combusted cigarettes." Given that they are on the US market now, the FDA needs to consider (and probably include in the report) the implications of either including heated tobacco products with combusted tobacco under the nicotine standard or treating them as non-combusted tobacco products (like smokeless tobacco and ENDS). In either case, the report might need to discuss the potential of heated tobacco products to serve as a substitute for combusted cigarettes and the resultant health implications, or at least acknowledge the existing lack of science on these topics.	

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"				
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**	**RESPONSE**
Reviewer #1	39-40		As stated in response to section I, question 4 above, the 2020 Perkins and Karelitz paper could contribute information to the discussion on levels of nicotine relative to "Choice" in section IV. B. b. iv.	
Reviewer #2	8		Update for new minimum age of cig purchase? Text says 18 but new law is 21 (as has been the case in several states in recent years). So, perhaps "Despite recent increase in age for purchase from 18 to 21 nationwide, surreptitious access to tobacco is likely to continue among adolescents and older teens." Later text in that paragraph, on very high rates of youth underestimating risks of dependence onset within a few years, is effective and could even be given more emphasis.	
Reviewer #2	216 (in refs)		Perkins et al. 2017 and 2018, each with 2 papers by same authors (marked "a" and "b" are actually the same paper, as one includes doi and the other does not).	
Reviewer #3			None provided.	
Reviewer #4	5	1/9	Insert comment that producing lowered nicotine content in VLNC is technically achievable.	

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"				
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**	**RESPONSE**
Reviewer #4	5	1/14	Insert 'possibly' before 'increased quit rates among current smokers'.	
Reviewer #4	5	1/16	Omit 'also' in the sentence beginning "There is ~~also~~	
Reviewer #4	5	1/21-22	The phrase 'substantial portion' is used twice in the same sentence. The sentence should be rewritten.	
Reviewer #4	6	1/7	After line 7, insert comment that FDA proposes to limit nicotine content in non-cigarette products .	
Reviewer #4	10	1/last line	Given the recent concern with Juul and other e-cigarettes, it seems rather incomplete that there is little discussion at any point in the manuscript about the possible addiction to nicotine via e-cigarettes, especially in terms of youth and young adults.	
Reviewer #4	11	2/5	As described below the evidence concerning the facilitation of quitting via VLNC is suggestive, but not so strong as that supporting the minimal addictiveness of VLNC. Therefore, I suggest that line 5 of paragraph 2 be slightly modified so that (2) reads as follows enhance the possibility that addicted users will be able to quit, or will switch to other products which are possibly less harmful	
Reviewer #4	13	2	FDA proposes to limit nicotine levels in 'all forms of combustible tobacco', as I understand it, not just cigarettes and cigars. Given this, the detailed description of the harms of cigars alone seems unbalanced. Suggest it be condensed, and some information on, or at least more detailed reference to, non-cigarette combustible products.	
Reviewer #4	13	2/3 and 4	Extensive discussion of cigars, in light of the many non-cigarette combustible products available, distracts from the flow of the document. Should be shortened, and at least passing reference made to other non-cigarette combustible products.	

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"				
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**	**RESPONSE**
Reviewer #4	17	1/5	Eliminate part of the sentence that begins with "potentially easier…. Rewrite this section to read, "potentially easier for smokers to make more successful quit attempts. Studies on the effects of reduced nicotine tobacco products on relapse have not been done. However, it is plausible that, under such a standard when more attractive and addictive nicotine products are not available, that relapse rates would also be impacted favorably". The next sentence would begin, "Former smokers who chose…:	
Reviewer #4	18	4/6	Replace "would" with "may well"	
Reviewer #4	24	2/all	In discussing Hatsukami et al. (2018), reports a significantly lower completion rate for immediate reduction than gradual reduction and control conditions. Concludes that immediate reduction is associated with positive outcomes (e. g, less toxicant exposure, less nicotine dependence, increased abstinence). Fails to discuss the possible effects of differential drop-out on the dependent variables or offer evidence that differential drop-out did not influence the outcome.	
Reviewer #4	24	2/7	Completion rates in the immediate reduction group were markedly lower than in the gradual reduction group. The report does not indicate whether these differences were statistically significant, nor does it discuss the possibility that they should be considered in interpreting differences between the two conditions. If neither of these concerns affects the results and the conclusions that can be drawn from them, there should be a statement to that effect.	

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"				
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**	**RESPONSE**
Reviewer #4	35	1/7	Insert the following paragraph after the sentence ending…and those uninterested in quitting. "of those studies addressing VLNC and abstinence, few meet most of the criteria that define major clinical trials that have abstinence as an endpoint, and results are sometimes inconsistent, especially with respect to long-term follow-up. Often, abstinence is assessed as a secondary endpoint in a study addressing another issue, and subsequently there is no control condition. Nevertheless, the preponderance of the evidence suggests that, when taken together, results from these studies…..	
Reviewer #4	35	2/1-6	At the end of the paragraph, insert "it should be noted that although significant differences were found at week 6, differences did not reach traditional levels of significance at weeks 1, 7 and 8'.	
Reviewer #4	35	3/9	After the sentence ending, "promoting continuous abstinence than VLNC cigarettes alone, insert, "However, as the authors note, abstinence at 3- and 6-month follow-up) could not adequately assessed due to attrition at those time points".	
Reviewer #4	35	3/16	After the sentence ending, ….received usual care (15%)", Insert, "Abstinence rates were based on self-report alone; further, the study lacked a placebo or other control for VLNC. Thus, abstinence rates may have been inflated, and it is unclear whether the results reported were biased due to the effects of receiving an novel intervention ".	
Reviewer #4	36	2/13	Remove sentence beginning with "Although 7%.... Insert sentence " Quit rates were low in both groups and did not reach traditional levels of statistical significance at any point up to 24 months.	
Reviewer #4	45	1/13-16	In discussing the results of several studies, reports somewhat contradictory ratings on items designed to measure subjective effects of VLNC without any attempt to integrate or explain the contradiction (e. g. VLNC both rated lower on aversiveness and sickness and higher on dislike and unpleasant.	

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"				
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**	**RESPONSE**
Reviewer #4	60	2/2	Consider updating data on use rates of e-cigarettes in high school students if they have changed substantially since the report was written.	
Reviewer #4	65	3/to end of page	Consider eliminating or summarizing	
Reviewer #4	66	3/to end of page	eliminate	
Reviewer #4	66	1&2/all	Consider eliminating or summarizing.	
Reviewer #4	67	Whole page	eliminate	
Reviewer #5	7	Paragraph 2	"In 2014, the Surgeon General estimated that, unless the current trajectory is changed dramatically, 5.6 million youth aged 0 to 17 years alive today will die prematurely from a smoking-related disease." This quote feels slightly outdated given the significant decline in middle and high school student smoking over the past 5 years. I recognize this is probably the most recent data available but perhaps somehow acknowledging that declines in smoking are occurring but a nicotine reduction policy could further render cigarettes unappealing to adolescents. Perhaps there are also differences in adolescent smoking by priority populations (e.g., LGBTQ+, those with mental health conditions) that could be included in this section and how a nicotine reduction policy could help reduce smoking in these populations. It feels a little disingenuous to reference an adolescent smoking epidemic that has changed substantially since this publication. Also, consider Wang et al., 2019 which reports that cigar use is the second most popular tobacco product, ahead of cigarettes, among high school students. This highlights the need for the product standard to apply to all combusted products and not just cigarettes.	
Reviewer #5	8	Line 8	The legal age to purchase tobacco is now 21	
Reviewer #5	10	Paragraph 2	Consider adding the 2020 Surgeon General's Report on Cessation	
Reviewer #5	10	Paragraph 3	First sentence consider dropping the 'escape and'; redundant with 'to avoid nicotine withdrawal.	

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"				
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**	**RESPONSE**
Reviewer #5	10	Paragraph 3	Minor comment: throughout the document your citation manager seems to include J.E. initials for Rose et al., 2004; 2006; 2010 citations. This occurs for a few repeated citations.	
Reviewer #5	17	Paragraph 1	"Smokers would be unable to obtain enough nicotine from cigarettes to sustain addiction no matter how they smoked them and eventually would stop trying to do so." I don't understand why the proceeding references were included to support that statement (vs other nicotine reduction references that were excluded). The majority of smokers using VLNC cigarettes for extended periods, including these citations, continue to smoke cigarettes.	
Reviewer #5	19	Paragraph 1	The rationale for references included vs excluded is not clear to me. Are the Benowitz et al., 2012; 2007 and Hatsukami et al., 2010 not included within the scope of the review and are instead background information?	
Reviewer #5	19	Paragraph 1	"FDA hypothesizes that a tobacco product standard limiting the nicotine level in combusted tobacco products could significantly increase the number of successful quit attempts by the majority of smokers seeking to quit smoking every year and potentially prevent experimenters from developing addiction to combusted cigarettes and becoming regular smokers." The hypothesis that the majority of smokers would be successful at quitting must be based on the Apelberg at al., 2018 *NEJM* policy simulation. If so, I would acknowledge the policy simulation data as the foundation. To my knowledge, most clinical trials have enrolled non-treatment-seeking smokers that continue to smoke so the cessation outcomes are potentially underestimated.	
Reviewer #5	23	Paragraph 2	Donny et al., 2015 *NEJM* reported increases in spontaneous quit attempts during the 30-day follow-up period for those in the VLNC conditions relative to NNC condition. This information is on page 15 of the online supplemental materials associated with the manuscript.	

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"				
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**	**RESPONSE**
Reviewer #5	24	Paragraph 2	Hatsukami et al., 2018 *JAMA* reported abstinence and cigarette-free days during the trial. This information is on page 13 of the second online supplemental materials associated with the manuscript.	
Reviewer #5	26	Paragraph 4	Consider adding one sentence about the commercial availability of Quest brand cigarettes.	
Reviewer #5	28	Paragraph 4	The Philip Morris citation does not include a date or any other identifiable information.	
Reviewer #5	29	Paragraph 4	Delete this last sentence about patents for genes since this information is also included on page 31, paragraph 2.	
Reviewer #5	31	Paragraph 2	Move the first and last sentences of Paragraph 2 to the previous paragraph and then focus only on 22nd Century products in Paragraph 2.	
Reviewer #5	31	Paragraph 3	This paragraph explains the differences between nicotine 'yield' vs 'content'. It would be better located much earlier in this section so unfamiliar readers can follow along with the different terms describing the different VLNC products.	
Reviewer #5	34	Paragraph 1	The quote from Benowitz & Henningfield 1994 includes "provide enough nicotine for taste and sensory stimulation." Is this something the FDA must consider with respect to nicotine reduction? If not, I would exclude this part of the quote. Studies indicated lower subjective ratings after smoking VLNCs.	

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"				
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**	**RESPONSE**
Reviewer #5	35	Paragraph 1	Additional studies of smokers not interested in quitting that report quit attempts or abstinence at the end of the trial: Donny et al., 2015 *NEJM* reported increases in spontaneous quit attempts during the 30-day follow-up period for those in the VLNC condition relative to NNC condition. This information is on page 15 of the online supplemental materials associated with the manuscript. Hatsukami et al., 2018 *JAMA* reported abstinence and cigarette-free days during the trial. This information is on page 13 of the second online supplemental materials associated with the manuscript. Smith et al., 2019a is a trial of VLNC+patch that included a 7-day abstinence assessment after 6-weeks of VLNC exposure. Denlinger-Apte et al,. 2019c is a secondary analysis of Hatsukami et al., 2018 - reported odds of Week 20 abstinence in the immediate reduction condition by menthol smoking status. n.	
Reviewer #5	35	Paragraph 1	The last sentence of the paragraph needs a citation (possibly Hatsukami, Heertsgard et al., 2013).	
Reviewer #5	35	Paragraph 3	Smith et al., 2019a is a trial of VLNC+patch that included a 7-day abstinence assessment after 6-weeks of VLNC exposure. The study did not report significant differences for VLNC+patch vs VLNC alone.	
Reviewer #5	36	Paragraph 2	Donny et al., 2015 *NEJM* reported increases in spontaneous quit attempts during the 30-day follow-up period for those in the VLNC condition relative to NNC condition. This information is on page 15 of the online supplemental materials associated with the manuscript.	
Reviewer #5	37	Paragraph 1	Tidey et al., 2019 is a VLNC trial among smokers with serious mental illness. It could be included in this section and/or the vulnerable populations section.	

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"				
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**	**RESPONSE**
Reviewer #5	37	Paragraph 1	The last sentence of the paragraph should cite Hatsukami et al., 2018 not 2015.	
Reviewer #5	37	Paragraph 2	Donny et al., 2015 *NEJM* reported increases in spontaneous quit attempts during the 30-day follow-up period for those in the VLNC condition relative to NNC condition. This information is on page 15 of the online supplemental materials associated with the manuscript.	
Reviewer #5	37	Paragraph 3	Cite the studies that did not account for non-study CPD.	
Reviewer #5	38	Paragraph 2	Add Smith et al., 2020a - In-patient study examining VLNC compensation.	
Reviewer #5	39	Paragraph 1	Denlinger-Apte et al., 2019d is a secondary analysis of Tidey et al., 2019 reporting VLNC smoking topography in smokers with serious mental illness. It could be included in this section and/or the vulnerable populations section.	
Reviewer #5	40	Paragraph 2	Cassidy et al., 2019a is a secondary analysis of Cassidy et al., 2018 *DAD* that reports Cigarette Purchase Task data among adolescent daily smokers. It could be included in this section and/or the vulnerable populations section.	
Reviewer #5	41		Since this section is about choice you might consider adding another paragraph about the Hatsukami et al., 2016 exploratory trial. Smokers could buy VLNC or alternative products.	
Reviewer #5	42	Paragraph 1	Hatsukami et al., 2018 *JAMA* reported significant reductions in CO between the immediate vs gradual and immediate vs control.	
Reviewer #5	42	Paragraph 1	Add CO outcomes for following studies: Smith et al., 2019a Smith et al., 2020a	
Reviewer #5	43	Paragraph 1	Add TNE outcomes for the following studies: Hatsukami et al., 2018 *JAMA* Denlinger, Smith et al., 2016 *Tob Reg Sci* Smith et al., 2019a Smith et al., 2020a	

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"				
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**	**RESPONSE**
Reviewer #5	43	Paragraph 2	Hatsukami et al., 2018 *JAMA* reported NNAL, 3-HPMA, and CEMA and many other biomarkers of exposure.	
Reviewer #5	44	Paragraph 4	Cassidy et al., 2018 *DAD* reported VLNC subjective effects. It could be included in this section and/or the vulnerable populations section.	
Reviewer #5	45	Paragraph 1	Higgins et al., 2017 *JAMA Psychiatry* reported VLNC subjective effects.	
Reviewer #5	45	Paragraph 3	Cassidy et al., 2019b is an age moderation manuscript of Donny et al., 2015 *NEJM*; reported VLNC subjective effects. It could be included in this section and/or the vulnerable populations section. Smith et al., 2019b is a secondary analysis of Hatsukami et al., 2018 *JAMA* that reports VLNC subjective effects. Tidey et al 2019 reports VLNC subjective effects. It could be included in this section and/or the vulnerable populations section.	
Reviewer #5	46	Paragraph 2	Streck et al., 2019 secondary analysis of Higgins et al., 2017 *JAMA Psychiatry*; gender moderation of VLNC subjective effects	
Reviewer #5	47	Paragraph 2	Hatsukami et al., 2018 *JAMA* reports FTCD and WISMD scores with reductions in immediate vs gradual and immediate vs control. No differences in gradual vs control. Tidey et al., 2019 reports FTCD scores but not significant differences between VLNC and NNC conditions.	
Reviewer #5	49	Paragraph 2	Hatsukami et al., 2018 *JAMA* reports MNWS and QSU scores	
Reviewer #5	49	Paragraph 4	Smith et al., 2019a reports MNWS and QSU outcomes	

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"				
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**	**RESPONSE**
Reviewer #5	52	Paragraph 2	Ribisl et al., 2019 reports strategies to mitigate illicit NNC market if a low nicotine product standard is implemented. It could be an informative addition to this section. Hall et al., 2019 reports interest is purchasing illicit cigarettes after a VLNC product standard. It could be an informative addition to this section.	
Reviewer #5	53	Paragraph 2	The last sentence of the paragraph about NTR needs a citation.	
Reviewer #5	54	Paragraph 3	Add Smith et al., 2019a - did not report differences in compliance based on NTR use.	
Reviewer #5	55	Paragraph 2	Citations for compensation are incomplete. Donny et al., 2015 *NEJM* - reductions in CPD, no differences in CO, reductions in total puff volume. Hatsukami et al., 2018 *JAMA* - reductions CPD and CO New citations to include: Denlinger-Apte et al., 2019d is a secondary analysis of Tidey et al., 2019 reporting VLNC smoking topography in smokers with serious mental illness. It could be included in this section and/or the vulnerable populations section. Smith et al., 2020b - Solanesol paper. Secondary analysis from Donny et al 2015 *NEJM*. CDC examined cigarette butt filters for solanesol to assess compensation. No evidence of increased compensation in VLNC groups.	
Reviewer #5	56	Paragraph 3	Denlinger-Apte et al,. 2019b is a secondary analysis of Cassidy et al., 2018 *DAD* that reports the Perceived Health Risk Scale by menthol smoking status. It could be included here and/or on pages 78-79 that report other risk perception studies.	
Reviewer #5	58	Paragraph 2	Add Tidey et al., 2019	
Reviewer #5	58	Paragraph 2	Tidey et al., 2019 reports MNWS, Craving and CES	

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"				
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**	**RESPONSE**
Reviewer #5	59	Paragraph 1	Denlinger-Apte et al., 2019d is a secondary analysis of Tidey et al., 2019 reporting VLNC smoking topography in smokers with serious mental illness.	
Reviewer #5	59	Paragraph 1	Other manuscripts to consider including as vulnerable populations: Dermody et al., 2016 *ACER*; Secondary analysis of Donny et al., 2015 *NEJM* examining alcohol outcomes. Pacek et al., 2016 *DAD*; Secondary analysis of Donny et al., 2015 *NEJM* examining cannabis use.	
Reviewer #5	60	Paragraph 1	This section should be revised to reflect the most recent data from December 2019. E-cigarettes and cigars were more commonly used than cigarettes among high school students. Update citation to Wang et al., 2019 *MMWR*	
Reviewer #5	60	Paragraph 2	This section should be revised to reflect the most recent data from December 2019. E-cigarettes and cigars were more commonly used than cigarettes among high school students. Update citation to Wang et al., 2019 *MMWR*	
Reviewer #5	61	Paragraphs 1-2	Update use percentages and citation to Wang et al., 2019 *MMWR*	
Reviewer #5	78	Paragraph 1	Add Byron et al., 2018 and Byron et al., 2019	
Reviewer #5	80	Paragraph 2	Add Denlinger-Apte et al,. 2019b which is a secondary analysis of Cassidy et al., 2018 *DAD.* Reports the Perceived Health Risk Scale by menthol smoking status.	
Reviewer #5	81	Paragraph 4	Add Denlinger-Apte et al., 2019a is a secondary analysis of Donny et al., 2015 *NEJM.* Reports support for a nicotine reduction policy did not different by treatment condition after 6-weeks.	
Reviewer #5	86	Paragraph 1	Poster abstracts were ineligible for review. On page 80, Joel, Hatsukami, Hertsgaard, Dermody & Donny, 2014 was referenced. It says the results were only published in abstract form so I'm not sure if this would be ineligible for inclusion.	

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"				
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**	**RESPONSE**
Reviewer #5	106	Paragraph 2	Arger et al., 2017 is only referenced in Table A.2: Reduced Nicotine Content Cigarettes. The findings are not reported anywhere in the review text.	
Reviewer #5	113	Paragraph 4	Perkins et al., 2018 - effects by menthol smoking status - Were these findings reported anywhere in the review?	
Reviewer #5	127	Paragraph 3	Dermody et al., 2018 - secondary analysis of Donny et al., 2015 *NEJM*. Should this be added to the withdrawal and craving section?	
Reviewer #5	129	Paragraph 3	Robinson et al., 2017 - secondary analysis of Donny et al., 2015 *NEJM.* Should this be added to sections about mental health or subjective effects?	
Reviewer #6	7-9		Pp. 7-8 present the arguments for why nicotine reduction would be beneficial for youth. The arguments are laid out and then a conclusion is made, "For these reasons, FDA is considering mitigating the addictiveness of combusted tobacco products by setting a product standard…" (middle of p. 9). Yet the next paragraph lists another reason for the standard "because age restrictions on the sale of tobacco products by themselves are not entirely effective"), and the end of this paragraph has another conclusion ("FDA is considering taking this additional step to ensure that even if youth do obtain access to cigarettes, they will be less likely to: (1) become addicted to these products; (2) progress to regular use; and (3) increase their risk of the many diseases caused by combusted tobacco product use (Grucza et al., 2013)."). It might be better to move the paragraph about ineffectiveness of age restrictions one paragraph up, and then have a single conclusion to the argument for the effects on youth.	

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"				
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**	**RESPONSE**
Reviewer #6	10	Line 4	Can add more recent citation to "In high-income countries, about 7 of 10 adult smokers say they regret initiating smoking and would like to stop (Prabhat & Chaloupka, 1999)": Nayak P, Pechacek TF, Slovic P, Eriksen MP. Regretting ever starting to smoke: results from a 2014 national survey. International journal of environmental research and public health. 2017 Apr;14(4):390. (Data from 2014 showing that among US smokers, 71.5% regretted starting smoking).	
Reviewer #6	11		Section **B. (Negative Health Effects of Combusted Tobacco Product Use)** starts with describing the effects of nicotine in facilitating addiction. This is not what I expected to see first in a section titled "**B. Negative Health Effects of Combusted Tobacco Product Use".** Given that there is a section on p. 14 titled "**C. Nicotine in Combusted Tobacco Products and Its Influence on Addiction"** it would be more appropriate to place the information on nicotine there.	

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"				
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**	**RESPONSE**
Reviewer #6	12		The two first paragraphs on p. 12 talk about deaths from three leading smoking-related causes, but the same information is repeated twice. It would be better to combine them to streamline. For example, instead of starting with the generic "Cigarettes are responsible for hundreds of thousands of premature deaths every year from many diseases" and then in the second paragraph explain the total death toll and the top three diseases, just start: "Cigarettes are responsible for at least 480,000 premature deaths each year (U.S. Department of Health and Human Services, 2014 at p.659)." Then continue with describing the specific causes and numbers (the rest of the first paragraph and a weave in the mention of the top three diseases ("The three leading causes of smoking-attributable death for current and former smokers were lung cancer, heart disease, and COPD" but make sure it is in line with the numbers ("163,700 deaths from cancer, 160,600 deaths from cardiovascular and metabolic diseases, and 131,100 deaths from pulmonary diseases" – are these all cancer deaths or just lung cancer?). Finish the paragraph with "163,700 deaths from cancer, 160,600 deaths from cardiovascular and metabolic diseases, and 131,100 deaths from pulmonary diseases".	
Reviewer #6	12	Paragraph 2	The sentence about other combusted products seem out of place ("However, this estimate does not include deaths caused by other combusted forms of tobacco…"). I would recommend moving it to the first full paragraph on p. 13.	

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"				
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**	**RESPONSE**
Reviewer #6	12	Bottom of page	Another example of sentences mixed into wrong paragraphs: paragraph on the bottom of p. 12 starts with the effects of secondhand smoke, but then jumps to the Surgeon General's Report that talks about general effects of smoking. It would be better to reorganize the paragraphs that are currently suffering from these issues (pretty much all paragraphs on p. 12) so each one only deals with a single topic: first one with the harms of smoking; second with the harms of secondhand smoke. If you want to close on the impressive note from the SG's report, put it in the separate paragraph that would be the conclusion to this section.	
Reviewer #6	13	First full paragraph	Recommend starting the first full paragraph on p. 13 with describing what "other combusted tobacco products" are (just briefly mention that they are "cigars, cigarillos, pipes, roll your own tobacco," etc.) This paragraph (on other combusted tobacco products) only focuses on cigars. It would be better to also briefly describe the evidence on the health effects of other combusted tobacco products, particularly cigarillos and roll your own tobacco. To make space for that, the research on cigars that is currently presented in a lot of detail, can be shortened and summarized.	
Reviewer #6	14		The section "**C. Nicotine in Combusted Tobacco Products and Its Influence on Addiction"** should start with describing the nicotine effects (2 last paragraphs from p. 11 mentioned earlier). It would also be helpful to then include the argument that these effects are the same for the other combusted tobacco products.	
Reviewer #6	14	Last paragraph	"meaning that they have tried smoking at least one puff of a cigarette (but smoked no more than 25 cigarettes in their lifetime)" – the parentheses should be removed since the second part is an integral part of the definition of the "early experimenters".	

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"				
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**	**RESPONSE**
Reviewer #6	14	Last paragraph	"The Centers for Disease Control and Prevention (CDC) and other researchers have estimated that 30 percent or more of experimenters become established smokers (Centers for Disease Control and Prevention, 1998; Choi, Pierce, Gilpin, Farkas, & Berry, 1997; Mowery et al., 2004)." – is it 30% of "early experimenters"? It would be good to keep the language consistent. If the "early experimenters" and "experimenters" are not the same, then need to define both.	
Reviewer #6	16	Second paragraph	The way the research is summarized in some sections makes it a bit hard for the reader to draw a single conclusion. For example, 2nd paragraph on p. 16 talks about success of quit attempts. It goes through the list of studies showing their results, but it does not synthesize the findings. This laundry list is confusing because it reports data not in chronological order and in different formats, for example: Babb et al.: 2015 data - 55.4% of smokers tried to quit - 7.4% of former smokers recently quit Fiore et al.: 2005 data - 19 million smokers tried to quit - 4-7% successfully quit IOM: 2004 data - -40.5% of smokers tried to quit - 3-5% were successful It would be better to summarize these data: "each year, about 40-55% of adults smokers try to quit, but only 3-7% succeed." (Then you can present the results of individual studies in chronological order brought to the common denominator – percent instead of numbers of smokers).	
Reviewer #6	16	Second paragraph	"Approximately 40.5 percent" – this number is pretty precise, so would recommend dropping "approximately".	

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"				
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**	**RESPONSE**
Reviewer #6	16	Last paragraph	The definition of relapse is a bit unclear: "Relapse refers to the point after an attempt to stop smoking when tobacco use becomes ongoing and persistent" – I think the part about restarting smoking is missing.	
Reviewer #6	17		Section "**c. Impact of a Nicotine Product Standard on Combusted Product Users"** does not mention youth (preventing progression to regular use). There might not be direct empirical evidence on that, but it is reasonable to hypothesize based on the evidence listed earlier on the progression to regular smoking among youth.	
Reviewer #6	19-20		Section **A. Maximum Nicotine Level** nicely describes the history on reduced nicotine products and what is possible technically. But it seems like this section should actually list the final target (in mg?) and succinctly describe the reason for it.	
Reviewer #6	20	Bottom of page	Cigarillos are not listed along other products when the "other combusted tobacco products" are introduced (here and in other places) (although they are discussed in specific studies).	
Reviewer #6	22		So, does gradual reduction lead to compensatory smoking or not? This section states both: "neither gradual nor immediate reduction of nicotine in cigarettes leads to compensatory smoking after individuals switch to VLNC cigarettes […]. Limited evidence also suggests that gradual reduction may lead to compensatory smoking during the intermediate steps of a gradual reduction approach when participants are smoking products with low to moderate nicotine content."	

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"				
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**	**RESPONSE**
Reviewer #6	23-24		"Studies have also shown that gradually reducing the nicotine content of cigarettes is associated with high levels of noncompliance when participants reach the VLNC cigarette phase of the intervention" (p. 23) – but noncompliance was lower under immediate reduction? This does not seem to be the case: "much like the gradual reduction studies, a secondary analysis showed that noncompliance was high in participants randomized to the VLNC cigarette group (Nardone et al., 2016)." (p. 23) and also "The immediate reduction group had higher rates of noncompliance with non-study cigarette use" (p. 24).	
Reviewer #6	25-26		Section "D. Analytical Testing Method" starts with describing the criteria FDA is considering for the analytical testing method for the nicotine content in combusted tobacco. Then, it lists several methods, but there is no conclusion. Also, the first two methods are described in great detail, the third briefly, and then a bunch are just mentioned. (And it is unclear if "CORESTA Method No. 62" is the same as one of the previous two CORESTA methods). What should the reader take away from this section? It needs to be clearly stated at the end if the FDA is still choosing the method or if one should be selected.	
Reviewer #6	27	Last paragraph	"manufacturers could replace more commonly used nicotine-rich varieties like *Nicotiana rustica* with lower nicotine varieties (Tengs, Ahmad, Savage, Moore, & Gage, 2005)" - would be helpful to provide an example of the variety with lower nicotine.	
Reviewer #6	27	Last paragraph	"Oriental Turkish-type cigarettes also deliver substantially less nicotine than cigarettes that contain air-cured Burley tobacco (Shelar, Bernasek, & Furin, 1992; Wayne & Carpenter, 2009)" - is it because they use different variety of nicotine or because they are cured differently? (If the former, how is it different from a previous sentence? If it's the curing process, then it would be helpful to be more specific about that.)	

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"				
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**	**RESPONSE**
Reviewer #6	30	Third paragraph	It was very interesting to learn about the effects of caterpillars on nicotine level, but it was not clear to me what happens to nicotine (I imagined that harvested leaves are treated with the salivatory extracts.) It might be worth slightly changing the explanation to mention "growing tobacco leaves" or something like that (as opposed to harvested leaves).	
Reviewer #6	33	Last paragraph	First paragraph in section "a. History of the Estimation of an Addiction Threshold" starts by talking about "chippers", but then does not mention how specifically studying this group led to the estimation of the threshold level of nicotine. I expected some sort of argument that because chippers smoked a certain number of cigarettes and were not dependent, this translates to xxx.	
Reviewer #6	51	First full paragraph	An introduction to section "C. Unintended Consequences" lists some unintended consequences (continued use of combusted VLNC products, switch or co-use of noncombustible products), but the subsequent sections detail completely other consequences (illicit products, noncompliance). It would be good to bring the introduction in line with the rest of the section. Related to the previous point, I am not sure that continued use of VLNC products or switch/dual use with noncombusted tobacco products are unintended consequences – complete switch to noncombusted tobacco products might be a benefit. Also, on p. 64 it is listed as an expected outcome: "It is FDA's expectation that once a nicotine product standard for combusted tobacco products is in place, a significant portion of combusted tobacco product smokers would choose to switch completely to a potentially less harmful nicotine delivery product (e.g., ENDS) (National Academies of Sciences, 2018) to maintain their nicotine dose."	

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"				
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**	**RESPONSE**
Reviewer #6	53	First full paragraph	"alternative combusted nicotine-containing products if a nicotine standard were implemented (e.g., full nicotine little cigars or cigarettes available through illicit trade, legally marketed non-combusted tobacco products)" (p. 53) - the first part of the sentence talks about "combusted" products, but the example in parentheses includes "non-combusted".	
Reviewer #6	59		Section "ii. Individuals with Symptoms of Mental Health and Substance Use Disorders" discusses lots of different effects and outcomes for VLNC cigarettes in populations with mental health symptoms, but concludes with a summary of only one effect: "In sum, results of studies reviewed in this document provide little to no evidence that VLNC cigarettes increase risk of adverse effects (e.g., exacerbations of psychiatric symptomatology) in smokers with symptoms of mental health disorders." (p. 59). It would be better to also summarize the rest of the section here.	
Reviewer #6	60	Top of the page	"Cigarette smoking prevalence rates among adults have also declined in recent years (from 20.9% in 2005 to 15.1% in 2015); however, in 2015 there were increased smoking prevalence rates among males, young adults,…" - does "increased" implies that the rates increased from 2005 to 2015 among males and young adults? Or that the smoking rates were higher among "males, young adults, …"?	

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"				
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**	**RESPONSE**
Reviewer #6	59-62		It would be helpful to make reporting in different sections under "A. Who Uses Combusted Tobacco Products?" more parallel. For example, the beginning of these sections currently flips the order of presentation for middle and high school students, the section on cigars lists other products, waterpipe section starts with the international use and adults, etc. Using the same structure for each section (middle and high school youth, followed by adults, followed by disparities in use) would make it easier. (If you want to keep some extraneous information, such as the information about different tobacco product use in the cigar section: "Among high school students, the most commonly used forms of tobacco other than cigarettes are e-cigarettes (11.7%), cigars (7.7%), smokeless tobacco (5.5%), hookah (3.3%), pipe tobacco (0.8%), and bidis (0.7%)(T. W. Wang et al., 2018)" reword it so the focus is on cigars: "Among high school students, cigars were as popular as cigarettes (7.7% vs. 7.6%) and second only to e-cigarettes (11.7%).")	
Reviewer #6	61		Is "Loose tobacco" roll-your-own and pipe tobacco? Would be helpful to specify from the outset.	
Reviewer #6	82		The conclusion to section VII that starts with "All together, these studies indicate that there is strong and consistent evidence to suggest that a substantial proportion of American adults falsely believe …" summarizes the findings in different order than the previous sections, and it would be better to start with the summary of the perceptions of nicotine followed by the perceptions of reduced nicotine cigarettes. (In addition, it is likely that the perceptions of nicotine drive perceptions of reduced nicotine cigarettes and not vice versa, so that order is justified for that reason as well.)	

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"				
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**	**RESPONSE**
Reviewer #6	82		What is "substantial proportion"? The conclusions paragraph to section VII uses this phrase to describe the proportion of American adults who a) falsely believe that nicotine is the main cause of harm from tobacco, b) falsely believe that reduced nicotine cigarettes are less harmful, and c) accurately believe that reduced nicotine cigarettes are less addictive. However, the proportions for these three beliefs are very different with a lot more people supporting a and b and fewer supporting c. It might be helpful to changes this to "majority" and "substantial minority" or something like that.	
Reviewer #6	82		"Regarding the belief held by some Americans that reduced nicotine cigarettes are less addictive, whether they held this belief seems to depend on the nicotine content of the cigarette." (p. 82) - this sentence is not very clear. Did it depend on the level of nicotine about which they were asked or on the level of nicotine in the cigarette they tried, as in some in-person studies?	
Reviewer #6	82	Second to last paragraph	"To ensure a positive net impact on population health, it will be important to ensure that consumers understand that nicotine is not a carcinogen nor a primary cause of smoking-related disease." - Rather than emphasizing this understanding, I think it is more important to directly address its derivative – the belief that VLNC cigarettes are less harmful, so I would emphasize this (or make sure it is mentioned in addition to the need to change perceptions of nicotine).	
Reviewer #6	208		Some of the references need to be updated, for example, Hatsukami et al., 2016 should be 2017 and include the journal volume and page numbers (Hatsukami, D. K., Luo, X., Dick, L., Kangkum, M., Allen, S. S., Murphy, S. E., ... & al'Absi, M. (2017). Reduced nicotine content cigarettes and use of alternative nicotine products: exploratory trial. *Addiction*, *112*(1), 156-167.)	

II. Specific Observations on "The Science of a Nicotine Standard for Combusted Tobacco Products"				
REVIEWER	**Page**	**Paragraph/ Line**	**Comment**	**RESPONSE**
Reviewer #6	212-213		Some references are listed twice, for example: Mercincavage, M., Saddleson, M. L., Gup, E., Halstead, A., Mays, D., & Strasser, A. A. (2017a). Reduced nicotine content cigarette advertising: How false beliefs and subjective ratings affect smoking behavior. *Drug and Alcohol Dependence, 173*, 99-106. doi:10.1016/j.drugalcdep.2016.12.022 Mercincavage, M., Saddleson, M. L., Gup, E., Halstead, A., Mays, D., & Strasser, A. A. (2017b). Reduced nicotine content cigarette advertising: How false beliefs and subjective ratings affect smoking behavior. *Drug Alcohol Depend, 173*, 99-106. Perkins, K. A., Karelitz, J. L., & Kunkle, N. (2017a). Sex differences in subjective responses to moderate versus very low nicotine content cigarettes. *Nicotine & Tobacco Research*. Perkins, K. A., Karelitz, J. L., & Kunkle, N. (2017b). Sex differences in subjective responses to moderate versus very low nicotine content cigarettes. *Nicotine Tob Res*. doi:10.1093/ntr/ntx205	