

CHARGE QUESTION 4. Are you aware of additional publicly available information which should have been included? If so, please specify.		
REVIEWER	COMMENT	RESPONSE
	<p>clinical trial. <i>Cancer, Epidemiology, Biomarkers & Prevention</i>, 29(4), 880-886. doi: 10.1158/1055-9965.EPI-19-0963</p> <p>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. <i>Cancer, Epidemiology, Biomarkers & Prevention</i>, 29(3), 643-649. doi: 10.1158/1055-9965.EPI-19-0905</p> <p>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. <i>Nicotine & Tobacco Research</i>, 21(Suppl_1), S38-S45. doi: 10.1093/ntr/ntz133.</p>	
Reviewer #6	<p>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.</p>	<p>In 2021 and 2022, we updated the Reproducible Transparent Document (RTD) Review of the Extant Social Science Literature Relevant to Low Nicotine and Very Low Nicotine Tobacco Products (Appendix B). This RTD updates the text found in Section VII; however, the conclusions remain the same.</p>
Reviewer #6	<p>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.</p>	<p>These studies were added to Section VII. (The Impact Perceptions Around Nicotine and Reduced Nicotine May</p>

CHARGE QUESTION 5. Provide any additional comments including limitations and outcomes not discussed, or editorial suggestions not addressed in the previous questions.		
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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 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.	This was addressed in response to an above comment. The following text has been added to Section II.A. (Purpose): "Decreasing the nicotine in cigarettes so that they are minimally addictive (using the best available science to determine a level that is appropriate for the protection of the public health) could help users restore some autonomy and quit if they want to-as the large majority of users say they do" (Centers for Disease Control and Prevention, 2011).
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?	These questions/comments are outside the scope of this scientific document. The nicotine standard ANPRM, published March 16, 2018, requested public comment on similar

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		issues, including technical feasibility and costs to tobacco farmers and processors.
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.	<p>We disagree on the lack of data in nondaily/light smokers and point the reviewer to several examples of studies investigating the effects of VLNC cigarettes in adolescent and adult nondaily smokers. Each of these studies are included in the report.</p> <p>Shiffman, S., Kurland, B. F., Scholl, S. M., & Mao, J. M. (2018). Nondaily Smokers' Changes in Cigarette Consumption With Very Low-Nicotine-Content Cigarettes: A Randomized Double-blind Clinical Trial. <i>JAMA psychiatry</i>. 75(10), 995-1002.</p> <p>Shiffman, S., Mao, J. M., Kurland, B. F., & Scholl, S. M. (2018). Do non-</p>

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		<p>daily smokers compensate for reduced cigarette consumption when smoking very-low-nicotine-content cigarettes? Psychopharmacology (Berl), 235(12), 3435-3441.</p> <p>Shiffman, S., Scholl, S. M., & Mao, J. M. (2019). Very-low-nicotine-content cigarettes and dependence among non-daily smokers. Drug Alcohol Depend, 197, 1-7.</p> <p>Kassel, J. D., Greenstein, J. E., Evatt, D. P., Wardle, M. C., Yates, M. C., Veilleux, J. C., & Eissenberg, T. (2007). Smoking topography in response to denicotinized and high-yield nicotine cigarettes in adolescent smokers. J Adolesc Health, 40(1), 54-60.</p>

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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?	Enforcement of a potential nicotine standard is outside the scope of this scientific document; however, we note several studies evaluating the potential effects of a nicotine standard in vulnerable populations. Across populations, there was little evidence of adverse effects (Section IV.C.c.). It is also important to clarify that FDA's enforcement of any nicotine standard for combusted tobacco products will only address manufacturers, distributors, wholesalers, importers, and retailers. The FDA cannot and will not enforce against individual consumer possession or use of tobacco products violating this standard.
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	In response to this comment, we added an

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		a nicotine product standard improves population health while still emphasizing the harms associated with using combustible cigarettes.
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.	An in-depth discussion of non-combusted tobacco products (including heated tobacco products) was outside the scope of this document, as we chose to limit the RTD search to combusted tobacco products only. Section V.C. (Potential for Non-Cigarette Combusted Tobacco Product Switching) briefly discusses non-combusted tobacco product switching, without referencing specific products or product categories.

IV. Specific Observations				
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.	We added this study to Section IV.B.b.iv. (Choice).
Reviewer #2	8		<p>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."</p> <p>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>	In response to this comment, we have updated the text on the legal age of cigarette purchasing. We agree with the reviewer on the importance of discussion on youth and dependence; however, we do not feel that additional discussion is necessary in this section as it is covered in more depth in Section II.C.a. (Youth Cigarette Smoking Initiation and Dependence).
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).	We edited these citations for accuracy.
Reviewer #3			None provided.	We appreciate the reviewer's support of the review.

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
Reviewer #4	5	1/9	Insert comment that producing lowered nicotine content in VLNC is technically achievable.	We added this addition to Section I. (Executive Summary).
Reviewer #4	5	1/14	Insert 'possibly' before 'increased quit rates among current smokers'.	The smoking cessation conclusions were modified slightly during revisions to the document to increase accuracy. The statement now reads: FDA concludes that extended exposure to combusted cigarettes containing very low nicotine content [VLNC] tobacco filler is associated with ... increased quit attempts among current smokers. As such, this comment is not longer relevant.
Reviewer #4	5	1/16	Omit 'also' in the sentence beginning "There is also	We made this edit to the document.
Reviewer #4	5	1/21-22	The phrase 'substantial portion' is used twice in the same sentence. The sentence should be rewritten.	We made this edit to the document.
Reviewer #4	6	1/7	After line 7, insert comment that FDA proposes to limit nicotine content in non-cigarette products.	We made this edit to the document.

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
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.	In response to this comment, we added text to Section V.C. (Potential for Non-Cigarette Combusted Tobacco Product Switching) to clarify that individuals who switch to non-combusted tobacco products (such as ENDS) may still sustain their nicotine dependence and that dependence on any tobacco product remains a health concern. However, complete switching would significantly reduce their risk of tobacco-related death and disease to the extent that the products they switch to result in less harm.
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	We edited this sentence to state "...give addicted users of combusted tobacco products the

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			addicted users will be able to quit, or will switch to other products which are possibly less harmful	choice and increase the likelihood that they may quit or switch to potentially less harmful tobacco products by reducing the nicotine to a minimally addictive level.”
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.	In response to this comment, we streamlined Section II.B. (Negative Health Effects of Combusted Tobacco Use) to more appropriately balance information on the health effects of all combusted tobacco 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.	In response to this comment, we streamlined Section II.B. (Negative Health Effects of Combusted Tobacco Use) to more appropriately balance information on the health effects of all combusted tobacco products.

IV. Specific Observations				
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...:	We made this edit to the document.
Reviewer #4	18	4/6	Replace “would” with “may well”	We made this edit to the document.
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.	In response to this comment, we added the following text: “The immediate reduction group had higher rates of noncompliance with non-study cigarette use and a higher drop-out rate, which may have impacted the various outcome measures (e.g., biomarkers of exposure). ”
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	The following was added to the text: “The immediate reduction group had

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			results and the conclusions that can be drawn from them, there should be a statement to that effect.	higher rates of noncompliance with non-study cigarette use and a higher drop-out rate, which may have impacted the various outcome measures (e.g., biomarkers of exposure). "
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.....	In response to reviewer comments, Section IV.B.b.i. (Smoking Cessation) was rewritten to address the limitations noted.
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'.	In response to reviewer comments, Section IV.B.b.i. (Smoking Cessation) was rewritten to address the limitations noted.

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
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”.	In response to reviewer comments, Section IV.B.b.i. (Smoking Cessation) was rewritten to address the limitations noted.
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 ”.	In response to reviewer comments, Section IV.B.b.i. (Smoking Cessation) was rewritten to address the limitations noted.
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.	In response to reviewer comments, Section IV.B.b.i. (Smoking Cessation) was rewritten to address the limitations noted.

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
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.	In response to this comment, we added the following text to Section IV.B.c.i. (Drug Liking and Other Subjective Effects): “These seemingly contradictory findings (e.g., lower liking and lower aversiveness) contribute to the understanding that positive and negative subjective effect subscales capture different aspects of reinforcing efficacy and abuse liability and these two subscales may independently predict preference for VLNC versus NNC cigarettes (Arger et al., 2017; D. K. Hatsukami, S. J. Heishman, et al., 2013).”

IV. Specific Observations				
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.	We updated the document to include the most recent use data.
Reviewer #4	65	3/to end of page	Consider eliminating or summarizing	As noted in our response above, we chose to retain these sections as they provide additional data that may be used as an indicator of potential product switching with a nicotine product standard.
Reviewer #4	66	3/to end of page	eliminate	As noted above, we chose to retain these sections as they provide additional data that may be used as an indicator of potential product switching with a nicotine product standard.
Reviewer #4	66	1&2/all	Consider eliminating or summarizing.	As noted above, we chose to retain these sections as they provide additional data that may be used as an indicator

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
				of potential product switching with a nicotine product standard.
Reviewer #4	67	Whole page	eliminate	As noted above, we chose to retain these sections as they provide additional data that may be used as an indicator of potential product switching with a nicotine product standard.
Reviewer #5	7	Paragraph 2	<p>“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</p>	In response to this comment, we edited this statement using updated projections of premature deaths from smoking that account for decreased smoking initiation rates, increasing cessation, and better screening for and treatment of smoking-related diseases (Warner, 2020).

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			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	We made this edit to the document.
Reviewer #5	10	Paragraph 2	Consider adding the 2020 Surgeon General's Report on Cessation	We added this report to the document.
Reviewer #5	10	Paragraph 3	First sentence consider dropping the 'escape and'; redundant with 'to avoid nicotine withdrawal.	We removed "escape and" from this sentence.
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.	We edited the document to remove initials from these 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.	Evidence suggests that dependence on cigarettes declines after smokers switch to VLNC cigarettes, and these cigarettes increase successful cessation attempts; however, many smokers who switch to VLNC cigarettes continue to smoke for various reasons, including continued access to NNC cigarettes. Therefore, we have included an additional reference

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
				<p>(the nicotine reduction policy simulation by Apelberg et al. (2018)) and revised the text to state:</p> <p>“Smokers would be unable to obtain enough nicotine from cigarettes to sustain addiction no matter how they smoked them (Benowitz et al., 2007; D. K. Hatsukami, L. A. Hertsgaard, et al., 2013; Hatsukami et al., 2010), making it potentially easier for smokers to make more successful quit attempts (Apelberg et al., 2018; Donny et al., 2015; Hatsukami et al., 2018).</p>
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?	We rewrote this sentence, and all references were removed from the executive summary

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
				to increase consistency.
Reviewer #5	19	Paragraph 1	<p>“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.”</p> <p>The hypothesis that the majority of smokers would be successful at quitting must be based on the Apelberg et al., 2018 <i>NEJM</i> 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.</p>	In response to this comment, we removed the phrase “by the majority” in order to more accurately represent the conclusions of the document.
Reviewer #5	23	Paragraph 2	Donny et al., 2015 <i>NEJM</i> 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.	This information was included in Section IV.B.b.i. (Smoking Cessation).
Reviewer #5	24	Paragraph 2	Hatsukami et al., 2018 <i>JAMA</i> 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.	This information was included in Section IV.B.b.i. (Smoking Cessation).
Reviewer #5	26	Paragraph 4	Consider adding one sentence about the commercial availability of Quest brand cigarettes.	We made this edit to the document.
Reviewer #5	28	Paragraph 4	The Philip Morris citation does not include a date or any other identifiable information.	We added additional clarifying information for this citation.

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
Reviewer #5	29	Paragraph 4	Delete this last sentence about patents for genes since this information is also included on page 31, paragraph 2.	We retained this sentence as it is applicable to both sections.
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.	We edited this paragraph to increase readability, but this editorial recommendation was not made.
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.	This comment is no longer applicable as this section was rewritten to focus on nicotine content rather than yield.
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.	We edited the document to remove this phrase.

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
Reviewer #5	35	Paragraph 1	<p>Additional studies of smokers not interested in quitting that report quit attempts or abstinence at the end of the trial:</p> <p>Donny et al., 2015 <i>NEJM</i> 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.</p> <p>Hatsukami et al., 2018 <i>JAMA</i> 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.</p> <p>Smith et al., 2019a is a trial of VLNC+patch that included a 7-day abstinence assessment after 6-weeks of VLNC exposure.</p> <p>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.</p>	We added these studies to Section IV.B.b.i. (Smoking Cessation).
Reviewer #5	35	Paragraph 1	The last sentence of the paragraph needs a citation (possibly Hatsukami, Heertsgard et al., 2013).	The paragraph in question has been rewritten and now includes several citations and descriptions of the studies therein.
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.	We added this study to Section IV.B.b.i. (Smoking Cessation).

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
Reviewer #5	36	Paragraph 2	Donny et al., 2015 <i>NEJM</i> 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.	We added this information to Section IV.B.b.i. (Smoking Cessation).
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.	We added this study to Section IV.C.c. (Impact on Vulnerable Populations).
Reviewer #5	37	Paragraph 1	The last sentence of the paragraph should cite Hatsukami et al., 2018 not 2015.	We made this edit to the document.
Reviewer #5	37	Paragraph 2	Donny et al., 2015 <i>NEJM</i> 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.	We added this information to Section IV.B.b.i. (Smoking Cessation).
Reviewer #5	37	Paragraph 3	Cite the studies that did not account for non-study CPD.	The majority of studies did not assess non-study CPD; therefore, we note in this paragraph in Section IV.B.b.ii. (Cigarettes Per Day) that the majority of studies did not account for use of non-study cigarettes, and we discuss the findings of those studies that did account for use of non-study cigarettes.

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
Reviewer #5	38	Paragraph 2	Add Smith et al., 2020a - In-patient study examining VLNC compensation.	We added this study to an earlier paragraph in this section, where it is appropriate to the narrative.
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.	We added this study throughout the document.
Reviewer #5	40	Paragraph 2	Cassidy et al., 2019a is a secondary analysis of Cassidy et al., 2018 <i>DAD</i> that reports Cigarette Purchase Task data among adolescent daily smokers. It could be included in this section and/or the vulnerable populations section.	We added this study to Section IV.C.c. (Impact on Vulnerable Populations).
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.	This study was discussed in depth in Section V.C.b. (Tobacco Product Switching in Clinical Studies).
Reviewer #5	42	Paragraph 1	Hatsukami et al., 2018 <i>JAMA</i> reported significant reductions in CO between the immediate vs gradual and immediate vs control.	We added this study to Section IV.B.b.v. (Biomarkers of Exposure).
Reviewer #5	42	Paragraph 1	Add CO outcomes for following studies: Smith et al., 2019a Smith et al., 2020a	We added these studies to Section IV.B.b.v. (Biomarkers of Exposure).

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
Reviewer #5	43	Paragraph 1	Add TNE outcomes for the following studies: Hatsukami et al., 2018 <i>JAMA</i> Denlinger, Smith et al., 2016 <i>Tob Reg Sci</i> Smith et al., 2019a Smith et al., 2020a	We added these studies to Section IV.B.b.v. (Biomarkers of Exposure).
Reviewer #5	43	Paragraph 2	Hatsukami et al., 2018 <i>JAMA</i> reported NNAL, 3-HPMA, and CEMA and many other biomarkers of exposure.	We added additional BOE assessed in this study to Section IV.B.b.v. (Biomarkers of Exposure).
Reviewer #5	44	Paragraph 4	Cassidy et al., 2018 <i>DAD</i> reported VLNC subjective effects. It could be included in this section and/or the vulnerable populations section.	We added this study throughout the document, where appropriate
Reviewer #5	45	Paragraph 1	Higgins et al., 2017 <i>JAMA Psychiatry</i> reported VLNC subjective effects.	We added this study throughout the document, where appropriate
Reviewer #5	45	Paragraph 3	Cassidy et al., 2019b is an age moderation manuscript of Donny et al., 2015 <i>NEJM</i> ; 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 <i>JAMA</i> 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.	We added these studies throughout the document, where appropriate

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
Reviewer #5	46	Paragraph 2	Streck et al., 2019 secondary analysis of Higgins et al., 2017 <i>JAMA Psychiatry</i> ; gender moderation of VLNC subjective effects	We added this study to Section IV.B.c.i. (Drug Liking and Other Subjective Effects).
Reviewer #5	47	Paragraph 2	Hatsukami et al., 2018 <i>JAMA</i> 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.	We added these studies to Section IV.B.c.ii. (Dependence).
Reviewer #5	49	Paragraph 2	Hatsukami et al., 2018 <i>JAMA</i> reports MNWS and QSU scores	We added this study to Section IV.B.c.iii. (Relief from Withdrawal Symptoms).
Reviewer #5	49	Paragraph 4	Smith et al., 2019a reports MNWS and QSU outcomes	We added this study to Section IV.B.b.i. (Smoking Cessation).
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.	We added these studies to Section IV.C.c. (Illicit Tobacco Products).
Reviewer #5	53	Paragraph 2	The last sentence of the paragraph about NTR needs a citation.	This is a summary paragraph. All citations appear later in this section.

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
Reviewer #5	54	Paragraph 3	Add Smith et al., 2019a - did not report differences in compliance based on NTR use.	We added this study to Section V.C.a. (Noncompliance).
Reviewer #5	55	Paragraph 2	<p>Citations for compensation are incomplete. Donny et al., 2015 <i>NEJM</i> - reductions in CPD, no differences in CO, reductions in total puff volume. Hatsukami et al., 2018 <i>JAMA</i> - reductions CPD and CO</p> <p>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.</p> <p>Smith et al., 2020b - Solanesol paper. Secondary analysis from Donny et al 2015 <i>NEJM</i>. CDC examined cigarette butt filters for solanesol to assess compensation. No evidence of increased compensation in VLNC groups.</p>	We added data from each of these studies to Section IV.C.a (Compensatory Smoking).
Reviewer #5	56	Paragraph 3	Denlinger-Apte et al., 2019b is a secondary analysis of Cassidy et al., 2018 <i>DAD</i> 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.	We added this study throughout the document, where appropriate.
Reviewer #5	58	Paragraph 2	Add Tidey et al., 2019	We added this study throughout the document, where appropriate.
Reviewer #5	58	Paragraph 2	Tidey et al., 2019 reports MNWS, Craving and CES	We added this study throughout the document, where appropriate.

IV. Specific Observations				
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.	We added this study throughout the document, where appropriate.
Reviewer #5	59	Paragraph 1	Other manuscripts to consider including as vulnerable populations: Dermody et al., 2016 <i>ACER</i> ; Secondary analysis of Donny et al., 2015 <i>NEJM</i> examining alcohol outcomes. Pacek et al., 2016 <i>DAD</i> ; Secondary analysis of Donny et al., 2015 <i>NEJM</i> examining cannabis use.	We added each of these studies to Section IV.C.c.ii. (Individuals with Symptoms of Mental Health and Substance Use Disorders).
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 <i>MMWR</i>	We updated the document to include the most recent use data.
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 <i>MMWR</i>	We updated the document to include the most recent use data.
Reviewer #5	61	Paragraphs 1-2	Update use percentages and citation to Wang et al., 2019 <i>MMWR</i>	We updated the document to include the most recent use data.

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
Reviewer #5	78	Paragraph 1	Add Byron et al., 2018 and Byron et al., 2019	We added these studies to Section VII.B.a (Perceived Relative Harm of Reduced Nicotine Cigarettes) and VII.B.b (Studies Examining Advertising and Messaging Interventions to Correct Misperceptions of Reduced Nicotine Content Cigarettes)
Reviewer #5	80	Paragraph 2	Add Denlinger-Apte et al., 2019b which is a secondary analysis of Cassidy et al., 2018 <i>DAD</i> . Reports the Perceived Health Risk Scale by menthol smoking status.	We added this study to Section VII.B.b. (Studies Employing the Use of Study Cigarettes).
Reviewer #5	81	Paragraph 4	Add Denlinger-Apte et al., 2019a is a secondary analysis of Donny et al., 2015 <i>NEJM</i> . Reports support for a nicotine reduction policy did not differ by treatment condition after 6-weeks.	We added this study throughout the document, where appropriate.
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.	Appendix A and Appendix B represent separate literature searches with slightly different exclusion criteria. Poster abstracts were

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
				ineligible for review for the literature search described in Appendix A. However, the abstract in question was a conference abstract printed in a peer-reviewed journal; therefore, it meets the inclusion criteria for the literature search described in Appendix B.
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.	We added this study to Section IV.B.c.i. (Drug Liking and Other Subjective Effects).
Reviewer #5	113	Paragraph 4	Perkins et al., 2018 - effects by menthol smoking status - Were these findings reported anywhere in the review?	We added this study to Section IV.B.c.i. (Drug Liking and Other Subjective Effects).
Reviewer #5	127	Paragraph 3	Dermody et al., 2018 - secondary analysis of Donny et al., 2015 <i>NEJM</i> . Should this be added to the withdrawal and craving section?	We added this study to Section IV.B.c.iii. (Relief from Withdrawal Symptoms).

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
Reviewer #5	129	Paragraph 3	Robinson et al., 2017 - secondary analysis of Donny et al., 2015 <i>NEJM</i> . Should this be added to sections about mental health or subjective effects?	We added this study to Section IV.C.c.ii. (Individuals with Symptoms of Mental Health and Substance Use Disorders).
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 (Gruza 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.	In response to this comment, we reorganized these paragraphs to increase readability.
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).	The data included in this section reflect the most current published statistics on this specific topic.
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	In response to this comment, we reorganized these sections and moved

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			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.	the discussion on nicotine to Section II.C. (Nicotine in Combusted Tobacco Products and Its Influence on Addiction).
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”.	In response to this comment, we reorganized these paragraphs to streamline and increase readability.

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
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.	We edited and streamlined this section, and as it currently reads, this sentence is appropriate for the paragraph in which it was originally included.
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.	We edited this section of the document to increase readability. The paragraphs on nicotine were moved to Section II.C. (Nicotine in Combusted Tobacco Products and Its Influence on Addiction), each paragraph now discusses one topic, the paragraph on secondhand smoke was moved to the bottom of this section, and it now ends with the quote from the SG report.

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
Reviewer #6	13	First full paragraph	<p>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.)</p> <p>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.</p>	We made these edits to the document.
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.	We reorganized section to start with a description of the addictive effects of nicotine and included a paragraph noting that these effects are the same for 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”.	We removed the parentheses, and this clause has been integrated into this sentence.
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	These definitions are slightly different. In response to this comment, we added additional

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			consistent. If the “early experimenters” and “experimenters” are not the same, then need to define both.	clarification to define the terms.
Reviewer #6	16	Second paragraph	<p>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:</p> <p>Babb et al.: 2015 data - 55.4% of smokers tried to quit - 7.4% of former smokers recently quit</p> <p>Fiore et al.: 2005 data - 19 million smokers tried to quit - 4-7% successfully quit</p> <p>IOM: 2004 data - -40.5% of smokers tried to quit - 3-5% were successful</p> <p>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).</p>	We revised the text in this paragraph to improve readability.
Reviewer #6	16	Second paragraph	“Approximately 40.5 percent” – this number is pretty precise, so would recommend dropping “approximately”.	We removed the word “approximately” from this sentence.
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.	<p>We added the following text:</p> <p>“Relapse refers to the point after an attempt to stop</p>

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
				smoking when tobacco use <i>begins again</i> and becomes ongoing and persistent (U.S. Department of Health and Human Services, 2010 citing Brandon et al., 1986).”
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.	The impact of a nicotine product standard on youth is discussed in Sections II.C.a. (Youth Cigarette Smoking Initiation and Dependence) and II.C.b. (Adults and Youth Cigarette Smoking Cessation and Relapse).
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.	In response to this comment, we added a conclusion paragraph to this section that describes the rationale for our recommended nicotine level.

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
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).	We added “Little cigars” and “Cigarillos” throughout the document, where appropriate.
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.”	We added text to explain that compensation occurs during the intermediate steps of gradual nicotine reduction, but it does not persist after participants switch to VLNC cigarettes.
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).	The text has been modified in line with this feedback to note it is the VLNC cigarettes, and not the gradual reduction procedure, that engenders participant noncompliance: “Studies have also shown high levels of noncompliance when participants reach

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
				the VLNC cigarette phase of interventions that gradually reduce the nicotine content of cigarettes (e.g., Benowitz, Nardone, Hatsukami, & Donny, 2015; Hammond & O'Connor, 2014)."
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.	We added text to this section to clarify that either international standard test methods or equivalent test methods may be used to analyze nicotine levels.
Reviewer #6	27	Last paragraph	"manufacturers could replace more commonly used nicotine-rich varieties like <i>Nicotiana rustica</i> with lower nicotine varieties (Tengs, Ahmad, Savage, Moore, & Gage, 2005)" - would be helpful to provide an example of the variety with lower nicotine.	We added clarification to this sentence.
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.)	We clarified in the document that the combination of different tobacco varieties, curing processes, and leaf position all contribute to the

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
				level of nicotine present.
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).	We added additional information to this paragraph to explain this process.
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.	In response to this comment, we added more detail this section to explain how data from chippers was used to estimate a nicotine threshold.
Reviewer #6	51	First full paragraph	<p>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.</p> <p>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.”</p>	We edited the introduction to make it consistent with the unintended consequences noted later in this section. This included removing the text on dual-use and switching from this section.

IV. Specific Observations				
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”.	We removed the word “combusted” from this portion of the sentence.
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.	We updated the summary to expand upon conclusions for additional outcomes.
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, ...”?	We revised this sentence to increase clarity.
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	We reorganized this section to improve parallel construction of the sub-sections.

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			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.	We added more detail on loose tobacco to this section.
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.)	In response to this comment, we reorganized this paragraph.
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.	In response to this comment, we reviewed and updated the conclusions paragraphs in Section VII and Appendix B, as well as the executive summary in Appendix B.

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
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?	We rewrote this paragraph to clarify the outcomes related to beliefs about nicotine.
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).	We added additional text on messaging around VLNC cigarette risks to this paragraph.
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. <i>Addiction</i> , 112(1), 156-167.)	We updated this reference throughout.
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. <i>Drug and Alcohol Dependence</i> , 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. <i>Drug Alcohol Depend</i> , 173, 99-106.	We removed duplicate references from the document.

IV. Specific Observations				
REVIEWER	Page	Paragraph/ Line	Comment	RESPONSE
			<p>Perkins, K. A., Karelitz, J. L., & Kunkle, N. (2017a). Sex differences in subjective responses to moderate versus very low nicotine content cigarettes. <i>Nicotine & Tobacco Research</i>.</p> <p>Perkins, K. A., Karelitz, J. L., & Kunkle, N. (2017b). Sex differences in subjective responses to moderate versus very low nicotine content cigarettes. <i>Nicotine Tob Res</i>. doi:10.1093/ntr/ntx205</p>	