

Tobacco Product Standard for N-Nitrosornicotine Level in Finished Smokeless Tobacco Products

Comment on proposed rule by Clive Bates and David Swenor

8 July 2017

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Summary

Request. We respectfully suggest that the proposed rule is withdrawn as soon as possible after the closure of the comment process. Instead of pursuing damaging interventions on the lowest-risk tobacco products, FDA should redeploy its resources to encourage and facilitate smokers to switch to low-risk alternatives to cigarettes such as smokeless tobacco, heated tobacco products and vapor technologies.

The reasoning underpinning our suggestion is in four parts:

1. **Overstates benefits.** The benefits of the rule are overstated because the risk, and hence risk reduction, are overstated. This arises as a result of inappropriate pooling of relative risk estimates for different types of smokeless tobacco, some of which are more harmful but rarely used.
2. **Understates disruption.** The FDA analysis is based on a *completely unrealistic* excessively optimistic assessment of the achievability of the standard for the products that dominate the US market. The analysis assumes unrealistically high compliance at baseline, though this conflicts with *measurement* data presented in the draft rule. The disruption of the smokeless market will therefore be much greater than FDA claims. That will make compliance more expensive, cause exit of firms and products, and affect the character of products with which smokeless tobacco users are familiar.
3. **Ignores unintended consequences.** If consumers' familiar products change in character, availability or price as a result of supply-chain disruption, it is not safe to assume that they will simply use these or other compliant smokeless products. The analysis is *extremely sensitive to any additional smoking* among the behavioral responses of smokeless tobacco users to supply chain disruption.
4. **Fails tests for public health and good regulation.** The proposed rule does not conform to the main principles of good regulation for federal agencies, and FDA has not shown that its rule would meet the public health test required for standard-setting under the Tobacco Control Act s907.

These four themes are elaborated in the four sections that follow.

1 Overstating the benefits by exaggerating the risks of smokeless tobacco use

1.1 Summary

The proposed rule significantly overstates the benefits of the standard because of the way it has characterized risks of oral cancer. The only persuasive evidence for a material risk from smokeless tobacco use is highly concentrated in a tiny niche of users: women using powdered dry snuff. The high risk associated with this product has been included in an average relative risk and used without justification to characterize risk for *all* smokeless tobaccos and *all* consumers, male and female.

1.2 The difference between studies of men and women

FDA bases its relative risk estimates¹ on two main studies, Boffetta *et al* (2008)² and Lee and Hamling (2009)³. The first source of error lies in the interpretation of Boffetta *et al* in the proposed rule. In this study, and several others, high relative risks found in dry powdered snuff, typically used by small numbers of women have been pooled with low or no significant risks found in the products typically used by men. In doing so, the authors created an average risk for all smokeless tobacco products and all users. However, US smokeless tobacco use is dominated by men and moist snuff. This approach was inappropriately adopted in Table 3 of Boffetta *et al*, in which a combined male-female relative risk, heavily weighted by *female* dry snuff use is applied to the *male* smokeless tobacco using population. An earlier study had identified dramatically different risks in the risks faced by moist snuff and dry snuff users, the latter being mainly women⁴.

The use of moist snuff and chewing tobacco imposes minimal risks for cancers of the oral cavity and other upper respiratory sites, with relative risks ranging from 0.6 to 1.7. The use of dry snuff imposes higher risks, ranging from 4 to 13.

1.3 Later studies properly conducted show no significant risks

FDA relies on Lee and Hamling (2009) for its relative risk estimate for oral cancer of 2.16. But this reveals the second serious source of error – reliance on old or improperly conducted studies. FDA has apparently overlooked an important conclusion drawn by Lee and Hamling:

The overall data for oropharyngeal cancer shows a significant increase in risk associated with ST use, but this is not evident for estimates adjusted for smoking and alcohol, or for studies published since 1990 (emphasis added)

¹ 82 FR 8012 [\[link\]](#)

² Boffetta P, Hecht S, Gray N, Gupta P, Straif K, Lim S. Smokeless tobacco and cancer. *Lancet Oncol*. IARC, Lyon; 2008 Jul 1;9(7):667–75. [\[link\]](#) Reference 100 in the proposed rule.

³ Lee PN, Hamling J. Systematic review of the relation between smokeless tobacco and cancer in Europe and North America. *BMC Med. BioMed Central*; 2009 Dec 29;7(1):36. [\[link\]](#) Reference 114 in the proposed rule.

⁴ Rodu B, Cole P. Smokeless tobacco use and cancer of the upper respiratory tract. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. : US Department of Health and Human Services, Washington, DC; 2002 May 1;93(5):511–5. [\[link\]](#)

It is quite likely that any NNN-related risk in smokeless tobacco use would change over time, through increased awareness of hazardous constituents, improvements in production techniques and changing patterns of product use. If analysis of this nature is going to be used to estimate benefits such as avoided cancers in the population, then it is essential to recognize that the products are *not homogenous* and *not constant* over time. If a pooled relative risk estimate is to be used to estimate benefits, it should at least be sales-weighted to reflect the actual consumption and aggregate risk.

1.4 Conclusion

There is no point in criticizing the rest of the calculations on the benefits side of the case for this rule because they are built on a meaningless assessment of risk. FDA should not proceed any further based on this analysis of benefits. It is far from clear there would be any benefits worthy of quantification.

2 Understating the difficulty of achieving the standard for most products and so ignoring the likely resulting supply chain disruption

2.1 Summary

The 1 µg/g standard is set towards the *market extremity*, not at a median or a level sufficient to remove outliers, which is a more responsible place to start with an untried standard. However, FDA's analysis assumes much higher rates of compliance or near compliances than actual measurements suggest. FDA does not, therefore, adequately characterize the potential disruption to the established smokeless tobacco supply chain that compliance with this rule would cause. The proposed rule fails to make a convincing assessment of the *achievability* of the NNN standard for the great majority of the products on the U.S. market, most of which are non-compliant by a factor of three or more.

2.2 Understating disruption by overstating the extent of baseline compliance

The analysis of the impact on the market or population should focus primarily on moist snuff, which accounts for 94% of the market and has an average NNN level of 3.01µg/g⁵. Thus the center of gravity of the market is *well outside* the area of compliance and 'nearly compliant', the term used in the Preliminary Regulatory Impact Analysis (PRIA)⁶ to refer to products with NNN levels of 1.0-2.0µg/g.

In the PRIA (Table 3), FDA gives estimates as follows:

- 30% of moist snuff products are already compliant (NNN ≤ 1.0µg/g)
- A further 59% moist snuff products that are 'nearly compliant' (NNN 1.0-2.0 µg/g)
- Only 12% that are 'not nearly compliant' (NNN > 2.0µg/g)

⁵ 82 FR 8014 Table 2 NNN Concentration and Market Share of Smokeless Tobacco Products Sold in the United State [\[link\]](#)

⁶ FDA. Tobacco Product Standard for N-Nitrosornicotine Level in Finished Smokeless Tobacco Products. Preliminary Regulatory Impact Analysis. January 2017. *Table 3.- Entities and Products Affected by the Proposed Rule* page 25 [\[link\]](#)

This paints a picture of a relatively effortless journey to market-wide compliance, on which the subsequent analysis of compliance costs is based. However, there are good reasons to believe these estimates are *completely unrealistic*.

- The estimates in Table 3, and used in FDA’s analysis, are based on 800 industry reports of harmful and potentially harmful constituents (HPHCs) provided under section 904 of the Tobacco Control Act. The reliability of these reports is open to doubt.
- These *reported* figures strongly conflict with the *measurement* data presented in Table 2 of the PRIA⁷. For moist snuff, the data given for an aggregation of nine measurement studies is a mean NNN level of 4.59µg/g and standard deviation of 2.01µg/g. To get a feel for how these measurements conflict with the assumptions used in FDA’s analysis, we assume the NNN measurements conformed to a normal distribution (mean=4.59, SD=2.01). Under this assumption, only 4% would be compliant ($\leq 1.0\mu\text{g/g}$) and only 6% would be nearly compliant 1.0-2.0µg/g – meaning 90% would be ‘not nearly compliant’. Nine-out-of-ten ‘not nearly compliant’ contrasts sharply with the one-in-eight (12%) FDA presents in Table 3 and uses for the analysis.
- The measured data presented in the PRIA Table 2 are also more consistent with FDA’s own study, Ammann *et al* (2015)⁸. In this measurement study, not one of the 18 moist snuff products surveyed is compliant and only one is ‘nearly compliant’. Using the assumptions FDA builds in to the analysis, Ammann *et al* might have expected to find five compliant products and eleven ‘nearly compliant’ and only two ‘not nearly compliant’ – rather than seventeen out of eighteen moist snuff products ‘not nearly compliant’ (i.e. $\geq 2.0\mu\text{g/g}$).
- It is difficult to know why there is such a sharp discrepancy between reported data and measured data. There remains justifiable concern that an elementary error in converting NNN concentration on a wet-weight basis to dry-weight basis made in the original proposed rule may have permeated parts of the analysis⁹. This error would have the effect of falsely lowering the NNN level when presented on a dry weight-basis, making compliance appear easier. FDA maintains the error was typographical and did not affect its analysis. However, it is impossible to verify that this is the case without more of the underlying data.

⁷ FDA. Tobacco Product Standard for N-Nitrosornicotine Level in Finished Smokeless Tobacco Products. Preliminary Regulatory Impact Analysis. January 2017. *Table 2.- NNN Levels in Marketed Smokeless Tobacco Products Drawn from a Convenience Sample* page 22 [\[link\]](#)

⁸ Ammann, J.R., K.S. Lovejoy, M.J. Walters, et al., “A Survey of N'-nitrosornicotine (NNN) and Total Water Content in Select Smokeless Tobacco Products Purchased in the United States in 2015,” *Journal of Agricultural and Food Chemistry*, 64(21):4400-4406, 2016 [\[link\]](#)

⁹ FDA statement: “The Agency also has received a request to clarify a formula in the Laboratory Information Bulletin (LIB) titled, “Determination of N-nitrosornicotine (NNN) in Smokeless Tobacco and Tobacco Filler by HPLC-MS/MS” (LIB No. 4620, January 2017). Upon further review, FDA has determined that the formula for converting NNN on a wet weight basis to a dry weight basis contains a typographical error—some of the terms and variables in the numerator and denominator were inadvertently switched. FDA has revised the LIB to correct this error (LIB No. 4623, March 2017, available at <https://www.fda.gov/downloads/ScienceResearch/FieldScience/UCM546874.pdf>). We note that the typographical error in the LIB did not affect our calculations in the preamble of the proposed rule or the supporting analyses”. [\[link\]](#)

- Another possible explanation is that these estimates do not appear to have been sales-weighted (they refer to number of products). So (likely) accurate reports of HPHCs from the largest companies with the highest-selling products and strongest incentives to comply may be ‘contaminated’ by poor reporting (i.e. underreporting of NNN) from niche companies, who may be more numerous but with a small share of the market and weaker incentives to comply.

The mismatch between measurement data and FDA’s analytical assumptions is very substantial. This is compounded by two further errors.

2.3 Disruption through the effect of changing products beyond recognition

FDA has simply assumed that products that are not nearly compliant (1 in 8 in FDA’s analysis, but more likely to be 9 in 10 in reality) will become compliant by ‘reformulation’ and a range of other measures that all contribute to reducing NNN¹⁰. It does not take into account how many of those measures have already been adopted in the industry in achieving reductions made so far. Neither does it show that these measures are sufficient to meet the standard (without changing the product beyond recognition).

The following statement in the proposed rule¹¹ betrays a simplistic appreciation of the diversity in the market and the difference between products, and hence the diversity of consumer preferences:

We note, however, that an NNN level of 1.0 µg/g of tobacco has been achieved in some smokeless tobacco products sold in the United States and is thus achievable using current technology.

So, it would be possible to change American moist smokeless tobacco to a product more like Swedish snus in order to become compliant. But then it becomes a very different product: like informing a wine lover that their preferred pinot will henceforth taste like beer. *The consumer response is unpredictable.*

2.4 Disruption through the exit of firms and withdrawal of products

FDA has not estimated the extent of the exit of firms or products from the market this rule will cause. It is quite possible that the costs and technical difficulty of complying – with the added risk that the reformulated product will no longer appeal to established customers – will drive smaller companies out of business or make more marginal products commercially unviable. In this event, users will find familiar products disappearing from the shelves. *The consumer response to this is unpredictable.*

2.5 Conclusion

FDA should base any rule making on measured and independently verified data about the extent and magnitude of baseline non-compliance. It should focus on what can be achieved with technically and economically feasible measures that retain the characterizing features of the product, otherwise it is implementing a *de facto* sub-category prohibition through rule-making. The Impact Analysis should assess the extent of supply chain disruption rather than just crudely approximating compliance costs.

¹⁰ 82 FR 2018 IV.E. Information on Technical Achievability [\[link\]](#) and FR 8013 IV.C.2 Factors that influence NNN levels [\[link\]](#)

¹¹ 82 FR 8014 D. Basis for the NNN Limit in the Proposed Standard [\[link\]](#)

3 Ignoring likely increased smoking arising from supply chain disruption

3.1 Summary

Disrupting the supply chain will have effects on tobacco-using behavior if it means that familiar American moist smokeless tobacco products are withdrawn from the market or their character changes significantly – perhaps to a taste or sensory experience that established users do not like. The behavioral response is unpredictable, but may include switching to or increasing smoking. It does not take much additional smoking to fully negate the case for the rule.

3.2 Ignoring likely harmful unintended consequences of supply chain disruption

FDA makes a heroic and wholly unjustified assumption that behavior will continue unaffected by the changes in the supply chain and benefits will arise from reduced NNN exposure to continuing smokeless users¹².

The analysis in section IV.C suggests that the estimated lifetime cancer risk (ELCR) would drop by approximately 65 percent under the scenario where the proposed product standard for smokeless tobacco products was fully implemented, and while assuming that all other variables remained constant (e.g., user habits). (emphasis added)

Why would user habits remain constant? This might be a valid assumption if compliance is not excessively expensive or disruptive, and does not significantly alter the character of the products. But as argued above, FDA appears to be greatly underplaying the degree of disruption that the proposed rule will cause.

3.3 Behavioral responses to supply chain disruption

The behavioral response to a supply chain disruption of the type likely to be caused by the proposed rule are difficult to predict, but could include several responses:

- switching to compliant smokeless products (a small to negligible reduction in risk),
- switching to non-compliant black market products (no reduction in risk)
- switching to smoking (very large increase in risk)
- migrating from dual use to a higher level of smoking (increase in risk)
- switching to vaping (little difference)
- quitting tobacco use (small to negligible reduction in risk)

The responses may evolve over time and may differ by age and demographic, and according to product substitutability. Though difficult to forecast with any confidence, these possible pathways are amenable

¹² 82 FR 8021 Estimated impact of proposed NNN standard on new and fatal cancers [\[link\]](#)

to 'break-even' sensitivity analysis of the form: "how many additional smokers caused by the rule would it take to negate the benefits of reduced NNN in smokeless tobacco?"

3.4 Rough break-even analysis - seven extra smokers per thousand smokeless users

It is possible to make a rough estimate for illustrative purposes. It is up to FDA to do such sensitivity testing to make its case that the proposed standard is appropriate for the protection of public health.

As FDA is drawing heavily on Lee and Hamling (2008), it could also draw on their estimate of the relative population impact of smokeless and smoking on the US population¹³:

Of 142,205 smoking-related male US cancer deaths in 2005, 104,737 are smoking-attributable. Smokeless tobacco-attributable deaths would be 1,102 (1.1%) if as many used smokeless tobacco as had smoked, and 2,081 (2.0%) if everyone used smokeless tobacco.

That estimate implies smoking is 95 times as lethal as smokeless use. Further, FDA asserts that the NNN rule would reduce cancer risk by 65%, not eliminate it¹⁴. So for every 1,000 smokeless users benefiting from the rule, it would require only seven (7) to switch to smoking to negate the value of the rule¹⁵. This is obviously a rough estimate, but serves to illustrate the sensitivity to smoking-related unintended consequences and the type of sensitivity analysis that FDA should do. This is without taking account of concern about exaggerating the risk and risk reduction (see [section 1](#) above). If the risk reduction is lower, then the sensitivity unintended consequences is greater.

3.5 Conclusion

FDA should base its analysis on a realistic assessment of supply chain disruption (see 2 above) and a realistic assessment of behavioral response, modelling scenarios that recognize the potential for harmful unintended consequences. The net value or costs of this rule is *extremely* sensitive to changes in smoking behavior triggered by unintended consequences of supply chain disruption.

¹³ Lee PN, Hamling J. Systematic review of the relation between smokeless tobacco and cancer in Europe and North America. *BMC Med. BioMed Central*; 2009 Dec 29;7(1):36. [\[link\]](#)

¹⁴ 82 FR 8017 IV.D.3. Conclusion [\[link\]](#)

¹⁵ If P_{SLT} is probability of smokeless-attributed death, n =breakeven number of extra smokers per thousand smokeless users, then: $1000 * 0.65 * P_{SLT} = n * 95 * P_{SLT}$ and so $n=7$

4 Poor regulatory practice and failure to meet the public health test

4.1 Summary

The argument laid out in this submission is that the benefits are exaggerated and the costs and risks have not been adequately assessed, in particular the sensitivity to unintended consequences. That means that it does not meet the standards required for federal agency regulation or to meet the public health test included in the Tobacco Control Act.

4.2 Inadequate economic and regulatory assessment

FDA's Preliminary Regulatory Impact Analysis is intricately detailed and highly precise, but wholly inaccurate. Without a realistic assessment of the disruption to the supply chain arising from the gulf between the extent and magnitude of baseline non-compliance and requirements of compliance with the standard, the PRIA simply does not do what it is there to do, assess the impacts of the rule. The proposed rule is not consistent with the regulatory principles set the Executive Orders governing Federal regulatory practice¹⁶, including the first three requirements:

(1) propose or adopt a regulation only upon a reasoned determination that its benefits justify its costs (recognizing that some benefits and costs are difficult to quantify);

The benefits of the proposed rule have been exaggerated and the costs and risks understated. The analysis does not address the danger of unintended consequences of disruption of the supply chain, including the sensitivity of the analysis to realistic behavioral responses including more smoking.

(2) tailor its regulations to impose the least burden on society, consistent with obtaining regulatory objectives, taking into account, among other things, and to the extent practicable, the costs of cumulative regulations;

The regulatory approach taken is reckless in establishing an aggressive but arbitrary standard which is very distant from the market norm. The supporting analysis of achievability amounts to only a list of measures and almost no analysis to show that the existing products on the market can be made to comply, other than through becoming unrecognisably different. The burdens to society arise from the costs and harms of the disruption to the established supply chain that such a rule would cause.

(3) select, in choosing among alternative regulatory approaches, those approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity);

Any approach to this issue needs to start with the risk of unintended consequences. The less burdensome route would have started with analysis of actual NNN levels and with the aim of validating the HPHC reporting (section 904 TCA). The next stage would be warning letters and threats to regulate¹⁷

¹⁶ 76 FR 3821 Executive Order 13563 of January 18, 2011 Improving Regulation and Regulatory Review [\[link\]](#) and 58 FR No. 190 Executive Order 12866 of September 30, 1993 Regulatory Planning and Review [\[link\]](#)

¹⁷ See for example, Tim Wu, Agency Threats, 60 DUKE L.J. 1841 (2011) [\[link\]](#)

if there were not improvements, especially in the outliers. The aim should be to find the technical and commercially practical technical frontier through voluntary action. In the process of this, FDA staff could have become more familiar with the technical challenges and constraints. In moving to a rule-based system, better practice would be to set the initial rule in such a way that it tackles outliers first and, if justified, tightens over time. Again, a graduated stepwise process would allow for learning and insight into potential unintended consequences. At each point, there has to be a recognition that even outliers in smokeless NNN levels are two orders of magnitude less risky than smoking and regulation can easily trigger adverse behavioural responses.

However, the greater issue is why FDA is spending its regulatory resources on products that are valuable low-risk alternatives to smoking, while doing nothing of substance about combustible tobacco products.

4.3 The failed public health test

The power to set standards is established in the Tobacco Control Act (TCA) Section 907¹⁸ (907a.3.A)

...the Secretary may adopt tobacco product standards [...] if the Secretary finds that a tobacco product standard is appropriate for the protection of the public health

The TCA elaborates that in making this determination the Secretary should consider risks and benefits to the whole population (Section 907a.3.B.i). The analysis provided in the proposed rule¹⁹ does not approach this test rigorously. Essentially, the analysis has been framed in way that can only show a public health benefit by ignoring the possibility of any adverse behavioural transitions and other unintended consequences, for example from smokeless use to smoking.

The ease with which the FDA concludes that its own rule meets this test sits in marked contrast to how it applies the same to test in the evaluation of Pre-Market Tobacco Product Applications (PMTAs) and Modified Risk Tobacco Product (MRTP) applications. In the case of the Swedish Match MRTP for snus, for example, FDA has taken every conceivable opportunity to find reasons of unintended consequences to deny the applicant the right to say something truthful and non-misleading about its products²⁰.

4.4 Conclusion

The proposed rule is poor quality and ill-conceived regulation which could have harmful economic and public health consequences. It should be withdrawn. The academic justifications for the rule do not address these issues²¹. FDA needs to rethink its regulatory strategy to prioritize interventions that will do most to reduce tobacco-related harms, primarily by addressing the risks of smoking.

¹⁸ FDA, Section 907 of the Federal Food, Drug, and Cosmetic Act - Tobacco Product Standards (2009) [\[link\]](#)

¹⁹ 82 FR 8020 V. Standard is appropriate for the protection of public health. [\[link\]](#)

²⁰ FDA Perspective: Lessons Learned from the First Review of Modified Risk Tobacco Product (MRTP) Applications, 16 December 2016 [\[link\]](#)

²¹ Berman ML, Hatsukami DK. Reducing tobacco-related harm: FDA's proposed product standard for smokeless tobacco. *Tob Control*. 2017 Jun 20;tobaccocontrol-2016-053612. [\[link\]](#)