Nicotine & Tobacco Research, 2019, S13–S15
doi:10.1093/ntr/ntz121
Supplement Article
Received May 13, 2019; Editorial Decision July 16, 2019; Accepted July 17, 2019

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Using Product Standards to Render the Most Harmful Tobacco Products Minimally Addictive: Maximum Nicotine Level, Non-Nicotine Constituents, and Scope

Cassidy M. White BA[1], Wallace B. Pickworth PhD[2], Alan F. Sved PhD[3], Eric C. Donny PhD[1]

[1]Department of Physiology and Pharmacology, Wake Forest School of Medicine, Winston-Salem, NC; [2]Center for Analytics and Public Health, Battelle Memorial Institute, Baltimore, MD; [3]Department of Neuroscience, University of Pittsburgh, Pittsburgh, PA

Corresponding Author: Eric C. Donny, PhD, Department of Physiology and Pharmacology, Wake Forest School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157, USA. Telephone: 336-713-1520; E-mail: edonny@wakehealth.edu

In the Advance Notice of Proposed Rulemaking issued in March 2018, the US Food and Drug Administration expressed interest in developing a tobacco product standard that would limit nicotine levels in cigarettes to make them minimally addictive.[1] This commentary highlights evidence relevant to the nicotine level that would most benefit public health, the scope of products to which maximum nicotine level product standard should apply, and whether other constituent standards are necessary to meaningfully minimize addictiveness.

What Maximum Nicotine Level Would be Best for Public Health?

The available evidence suggests that reducing nicotine content in cigarettes by at least 95% relative to typical commercially available cigarettes would produce the greatest benefit across the population of smokers. In a large clinical trial of daily smokers randomly assigned to investigational cigarettes with various nicotine levels, participants in the 2.4, 1.3, or 0.4 mg of nicotine per gram of tobacco conditions smoked fewer cigarettes after 6 weeks and reported less craving following abstinence than those randomized to normal nicotine content cigarettes (15.8 mg/g).[2] However, composite measures of nicotine dependence decreased only among those using cigarettes with 1.3 mg nicotine per gram of tobacco (one measure) and 0.4 mg nicotine per gram of tobacco (multiple measures). Furthermore, quit attempts during the follow-up period were significantly more likely to occur among only those using 0.4 mg per gram of tobacco cigarettes, which is consistent with other findings demonstrating that smokers who experience the largest reductions in nicotine exposure when assigned to reduced-nicotine cigarettes are those most likely to quit.[3–5] Studies assigning cigarettes with varied nicotine content to individuals vulnerable to tobacco addiction (such as those with opioid dependence, affective disorders, and socioeconomic disadvantages) also demonstrate a clear dose-dependent relationship between the magnitude of nicotine reduction and decreases in abuse liability.[6] In addition, although most smokers cannot discriminate between different doses of low-nicotine cigarettes, some can, and they indicate a preference for cigarettes with 2.4 mg nicotine per gram of tobacco over cigarettes with 0.4 mg.[6–8] This suggests even within the low end of the nicotine-dose range, reductions can further minimize abuse liability. Thus, a maximum nicotine level less than or equal to 0.4 mg nicotine per gram of tobacco may affect more smokers than even slightly higher levels. It is also important to caution that setting a maximum nicotine level too high could risk increased smoke exposure among some individuals. Compensatory smoking has been reported in smokers from multiple studies after extended use of cigarettes with only moderate reductions, such as a nicotine content of 5.2 mg per gram of tobacco.[3,9,10] Taken together, this evidence indicates a maximum nicotine level of 0.4 mg per gram of tobacco, which is technically feasible and the lowest dose tested in clinical trials to date, would most extensively benefit public health.

A maximum nicotine level should apply to the nicotine content per weight of tobacco intended for combustion and inhalation. Given the potential for some product wrappers to contribute significantly to nicotine delivery, a product standard applicable to both the tobacco filler and wrapper is necessary to ultimately limit nicotine exposure.[11] Product changes that could affect bioavailability or emissions should be monitored closely. Limiting emissions as a secondary standard may reduce the chance that product design changes could dramatically increase the nicotine yield of low-nicotine content cigarettes.[2]

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However, emissions standards should not supersede content standards since machine yields inaccurately reflect user exposure.[12]

Which Products Should Fall Within the Scope of a Maximum Nicotine Level Standard?

A maximum nicotine content product standard should apply to cigarettes and combusted substitutes for cigarettes. A good exemplar is little cigars. Although no studies have directly investigated nicotine reduction in little cigars, the design of little cigars is similar to cigarettes, so much so that some argue they meet the legal definition of cigarettes under the Tobacco Control Act.[13] For example, little cigars are about the same size as cigarettes (available in both 85 and 100 mm), sold in packages of 20 and filtered with the same cellulose-acetate material.[14] Studies indicate little cigars are smoked like cigarettes, as evaluated by puff volume, puff duration, number of puffs per article, and grams of tobacco burned.[15] Inhaling little cigar smoke increases plasma nicotine levels and exhaled carbon monoxide levels similarly to cigarette smoking.[15] The composition of mainstream little cigar smoke is qualitatively and quantitatively like that of cigarette smoke, thereby exposing consumers to known carcinogens and irritants.[16] Furthermore, recent sales data indicate little cigar use is rising, particularly in minority populations, as the price and regulation of cigarettes increases.[17,18] Sharing many characteristics with cigarettes while carrying the added appeal of flavor and affordability, little cigars would be an especially attractive and similarly harmful product for smokers looking to maintain their nicotine intake.[13] Therefore failing to include little cigars could greatly limit the public health impact of a nicotine product standard. The ideal product standard would also extend to roll-your-own tobacco and other products, such as cigarillos, which also function as ready substitutes for machine-made cigarettes. In contrast, cigarette-like nicotine delivery via appealing non-combusted sources, such as vaping devices, may be necessary to reduce illicit cigarette use and could play a key role in further diminishing tobacco-related harm.[19]

Are Other Maximum Constituent Standards Necessary to Achieve Minimal Addictiveness?

Analyses characterizing the properties of the SPECTRUM investigational cigarettes suggest they contain levels of most non-nicotine constituents similar to those of commercially available brands.[20] Therefore, data from clinical studies using these cigarettes already incorporate the impact of current levels of other constituents within the context of a reduced-nicotine cigarette. Furthermore, changes to commercial products resulting in significant differences in psychoactive constituents would render those products no longer substantially equivalent and require premarket approval under the Tobacco Control Act, which serves as an important barrier to product changes that could maintain the high abuse liability of cigarettes.[21]

Non-nicotine tobacco constituents are unlikely to have a significant impact if nicotine content is adequately reduced. There are thousands of chemicals in cigarette smoke, some of which could contribute to abuse liability. However, preclinical research investigating the relationship between non-nicotine constituents and abuse liability has yielded mixed results and highlight the primary importance of nicotine as a determinant of behavior. One study observed that a mixture of minor alkaloids, at cigarette-smoke-like concentrations, and nicotine produced a small increase in low-dose nicotine self-administration in adult male rats.[22] Other research has demonstrated that acetaldehyde, at a dose based on what might be present in cigarette smoke, mixed with nicotine increased nicotine self-administration in rats when tested during early adolescence, but not at older ages; slightly higher or lower doses had no effect.[23] A single study found that adult male rats self-administer norharmane at doses approximately 10-fold of those found in cigarette smoke and increased nicotine self-administration with norharmane present.[24] However, a more extensive study found that a mixture of minor alkaloids, acetaldehyde, harmane, and norharmane did not significantly alter nicotine self-administration, even when increasing the doses 10-fold from levels expected in cigarette smoke.[25] When comparing nicotine with aqueous cigarette smoke extract to nicotine alone, a study found that the aqueous smoke extract resulted in slightly higher self-administration in adult male rats, suggesting other chemicals in cigarette smoke may increase in the reinforcing properties of nicotine.[26] However, subsequent studies failed to provide support for this notion.[27]

Investigations of flavorants, such as menthol, suggest such additives can influence the appeal and abuse liability of tobacco products through multiple mechanisms. For example, flavors can mask initially aversive aspects of smoking and become reinforcing sensory cues over time.[28] Preclinical studies further suggest that menthol in particular may interact with nicotine to directly affect the central nervous system, by altering cholinergic neuron structure and function and/or nicotine pharmacokinetics.[28–30] These findings suggest that the effects of nicotine reduction could differ between menthol and non-menthol products; however, analyses of clinical trials to date suggest that both menthol and non-menthol smokers would likely benefit from nicotine reduction even when their reduced-nicotine cigarettes reflect their menthol preference (see Denlinger-Apte et al.[31]).

The ability of cigarette smoke to inhibit monoamine oxidase (MAO) might enhance the reinforcing properties of low-dose nicotine. Unfortunately, the chemicals responsible for this action have not been fully characterized. In animal studies, MAO-inhibition results in making previously subthreshold doses of nicotine reinforcing. Partially inhibiting MAO, to the extent seen in smokers, can also sufficiently increase self-administration of low doses of nicotine.[32] The potential for MAO-inhibiting effects of tobacco smoke to reduce the addictive threshold of nicotine supports developing a product standard that caps nicotine levels as low as possible. Furthermore, to ensure that increasing MAO-inhibition caused by cigarettes cannot be used to offset a lowered nicotine content, tobacco constituents that inhibit MAO could be identified, tracked, and potentially regulated. The level of MAO-inhibition induced by product use could be monitored and used to determine if products can stay on or enter the market.

Overall, there is no compelling evidence that non-nicotine constituents, at the levels present in tobacco smoke, are sufficient to sustain robust self-administration in animal models. Nevertheless, several studies indicate that other chemicals in cigarette smoke may modify the reinforcing actions of nicotine, suggesting that limiting nicotine to the lowest level possible and monitoring levels of other constituents would be prudent.

Conclusion

The current scientific literature offers many findings relevant to developing a nicotine content product standard that will maximize net benefits to the population. First, evidence suggests a maximum nicotine level, specifying nicotine content per weight of tobacco,

should be set equal to or less than 0.4 mg per gram to minimize addictiveness. Second, to adequately minimize harm, this standard should apply to cigarettes and other combusted tobacco products that act as substitutes for cigarettes. Finally, although non-nicotine constituents are unlikely to maintain abuse liability, implementing a reduced-nicotine product standard does not preclude additional standards for other constituents should data emerge suggesting such standards would further improve public health.

Funding

Research reported in this publication was supported by the National Institute on Drug Abuse and the Food and Drug Administration Center for Tobacco Products (U54-DA031659). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health or Food and Drug Administration.

Declaration of Interests

None.

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