Evaluation of Evidence for a Smoked Tobacco Product Nicotine Standard

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The purpose of this document is to represent the current state of the science and may not necessarily reflect the views of all individual SRNT members or PRSN members.

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1. The Problem to be Addressed and the Proposed Standard

1A. The Problem

Cigarettes and other smoked tobacco products, like all tobacco products, are addictive. Nicotine is the tobacco constituent that causes this addictiveness. This addictiveness results in repeated use of the tobacco product and difficulty quitting.

1B. Purpose of a Nicotine Standard

To reduce the addictiveness of cigarettes and other smoked tobacco products so that (1) fewer people who try them would become long-term users, and (2) persons who currently smoke would find it easier to quit using them.

1C. Description of the Standard

A nicotine standard would limit the manufacture and sale of smoked tobacco to products with a nicotine content that is not sufficient to lead to the development and/or maintenance of addiction.

2. Background

Tobacco use is recognized by the World Health Organization as the single most important cause of preventable morbidity and premature mortality, accounting for more than 8 million deaths each year [1,2]. However, despite the overwhelming evidence of the harms caused by tobacco use [3], an estimated 1.3 billion people worldwide smoke cigarettes, with over 80% living in low- and middle-income countries (LMICs) [1]. Most tobacco-related deaths occur in LMICs, which are often targets of intensive tobacco industry interference and marketing [4,5].

The implementation of strong, evidence-based approaches to combating the tobacco epidemic has the greatest potential to reduce the global burden of premature morbidity and mortality [1,6–9]. While significant declines in smoking prevalence have occurred in many countries over the last several decades [10,11], additional efforts are needed to reduce the number of people who smoke and use other dangerous tobacco products, particularly in LMICs with the greatest burden. However, even in high-income nations that have set aggressive targets to reduce smoking prevalence to minimal levels, these goals will not be achieved without the implementation of more aggressive measures [12–16].

The death and disease from smoking are primarily caused by the byproducts of combustion, while the addiction to tobacco products is caused mainly by nicotine [17–19]. Nicotine dependence is considered a chronic, relapsing disease, with a compulsive need to use the drug despite social consequences, loss of control over drug intake, and withdrawal symptoms [20–23]. Nicotine is not known to be the primary cause of diseases caused by tobacco smoke, but rather contributes indirectly to the harm caused by smoking through its role in sustaining dependence, thus maintaining exposure to toxicants in cigarettes. Indeed, in 1976, researcher Michael Russell famously wrote, "people smoke for the nicotine but they die from the tar" [24].

Tobacco initiation, use, and dependence could be significantly abated by reducing nicotine to minimally addictive or non-addictive levels in commercial tobacco products [25]. The idea of a mandated reduction in nicotine content was first proposed in 1994 in a seminal article published in the New England Journal of Medicine[26], but it is only over the past 20 years that the research base for nicotine regulation has been established. In 2015, a World Health Organization (WHO) expert committee published an advisory report that promoted a "global nicotine reduction strategy" [27], which would limit the sale of commercial cigarettes to brands with a nicotine content that is not sufficient to lead to the development and/or maintenance of addiction. Importantly, limits on nicotine are proposed based on the nicotine content of cigarette tobacco, not the nicotine delivery yield; reductions in yield through cigarette design changes without reductions in nicotine content (e.g., filter ventilation) are often circumvented by changes in behavior (e.g., placing fingers over ventilation holes). If nicotine content is low enough, the user cannot obtain a high enough level of nicotine from smoking to sustain addiction. The goal of a mandated reduction in cigarette nicotine content is to improve public health by reducing the prevalence of smoking [28,29]. The premise is based on the well-documented role of nicotine in increasing cigarette smoking initiation, maintaining cigarette smoking, and reducing the ability to quit smoking [30]. Indeed, the tobacco industry has long recognized the role of nicotine in cigarette addiction. In 1991, a report from R.J. Reynolds states, "We are basically in the nicotine business" [30], and a memo from Philip Morris in 1980 stated, "I believe the thing

we sell most is nicotine" [31].

The regulatory framework for implementing a mandated reduction in cigarette nicotine content already exists in many countries. Article 9 of the WHO Framework Convention on Tobacco Control, ratified by 183 Parties, provides for the regulation of tobacco product contents and emissions. In the United States (US), the Family Smoking Prevention and Tobacco Control Act (2009) allows the Food and Drug Administration (FDA) to regulate nicotine, although nicotine cannot be reduced to zero [32]. In 2018, the US FDA announced its intention to implement a nicotine reduction policy with the release of an Advanced Notice of Proposed Rulemaking, and in 2025, the FDA released a Proposed Rule [33]. In New Zealand (NZ), a nicotine reduction policy was passed into law in 2022 and intended to take effect in 2025; however, the law was repealed in early 2024 by a new government [34], and the future of the policy is unclear.

If a mandated reduction in nicotine were implemented in any country, it is likely that the prevalence of smoking would be reduced, resulting in reductions in tobacco-related disease and death [35–40]. Reductions in the prevalence of smoking would be the result of reductions in the rate of smoking initiation and increases in the rate of smoking cessation. Some people who quit smoking may switch to other nicotine products in communities where alternative products are still available. While the full impact of a mandated reduction in nicotine content cannot be determined because no country has yet implemented one, there is now a wealth of primary and secondary evidence that offers policymakers insight into the potential benefits of such a policy.

3. Executive Summary

3A. Summary of the Scientific Evidence:

Data from randomized clinical trials found that providing people who smoke with very low nicotine content (VLNC) cigarettes reduces smoking, exposure to toxicants, craving, and dependence on cigarettes while promoting cessation without serious negative unintended consequences. Peer-reviewed studies have also found that a mandated reduction in nicotine content would likely reduce smoking behavior as well as cigarette appeal among adolescents and young adults who already smoke and thus may reduce the likelihood of transitioning from cigarette experimentation to established smoking for those who have not yet initiated. Rodent self-administration experiments have replicated many fundamental findings in people who smoke and have contributed additional evidence that a mandated reduction in nicotine content is likely to reduce smoking initiation among adolescents and adults who have not smoked before. When people are asked how they would respond to a hypothetical mandated reduction in nicotine content, most adults who smoke anticipate that they would continue to smoke VLNC cigarettes. Some adults also reported interest in quitting smoking altogether or purchasing illicit, normal nicotine content (NNC) cigarettes, and switching to other sources of nicotine. Several qualitative studies have been conducted, and most support the findings of quantitative assessments. These studies have found that people who smoke mostly do not like the taste of smoking VLNC cigarettes, and many anticipated stopping smoking, cutting down, or switching to alternative products like e-cigarettes if a mandated reduction in nicotine content were implemented. Research investigating the impact of nicotine reduction on health equity has generally shown that a mandated reduction in the nicotine content of cigarettes is likely to benefit people who have historically shouldered a disproportionate share of the tobacco-related disease burden. Several modeling studies have estimated the impact of a mandated reduction in nicotine on the population as a whole and found that a mandated nicotine standard is likely to result in substantial and rapid reductions in smoking prevalence and profound population health benefits.

3B. Addressing Common Concerns about a Nicotine Standard

The document addresses several common concerns about a nicotine standard. First, one concern is that a nicotine standard might result in 'compensatory smoking' (i.e., people might smoke more). Together, across trials and outcome measures, the weight of evidence shows that there is no sustained compensatory smoking when nicotine is reduced to a very low level (≤0.4 mg nicotine/g tobacco) and instead shows that the opposite is true; a nicotine standard is expected to reduce smoking behavior and smoke exposure. Second, a nicotine standard has the potential to increase the size of the illicit tobacco market. However, the level of illicit purchasing will depend on the price and availability of illicit products, as well as the rigor and effectiveness of enforcement measures. Furthermore, as demand for NNC smoked products is likely to decline with the reduction in smoking prevalence, the absolute size of the illicit market will decline. Third, some people have questioned whether a nicotine standard is equivalent to a prohibition of smoking or a prohibition of nicotine use. Such criticisms ignore the freedom from addiction to smoked tobacco products that will result from the policy. In addition, a mandated reduction in nicotine content within smoked tobacco is fundamentally different from a ban on cigarettes or a ban on nicotine products. Cigarettes and, in most jurisdictions, other nicotine products

will remain legally available to purchase. The policy removes most of the nicotine from the most harmful forms of tobacco available, thus allowing people the freedom to use smoked tobacco if they want to continue to smoke and the option to obtain nicotine from alternative sources where they are available. Fourth, some have been concerned that the public will not support a nicotine standard. However, the evidence from multiple settings shows a high level of support for a mandated reduction in nicotine content among the public and among people who smoke. This evidence comes from large population-based surveys in many countries, as well as participants in clinical trials who have experienced smoking VLNC cigarettes for several weeks. Fifth, there have been concerns that a nicotine standard might result in extreme discomfort among people who smoke. The evidence indicates that VLNC cigarettes typically do not substantially increase immediate cravings or other withdrawal symptoms or negatively impact well-being. Finally, concerns have been raised about whether such a standard is technically achievable and verifiable. There are multiple methods for lowering the nicotine levels within cigarettes, including ammonia in chloroform solvent extraction and supercritical fluid extraction. In addition, genetic engineering and plant breeding may be other avenues to produce tobacco with nicotine content that meets the standard. There are also validated methods for verifying that products meet the nicotine standard by gas chromatography with either flame ionization detection or mass spectrometry.

3C. Other Consequences of a Mandated Reduction in Nicotine Content for Smoked Tobacco

In addition to a decrease in smoking prevalence, several other outcomes are expected consequences of a nicotine standard. First, a mandated reduction in nicotine content is likely to cause some people who smoke to gain weight. However, the potential health benefits of a nicotine standard far outweigh the unintended health consequences of modest weight gain, much as it is generally accepted that the benefits of smoking cessation programs outweigh any risks from weight gain. Second, randomized trials indicate that switching to non-combusted alternative nicotine delivery systems (ANDS) among people who smoke is a likely outcome. Finally, the anticipated decrease in the prevalence of smoking will reduce government tax revenue from cigarettes if tax rates remain the same. However, such considerations would apply to any effective tobacco control intervention, and allowing concerns about reduced tax revenues to drive government decisions about public health interventions would be irrational. Furthermore, economic benefits will accrue from reductions in smoking prevalence through lower health service costs and productivity gains from improved health.

3D. Other Paths to Achieve the Same Benefit

This report considers two other paths that have been suggested as potential avenues to achieve the same public health benefits as a nicotine standard. First, the report considers whether commercial marketing of VLNC cigarettes alongside NNC cigarettes would yield the same benefits as a mandated reduction in nicotine content requiring that all smoked tobacco have a VLNC and concludes that such a pathway would not yield the same benefits. Second, the report considers whether reductions in smoking because of the availability of ANDS are likely to result in the same benefits and concludes that the greatest public health benefits would come from a mandated reduction in nicotine content for smoked tobacco and a marketplace with a wide range of ANDS available for people who smoke.

3E. Loopholes to Address

The report considers several possible loopholes that are important to address when implementing a nicotine standard. First, the scope of the standard is a critical issue. Scientific evidence indicates that a mandated reduction in nicotine content that includes all smoked tobacco products, including cigarettes, little cigars, cigarillos, large cigars, pipe tobacco, and roll-your-own (RYO) tobacco, would have the most public health benefit. If these other products are not included in the scope, people who smoke are likely to substitute these combustible products for cigarettes, mitigating the health benefits of a product standard. Second, in addition to setting a limit on the content of nicotine in tobacco, tobacco products that contain nicotine in the paper, filter, capsule, or any other part would negate the public health benefit of reducing nicotine in tobacco. This is also the case for any product, such as separately sold cigarette holders or mouthpieces that contain nicotine.

3F. Maximizing the Public Health Benefits

The impact on smoking prevalence and the public health benefits of a nicotine standard will be largest if the standard is implemented immediately (rather than a gradual step-down approach), if the standard is paired with an educational campaign explaining the policy rationale, and if additional behavioral and pharmacological cessation support is made available for people who smoke and want to stop.

3G. Implementation Issues

The effectiveness of a mandated reduction in nicotine content will only be fully realized if governments have the capacity to ensure compliance with the standard, evaluate the population impact of the standard, and place limits on potential industry interventions that could undermine the standard's health benefits. More detailed suggestions are found in this report.

4. Scientific Evidence Supporting a Standard

4A. Clinical Trials in Adults who Smoke

The strongest evidence that a nicotine reduction policy would improve public health comes from randomized clinical trials (RCTs) in which people who smoke cigarettes are given VLNC cigarettes and asked to exclusively use those cigarettes. At least a dozen randomized clinical trials conducted across a variety of settings and participant populations and with variable designs have assessed the impact of extended use of VLNC cigarettes in recent years. These trials, many of which have been summarized in prior reviews [41,42], show that switching to cigarettes with approximately 95% less nicotine reduces the number of cigarettes smoked per day, reduces biomarkers of exposure to tobacco, reduces cigarette appeal and reinforcement, reduces cigarette dependence, and does not produce significant compensatory smoking or other potential adverse outcomes [43–54]. Several studies have also reported increases in quit attempts, the number of smokefree days, and/or biochemically verified abstinence relative to NNC cigarettes [43,44,48–50,53,54]. The concordance of data from multiple studies increases confidence in the conclusion that nicotine reduction is likely to decrease smoking prevalence and improve public health.

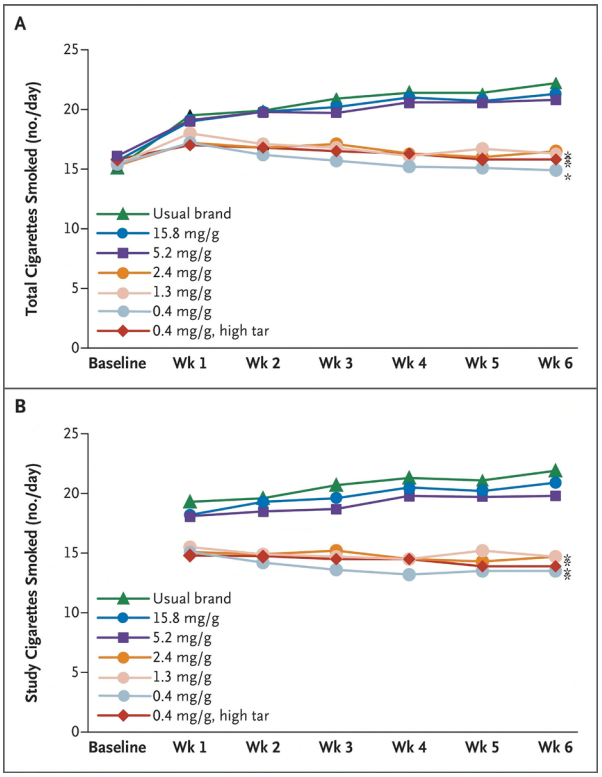


Figure 1

RCTs provide evidence on three fundamental aspects of implementing a nicotine product standard. The first is the relationship between cigarette nicotine content and key outcomes, which is critical to defining the product standard. Donny et al. compared the impact of five different levels of nicotine content in cigarettes over a 6-week RCT [43]. Nicotine contents were expressed as mg of nicotine per gram of tobacco (mg/g). As shown in Figure 1, participants randomized to 2.4 mg nicotine/g tobacco or less smoked fewer cigarettes per day (provided free of charge after baseline) than those assigned to cigarettes with NNC (15.8 mg/g), while participants assigned to 5.2 mg/g did not differ from controls. Nicotine content cigarettes with 0.4 mg/g produced the most robust benefits (decreased dependence, increased quit attempts). These data are consistent with laboratory assessments demonstrating that cigarettes with higher nicotine content are reliably chosen over cigarettes with lower nicotine content [55]. Higgins et al. (2020) observed similar differences between 0.4 and 2.4 mg/g vs 15.8 mg/g; both reduced nicotine cigarette conditions reduced the number of cigarettes smoked per day and dependence in people who smoke from three different vulnerable populations, with little difference between 0.4 and 2.4 mg/g [48]. Differences in outcomes between cigarettes with different nicotine content below 2.4 mg/g tend to be small; however, because the empirical evidence is most extensive for 0.4 mg/g, there may be heterogeneity in sensitivity to nicotine between people, and maximizing reductions in exposure is likely to have the greatest impact on dependence, product standards should be set with the goal of reducing nicotine content to as close to 0.4 mg/g as possible. Countries will need to decide on the appropriate standard for attaining this goal based on regulatory infrastructure and product testing capacity. NZ and the US targeted 0.8 and 0.7 mg/g, respectively, as the upper

limit [28,56].

The second line of evidence is that an immediate reduction to 0.4 mg/g, as opposed to a stepped or gradual reduction, produces the most rapid benefits with minimal evidence of unintended negative consequences such as compensatory smoking, which may occur at more intermediate doses (described in detail in Section 9A) [44].

Finally, the results of RCTs are remarkably similar across diverse populations, including people with anxiety or mood disorders [50], people with serious mental illness [47], people with less than a college degree [49], and people who smoke nondaily intermittently [45], when nicotine is reduced to 0.4 mg/g (described in detail in Section 4F).

Reducing the nicotine content of cigarettes has several noteworthy effects. The first is a reduction in smoking. Most RCTs have provided study cigarettes to people who are not interested in quitting. When participants are randomized to VLNC cigarettes, they generally continue to smoke for the duration of the trial, but they report smoking fewer cigarettes, and biomarkers of smoke exposure are typically reduced. The magnitude of the reduction observed in RCTs after 6-20 weeks of use is generally around 25-40% or 4-7 cigarettes per day [43,44,48–50]. Importantly, there is no evidence that switching to VLNC cigarettes produces prolonged increases in smoking (i.e., compensatory smoking) as measured by self-report, puff topography, or biomarkers [43,44,50,57,58]. Second, participants report reduced positive subjective effects from smoking and experience less craving for VLNC cigarettes [43,59,60]. After smoking VLNC cigarettes for 6 weeks, participants who were abstinent from smoking for 24 hours reported little increase in craving compared to participants who had been smoking NNC cigarettes [43]. Third, people who smoke daily report fewer symptoms of nicotine dependence across multiple well-validated scales after 6-20 weeks of VLNC cigarettes relative to the persistent level of dependence observed in people who smoked NNC cigarettes, including for subscales shown to predict relapse [61], and reductions in dependence appear to persist for at least 1 month after participants return to regular smoking [43,44,48,50]. Fourth, withdrawal and other potential negative consequences tend to be mild [43,44,48,50]. Fifth, some participants, despite not planning to quit at the start of the trial, are more likely to try to quit and, in some cases, succeed. For example, Hatsukami and colleagues reported that participants who were provided with VLNC cigarettes for 12 or 20 weeks were over 3 times more likely to be abstinent at the end of the 20-week trial [44; supplementary materials,53]. Likewise, Foulds et al. found that when participants randomized to VLNC cigarettes were given the option to quit smoking at the end of the trial, they were more likely to achieve abstinence than participants who chose to try to quit smoking in the control arm [50]. Providing VLNC cigarettes to use in lieu of regular cigarettes for people engaged in a quit attempt to use when they experience cravings has also been shown to reduce relapse [62]. Finally, although nicotine exposure is drastically decreased when smoking VLNC cigarettes compared to NNC cigarettes, VLNC cigarettes do produce measurable nicotine exposure compared to people who do not smoke [62–64] and likely produce some physiological and subjective effects [65–69], albeit reduced in magnitude compared to NNC cigarettes. **Taken together, the evidence from RCTs is clear. Switching to VLNC cigarettes reduces smoking, exposure to toxicants, craving, and dependence on cigarettes while promoting cessation without serious negative unintended consequences** [63].

4B. Studies in Adolescents and Young Adults

It is not ethical to prospectively assess the impact of VLNC cigarettes on smoking initiation through experimental intervention studies. Direct evidence of the impact on initiation will only emerge after the actual implementation of a low-nicotine product standard (VLNC standard). However, several laboratory studies and clinical trials have examined the impact of a mandated reduction in nicotine content among adolescents and young adults who already smoke [51,59,64–67]. Together, these studies indicate that such a policy will likely be beneficial for adolescents and young adults by reducing the appeal of cigarette smoking.

Laboratory studies have assessed the effects of VLNC cigarettes among adolescents and young adults on the positive subjective responses and reinforcement from smoking. During a multi-session laboratory study by Cassidy et al., adolescents aged 15-19 who smoked daily reported reduced positive subjective responses (e.g., "Did you enjoy smoking?") after smoking VLNC cigarettes following overnight abstinence compared to after smoking NNC cigarettes, indicating potentially reduced abuse liability of VLNC cigarettes among this population (Figure 2) [64]. The adolescents also reported higher economic demand indices for their usual brand cigarettes relative to all of the reduced nicotine content research cigarettes administered, which indicates reduced reinforcing efficacy of VLNC cigarettes [65]. In a multi-session laboratory study, young adults aged 18-25 who smoked infrequently reported reduced positive and negative reactions after smoking VLNC cigarettes relative to NNC cigarettes [68], indicating lower cigarette appeal but also potentially lower aversiveness to VLNC cigarettes. Some laboratory data have even suggested that younger people may experience greater reductions in smoking reinforcement as a result of a mandated reduction in nicotine content compared to older adults [74. Indeed, a secondary analysis by Higgins et al. 2017—a multi-session laboratory study that recruited adults with socioeconomic disadvantage or psychiatric comorbidities who smoke daily—found that participants aged 18-24 had lower economic demand indices when completing the Cigarette Purchase Task for reduced nicotine research cigarettes relative to participants aged 25+ [74]. Overall, across laboratory studies, adolescents and young adults report reduced cigarette appeal, which is one marker for reduced abuse liability, after acute exposure to VLNC cigarettes.

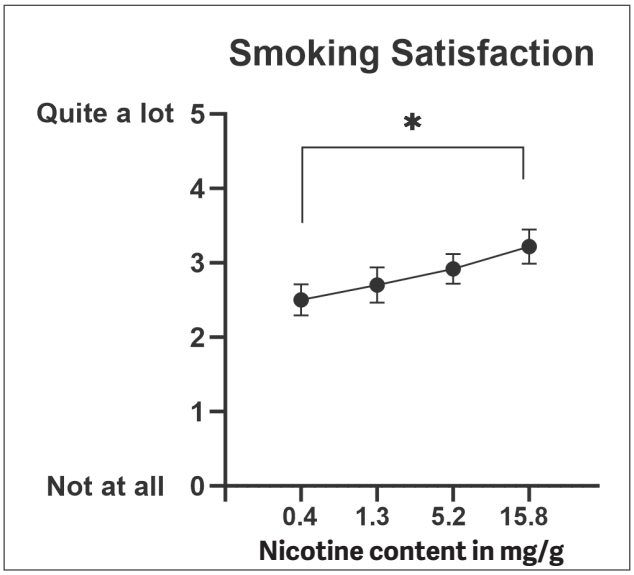


Figure 2

Randomized clinical trials have demonstrated that adolescents and young adults are likely to reduce cigarette smoking as a result of a mandated reduction in nicotine content. In a randomized clinical trial of adolescents aged 15-19 who smoke daily, adolescents randomized to receive VLNC cigarettes for three weeks reported an average reduction of 2.4 cigarettes per day relative to adolescents randomized to receive NNC cigarettes [51]. Adolescents in the VLNC cigarette group also reported reduced craving relative to those in the NNC group. Secondary analyses of large randomized clinical trials have assessed whether young adults (18-24 year olds) experience similar benefits from VLNC cigarettes as older adults in the same trials. In a secondary analysis of Donny et al. [42], a multi-site randomized clinical trial of adults who smoke daily, participants aged 18-24 assigned to VLNC cigarettes had significant reductions in cigarettes smoked per day and positive subjective smoking effects at the end of the 6-week trial compared to those assigned to NNC cigarettes [59]. In a secondary analysis of Hatsukami et al. [43], a multi-site randomized

clinical trial of adults who smoke daily, both younger participants aged 18-24 and older participants aged 25+ assigned to VLNC cigarettes smoked fewer cigarettes per day at the end of the 20-week trial compared to participants assigned to NNC cigarettes [66]. Interestingly, participants aged 18-24 in the VLNC cigarette group had greater reductions in positive subjective smoking effects relative to participants aged 25+ in the VLNC cigarette group.

Overall, these studies indicate that a mandated reduction in nicotine content would reduce smoking behavior as well as cigarette appeal among adolescents and young adults who already smoke, and thus it is highly plausible that introducing a nicotine standard may also reduce the likelihood of transitioning from cigarette experimentation to established smoking for those who have not yet initiated.

4C. Rodent Self-administration Experiments

Rodent nicotine self-administration has been used to address research questions related to a mandated reduction in nicotine content that might be difficult or unethical to address in humans. In these studies, rodents make a response (e.g., nose poke, lever press) to earn intravenous infusions of nicotine. The nicotine dose per infusion is tightly controlled, allowing researchers to reduce the dose of nicotine received to understand the impact of nicotine dose reduction on responding for nicotine. These experiments have generally converged with clinical data to show that large reductions in nicotine dose can reduce the rate at which animals will self-administer nicotine and decrease the likelihood of animals initiating nicotine self-administration.

Rodent self-administration experiments have replicated many of the findings from human RCTs (for a review see [69]). Self-administration experiments have shown that there is a threshold nicotine dose, below which responding for nicotine is reduced. These data are in line with data from clinical trials showing a clear threshold nicotine dose, below which humans will smoke fewer cigarettes per day and be more likely to quit smoking [43,44]. Self-administration studies have not shown a difference in the threshold dose of nicotine by sex [69], consistent with clinical data that have not shown a difference in the impact of VLNC cigarettes on smoking behavior by gender [70]. Large reductions in nicotine dose, below the threshold for reinforcement, do not result in compensatory responding for nicotine [increased responding to obtain more nicotine; 71], consistent with the evidence that humans who smoke don't compensate by smoking more cigarettes or changing how they smoke if the reduction in nicotine content is large enough.

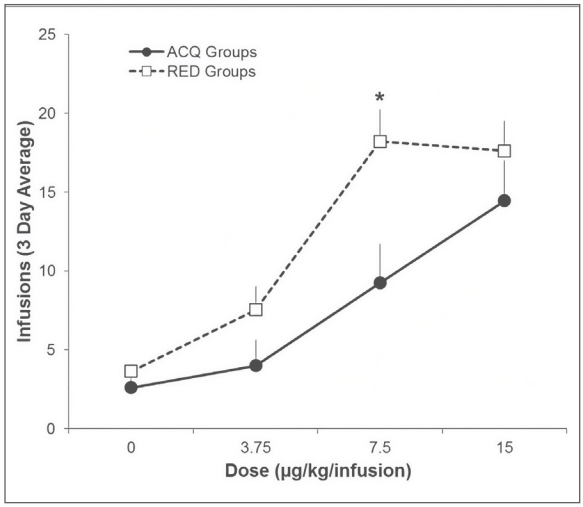


Figure 3

One of the most critical aspects of a mandated reduction in nicotine addressed by rodent self-administration experiments is the impact of nicotine reduction on adolescents and adults naive to nicotine. This work is important because we cannot ethically assess the impact of VLNC cigarettes on youth initiation of smoking (See Section 4B). Smith et al. [72] directly compared nicotine self-administration across different low doses for adult rats that have a history of nicotine self-administration at higher doses (similar to the history of adults who smoke) and those that do not (similar to the history of individuals who have never smoked) and found that the threshold nicotine dose for acquiring nicotine

self-administration in adult male rats was similar to or even higher than the threshold nicotine dose for maintaining self-administration following reduction (Figure 3). These data suggest that a reduction in the nicotine content of cigarettes to levels that reduce smoking in adults who smoke would be sufficient to reduce smoking initiation in people who are naive to smoking. Several studies have assessed whether there are developmental differences in nicotine reinforcement between adolescent rats and adult rats. These experiments have produced mixed results, with some suggesting that adolescents may find low doses of nicotine more reinforcing than adults [80–88] and some that adolescent rats may require an even higher dose of nicotine to acquire self-administration behavior [73,74]. However, these discrepant results in rodents are outweighed by clinical research in adolescent people who smoke (discussed in Section 4B) showing that VLNC cigarettes reduce positive subjective responses to smoking, smoking reinforcement, and cigarettes smoked per day, consistent with results from adult randomized trials.

Taken together, rodent self-administration experiments have replicated many fundamental findings in people who smoke and have contributed additional evidence that a mandated reduction in nicotine content is likely to reduce smoking initiation among adolescents and adults who have not smoked before.

4D. Qualitative Evidence

There have been at least nine qualitative studies to date exploring with the public (mainly people who smoke) actual and anticipated experiences of using VLNC cigarettes and views about a mandated reduction in nicotine content. These include six studies (described in eight papers) carried out in the USA [75–82] and three from New Zealand [83–85]. Most of the studies used semi-structured interviews and a thematic analysis approach. One study used a longitudinal qualitative design and a theory-informed analysis [85]. All the studies except one included only people who currently smoke. The exception was one study (reported in three papers) that included people who currently smoke as well as people who formerly smoked and 18-30-year-olds who had never smoked regularly [94, 96].

Four out of five studies in which people received VLNC cigarettes found that participants disliked them, usually because of their taste, smell, or lower satisfaction [75,76,82,84]. The exception was a confinement study in which adults who smoked only had VLNC cigarettes available to smoke for five days [77]. The participants in this study anticipated that the VLNC cigarettes would be less satisfying than their usual cigarettes, but for most participants, this did not eventuate. In one of the blinded studies with young people, dislike of the study cigarettes was similar for participants who received NNC cigarettes and VLNC cigarettes [77].

In two of these five studies, support for a low-nicotine-content product standard was assessed. In one study, around half of adolescents and young adults were supportive [76], whereas in another study from New Zealand, most adult participants were opposed [84]. The most frequently cited reasons for supporting a mandated reduction in nicotine content in these studies were that it would likely help people to quit smoking or reduce the number of young people starting to smoke. Common reasons given for opposing the policy included that it infringed on the choice to smoke, would result in the use of alternative products such as illicit tobacco, or that the policy might not be effective.

Anticipated responses to a low nicotine content product standard were assessed in both of the adolescent and young adult focused studies, with most participants believing that if the standard was introduced, they would quit or reduce their smoking, and a substantial

minority suggesting they would switch to (or at least try) non-combusted alternative products such as e-cigarettes [76,82]. Some participants in the confinement study suggested they would seek illicit sources of NNC cigarettes if a mandated reduction in nicotine content were introduced.

Support for a low-nicotine-content product standard was also assessed in three out of four studies, which included adults who smoke with no direct experience of using VLNC cigarettes. Most participants were supportive of a VLNC policy in two studies, with the most common reason cited being that it would likely help people to quit smoking [79,83]. In one study, most participants opposed the policy [85]. The latter study included only people who did not want to quit smoking or believed that they would quit, and hence represented the views of a highly select group of people who smoke. A further caveat is that this study was funded by the Foundation for a Smokefree World, which was established and funded by Philip Morris International. Reasons for opposing the policy among participants in these three studies included that it might cause excessive stress (particularly to heavily addicted people who smoke or people with mental health conditions), compensatory increased smoking, or a growth in the illicit market. Others had concerns that it would be ineffective and represented regulatory overreach and an unwarranted restriction on freedom of choice.

Authors of several qualitative studies concluded that implementing the policy should be accompanied by comprehensive communication and engagement to articulate its rationale. Given the concerns expressed about possible adverse consequences for people who smoke, authors in several papers argued that comprehensive smoking cessation support and non-combusted alternative nicotine products should be available to people who smoke following implementation of the low-nicotine product standard.

The findings from these qualitative studies were mixed, but most studies found that most people who smoke did not like smoking VLNC cigarettes, and many anticipated stopping smoking, cutting down, or switching to alternative products like e-cigarettes if a low-nicotine standard were introduced. Support for a low-nicotine product standard was variable within and between studies. The main reasons for supporting the standard were that it would likely help people to quit smoking or minimize uptake among young people. However, a range of concerns were also expressed, underlining the need for careful implementation with appropriate support provided for people who smoke.

4E. Anticipated Behavior with the Implementation of a Nicotine Standard for Cigarettes

The potential impact of a nicotine reduction standard can be estimated from surveys that have asked people who smoke cigarettes how they anticipate they might respond to a mandated reduction in nicotine content. This has been done for other policies such as menthol bans and cigarette price increases [86–89].

A handful of population-level studies have assessed possible behavioral responses to a nicotine reduction standard among adults who smoke cigarettes. These studies have limitations, being cross-sectional and hypothetical in nature, and it is unclear whether any of the participants have ever tried a VLNC cigarette [90–95]. All studies included adults aged 18+ years, and some included participants from more than one country.

Across all studies, the most common response to a mandated nicotine reduction in nicotine

content was that people who smoke would try VLNC cigarettes [92] or continue to smoke using VLNC cigarettes. Other anticipated responses were mixed across and within studies, including quitting smoking completely, switching to e-cigarettes, cutting down on their smoking, and finding a way to get NNC cigarettes.

Across all studies, except Patel et al. [93], up to a quarter of adults reported anticipating quitting smoking. A smaller proportion responded that they would seek out ways to find NNC cigarettes. For example, in a study from New Zealand (where introducing a nicotine standard was under consideration), just over a third (35%) anticipated continuing to smoke using VLNCs, and 19% stated they would find a way to get the cigarettes they wanted to smoke. However, almost half anticipated that they would quit smoking entirely (13%), switch to vaping (14%), or reduce the amount they smoked (18%). Anticipated quitting or switching to vaping was much higher among people who smoked less than daily and much lower among people who smoked daily who had no intention to quit.[90].

Taken together, these data suggest that most adults who smoke anticipate that if a mandated reduction in nicotine content were implemented, they would continue to smoke VLNC cigarettes. However, a variable but substantial proportion also stated that they would likely quit smoking completely, switch to vaping, or cut down on the number of cigarettes smoked, while a minority reported that they would seek to access NNC cigarettes. Adults who smoked daily and were not motivated to quit (or for whom higher nicotine dependence was indicated) appear to be more likely to continue smoking VLNC cigarettes and/or seek out ways to purchase NNC cigarettes, while people who smoked less than daily were more likely to quit smoking or switch to vaping. It is unclear whether youth who smoke cigarettes would anticipate responding in similar ways. Data from these studies is a relatively weak line of evidence about likely outcomes of a nicotine standard, as almost all survey participants will have had no experience of smoking VLNC cigarettes.

4F. The Potential Impact of Nicotine Reduction on Health Equity

Some people are at higher risk for experiencing tobacco-related harms from smoking due to disparities in smoking prevalence and cessation rates. Unfortunately, many tobacco control interventions widen tobacco-related health disparities. Thus, it is important to understand the impact of a mandated reduction in nicotine content among people who disproportionately experience the disease burden of cigarette smoking to understand whether a mandated reduction in nicotine content is likely to widen or shrink existing health disparities. Both RCTs and secondary analyses of RCTs have been used to assess the impact of nicotine reduction on people with mental illness, people with substance use disorders, people with lower educational attainment, different demographic groups, and people who smoke menthol-flavored cigarettes [for a review, see 96]. Overall, these studies have found that vulnerable subgroups would experience the same benefit of nicotine reduction as the general population of people who smoke, without any significant safety concerns. Nonetheless, it will be important for regulators to be thoughtful in implementing a mandated reduction in nicotine content so that these subgroups do not bear any additional burden.

In lab studies and clinical trials among people with serious mental illness, including

schizophrenia and bipolar disorder, VLNC cigarettes reduce craving, withdrawal symptoms, cigarette reinforcement, cigarette smoking, and biomarkers of cigarette smoking (expired carbon monoxide) without increasing psychiatric symptoms [47,97–99]. In an RCT by Tidey et al. among people with schizophrenia (n=58), schizoaffective disorder, or bipolar disorder, assignment to VLNC cigarettes for six weeks reduced cigarettes smoked per day, smoke exposure, cigarette craving, and cigarette appeal more than assignment to NNC cigarettes [47]. There was no increase in psychiatric or extrapyramidal symptoms. However, participants assigned to VLNC cigarettes did not have lower biomarkers of nicotine exposure than participants assigned to NNC cigarettes, suggesting there were high rates of nonadherence with the VLNC cigarettes. High rates of nonadherence in this population might suggest that individuals with serious mental illness may seek out alternative sources of nicotine following implementation of a mandated reduction in nicotine content.

Several trials have assessed the impact of VLNC cigarettes among people with affective disorders. In a multi-site lab study that included people with depression and anxiety, VLNC cigarettes reduced craving, withdrawal, appeal, and preference for smoking without increasing depression or anxiety symptoms or severity [55]. Two clinical trials have assessed the impact of VLNC cigarettes on people with depressive symptoms [100] or people with anxiety and depression [48]. In both trials, VLNC cigarettes reduced cigarettes smoked per day and cigarette dependence [116]. One analysis focused on people with depressive symptoms and found that assignment to VLNC cigarettes reduced depressive symptoms [100], while the other trial focused on people with depression and anxiety diagnoses and found that depressive symptoms increased during the trial, but symptoms remained within a minimal range [48,50,54].

Several studies have investigated the impact of nicotine reduction among people who use other drugs of abuse and generally found similar effects of nicotine reduction to studies conducted among general populations with no concerns about increases in use. One laboratory study among people receiving methadone or buprenorphine maintenance treatment found that VLNC cigarettes reduced reinforcement from smoking [55], and a clinical trial among the same population found that VLNC cigarettes reduced the number of cigarettes smoked per day and smoke exposure (expired CO) although to a lesser extent than they did for individuals from other populations in the trial, possibly as a result of having lower adherence with the instruction to only use study cigarettes [48,54]. Secondary analyses of larger clinical trials have examined the impact of VLNC cigarettes among people who use alcohol or cannabis. These analyses have shown that alcohol and cannabis users experience similar benefits from VLNC cigarettes as the general population, with either no effect on use [cannabis; 101] or a reduction in use [alcohol; 102].

The effects of nicotine reduction across demographic variables (race, gender, educational attainment, and socioeconomic status) have been assessed through both secondary analyses of RCTs and RCTs conducted in specific demographic subgroups. One secondary analysis of a large RCT (n=1250) tested whether race, gender, or educational attainment moderated the effects of nicotine reduction over 20 weeks [70]. Researchers found that assignment to VLNC cigarettes reduced cigarette smoking and biomarkers of nicotine and tobacco exposure for both white and black participants, men and women, and individuals with lower and higher educational attainment, although effects of nicotine exposure were smaller for Black participants than for White participants. Several studies have assessed the impact of nicotine reduction among people with lower educational attainment or

lower socioeconomic status and have shown that a mandated reduction in nicotine content is likely to provide the same benefits for people in these groups. Laboratory studies and randomized controlled trials among women of reproductive age with low socioeconomic status have found that VLNC cigarettes reduce cigarette reinforcement, do not produce compensatory smoking [55], and reduce the number of cigarettes smoked per day [48,54]. In another randomized controlled trial, VLNC cigarettes reduced the number of cigarettes smoked per day among adults with 16 or fewer years of education [49]. Participants in this trial were also more likely to choose to make a quit attempt and quit smoking than individuals in the NNC control group. In a secondary analysis of a larger clinical trial [44], low-nicotine cigarettes reduced smoking and toxicant exposure among adults with 12 years or less of education [70].

Results have been mixed as to whether the benefits of a mandated reduction in nicotine content are likely to be as large for people who smoke menthol cigarettes as for people who smoke non-menthol cigarettes. A secondary analysis of a large randomized clinical trial found that people who smoked menthol cigarettes experienced smaller reductions in smoking when assigned to VLNC cigarettes than those who smoked non-menthol cigarettes [103]. Low-nicotine cigarettes also did not increase smoking abstinence for people who smoke menthol cigarettes, whereas they did increase abstinence for people who smoke non-menthol cigarettes. However, other randomized controlled trials did not find that menthol status moderated the impact of nicotine reduction on smoking [43,104].

In sum, research investigating the impact of nicotine reduction on subpopulations that are disproportionately affected by the harms from tobacco has generally shown that a mandated reduction in the nicotine content of cigarettes is likely to benefit people who have historically shouldered a disproportionate share of the tobacco-related disease burden, without safety concerns. These data suggest that a mandated reduction in nicotine content is likely to improve health equity by reducing the prevalence of smoking in these populations. However, regulators and policymakers can ensure that vulnerable subgroups do not experience adverse consequences (e.g., withdrawal, craving, increased depression) by providing increased access to alternative forms of nicotine (e.g., nicotine replacement therapy).

4G. Quantitative Estimate of the Public Health Benefit of Nicotine Reduction

The best estimates of the population impact of a mandated reduction in nicotine content come from studies that use modeling to estimate changes in population outcomes over long time horizons. To date, seven modeling studies have examined the impact of a mandated reduction in nicotine content. These have produced estimates for the impact of these policies in the US [29,36,37,105], New Zealand [38,39], and Singapore [40]. Six of the modelling studies estimated the impact of a low-nicotine-content product standard on future smoking prevalence relative to no policy, using the counterfactual of not implementing a policy [29,37–40]. The other study estimated retrospectively that the change in smoking prevalence would have been different if tobacco companies had only produced and marketed VLNC cigarettes from 1965, 1975, or 1985 [36]. Some studies also estimated the health impacts of a low-nicotine content product standard on Quality-Adjusted Life Years (QALYs) [37], the number of smoking-related deaths averted and life years lost (LYL) [29,36,105], or Health-Adjusted Life Years (HALYs) [38].

Timeframes of the studies varied, but most modelled prevalence and health impacts over prolonged periods, ranging from 20 years [38] to 50 years [37,40], or even 85-100 years [29,36,38,105]. Ait Ouakrim et al. modelled prevalence over 20 years but assessed health impacts over the lifespan of a 2020 population cohort. Wilson et al. assessed relatively short-term outcomes from 2020-2025. Most studies modelled outcomes of a low-nicotine standard in the whole population. The two studies modelling the policy's outcomes in the New Zealand population also included an investigation of equity effects by comparing impacts across the Māori (the Indigenous peoples of New Zealand) and non-Māori populations.

A key assumption underpinning the modelling in all studies was the predicted impact of the low nicotine product standard on initiation of smoking and on smoking cessation (and relapse) among people who smoke. In five studies [29,36,38,40,105], these assumptions were primarily based on expert elicitation, and this method was also used to inform a secondary estimate in Wilson et al. [39]. In all except the study by Ait Ouakrim et al., the expert elicitation was derived from estimates by Apelberg et al. [29] or an updated version [105].

All the studies estimated that the standard would result in rapid and profound declines in smoking prevalence, with concomitant substantial impacts on reducing the health impacts due to smoking, and with substantial pro-equity effects by ethnicity where this was studied. Apelberg et al. estimated that a low nicotine standard implemented in the US in 2015 would save millions of lives (e.g., 2.8 million by 2026) and tens of millions of life years (e.g., 33.1 million by 2026) over the next several decades. Where the impact was compared to other tobacco control policies, the low-nicotine product standard policy resulted in the largest impact on smoking prevalence [38,40]. The modeled impacts remained very substantial, and sensitivity analyses and uncertainty estimates incorporated lower-bound impact estimates from the expert elicitations.

All modelling studies suffer from the limitation that estimates of the policy effects are not based on evidence from the evaluation of real-world policy implementation, as this has yet to occur. However, as demonstrated in the preceding sections, there is supporting theory and empirical evidence of a likely substantial impact, based on anticipated responses and simulation trials among people who smoke from diverse populations and settings. Other weaknesses of the modeling studies include that some do not consider the impact of people who smoke switching to illicit tobacco products, nor model the use of alternative products such as e-cigarettes. However, when included in sensitivity analyses, they did not greatly affect the estimated impact of the low-nicotine standard and are therefore unlikely to negate the very large positive modelled effects of a low-nicotine product standard. Some studies could also be criticized for assumptions about smoking prevalence that may have resulted in overestimates of impacts of the product standard because baseline smoking prevalence was too high [38] or predicted reductions in smoking prevalence in the counterfactual scenario were too conservative [37–39]. However, such biases will only reduce but not eliminate the modelled impacts of a low-nicotine product standard if the core assumptions about the effects of mandated reduction in nicotine content on reducing smoking initiation and increasing cessation are reasonably accurate.

Taken together, modeling studies estimate very substantial reductions in smoking prevalence and population health benefits associated with the introduction of a low-nicotine content product standard for cigarettes.

5. Addressing Common Questions and Concerns about a Nicotine Standard

5A. Will People Compensate?

The most common criticism of a mandated reduction in nicotine content is that people will smoke more to "compensate" for the reduction in nicotine content. Compensatory smoking would be a negative outcome for a mandated reduction in nicotine content because it would increase exposure to toxicants and potentially result in increased harm. These criticisms are based on historical data showing that moderate reductions in nicotine content or yield can result in people smoking more cigarettes per day or changing the way they smoke each cigarette (i.e., puff topography) to compensate for reductions in nicotine [106]. However, there is a convergence of data demonstrating that reductions in the nicotine content of cigarettes to a very low level (≤0.4 mg nicotine/g tobacco) do not result in compensatory increases in the number of cigarettes smoked per day or changes in puff topography to obtain more nicotine.

RCTs have assessed compensation when people who smoke switch to VLNC cigarettes and found minimal or no evidence for compensation [106]. Compensation has been assessed using multiple measures, including cigarettes smoked per day, nicotine exposure, exposure to toxicants, and smoking topography. Studies of short-term exposure to VLNC cigarettes have shown that puff topography may be increased across the first several cigarettes [107]. However, studies that have examined changes in smoking in people who smoke VLNC cigarettes for several weeks or as long as one year show that there are significant decreases in cigarettes smoked per day, with no increase in expired carbon monoxide or toxicants [43,44,53,104,108–110]. When smoking topography is assessed after six weeks of VLNC cigarette use, puff volume is decreased rather than increased [43]. One limitation of these studies is that people who smoke VLNC cigarettes will sometimes use non-study NNC cigarettes [42, 126], which might result in an inability to measure compensatory smoking, as people are obtaining nicotine through another source that would not be available following a policy implementation. However, one trial that confined people who smoked to an inpatient setting in which NNC cigarettes were completely unavailable for four days did not show any increases in the number of cigarettes smoked per day or expired carbon monoxide by day 4 [58]. **Together, across trials and outcome measures, the weight of evidence shows that there is no sustained compensatory smoking when nicotine is reduced to a very low level (≤0.4 mg nicotine/g tobacco).**

5B. Will a Standard Create an Illicit Market?

The implementation of a mandated reduction in nicotine content has the potential to significantly reshape both the legal and illicit tobacco markets. In terms of the legal market, the policy is expected to reduce overall consumption due to higher quit rates and lower cigarettes per day, as mentioned in previous sections. However, as reports suggest, [42,111,112] the illicit tobacco market may also evolve as a result. Illicit purchasing can occur through multiple channels, including online purchases from overseas vendors, diversion of legally exported products back into the domestic market, or local informal sources such as street sales or social networks.[112]

Studies that have examined the effect of the nicotine reduction standard on illicit purchases are largely prospective, as no jurisdiction has yet implemented such a standard. In this

sense, a few studies have examined the impact of a cigarette nicotine standard on illicit tobacco purchases, with some suggesting that a reduced nicotine content may increase the willingness to buy illicit NNC cigarettes [93,113]. However, others have found that the availability of lower-priced e-cigarettes could reduce illicit-market engagement, as people who smoke may choose e-cigarettes over illicit cigarettes [114]. This suggests that while a nicotine standard may drive some consumers to the illicit market, the availability of alternative products could help mitigate this effect. A major limitation of these studies is that they were conducted without prior experimentation or familiarity with VLNC cigarettes. Although clinical trials, where participants smoke VLNC cigarettes, do not directly assess the illicit market, they reveal that demand for participants' usual brand of cigarettes drops significantly during and after exposure to VLNC cigarettes. In these trials, many participants quit smoking entirely or reduced their consumption to the point where cravings for regular nicotine levels were less pronounced [42]. This suggests that, similar to the behavioral shifts observed in these trials, individuals might experience a reduction in demand for illicit cigarettes after sustained exposure to VLNC products.

From a response cost perspective, if NNC cigarettes were to become illicit due to a nicotine reduction policy, their prices would likely increase in the illicit market due to higher demand and reduced availability in the legal market. However, as the cost of obtaining NNC cigarettes rises, preference may shift toward VLNC cigarettes. Research suggests that when the response cost for a higher nicotine dose increases—such as in the case of illicit cigarettes—the preference for VLNC cigarettes can increase [55]. This shift in preference could lead to greater acceptance of VLNC cigarettes, especially if they are more accessible and affordable compared to illicit cigarettes.

Moreover, even though a nicotine reduction policy could lead to an increased portion of the overall cigarette market being illicit, the overall decline in cigarette consumption expected from such a policy could result in a smaller absolute illicit market, even if the proportion of consumers turning to illicit sources increases. This was observed in New Zealand, where strict tobacco regulations led to a rise in the share of the illicit market, from 11.5% to 12.1%. However, despite the increase in illicit market share, the absolute size of the illicit market shrank by 27%, driven by a dramatic decline in legal cigarette consumption [115]. This suggests that, although the percentage of people turning to illicit tobacco may rise, the significant decline in legal cigarette consumption could result in a net reduction in the volume of illicit trade.

Further, lessons from past regulatory actions, such as menthol bans in Canada and the European Union, suggest that changes in the legal market do not always correlate with significant increases in illicit trade. In both jurisdictions, menthol bans led to concerns about illicit tobacco proliferation, yet evidence showed that the illicit market did not expand. For example, in Nova Scotia, following the 2015 menthol ban, an analysis of illicit cigarette seizures from 2012 to 2018 showed no evidence of an increase in illicit trade, either for menthol or non-menthol cigarettes [116]. Another study using brand validation analysis found no change in the purchasing patterns of menthol, non-menthol, or both types of cigarettes on First Nations reserves, providing no support for the claim that a menthol ban drives an increase in illicit purchases [117]. In the Netherlands, evidence indicated that illicit purchasing remained consistently low both before and after the ban, with no significant difference between people who smoke menthol and non-menthol cigarettes [118]. Although these examples involve different cigarette feature restrictions, they highlight how effective

regulation can mitigate the unintended consequences of reduced legal product availability.

In sum, a nicotine standard may increase the size of the illicit tobacco market. However, any increase in illicit purchasing is likely dependent on the price and availability of illicit products. Over time, demand for NNC smoked products is likely to decline, decreasing the size of the illicit market.

5C. Is a Nicotine Standard Prohibition?

One concern about a nicotine standard is that such a policy is tantamount to prohibition or a ban on cigarettes. **However, a mandated reduction in nicotine content is not a ban on cigarettes or a ban on nicotine. Cigarettes and other nicotine products will remain legally available to purchase. Instead, the policy removes most of the nicotine from the most harmful forms of tobacco available, giving people the freedom to use cigarettes if they want to continue to smoke and the option to use higher doses of nicotine in alternative sources. Without a standard, the choice to continue or quit smoking is constrained by nicotine dependence.**

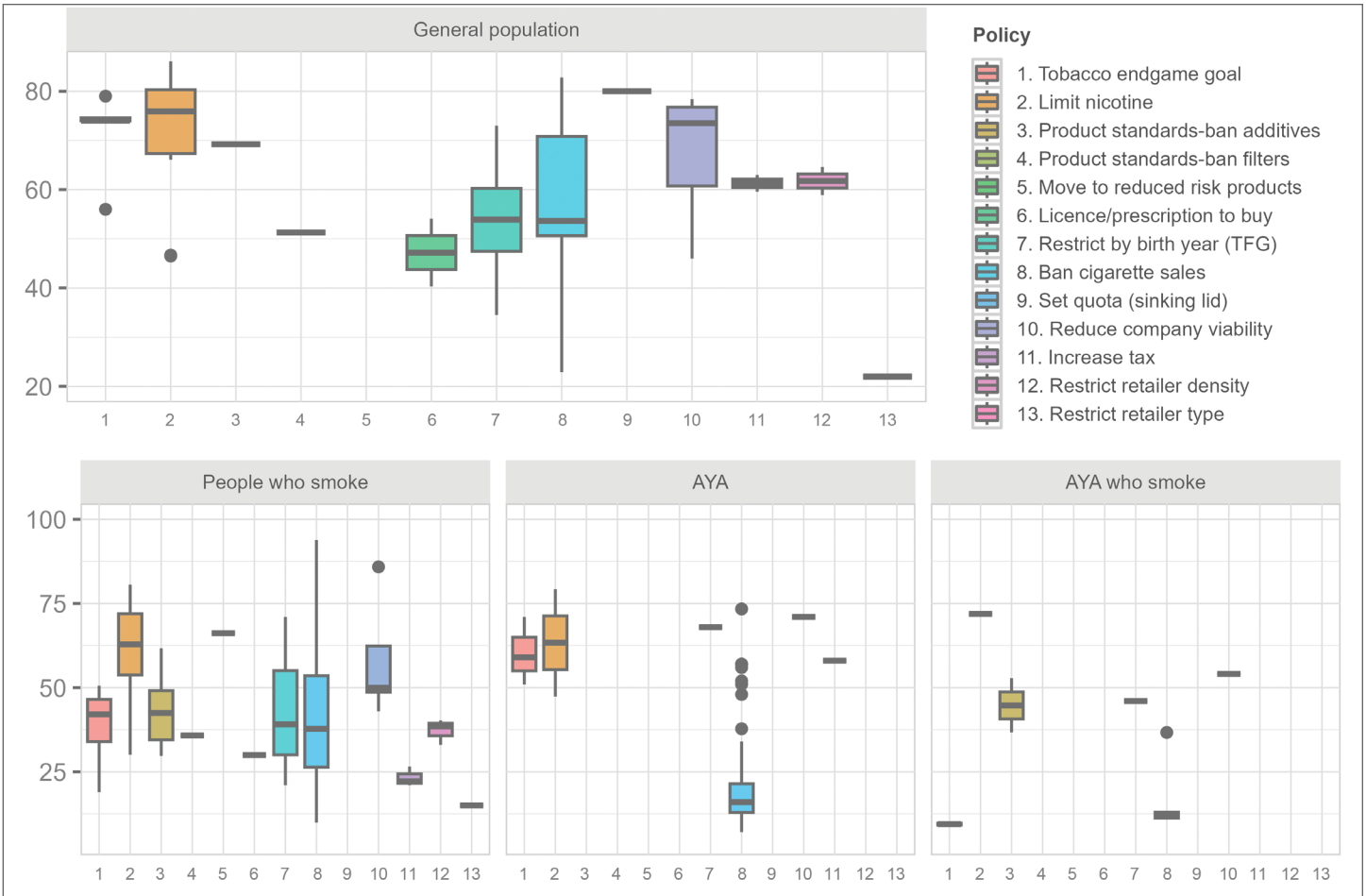
Scientific evidence suggests that VLNC cigarettes are an acceptable product to people who smoke. As discussed in Section 4D, when people who smoke cigarettes are asked how they would respond to a nicotine reduction policy, the most common response is to continue to smoke VLNC cigarettes. Further, in clinical trials where participants are assigned to VLNC cigarettes, most participants continue to smoke them. These data contradict the argument that a mandated reduction in nicotine is equivalent to cigarette prohibition.

People who have a persistent desire for nicotine will have nicotine available in alternative forms. A mandated reduction in nicotine content does not remove nicotine from all products—only from the products that cause the greatest rates of death and disease. Many people are likely to continue using nicotine in non-combusted products (e.g., e-cigarettes, oral nicotine pouches) or in medicinal products (i.e., nicotine replacement therapy).

5D. Would the Public Support a Nicotine Standard?

As governments consider bolder tobacco product standard actions to reduce smoking prevalence, evidence of strong public support—particularly among those who would be affected by mandated product standards (e.g., those who smoke)—has the potential to accelerate government action and implementation of such policies, as well as justify and establish that they are politically feasible and/or desirable. Several publications and policy reports have examined public support for a broad range of tobacco policies that would pertain to tobacco product standards, including menthol bans [92,119–121], banning cigarette filters [122–124], mandating reduced-nicotine content in cigarettes [92,94,125–134], and banning the sale of commercial cigarettes altogether [120,135–137].

Published studies and policy reports examining public support or opposition to a mandated reduction in cigarette nicotine content have found high levels of support (>50%). A recently published systematic review and meta-analysis [125] assessed public support for various commercial tobacco endgame policies across several countries, including banning cigarette sales, banning additives, prohibiting the manufacture of cigarettes with filters, increasing taxes, implementing a tobacco-free generation policy, and restricting the number of retail suppliers. The authors reported that support was highest for mandating a VLNC in tobacco products among the general population, as well as among people who smoke. Fourteen



Subgroup	Policy.1	Policy.2	Policy.3	Policy.4	Policy.5	Policy.6	Policy.7	Policy.8	Policy.9	Policy.10	Policy.11	Policy.12	Policy.13
General population	74.0%	75.9%	69.2%	51.3%	-	47.2%	53.9%	53.7%	80.0%	73.5%	61.3%	61.8%	22.0%
People who smoke	42.1%	62.9%	42.5%	35.8%	66.2%	30.0%	39.1%	37.8%	-	50.0%	22.2%	38.5%	15.0%
AYA	59.0%	63.3%	-	-	-	-	68.0%	16.0%	-	71.0%	58.0%	-	-
AYA who smoke	9.5%	71.9%	44.8%	-	-	-	46.0%	12.5%	-	54.1%	-	-	-

studies were included in a meta-analysis, which showed that, overall, 76% of the general population in six high-income countries supported a mandated reduction in nicotine content, with support only somewhat lower among smokers (63%) than in the general population (See Figure 4). The only LMIC country included in this review was Pakistan, which did not assess support for a mandated reduction in nicotine content; however, 80% of adults in Pakistan did support banning cigarette sales altogether, which may indicate that there would be high support for reducing nicotine in cigarettes.

Most research that has examined support or opposition to a mandated reduction in nicotine content has been conducted in Westernized high-income countries. There are few studies from non-westernized and/or LMICs, many of which have less advanced tobacco control measures and may have lower political will and resources to pass and implement such policies [138]. However, a study from the Republic of Korea found high levels of support among adults for limiting the nicotine content in cigarettes (68%) compared to other endgame policies [126]; thus providing evidence that support in non-Westernized countries may be comparable to that found in high-income Westernized countries.

Aotearoa New Zealand is the only country to have passed legislation mandating a reduction

in cigarette nicotine content [139]. High levels of support in the general population (78%) for this policy suggest it was well received [140]. There was also strong support for the legislation among people who smoke (48% support vs. 32% oppose) and people who have recently quit smoking (75% support vs. 16% oppose) (See Figure 5A). Similarly, a large proportion of youth (65%) and young adults (69%) in New Zealand supported the legislation (See Figure 5B [129]). However, despite receiving strong support, the newly elected National-led coalition government repealed the law in 2024 [34].

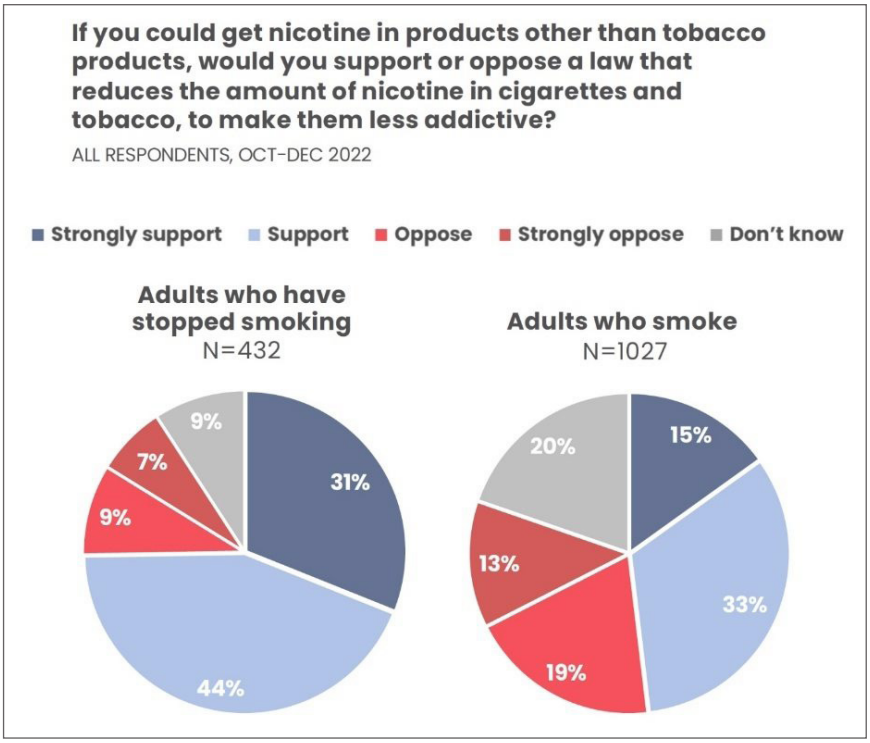


Figure 5A

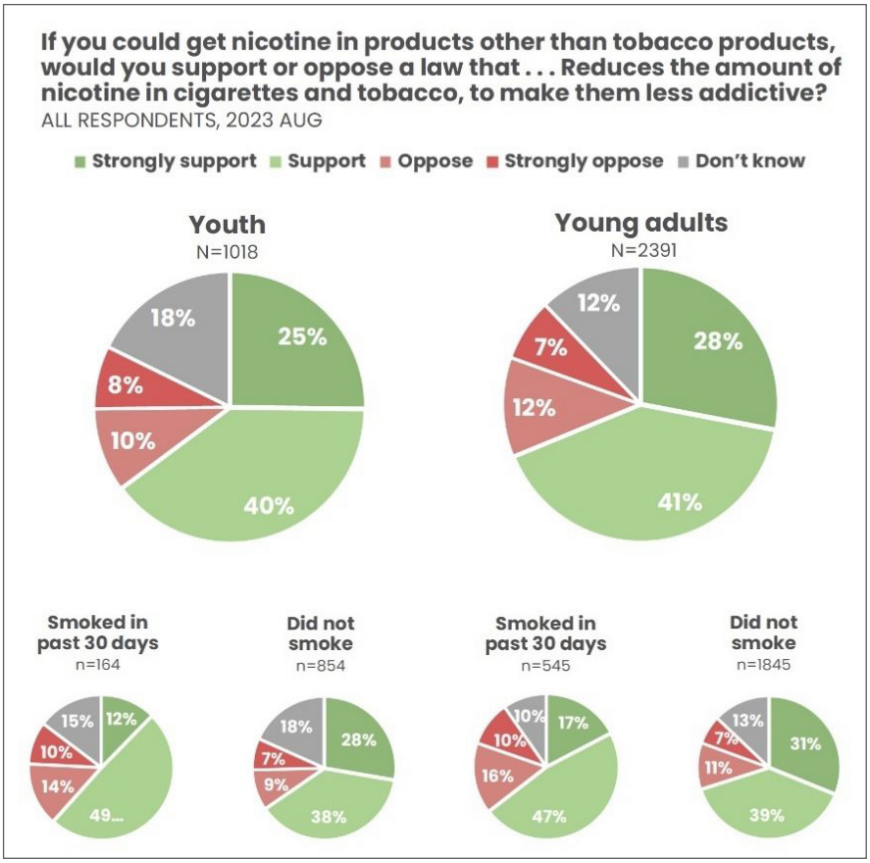


Figure 5B

Most studies that have assessed support for a mandated reduction in the nicotine content of cigarettes have been conducted in the general public, including people who smoke, but there has been less attention to subgroups who smoke cigarettes at higher rates (e.g., marginalized groups, people with mental health conditions). For example, in many countries, indigenous people smoke cigarettes at much higher rates compared to non-Indigenous populations [154–158]; thus, assessing levels of support among this priority population is important [141]. One study conducted among Māori adults who smoke in New Zealand found that 59% supported the policy, and only 17% opposed it [134].

Few studies have assessed support or opposition to a mandated nicotine reduction in nicotine content among people who have experience using VLNC cigarettes, which theoretically could impact support or opposition to such a policy. Two published randomized trials have assessed support for a law reducing the amount of nicotine in cigarettes among non-naïve US subjects who were randomized to smoking VLNC cigarettes (0.4 mg/g) for 6 weeks [142] or 20 weeks in clinical trials of VLNC cigarettes versus NNC cigarettes [143].

In the first study, 59% of participants supported the policy (18% opposed) at baseline, with only a small reduction in support at the end of the 6-week trial[142]. Support at follow-up did not differ significantly between participants who were randomized to smoke VLNC

cigarettes (50% support, 26% oppose) and those who smoked their usual brand (55% support, 20% oppose).

In the second study, at the end of the 20-week trial, 60-61% of participants in all study arms (participants randomized to immediate reduction and gradual reduction of nicotine level to 0.4 mg/ml and control group provided with normal-strength cigarettes) supported the policy, and 15-19% opposed it. Support was higher among those who were adherent to smoking only VLNC cigarettes (65%) compared with those who were non-adherent (44%) [143]. Older participants and those interested in quitting had increased odds of support; there were no differences by sex, ethnicity, or education level. These findings suggest that there is substantial support for a nicotine standard law among people who smoke and who have experienced smoking these products.

In sum, the evidence collectively shows a high level of support for a mandated reduction in nicotine content among the public and among people who smoke in large population surveys in many countries, as well as participants in clinical trials who have experienced smoking VLNC cigarettes for several weeks. This is important evidence for policymakers to justify introducing this measure and counter claims that such policies would be unpopular among the public and those most impacted. The high level of support is perhaps unsurprising given 1) the overwhelming evidence that most people who smoke want to quit but find it hard to do so and 2) the compelling evidence and logic that reducing or eliminating nicotine to make smoked tobacco products less addictive will reduce the number of cigarettes people smoke, facilitate quitting, and reduce the risk of relapse [42,144].

5E. Will a Nicotine Standard Result in Extreme Discomfort among People Who Smoke?

The overall evidence indicates that VLNC cigarettes typically do not produce greater reports of immediate craving or other withdrawal symptoms. While there are results from studies of brief exposure that are mixed, the findings of many investigations indicate that both short and long-term use of VLNC cigarettes can suppress craving and withdrawal as successfully as NNC or usual brand cigarettes [62,145–147]. Craving and withdrawal suppression from smoking VLNC cigarettes is likely due, at least in part, to the learned connection in people who smoke between the sensorimotor stimuli associated with smoking and the physiological response due to nicotine. Because of the conditioning, these stimuli can suppress craving and some other withdrawal symptoms even when very little nicotine is delivered [148].

5F. Is a Nicotine Standard Technically Achievable and Verifiable?

There is clear evidence that cigarettes can be successfully manufactured at nicotine contents that meet the requirements of a product that is non- or minimally addictive. The achievability of producing tobacco at very low levels of nicotine is supported by internal tobacco industry documents, the development of low-nicotine products for research, and the marketing of products that meet the requirements of a VLNC product standard. In addition, analytical methods exist that can verify that products meet the standard and distinguish them from those that do not. Countries considering a mandated reduction in nicotine content should require that all testing and verification costs be borne by companies seeking to market their products. These costs should not be borne by the government

regulatory agency or non-governmental organizations.

5F1. Achievability

5F1a. Industry Documents

Industry documents made available through litigation in the United States have provided insight into activities that the tobacco industry has undertaken to remove nicotine from tobacco. While some efforts were more successful than others, through various research efforts, these companies have successfully developed methodologies to lower nicotine levels in a wide variety of tobacco types.

These efforts date back to 1964, when Backhurst, in a British American Tobacco industry file note, discussed how up to 99% of nicotine can be removed from tobacco using 1% ammonia in chloroform solvent extraction, with only a 5% loss of other tobacco materials [149,150]. Lorillard tried a somewhat different approach [151]. Their goal was to isolate nicotine to add it back to tobacco to create higher-nicotine cigarettes with the same tar level. Nonetheless, they were able to extract 80-85% of the nicotine with either water or freon, but treatment with ammonia was required to achieve these results. A report by Schmekel and Rodemeyer of Brown & Williamson describes the use of CO2 supercritical fluid extraction, a process that can also be used to extract caffeine from coffee [152]. The objective was to achieve tobacco with less than 0.05 mg of nicotine per cigarette as measured in the smoke.

A patent was applied for by Philip Morris (PM) for the process of semi-continuous extraction of nicotine from tobacco with supercritical CO2 [153]. When supercritical CO2 is used to extract caffeine from coffee, it also removes aroma compounds, so a multi-step process is needed. But aroma compounds can be added back to the tobacco during the process. A document from Lorillard describes efforts to apply supercritical fluid extraction to produce tobacco with reduced nicotine levels while maintaining acceptable sensory qualities [154]. They identified ways to extract flavors first, with little nicotine removal. This allows flavors to be reintroduced onto the tobacco.

An alternative approach was developed that used supercritical fluid extraction with CO2 under conditions that remove nicotine while retaining flavor compounds. A report by Roselius et al. [155] of Brown & Williamson describes a patent application for extracting nicotine from tobacco using high-pressure CO2 extraction. They identified conditions in which aroma constituents are not extracted. The addition of ammonia improved the results. This can also be accomplished in the subcritical state. They give examples showing a reduction in nicotine of about 95% or more, with no loss of aroma, across multiple tobacco types. A particular cost-saving advantage of this approach is that, once the CO2 is no longer supercritical, the nicotine precipitates, allowing the solvent to be reused.

PM has moved forward with a more complete consideration of how to move these research results into production. PM's nicotine reduction process uses tobacco stem to remove nicotine from CO2 that has extracted nicotine from tobacco, thus recycling the CO2 [156]. PM went so far as to design a new facility to remove 97% of nicotine from tobacco using supercritical CO2 extraction [157]. The report estimated that the facility could produce enough tobacco for 12 billion cigarettes per year. Ammonium bicarbonate and monopotassium citrate are used. About 3 ½ hours were needed for the process. It is possible to extract nicotine virtually exclusively and retain flavor compounds.

Other approaches that have been shown by the tobacco industry as means for reducing

levels of nicotine in tobacco leaves include genetic engineering [158,159] and tobacco blending [160].

A tobacco industry document lists a series of patents for reducing nicotine in tobacco and may be useful for demonstrating the success of industry efforts [161]. Patent holders include Philip Morris, Brown & Williamson, and R.J. Reynolds.

5F1b. Commercially Available VLNC Cigarettes

Quest cigarettes (Vector Tobacco) utilized genetically engineered tobacco and were marketed in the United States from 2002 to 2010 [162]. They were available at three different nicotine levels, with the lowest nicotine level being comparable to a VLNC cigarette and reported to be 0.4 mg nicotine per gram of tobacco. Next (Philip Morris) was introduced onto the US commercial cigarette market in 1981 [163]. The cigarette delivered comparable nicotine levels to VLNC cigarettes, and Philip Morris claimed it was indistinguishable from regular cigarettes. Finally, in 2019, the US FDA granted 22nd Century Group, Inc. marketing authority for Moonlight and Moonlight Menthol cigarettes after determining that these products met the statutory requirement for marketing and were appropriate for the protection of public health. FDA determined that these products presented no additional disease risk than current products but would have lower abuse liability than the comparator brand and facilitate abstinence from smoking. This decision was based on the company's products tested containing very low levels of nicotine per gram of tobacco, similar to their VLN test cigarettes (97-98% lower nicotine content, 0.46-0.5 mg/g) [164]. These products are now being sold in the US under the name VLN.

5F1c. Research Cigarettes

Before 1999, the United States National Institute on Drug Abuse (NIDA) contracted with Ultratech/Lifetech Corporation to produce VLNC cigarettes for research purposes that contained 0.6-0.7 mg nicotine per gram of tobacco [147]. Later, working through a contract with 22nd Century, NIDA produced Spectrum cigarettes, a series of products with various content levels of nicotine [165], both menthol and non-menthol versions. In a paper by Richter et al. [165], the investigators reported that Spectrum cigarette nicotine levels were 0.3, 1.0, 2.0, 5.0, 10, 16, and 24 mg nicotine/g tobacco. The company used a combination of genetic engineering and plant breeding to produce tobacco with reduced nicotine content. These cigarettes were made available to researchers through NIDA's drug supply program, and most of the clinical trials discussed above utilized these products.

5F2. Verifying Cigarettes Have Met the Standard

Methods have been developed to measure nicotine levels in cigarette tobacco by the US Centers for Disease Control and the World Health Organization [165]. Richter et al. [165] characterized the physical characteristics (weights, cigarette length, pressure drop, filter ventilation, filter circumference, rod circumference, filter length, tobacco length, and overwrap length), nicotine content, and other HPHCs (TSNAs, PAHs) in tobacco filler from Spectrum research cigarettes. For nicotine analysis, the following method was used: 5 mL of 2N NaOH was added to 1.0 g of tobacco filler in a 60-mL amber vial. A simple extraction was performed with 50 mL of an MTBE stock containing quinoline as an internal standard, and gas chromatography/mass spectrometry was used for quantification. Detection limits (0.16 mg/g) were set using Taylor's method [166]. This study reported tobacco nicotine levels as low as 0.28 mg nicotine/g tobacco, but lower detection levels would likely be

achievable using this method if additional standards at lower levels were used.

The World Health Organization (WHO[167]) has developed a detailed standard operating procedure for measuring nicotine in cigarette tobacco. After conditioning, the cigarette tobacco filler is ground and mixed. Nicotine is extracted from the cigarette tobacco filler with a mixture of n-hexane, sodium hydroxide solution, and water using an internal standard of n-heptadecane. Other suitable internal standards include quinaldine, iso-quinoline, and quinoline. The organic layer is analyzed by gas chromatography with a flame ionization detector. The lowest standard reported using this method was 1.3 mg of nicotine per g of tobacco. However, nicotine quantification at lower levels is likely achievable using this method if lower standards are applied.

In addition, the US FDA tobacco laboratory has developed and validated a method for measuring nicotine in tobacco with a detection limit of 0.05 mg/g and a limit of quantification of 0.1 mg/g. The method uses sodium hydroxide treatment, extraction, and gas chromatography/mass spectrometry [168].

Finally, in 2021, CORESTA (Cooperation Centre for Scientific Research Relative to Tobacco) an industry-led organization updated CRM (CORESTA Recommended Method) No. 62 (Determination of Nicotine in Tobacco and Tobacco Products by Gas Chromatographic Analysis) and, in 2020 CRM No. 87 (Determination of Nicotine in Tobacco Products by Gas Chromatography-Mass Spectrometry (GC–MS)) by lowering the calibration range to measure nicotine in tobacco as low as 0.117 mg per gram tobacco [169].

If an alternative to these analytical methods is used, analyses should be carried out in a laboratory that is accredited to the most recent version of ISO/IEC 17025. Tests should be carried out using an appropriate chromatography-based analytical method (such as gas or liquid chromatography) and a sensitive detection technique, such as flame ionization or mass spectrometry. To demonstrate fitness for use, the analytical method should meet adequate analytical parameters, be fit for purpose, and be fully validated at the laboratory performing the analysis, including accuracy, precision, specificity, selectivity, detection limit, quantification limit, linearity, and range.

Verification of compliance with a product standard through product testing should be required before specific products can be marketed. All method validation and testing costs should be borne by the company marketing the product, as discussed and supported by WHO [170]. These costs should not be the responsibility of a country's regulatory body.

Importers or manufacturers should provide the following product information for each brand and variant, demonstrating compliance before marketing and every year that the product is on the market.

1. a specific description of the product type, brand, variant, and unique product code (e.g. EAN or UPC number) which can be used to make a clear identification.
2. a summary of test results for nicotine content for the tobacco for multiple lots of products manufactured according to the actual standards for products on the market (this may be for at least three batches and may require testing of products during different times of the year)
3. a summary of information on the testing methodology used, including validation results as described above.

In addition, countries may choose to conduct spot checks by purchasing products from retail establishments and testing them separately from industry results, using laboratories independent of the industry. WHO has developed laboratory capabilities for this particular purpose as part of the Tobacco Laboratory Network (TobLabNet). As mentioned above, means should be in place, for example, through user fees, to require companies that sell products to bear these costs.

In sum, there are multiple methods for lowering the nicotine levels within cigarettes, including ammonia in chloroform solvent extraction and supercritical fluid extraction. In addition, genetic engineering and plant breeding may be other avenues to produce tobacco with nicotine content that meets the standard. There are validated methods for verifying that products meet the nicotine standard by gas chromatography with either flame ionization detection or mass spectrometry. Cigarette companies should be required to bear the costs of manufacturing VLNC cigarettes and verifying that their products meet the standard.

6. Other Consequences of a Mandated Reduction in Nicotine Content, Their Costs and Benefits

6A. Weight Gain

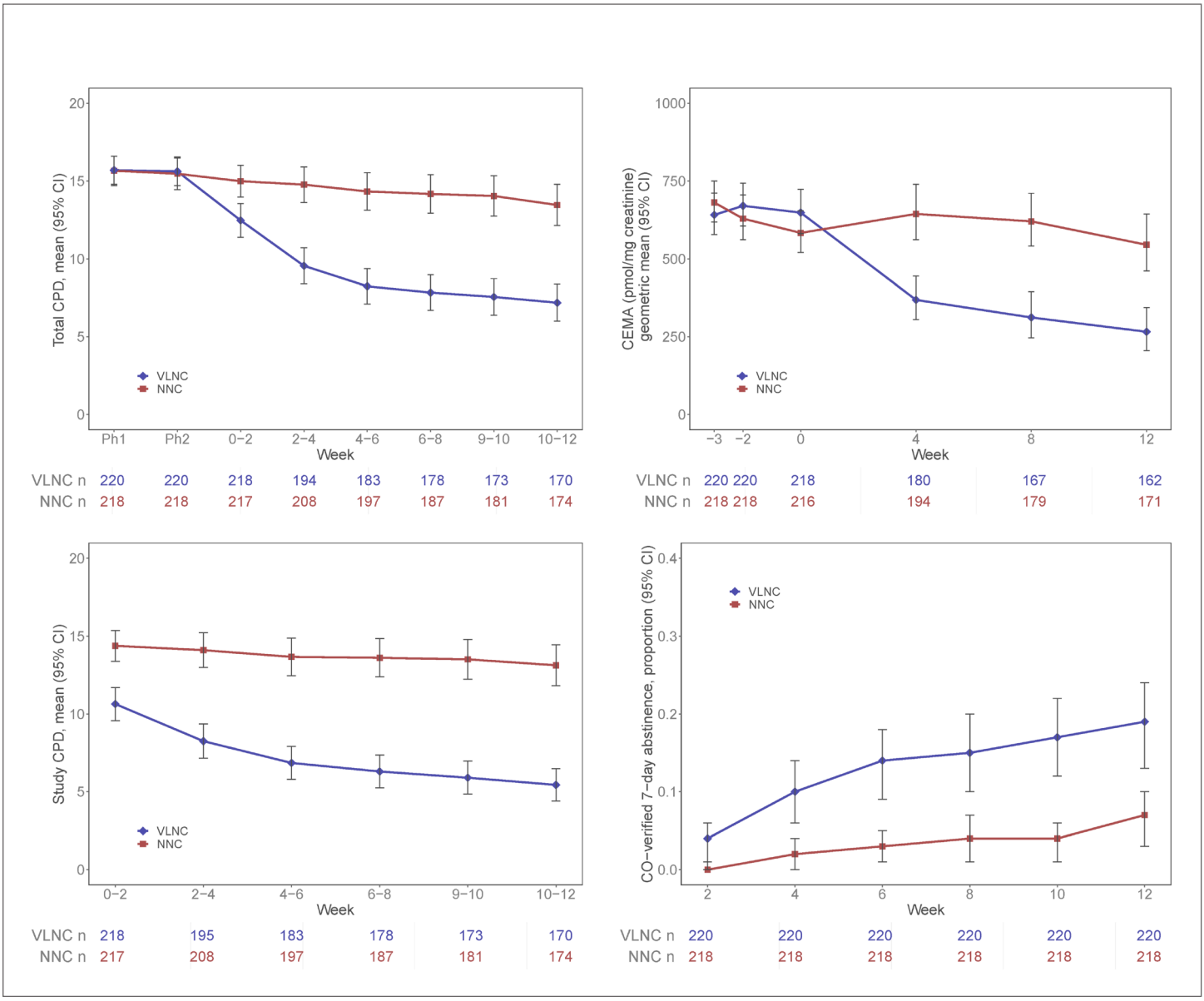
Reductions in nicotine exposure may lead to weight gain in some individuals, a phenomenon that is often seen following smoking cessation. A randomized clinical trial found that people who smoked were assigned to VLNC cigarettes and were adherent to the request to use only those cigarettes, gained, on average, 1.2 kg over the course of six weeks, particularly those who adhered to the study's low-nicotine conditions [171]. **This finding suggests that a decrease in nicotine exposure, like smoking cessation, may trigger weight gain in some people who smoke. Despite this, the potential health benefits of reducing nicotine levels—such as decreased dependence and reduced exposure to cigarette smoke—likely outweigh the unintended consequence of weight gain, much as the broader benefits of smoking cessation programs outweigh the risks of weight gain.**

6B. Switching to Other Nicotine Products

A mandated reduction in nicotine content is likely to result in switching from combusted to non-combusted forms of nicotine among individuals who smoke and are unable or unwilling to quit nicotine altogether. Indeed, the framework proposed by Gottlieb and Zeller from the US FDA includes the expectation that reducing nicotine in the most harmful combusted products (e.g., cigarettes) will result in a shift to alternative non-combusted products [172]. To date, several randomized trials have investigated this possibility with alternative nicotine delivery systems (ANDS; [53,54,173,174].

Hatsukami et al. [173] randomized adults who smoke (N=136) to receive eight weeks of VLNC cigarettes with access to 1) an array of alternative combusted (cigars, little cigars, cigarillos) and non-combusted (smokeless tobacco, snus, e-cigarettes, nicotine replacement therapy (NRT) patch, NRT gum/lozenge) products or 2) only non-combusted products, and compared both conditions to 3) continuing to smoke NNC cigarettes with access to an array of combusted and non-combusted alternative products. Findings demonstrated that switching to VLNC cigarettes increased uptake of alternative nicotine products, reduced use of combusted tobacco products, increased quit attempts, and reduced overall nicotine exposure. Importantly, limiting access to only non-combusted alternatives also reduced exposure to toxicants and further decreased nicotine exposure compared with those who had access to both combusted and non-combusted alternatives. Combined, findings demonstrate that reducing the nicotine in cigarettes could result in increased uptake of alternative products and reductions in smoking, with the most significant reduction in biomarkers of harm experienced when available alternatives are limited to non-combusted products only.

The second study of ANDS [174] was a factorial trial in which adults who smoke (N=50) were randomized to receive 12 weeks of VLNC vs NNC cigarettes as well as e-cigarettes containing low (0.3%) vs moderate (1.8%) nicotine concentrations in tobacco flavor only vs tobacco, fruit, dessert, and mint flavors. Though underpowered to adequately test interactions, uptake of e-cigarette use appeared greatest among participants in the VLNC cigarette conditions. Trends indicated that the greatest reduction in cigarette smoking was



achieved among those assigned to VLNC cigarettes in combination with higher nicotine content e-cigarettes in an array of flavors. Taken together, the findings are consistent with the hypothesis that a product standard mandating VLNC cigarettes may maximize migration to alternative non-combusted products if sufficiently appealing alternatives are available.

The third trial of ANDS [53] randomized adults who smoke (N=438) to 12 weeks of an experimental marketplace in which either VLNC or NNC cigarettes were available. In addition, all participants had access to a range of ANDS products, including e-cigarettes, oral nicotine pouches, snuff, snus, NRT patches, and NRT gum/lozenges. Participants in both conditions received points redeemable for the product(s) of their choice, allowing them to purchase their assigned study cigarettes (VLNC or NNC) and/or alternative non-combusted products. Consistent with prior research, the VLNC cigarette condition resulted in greater reductions in smoking, more days of cigarette abstinence, and a greater reduction in biomarkers of exposure (Figure 6). The VLNC cigarette condition also resulted in more use of non-combusted nicotine products, with e-cigarettes representing the most popular non-combusted alternative to smoking. These findings provide further evidence that a nicotine content product standard for cigarettes would likely accelerate the rate of switching to alternative non-combusted products.

The most recent study to investigate switching to ANDS [54] conducted three parallel RCTs in samples of adults who smoke with 1) affective disorders and 2) opioid use disorder, as well as 3) women of reproductive age (21-44) with lower educational attainment (<high school). Participants (N=326) were randomized to receive 16 weeks of 1) NNC cigarettes, 2) VLNC cigarettes, 3) VLNC cigarettes plus tobacco-flavored e-cigarettes, or 4) VLNC cigarettes plus e-cigarettes in a range of commonly preferred (e.g., sweet and fruity) flavors. Consistent with prior studies, VLNC cigarettes resulted in reduced cigarette smoking. However, participants who received VLNC cigarettes plus e-cigarettes in a range of commonly preferred flavors had the greatest uptake of e-cigarette use, reduction in cigarette smoking, and reduction in biomarkers of harm. As such, findings demonstrate that VLNC cigarettes with access to e-cigarettes in an array of commonly preferred flavors maximized switching among adults in high-risk populations.

Taken together, randomized trials to date indicate that switching to ANDS is likely to occur in the context of a mandated reduction in nicotine content among people who smoke. Further, findings suggest that the greatest reduction in use is likely to be achieved if appealing non-combusted alternative nicotine products remain accessible while normal nicotine non-cigarette combusted tobacco products do not. These findings provide further support for a nicotine-limiting standard that includes all combusted products.

6C. Decreases in Tax Revenue

A mandated reduction in nicotine content will reduce the prevalence of smoking, which in turn will reduce government tax revenue from cigarettes if tax rates remain the same. However, tax revenues should not drive government decisions about public health, and policymakers can be thoughtful about how to recoup losses in revenue because of a nicotine standard for smoked tobacco. The effect on tax revenue will depend on how quickly tobacco use behavior is changed. An immediate reduction in nicotine content is best for changing smoking behavior. In countries where alternative nicotine delivery systems are also available, uptake and use of these products are likely to increase, and the tax burden could shift to them. Just as industry is transforming, the tax system should transform with it.

7. Other Paths Suggested That May Achieve the Same Benefits

7A. Allowing VLNC cigarettes on the Market Alongside NNC Cigarettes

An alternative option to a VLNC standard is a market-driven approach in which countries could authorize the sale of VLNC cigarettes—potentially with modified risk claims such as "Helps you smoke less"—while maintaining the availability of conventional cigarettes. People who want to quit or reduce their smoking would have the option to buy VLNC cigarettes, and those uninterested in changing their smoking behavior would remain unaffected. However, the evidence suggests that having VLNC cigarettes commercially available along with NNC cigarettes would attenuate the potential benefits of nicotine reduction for at least two reasons. First, in a market-driven approach, many people who use VLNC cigarettes are likely to also use NNC cigarettes sometimes, which has been found to reduce the benefits of VLNC cigarettes. For example, one study found that participants with higher urinary nicotine levels when smoking VLNC cigarettes prior to a quit attempt had poorer cessation outcomes [175]. The increased urinary nicotine levels were likely the result of participants using both VLNC cigarettes and NNC cigarettes. Indeed, non-adherence is common in real-world trials where participants are asked to exclusively use VLNC cigarettes, which may contribute to why most participants enrolled in VLNC trials continue smoking rather than quitting [41]. Primarily smoking VLNC cigarettes while intermittently smoking NNC cigarettes (i.e., intermittent reinforcement) would likely sustain behavior and not lead to extinction [176,177]. Second, in a market-driven approach, only some people who smoke are likely to use VLNC cigarettes. As discussed above, VLNC cigarettes have previously been available in the US with little commercial success, suggesting VLNC cigarettes are unable to compete when the market includes NNC cigarettes. **Thus, the commercial availability of VLNC cigarettes alongside NNC cigarettes would not result in the same benefits as a mandated reduction in nicotine content.**

7B. Shifting the Nicotine Marketplace Towards Non-Combusted Products

Others have argued that a mandated nicotine content reduction policy is unnecessary because smoking is already declining and the market is shifting away from cigarettes towards alternative nicotine delivery systems (ANDS), such as e-cigarettes. However, the evidence suggests that a nicotine standard and ANDS can work together to produce the greatest public health benefit [144]. Globally, cigarette smoking has declined since 1990, with the largest reductions occurring in high-income countries [11]. For example, in the US, the adult smoking prevalence in 2021 was 11.5% [178], and the adolescent smoking prevalence in 2024 was 1.4% [179], both historic lows, and some of the reduction in smoking may be due to the availability of ANDS. However, 28.3 million adults and 2.8 million adolescents in the US still smoke cigarettes, and as noted above, people who continue to smoke are often those who are more likely to experience tobacco use disparities. A complete transition to ANDS will take decades. Clinical trials demonstrate that a nicotine standard would accelerate the transition to ANDS [53,54], which will save lives. Indeed, these data are likely the reason that e-cigarette companies like JUUL Labs support a nicotine standard [180].

The availability of ANDS may also increase the benefits of a nicotine standard. Although modeling studies indicate that a substantial proportion of the population will quit after policy implementation, not all people who smoke will be able or willing to stop using nicotine. This may be especially true in countries with high smoking prevalence or among populations particularly vulnerable to smoking. Thus, the availability of legal ANDS, including e-cigarettes, smokeless tobacco, and oral nicotine products, as well as nicotine replacement therapies, is likely to be helpful within the context of a low-nicotine product standard for combusted tobacco. **The greatest public health benefits would come from a mandated reduction in nicotine content for smoked tobacco and a marketplace with a wide range of available ANDS.**

8. Loopholes to Address

8A. Other Combustible Products Including Cigars

The science indicates that it is critical that a mandated reduction in nicotine content include all smoked tobacco products, including cigarettes, pipe tobacco, little cigars, cigarillos, large cigars, and roll-your-own (RYO) tobacco. If these other products are not included in the scope, people who smoke are likely to substitute these combustible products for cigarettes, mitigating the health benefits of a product standard. As discussed earlier in this document, when people who smoke are asked how they would respond to a nicotine standard, switching to other combustible products is a common response [181]. In one clinical trial, the availability of other combustible products was manipulated following assignment to VLNC cigarettes [182]. Participants who did not have access to NNC non-cigarette combustibles had reduced exposure to toxicants and decreased nicotine exposure compared to those who had access to both combusted and non-combusted alternatives. These data demonstrate that extending a mandated reduction in nicotine content to non-cigarette combustibles is critical to ensure the greatest population health benefits.

Given their shape, size, use of filters, and packaging, little cigars are like cigarettes and can easily serve as substitutes. There have been several studies that provide evidence that supports that nicotine delivered from cigar smoking is sufficient to produce and maintain nicotine dependence. [183,184]. In addition, other studies have shown that RYO and pipe tobacco smoking is adequate to produce and maintain nicotine dependence when used [185]. To minimize migration to these products by people who smoke who look to maintain their nicotine exposure from combusted products, these products also should be subject to a maximum allowed nicotine content.

Studies examining the impact of VLNC cigars or RYO on tobacco use are limited, primarily because these products have not been available in a range of nicotine content that would be appropriate for study. However, research documenting the use patterns associated with these products shows that they are used in the same way as cigarettes by people who smoke, and a reduction in nicotine content to 0.4 mg nicotine/g tobacco would be expected to be below the threshold required to maintain dependence. Little cigars are similar to cigarettes in size, filtered like a cigarette, and most commonly used by people who also smoke cigarettes [186], making them particularly likely to serve as substitutes for people who smoke following a mandated reduction in nicotine content [186]. Indeed, behavioral economic purchase tasks demonstrate that little cigars substitute for cigarettes among adults who smoke [187,188]. Although cigar products typically contain a greater weight of tobacco per unit than cigarettes, a nicotine standard that limits the nicotine content per weight of tobacco is appropriate for products of different tobacco weights. Indeed, in laboratory studies that have assessed smoking topography and toxicant exposure for cigarettes and cigars, the plasma nicotine boost following use is similar for all products [189], indicating that the relationship between nicotine dose and reinforcement is consistent across these tobacco products.

8B. Manipulation of the Product or Non-nicotine Constituents

Manufacturers could attempt to alter the content or design of VLNC cigarettes to increase

their addictive potential. A wide range of manipulations is possible. Changes that aim to improve the bioavailability of nicotine from the product to the person (e.g., pH, back-loading of nicotine near the mouth end of the cigarette) would likely be ineffective given the low nicotine content of VLNC cigarettes [190]. However, other constituents of tobacco do have the potential to impact smoking behavior, including other alkaloids (e.g., nornicotine), beta-carbolines, and acetaldehyde [191–199]. Rodent self-administration studies have suggested that the content of these constituents would need to be increased well above current levels to maintain reinforcement [69]. Cigarette flavoring may also increase the appeal of cigarettes on its own, independent of nicotine, and tobacco manufacturers could add flavor capsules or flavoring to the cigarette filter. Further, there are now a variety of nicotine analogs that have similar pharmacodynamic actions as nicotine, have been used in non-cigarette products, and would likely reinforce smoking behavior and maintain addiction, even in the absence of nicotine.[200–202] Manufacturers could attempt to include these nicotine analogs along with nicotine if a mandated reduction in nicotine content were implemented.

The potential for product manipulation and alteration of non-nicotine constituents makes it critical that regulators do not allow manufacturers to change products without a thorough review of the impact of these changes on reinforcement and appeal. In the US, changes to currently marketed cigarettes or the legal sale of new cigarettes must be evaluated by the Food and Drug Administration (FDA), and the FDA needs to be aware of the impact of such manipulations. Effective implementation of a nicotine standard requires the capacity to monitor nicotine levels and levels of other constituents. Methods for assessing changes in product design and ingredients are available (see Section 5F).

8C. Addressing Misinformation

Many people believe that nicotine is the primary cause of cancer among people who smoke.[203–205] **It is essential for countries implementing a mandated reduction in nicotine content to tightly control packaging, advertising, and marketing of these products to prevent manufacturers from using language that could further contribute to misperceptions about their perceived safety** [206]. Even in the absence of manufacturer messaging, misperceptions that VLNC cigarettes are safer than NNC cigarettes should be corrected (see Section 9B).

8D. Regulation of Nicotine Delivered in Other Parts of the Tobacco Product or Accessories:

Because this regulation is aimed at reducing the nicotine content in tobacco, manufacturers may seek alternative ways to deliver nicotine to the user by incorporating nicotine into other parts of the product or accessories made just for this purpose. **In addition to setting a limit on the nicotine content of tobacco, countries may consider regulating products that contain nicotine in paper, filters, capsules, or other parts. Countries might consider regulating or prohibiting any product, such as separately sold cigarette holders or mouthpieces that contain nicotine.**

9. Maximizing the Public Health Benefits

9A. Immediate Versus Gradual Change:

Maximizing the public health benefit of a product standard to reduce nicotine content in cigarettes and other selected combusted tobacco products requires assessing the best approach for nicotine reduction (e.g., a step-down vs. immediate reduction to the targeted nicotine level on a set date). A ten-site randomized controlled trial was conducted in which people who smoked daily were randomized to either an immediate reduction to VLNC cigarettes (0.4 mg nicotine/g tobacco, n=503), a gradual or step-down approach to VLNC cigarettes (n=498), or a control condition of NNC cigarettes (15.8 mg nicotine/g tobacco, n=249) [44]. The results demonstrated greater reductions in cigarettes per day and in biomarkers of toxicant and carcinogen exposures, a greater number of smoke-free days, and a higher rate of biochemically verified end-of-intervention 7-day point prevalence abstinence in the immediate vs. gradual and control groups. The results also suggested the occurrence of compensatory and more intense smoking at the moderate levels of nicotine reduction in the gradual reduction group, signifying that with this approach, there might be a period where some people who smoke will experience greater exposure to toxicants. On the other hand, participants in the immediate reduction group experience greater severity of withdrawal symptoms and higher rates of dropouts and non-compliance in only using study cigarettes than the other two groups. **These findings suggest that an immediate reduction in nicotine is likely to result in the greatest public health benefits and that methods to limit discomfort or use of alternative (illicit) combusted products must be considered.**

9B. Health Communications

Many people believe that nicotine is the primary cause of cancer among people who smoke [203–205], even though other constituents primarily contribute to cancer and other disease risks [207]. This misperception could mitigate the benefits of a mandated reduction in nicotine content if people who smoke believe VLNC cigarettes are less harmful [208]. One concern is that people who smoke might not reduce their cigarette smoking or might have reduced intention to quit smoking following a mandated reduction in nicotine content because they incorrectly believe VLNC cigarettes are less likely to cause physical harm. Indeed, many people who smoke incorrectly believe that cigarettes with reduced nicotine yield (i.e., "light" cigarettes) are less harmful than full-flavor cigarettes,[209] largely as a result of marketing. Similarly, lab studies and clinical trials have demonstrated that people who smoke believe VLNC cigarettes to be less harmful than NNC cigarettes [210]. However, there is no current evidence that these misperceptions negatively impact smoking behavior. Mercincavage et al. [226] found that viewing an advertisement for reduced nicotine cigarettes increased beliefs that reduced nicotine cigarettes were healthier than regular cigarettes, but these false beliefs did not affect smoking behavior. Pacek et al. [227] completed a secondary analysis of a multi-site RCT in which participants were not told the nicotine content of the cigarette they received (i.e., nicotine was blinded), but participants who believed they had received a low-nicotine cigarette were more likely to believe their assigned cigarette was less harmful. However, these misperceptions did not reduce the benefits of VLNC cigarettes on smoking behavior in the trial.

Educational materials about VLNC cigarettes have produced inconsistent results on harm perceptions [78,80,211], but Villanti et al. [212] provided nicotine corrective messages to a

sample of US adults who smoke and found that the intervention reduced false beliefs about nicotine over 3 months. Differding et al. [213] found that providing messages about the potential health harm of VLNC cigarettes increased accurate perceptions of the health risks of VLNC cigarettes, but misperceptions remained among one-third of participants.

Pairing a mandated reduction in nicotine content with an educational campaign could increase the benefits of a nicotine reduction policy. [214,215] Educational campaigns might focus on both the risks and benefits of VLNC cigarettes. For example, campaigns could aim to inform people who smoke that VLNC cigarettes will reduce their addiction and help them smoke less or improve their chances of quitting smoking, but that long-term use of VLNC cigarettes will confer the same health risks as conventional cigarettes. Education about the public health benefits of a policy could empower people who smoke to try to reduce smoking or make a quit attempt. In the US, VLN King® cigarettes have authorization from FDA (modified risk tobacco product [MRTP] authorization) to use language in their marketing informing consumers that these products "greatly reduce nicotine consumption" and "help you smoke less." Additionally, improving knowledge about the relative risk of different tobacco products might engender switching from VLNC cigarettes to alternative nicotine products like e-cigarettes.

9C. Cessation Support:

Although people who smoke and have switched to VLNC cigarettes experience an increased likelihood of quitting, most continue to smoke at least for the limited duration of clinical trials [e.g., 43,44,48,50,53,54]. Some experience withdrawal symptoms [44,53], although at lower severity than people who are asked to abstain from higher nicotine content cigarettes [173]. These individuals could benefit from the provision of behavioral and pharmacological smoking cessation treatments. The availability of resources for treatment can be made through educational campaigns such as FDA's Every Try Counts campaign, referrals to state quit lines or Smokefree.gov, or discussions with a healthcare provider [230, 231]. The World Health Organization has also noted that a nicotine reduction strategy should be accompanied by the provision of cessation treatments to help people quit. These may include behavioral support and NRT or other medications [216]. **In sum, the provision of behavioral and pharmacological smoking cessation support could increase the public health benefits of a nicotine standard.**

9D. Alternative Non-combusted Products:

Those individuals who continue to use a nicotine-containing non-medicinal product or have tried and failed in using FDA-approved medicinal smoking cessation products could be informed about the continuum of risk for tobacco and nicotine products. One randomized controlled trial found a high uptake of non-combusted ANDS from an experimental marketplace, particularly vapes, among those assigned to use VLNC cigarettes vs. NNC cigarettes and who quit smoking [53]. Another clinical trial observed that the fewest cigarettes smoked occurred among those participants assigned to VLNC cigarettes and the preferred flavor of e-cigarettes (See Section 6B). Similarly, in a laboratory study with early young adults, fewer cigarette puffs were chosen among those assigned to use VLNC cigarettes and flavored e-cigarettes vs. VLNC cigarettes with tobacco flavor only, e-cigarettes, or NNC with tobacco or other flavored e-cigarettes [217]. These results suggest that having access to appealing alternative, non-combusted nicotine delivery products might have the most beneficial effect. It is important to note which products have been

authorized for sale by government regulators (e.g., some countries have banned certain products or authorized only some brands/sub-brands or product types). It is also important to communicate that the use of any tobacco or non-medicinal nicotine product is not considered to be safe, and the long-term health consequences for many of these products are yet unknown.

In summary, a nicotine product standard must be implemented alongside other tobacco control efforts (e.g., taxation, tobacco-free environments, smoking cessation treatments). Furthermore, preparing the landscape for a nicotine content reduction product standard by educating the current and potential consumers and making accessible off-ramps away from tobacco smoking will be essential components for the maximal public health benefit of this standard.

10. Implementation Issues

As discussed throughout this document, to strengthen implementation of a mandated reduction in nicotine content, governments should have the capacity to ensure compliance with the standard, evaluate the population impact of the standard, and place limits on possible industry steps that could undermine the standard's health benefits. Many of these have been discussed elsewhere in this document but are briefly covered here.

To maximize the benefits of a mandated reduction in nicotine content, the government will need to be thoughtful about restrictions that ensure compliance with the standard. The World Health Organization has previously published documents to aid countries in planning for the implementation, compliance, and enforcement of tobacco control policies [218,219], which may be useful for this purpose. For example, when appropriate under a specific country's legislative and regulatory authority, governments might require that tobacco product manufacturers conduct regular testing of their finished tobacco products to ensure compliance with the standard, using analytical test methods validated in an analytical test laboratory. Manufacturers would need to maintain documentation of all test results, which can be produced upon request. The cost of this testing and documentation may be borne by the manufacturer. Manufacturers might be required to provide a sampling plan that is reviewed and approved by the government. The sampling plans should ensure that the samples are representative of the batch being sampled, that the number of samples is based on a valid scientific rationale, and that the number of samples is sufficient for the intended purpose [220]. The government might require that all test samples be stored in accordance with the intended storage conditions of the finished tobacco product and that they be representative of all storage facilities, including factories, stockrooms, warehouses, and other locations that contain finished tobacco products. The sampling plan could also specify the criteria for deciding whether to accept or reject each batch. Regulatory bodies may wish to impose a limit on the length of time between when a batch is manufactured and when it is tested. Governments may wish to ensure that sampling is conducted by individuals with the required expertise to conduct the analytical test method. When a product or batch is found not to conform to the standard, manufacturers may be required to have approved standard operating procedures for its disposal to prevent its distribution into the tobacco marketplace. Tobacco manufacturers may also be required to investigate to determine the extent of nonconformity when a test article fails to comply with the standard. Tobacco products included in the standard should be required to include a manufacturing code that can be used to identify the production batch, allowing governments to identify and remove nonconforming products if testing reveals that a commercialized product does not meet the standard.

In addition to requiring that manufacturers demonstrate their product meets the standard prior to commercial sale, when appropriate under a specific country's legislative and regulatory authority, the government would ideally require manufacturers to submit testing demonstrating that their product does not contain additives or constituents that could mimic the reinforcing effects of nicotine. Strict limits would be placed on manufacturers regarding packaging, advertising, and health messaging that clearly conveys the nuance that smoking VLNC cigarettes may reduce dependence, which could help people quit, but long-term use will convey similar health risks as conventional cigarettes.

To maximize the benefits of a mandated nicotine standard, governments should set a clear, effective date by which all combustible products must meet the standard. The effective date could be far enough into the future to allow manufacturers to produce cigarettes that meet the standard, submit product testing and plans for future testing to the government, and for the government to review those products and plans to ensure they meet the requirements of the standard. In the US, the effective date is proposed to be two years after publication of the final rule for a nicotine standard [220].

Governments may wish to regularly survey the population to understand the population's impact of a mandated reduction in nicotine content following implementation. At least one wave of survey data collection could take place before the standard is implemented, followed by regular intervals after implementation. Surveys could include items about the use of different tobacco product categories, recent quit attempts, and purchasing through illicit sources. The sample should be representative of the population, including individuals in the age range when tobacco initiation is most common (12+ years).

11. Summary

The evidence base for a mandated reduction in nicotine content has been growing for the past decade. While no country has yet implemented such a policy, New Zealand and the United States have both proposed rules. As discussed above, the evidence is clear that a mandated reduction in nicotine content to a level comparable to 0.4 mg nicotine/g tobacco would reduce the prevalence of smoking by increasing rates of smoking cessation, decreasing rates of smoking initiation, and increasing rates of switching to available noncombustible tobacco products. While many concerns have been raised about a nicotine standard (e.g., compensation or illicit trade), the evidence does not suggest that any of these concerns would outweigh the public health benefits of such a standard. Regulators must be careful in crafting and implementing such a policy to ensure that loopholes are closed and the public health benefit is maximized. A nicotine standard requires that the government has the capability to ensure compliance with the standard, monitor its impact, and place limits on industry counter-responses.

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Tracy T. Smith has received grants as a Principal Investigator, Co-Principal Investigator, or Co-Investigator from the following agencies: US National Cancer Institute, US National Institute on Drug Abuse, the Food and Drug Administration, and the American Cancer Society. Grants received over the past 3 years are not related to the content of this report. She received funds as a consultant for Versar related to the work contained in the report. She has received honoraria from the Ohio State University and Fralin Biomedical Research Institute at Virginia Technical College unrelated to the work in this report.

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Victor Lasebikan has no financial support or conflicts to report.

Roberta Freitas-Lemos reports previously serving as a consultant to Virginia Commonwealth University on an academic research project and currently receiving a non-commercial research fellowship administered by FUNDEP (Fundação de Apoio da UFMG), funded by the Brazilian Ministry of Social Development, to supervise research activities on healthy eating and point-of-purchase interventions. These activities are unrelated to the work presented herein.

Dorothy Hatsukami has received grant funding from the National Institutes of Health and the Food and Drug Administration for research that was directly relevant and not relevant to the document. She is currently a consultant to Eli Lilly and Achieve Life Sciences and an advisor to Antidote Therapeutics. She serves or has served on the scientific advisory boards on NIH funded projects relevant to tobacco for Yale University, Pennsylvania State University, Medical School of South Carolina, University of Kentucky, University of Michigan (for which she is currently a consultant). She has served on the advisory boards for MD Anderson Cancer Center, Rutgers Cancer Institute of New Jersey and Penn State Cancer Institute. She recently stepped down from the National Cancer Institute Scientific Board of Advisors but is currently serving on the World Health Organization Study Group on Tobacco Product Regulation.

Richard Edwards been an investigator on research grants funded by the Health Research Council of New Zealand, The Cancer Society of New Zealand, Universities of Otago (New Zealand), the Medical Research Future Fund and National Health and Medical Research Council (Australia), University of Queensland (Australia), South Australian Department of Health and the US National Institutes of Health-funded whilst at University of Otago, New Zealand and Flinders University, Australia. He has also received honoraria for serving on a National Health and Medical Research Council panel and on the Council of Preventive Health South Australia, and for occasional invited talks at international scientific meetings. These sources of funding have not supported the work presented herein. He has been an unpaid member of several expert advisory committees including chairing the Public Health Communication Centre Expert Advisory Board from 2021 to 2024, and is current President of SRNT-Oceania. He was a deputy editor of Nicotine and Tobacco Research until mid 2024.

Elias M. Klemperer has received funds for serving as an investigator on Food and Drug Administration and National Institutes of Health-funded research grants at the University of Vermont. He has also received funds as a consultant for the National Center of Excellence for Tobacco-Free Recovery and for serving on a Study Section of the National Institutes of Health. His grant-funded work includes research evaluating very low nicotine content cigarettes. All other interests are unrelated to the work presented herein.

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