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Review
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Review

Regulatory Approaches and Implementation of Minimally Addictive Combusted Products

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Abstract

Introduction: A joint meeting was held by the World Health Organization (WHO) and the Convention Secretariat of the WHO Framework Convention on Tobacco Control to examine the potential effects of a regulatory policy to reduce nicotine in cigarettes to minimally addictive levels. This paper reviews the feasibility of and approaches to implementing a nicotine product standard.

Methods: Prior WHO reports on this topic were consulted and a systematic review of the scientific literature was conducted. The paper was reviewed by the participants at the aforementioned meeting and their feedback was incorporated.

Results: The nicotine dose most likely to consistently reduce smoking behavior and dependence is ≤0.4 mg nicotine/g tobacco. An immediate rather than a gradual nicotine reduction approach appears to be more beneficial. Smokers are likely to seek nicotine from alternate sources (e.g., nicotine replacement therapies, e-cigarettes) or potentially, the illegal market. As such, the availability of alternative products, as well as strong policies against illegal markets, can potentially mitigate unintended consequences. An effectively reduced nicotine regulation must be imbedded in a comprehensive and strong tobacco control program that includes public education and surveillance. Barriers and challenges to implementing a nicotine product standard exist, particularly in low-capacity countries.

Conclusions: Not all countries will have the capacity to implement a regulation to reduce nicotine in cigarettes (and preferably other combusted tobacco products) to minimally addictive levels. However, for the countries that choose to implement it, such a policy could potentially dramatically reduce the burden of tobacco use.

Implications for tobacco regulatory science: Article 9 of the Framework Convention on Tobacco Control provides signatory governments the authority to implement a product standard for reducing nicotine in tobacco products to minimally addictive levels. This product standard has the potential to result in a dramatic reduction in cigarette and other combusted tobacco use and therefore, smoking-caused mortality and morbidity. This article describes the growing scientific evidence to support nicotine regulation in cigarettes, potential regulatory approaches and describes the infrastructure and tobacco control policies needed to implement a reduced nicotine product standard.

Introduction

The Seventh Conference of the Parties for the Framework Convention on Tobacco Control (FCTC) held in November 2016 requested the Conference Secretariat and the World Health Organization (WHO) to convene a meeting to address the issue of reducing the addictiveness of tobacco products (http://www.who.int/fctc/cop/cop7/FCTC_COP7(14)_EN.pdf?ua=1). One method for reducing addictiveness is to decrease levels of nicotine, the principal addictive

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agent in tobacco.[1] A product standard for nicotine can be implemented through Articles 9 and 10 of the FCTC, which involve the disclosure, testing, and regulation of the contents and emissions of tobacco products. The meeting was convened on 15–16, May 2018 in Berlin, Germany. The meeting participants included individuals with diverse expertise and relevant stakeholders. Tobacco industry representatives were not invited to this meeting. The goal of the meeting was to present and discuss the extant scientific and empirical evidence on the potential public health impact of reducing nicotine in cigarettes to minimally addictive levels as a regulatory measure. The topics that were examined included the individual and societal impact, both positive and negative, the feasibility, regulatory approach and implementation, and barriers associated with this potential regulation (https://apps.who.int/iris/bitstream/handle/10665/274955/WHO-NMH-PND-18.8-eng.pdf?sequence=1).

To date, considerable evidence exists from both scientific research[2,3] and industry documents demonstrating that a substantial reduction of nicotine in tobacco filler could significantly affect smoking behavior and dependence and as a consequence could potentially have a profound beneficial effect on public health. However, the necessary steps involved in implementing a product standard for nicotine have not been described. Furthermore, even within the public health community, there are skeptics who believe this approach smacks of prohibition with potential unintended consequences, is unwarranted if smokers have access to less harmful alternative nicotine products, and can potentially mislead consumers into believing they are smoking a less toxic cigarette. The goal of this paper is to describe the feasibility of and regulatory approaches for the implementation of a nicotine product standard for cigarettes, and ideally other combusted products, potential barriers for implementation, and recommendations to overcome these barriers.

Methods

The content of this paper was based on the 2015 advisory note, *Global Nicotine Reduction Strategy,* issued by the WHO Study Group on Tobacco Product Regulation (TobReg).[2] This advisory note was a comprehensive review of the scientific literature focused on the effects of reducing the addictiveness of cigarettes. To update this advisory note, a search for relevant articles spanning the years not covered by the WHO advisory note (mid-2015 through mid-2018) was conducted through PubMed and Scopus. Key words included nicotine reduction, reduced nicotine cigarettes, very low nicotine cigarettes, minimally addictive cigarettes, and non-addictive cigarettes. Only English language articles were reviewed. The resulting update was presented and reviewed at the 2018 WHO meeting held in Berlin and modifications were made based on the feedback received during this meeting. A subsequent WHO TobReg report was published in 2019, *A Global Nicotine Reduction Strategy: State of the Science*,[3] in the Technical Report Series 1015, updating the review conducted in the 2015 advisory report. Any new and relevant findings were incorporated into the present paper. Another search for articles published after the second WHO TobReg report, spanning mid-2018 to mid-2020, was conducted using the same terms as the previous search. Scientific findings from this updated search have also been included.

Results

Policy Approaches to Nicotine Reduction

The 2015 WHO TobReg Advisory Note was supportive of a policy "limiting the sale of cigarettes to brands with a nicotine content that is not sufficient to lead to the development and/or maintenance of an addiction." The 2019 Technical Report 1015 similarly concluded that in countries that have the appropriate infrastructure and capacity, a reduced nicotine policy has the potential to significantly benefit public health, substantially reducing the prevalence of smoking by preventing addiction and facilitating smoking abstinence. In the United States (U.S.) alone, adoption of this approach has been estimated as reducing the prevalence of smoking to 1.4% and averting cigarette-caused death by 8.5 million by the year 2100.[4] Further modeling has indicated that if a nicotine product standard had been implemented in the U.S. in 1965, when cigarette manufacturers had already recognized that cigarettes were deadly and addictive, 21 million smoking attributable deaths and 272 million life years lost could have been averted from 1965 to 2064.[5] Because there was sufficient evidence for the promise of this approach to benefit the population health as a whole, in March of 2018, the U.S. Food and Drug Administration (FDA) issued an Advance Notice of Proposed Rulemaking (ANPRM) to reduce nicotine in cigarettes to minimally addictive levels. In this ANPRM, the FDA requested input on several issues, including the potential allowable nicotine dose that would render a cigarette minimally addictive, and the best approach to reduce the level of nicotine in cigarettes, that is, an immediate versus gradual nicotine reduction strategy.

Establishment of a Product Standard for Nicotine Dose

Regulating the nicotine in cigarettes was first described in 1994 by Drs. Neal Benowitz and Jack Henningfield,[6] who proposed a reduction in nicotine in cigarettes to 0.5 mg per cigarette rod implemented over the course of 10–15 years with the main goal of minimizing the progression to dependence. Their proposal remained relatively dormant for many years because, at that time, there was no governmental regulatory agency that could implement a product standard for nicotine. Nevertheless, several studies were conducted to examine if this approach to reducing the prevalence of smoking was reasonable and to better understand the role of nicotine and the sensory aspects of smoking in maintaining smoking behavior.[7–15] It was not until the 2009 U.S. Smoking Prevention and Tobacco Control Act, which gave the U.S. FDA jurisdiction over tobacco products, that research in this area burgeoned.[16–62] These predominantly U.S. conducted studies have established that ≤0.4 mg nicotine/g tobacco, representing at least a 95% nicotine reduction compared to a typical conventional cigarette which contains about 10 to 15 mg/nicotine, is most likely to lead to reduced addictiveness.[2,3] This reduction in nicotine content is unlike the reduced nicotine yield of cigarettes formerly labeled as "light" and "ultralight," in which the reduction in yields was achieved by cigarette design features such as filter ventilation rather than through reduction of nicotine in the tobacco itself. Most significantly, there is minimal evidence of compensatory smoking with these very low nicotine content cigarettes[33,53,59–62] unlike with cigarettes that reduced nicotine yield through these other means.[63]

It should be noted that both clinical[16,34] and laboratory studies[28–30] indicate that cigarettes with nicotine/g tobacco doses of ≤2.4 mg (referred to as reduced nicotine content cigarettes, RNC) can also support attenuation of nicotine reinforcement, cigarette use, and dependence, with potentially no differences in effect between 2.4 and 0.4 mg nicotine doses.[34] However, prior and current large clinical trials have focused on the effects of the 0.4 mg nicotine dose (referred to as very low nicotine content [VLNC] cigarettes), leading to greater support for this dose as a product standard. Furthermore, more consistent reduced reinforcement effects have been found

with the 0.4 mg dose relative to other reduced doses of nicotine.[22,33] Intuitively the lower the nicotine dose, the less abuse potential for a product and greater probability of being effective in consumers more sensitive to nicotine.[28] Relative to normal nicotine content cigarettes (NNC, ≈15.8 mg nicotine/g tobacco), use of VLNC cigarettes in clinical trials of a general population of smokers has consistently led to reductions in smoking and cigarette dependence, *and* increased quit attempts and smoke-free days.[16,26] In laboratory studies, smokers abstaining from cigarettes overnight experience reduced craving, withdrawal, and number of cigarettes smoked *ad libitum* and increased ability to resist smoking after smoking a VLNC cigarette compared to sham smoking,[35] demonstrating some psychoactive effects even at this low dose. At the same time, abstinence from VLNC cigarettes produces relatively mild and transient withdrawal symptoms.[36]

Similar effects have been demonstrated across vulnerable populations of smokers at the VLNC or RNC dose. In secondary data analyses from the aforementioned 6-week clinical trial and other studies including a 20-week trial,[26] VLNC or RNC vs. NNC doses were found to decrease smoking behavior and dependence in smokers with a history of cannabis use,[37,38] with elevated depression scores,[39] in menthol and non-menthol smokers (although menthol smokers were less responsive than non-menthol smokers),[40] and in young adults.[41] Furthermore, smokers assigned RNC cigarettes experienced reduced score on a depression scale[39] and alcohol consumption[31,32] but increased weight[42] compared to NNC cigarettes. In laboratory studies, VLNC cigarettes were observed to be consistently less reinforcing than NNC cigarettes in smokers who are socioeconomically disadvantaged, diagnosed with opioid use or affective disorders[22,33] and with varying severity of tobacco dependence[43] or who are pregnant.[44] Attenuated reinforcing effects were also found with RNC cigarettes in smokers who experience other mental health conditions,[35] chronic health conditions[45] and among youth.[46] A randomized 12-week clinical trial demonstrated that smokers with opioid use or affective disorders and women smokers of lower socioeconomic status exhibited reduced cigarettes per day and dependence with the RNC vs. NNC cigarette.[34] In another 6-week clinical trial, smokers with serious mental illness demonstrated fewer cigarettes per day, lower smoke exposure, and lower scores on a cigarette evaluation scale, with no increase in psychiatric symptoms for the VLNC compared to the NNC cigarette.[47] While the aforementioned studies involved daily smokers, non-daily smokers also responded to RNC (≈ 1 mg nicotine/g tobacco) cigarettes with less intense smoking,[48] smoking fewer cigarettes and reporting less dependence.[49]

For ethical reasons, research on determining the development of cigarette dependence with VLNC cigarettes among adolescents and young adults naïve to tobacco cannot be conducted. However, the laboratory research described above with adolescent smokers, including among vulnerable young adult populations,[50] coupled with findings from animal studies,[51,52] suggest that adolescents and young adults may be less sensitive to the reinforcing effects of low dose nicotine than adults. Therefore, low nicotine doses that do not support self-administration and continued use in adults are likely not to lead to the acquisition of self-administration or continued use in adolescents.[52,53]

Gradual Versus Immediate Policy Implementation

Once the nicotine dose was established, the next urgent question that needed to be addressed was the optimal temporal approach to reducing nicotine in cigarettes, that is, whether a specific date should be set at which time all cigarettes sold in a country would be below a threshold for nicotine addiction (immediate reduction), or whether a gradual reduction of nicotine be implemented over the course of several years. To date, only one large clinical trial has been conducted to directly address this question. In this clinical trial, 1250 smokers who were uninterested in quitting in the next 30 days were randomized to three experimental conditions over the course of 20 weeks: 1) an immediate reduction to 0.4 mg nicotine/g tobacco (n = 503); 2) gradual reduction in nicotine from 15.5, 11.7, 5.2, 2.4 to 0.4 mg nicotine/g of tobacco, with doses changed on a monthly basis (n = 498); and 3) a control group of 15.5 mg nicotine/g tobacco cigarettes (n = 249).[26] In general, the results from this study showed a greater benefit from the immediate compared to the gradual nicotine reduction approach. Specifically, smokers in the immediate reduction approach demonstrated significantly fewer cigarettes smoked than the gradual and control groups, with significantly greater reductions in overall smoke exposure across multiple biomarkers of exposure compared to the other two groups. This overall difference was observed in Whites and African Americans, in males and females, and across educational levels.[54]

A specific concern with the gradual reduction approach was the observed modest increase in a few smoke exposure measures at the 5.2 mg dose. This finding would suggest that if a gradual reduction approach was implemented, there might be a period of time during which smokers may experience greater exposure to toxicants due to compensatory smoking behavior. The occurrence of compensatory smoking as assessed by carbon monoxide exposure and/or cigarettes per day has been observed at moderate nicotine doses in other studies.[10,13,23] That is, smokers would smoke cigarettes more intensely to obtain the desired level of nicotine, which could be achieved at moderate nicotine dose reductions. The other findings that would support an immediate reduction approach included a significantly greater reduction in cigarette dependence compared to the other two groups, which would make quitting easier. In fact, a higher number of days abstinent from cigarettes was observed (10 days in the immediate nicotine reduction and 3 days in both the gradual nicotine reduction and control groups). Furthermore, smokers assigned to the gradual reduction group experienced greater satisfaction and other positive subjective effects of smoking with the 0.4 mg/g nicotine content cigarettes compared to the immediate group at the end of treatment.[55] The higher level of positive subjective cigarette effects was observed even when controlling for the duration of VLNC cigarette assignment. This finding would suggest an adaptation to the reduced nicotine content in the gradual reduction group.

However, a few concerns were observed for the immediate compared to the gradual reduction approach. There was a higher drop-out rate and non-compliance with only smoking study cigarettes (e.g., participants smoked their usual brand cigarettes even when asked to only smoke study cigarettes), which suggests that smokers might find this approach less tolerable than the gradual reduction approach. To reinforce this observation, smokers in the immediate group experienced greater nicotine withdrawal symptoms and adverse events related to withdrawal during the first week, although not thereafter. These findings indicate that particularly in the case of an immediate nicotine reduction approach, some smokers will likely seek other sources of nicotine, which may include NRT, alternative nicotine delivery systems (ANDS) (e.g., smokeless tobacco, heat-not-burn tobacco, electronic nicotine delivery systems [ENDS]), or illegally marketed cigarettes.

In summary, there is sufficient research indicating that ≤0.4 mg/g nicotine is appropriate as a product standard to achieve reductions in number of cigarettes per day, dependence, and an increase in quit

attempts among different populations of smokers. The immediate nicotine reduction approach is associated with a greater and more rapid overall reduction in smoke exposure, decrease in dependence and higher number of abstinence days compared to the gradual reduction group. Therefore, this approach would result in public health benefit substantially sooner than one in which nicotine is reduced in cigarettes over several years. However, this approach may also lead to greater short-term discomfort among smokers, which would potentially lead them to seek nicotine from other sources.

Mitigation of Negative Impacts From a Reduced Nicotine Policy

Several measures can be implemented to mitigate any negative impact from reducing nicotine in cigarettes (and other combusted tobacco products). These measures include: 1) making access to NRT or other pharmacological products widely available and less costly; 2) for some countries, approving and/or supporting other alternative sources of nicotine which have been demonstrated to be less harmful than combusted products (e.g., ENDS and other tobacco products that are not combusted), provided that these products are also regulated for toxicity, appeal and addictiveness by a government agency; and 3) controlling illegal markets.

Access to Pharmacological Agents and Cigarette Cessation Services

A dramatic reduction in nicotine can lead to withdrawal symptoms in some smokers,[36] although the intensity of withdrawal is likely to be less than observed from total abstinence from cigarettes and has been observed to be similar to that experienced when using NRT.[56] Other studies have shown a decrement in cognitive function or performance while smoking reduced nicotine cigarettes.[57,58] Pharmacological agents such as NRT, bupropion SR or varenicline can alleviate some of these symptoms.[64–67] A few studies have examined the effects of NRT when they are combined with VLNC cigarettes. These studies showed that if smokers assigned to VLNC were provided NRT such as the nicotine patch, they experienced reduced withdrawal symptoms,[56,58,68] and greater reductions in the amount of cigarettes smoked[56,68] and smoking intensity[68] compared to smokers who were not assigned NRT. Another study in non-treatment seeking smokers showed adding NRT to VLNC cigarettes did not enhance reductions in cigarettes per day or withdrawal symptoms or increase time to lapse or smoke-free days compared to VLNC alone. On the other hand, compliance with VLNC cigarettes was enhanced with the use of NRT.[69] This later finding might suggest that smokers using NRT will be less inclined to seek illegal NNC cigarettes.

Cessation trials using VLNC cigarettes have been conducted to determine if, by reducing the reinforcing effects of cigarettes, smoking behavior would extinguish. In one clinical cessation trial, smokers seeking treatment through a smoking cessation telephone Quitline that provided behavioral counseling and NRT were randomized to a VLNC cigarette or only usual care. Those assigned to the VLNC cigarettes demonstrated significantly higher smoking cessation abstinence at six months follow-up and a substantially longer time to relapse (2 months vs. 2 weeks).[25] In another trial, smokers randomized to nine-week standard smoking cessation treatment that included both behavioral and pharmacological treatment and a two-week supply of VLNC cigarettes experienced significantly higher short-term but not long term abstinence rates than standard treatment alone.[70] These findings would suggest that reduced nicotine content cigarettes might facilitate abstinence. It is important to note that reducing nicotine in cigarettes has led to increased smoking quit attempts[16]; therefore, making cessation tools, including behavioral counseling or cessation support materials, available to smokers would be critical.

Availability of Alternative Nicotine Delivery Systems

For some countries, a harm reduction approach has been considered one of the three pillars of tobacco control that also includes prevention and cessation of tobacco use. Harm reduction targets smokers who find it difficult or are unwilling to quit smoking or use of nicotine. It is posited and observed that if smokers completely switch to *scientifically proven* less harmful products, then tobacco-caused morbidity and mortality would be reduced.[71–74] In countries that adopt a harm reduction approach, the availability of less harmful nicotine containing products may help reduce negative consequences associated with an immediate nicotine reduction in cigarettes. To explore this area, a pilot study was conducted in the U.S. in which smokers not interested in quitting were randomized to: 1) RNC (defined as 1.3 mg nicotine /g tobacco) cigarettes with access to both non-cigarette combusted tobacco products (little cigars, cigarillos, premium cigarettes) and non-combusted nicotine products (NRT, ENDS and smokeless tobacco); 2) RNC cigarettes with access to only non-combusted nicotine products; and 3) NNC cigarettes with access to both non-cigarette combusted and non-combusted nicotine products.[21] Several key findings emerged. First, regardless of the types of products that were accessible to smokers, those smokers assigned to the RNC cigarettes demonstrated a reduction in cigarettes smoked per day, dependence, increase in the number of quit attempts, and greater uptake of alternative nicotine products. The product associated with the greatest uptake was the ENDS, likely the most appealing of the non-combusted alternative products for cigarette smokers.[75–79] The results also showed that smokers who were assigned to RNC cigarettes and only the non-combusted products experienced significantly less toxicant exposure (CO and NNK) compared to the NNC group, but the smokers assigned to RNC cigarettes with access to both combusted and non-combusted products did not. This finding is most likely due to the increasing uptake of non-cigarette combusted products in smokers assigned to the RNC condition with access to both combusted and non-combusted products. This observation would indicate that if a reduction in nicotine were to be instituted, this standard should be implemented for all combusted products (with the possible exception of premium cigars and waterpipes because of the different patterns of use). Little cigars and cigarillos are likely a better substitute for cigarettes than other less harmful nicotine-containing products because of their similar pharmacokinetics with cigarettes[80,81]; but unfortunately these products also result in similar toxicity to cigarettes.[80] Indeed, one study that examined the effects of price change in cigarettes on the sales of little cigars found that a 10% increase in cigarette price was associated with a 27% increase in purchase of little cigars in convenience stores and food, drug, and mass merchandisers.[82] These studies indicate that unless other combusted products are also required to reduce nicotine to minimally addictive levels, the public health benefit may not be substantial.

The pilot study results were also notable in demonstrating that the greater the uptake of the non-combusted products, the fewer cigarettes smoked, the greater the number of quit attempts, and the greater the reduction in toxicant exposure (e.g., total NNAL). This finding is not unlike observational studies conducted with ENDS

in which the more frequent the use of these products, the higher the likelihood of cigarette cessation.[83–86] The availability of alternative nicotine delivery systems such as ENDS might facilitate cessation. A recent Cochrane Review, *Electronic Cigarettes for Smoking Cessation*, reported that there is "moderate certainty evidence" that e-cigarettes with nicotine increased smoking cessation success at six months compared to NRT, although the number of studies on which this conclusion was based was small.[87]

In summary, the results suggest that the availability of other nicotine products, specifically non-combusted products such as NRT or ANDS, might facilitate the cessation of cigarettes and also provide withdrawal relief. Regulation of the toxicity of the non-combusted tobacco products would be important. For example, tremendous variability has been observed in the levels of carcinogens and other toxicants in smokeless tobacco products[73,88–90] and ENDS,[91] yet few countries have regulated the contents of these products. Therefore, as stated in the WHO Advisory Note *Global Nicotine Reduction Strategy* and subsequent update, a comprehensive regulation of ***all*** nicotine- and tobacco-containing products would be warranted. This regulation should be implemented whether or not a reduced nicotine cigarette approach is adopted and should focus on reducing the toxicity of these products and minimizing uptake in youth and tobacco-naïve young adults. For example, some of the toxicants in the smokeless tobacco[3,92] and ENDS fluids could be eliminated or reduced. Flavors that appeal to youth and tobacco-naïve users could also be regulated[3] keeping in mind that bans on certain flavors might also dissuade smokers unmotivated to quit from pursuing less harmful sources of nicotine. For ENDS, other sources of appeal and toxicity[3,91,93] could be regulated including product design, materials used in the manufacturing of the device (e.g., coils), batteries and wattage of the device, and potential amount of nicotine delivery (e.g., no higher than combusted products). Additionally, other regulations could include increasing age of purchase, adult-only store access to these products, and marketing specifically aimed at existing smokers (see Kennedy et al.[94] and Du et al.[95] for examples). It should be recognized that some tobacco control researchers and advocates strongly believe that the restrictiveness of the regulations should be commensurate with the extent of harm of the product (e.g., greater regulations and restrictions on combusted products compared to less harmful ANDS).

As a final note, the ultimate goal is to support abstinence from all nicotine containing products, including NRT. However, for those who find it difficult to stop using these products, complete switching to ANDS and preferably medicinal nicotine (for some countries, under the direction of a physician) is likely to be significantly less harmful than continued smoking.[91,96] In the study referenced above that modeled the U.S. public health effects of reducing nicotine levels in cigarettes, it was estimated that by 2060, any tobacco use, which included cigarettes, non-combusted tobacco (e-cigarettes, smokeless tobacco), and dual cigarette plus non-combusted tobacco use, was projected to be a median of 11.6%, with almost 90% of this figure attributed to non-cigarette use. The number of U.S. tobacco-related deaths averted in this scenario was estimated to be a median of 2.8 million by 2060, continuing to 8.5 million by 2100.[4]

Illicit Markets

One of the greatest concerns with implementation of a nicotine reduction policy is the illicit markets that might surface in response. While the availability of NRT and other less harmful ANDS might significantly reduce the number of smokers seeking cigarettes on the black market, these markets will likely exist.[97] Illegal cigarettes can be sold through various venues: retail locations, on the streets, and through the internet.[3] The most recent estimate of the percent of illicit sales of the total cigarette market in the U.S. and globally is between 9% and 21%; illicit cigarettes accounted for 11.6% of the cigarettes consumed in 84 countries in 2007.[3,98] In a brief online survey of a national convenience sample, smokers who were informed about a potential low nicotine product standard reported significantly increased interest in purchasing normal nicotine content cigarettes illegally compared to controls, but the magnitude of the difference was modest (36% vs. 30% across three sources for illicit cigarettes, respectively).[97] Another national survey found just under 12% would seek ways to get their usual brand cigarettes.[99] Based on these estimates, the actual magnitude of the illicit market is likely to be low, especially if regulatory measures to mitigate the illegal market and trade are established.

Measures to reduce illegal cigarette sales can be inferred from policies that have been employed to reduce black market cigarettes that have resulted from increased cigarette taxes.[98,100] Policies to mitigate black markets include the following[98,100,101] and should be considered in concordance with Article 15 of the FCTC and international collaboration to overcome illicit trade:

- Prohibit the country's manufacturers from making nicotine cigarettes above a certain threshold, importers from introducing products on the market that do not meet the nicotine standard, and retailers and internet vendors from selling above nicotine threshold cigarettes.
- Regulate the tobacco grown to be used by cigarette manufacturers.
- Impose licensing requirements on tobacco growers to retailers.
- Institute a robust track and trace system that follows a product from the manufacturer, distributor, to retailers and that includes strong custom controls and encrypted tax stamps on cigarette packs.
- Adopt a policy that includes strong penalties, can lead to illicit cigarette detection, has a strong surveillance system, and involves sufficient enforcement personnel. Penalties and enforcement efforts should be targeted towards manufacturers, importers, retailers, and internet vendors and not the consumer.
- Institute regular compliance testing (including independent product testing) with manufacturers, importers, retailers, and internet vendors.
- Restrict online payment processing and shipping companies from sending products to consumers and prohibit sales of supplemental nicotine.
- Coordinate policies across countries or jurisdictions and efforts among regulators.

Structural Capacity Needed to Support a Nicotine Reduction Approach

Comprehensive Tobacco Control

A regulation to reduce nicotine in cigarettes must be one component of a comprehensive tobacco control program, as described in the WHO FCTC. This program should include increased taxes on cigarettes and other combusted tobacco (Article 6), anti-smoking media campaigns (Article 12), comprehensive smoking bans (Article 18), and accessibility of evidence-based treatments (Article 14). These tobacco control measures have made substantial contributions towards reducing the rates of smoking.[102] Increasing taxes on cigarettes

with reduced nicotine content following successful implementation of a nicotine reduction policy may further facilitate smoking cessation. The price at which smokers would rather quit than sustain smoking is much lower with reduced nicotine content cigarettes compared to conventional nicotine cigarettes.[103,104] Some researchers have advocated for differential taxation based on the relative risk of a nicotine product, with the highest taxes leveraged on combusted tobacco products. This approach would promote a shift away from more highly toxic products. At the same time, taxation of lower risk products should be sufficient to minimize initiation among youth.[105]

Education About the Health Effects of Nicotine

Educating the public about the health effects of nicotine is clearly important. The promise of reducing nicotine in cigarettes to benefit public health is not a function of reducing the overall toxicity of the cigarette.[106] Rather, the public health benefit results from reducing the prevalence of smoking by decreasing initiation and facilitating cessation, and possibly by decreasing the amount and duration of smoking. A significant portion of the public has misperceptions regarding the toxicity of nicotine,[2,107,108] which might lead consumers to misperceive cigarettes that have reduced nicotine to be less harmful to health than cigarettes that contain conventional nicotine levels,[107,109–113] thereby promoting continued smoking behavior.[109] Conversely, if consumers perceive nicotine to be highly toxic, smokers may not seek out other sources of nicotine including NRT[114–117] that might reduce any discomfort with the use of VLNC cigarettes and thereby might promote seeking cigarettes through illegal sources. For these reasons, an education campaign should be aimed at increasing public support, educating consumers about the rationale for reducing nicotine in cigarettes (to reduce addictiveness and facilitate smoking cessation), and preparing smokers for the reduced nicotine regulation. Additionally, it would be important to dispel any false beliefs and perceptions regarding nicotine (e.g., other chemicals in smoke are primarily associated with causing diseases), the harms of smoking VLNC cigarettes (e.g., smoking VLNC cigarettes can be just as toxic to health as conventional cigarettes) and effects of VLNC on smoking behaviors (VLNC cigarettes help you smoke fewer cigarettes, not more).[108,112,118,119]

Laboratory Testing

A laboratory that can conduct product testing is vital to monitor the development of illicit cigarette markets as well as any attempts to alter cigarettes to increase their addictiveness and appeal. To avoid market manipulation of cigarettes or combusted products, a regulatory agency can also set limits on non-nicotine constituents at levels not higher than those found in currently available cigarettes and can prohibit the addition of new constituents or design features.[120] Laboratory testing could conceivably be supported through TobLabNet or government laboratories for countries that have them. Laboratory testing could be routinely conducted on random samples of cigarettes collected at the levels of the manufacturer, importer, and retailer. Additionally, cigarette companies should be required by the government to disclose all ingredients, yields of harmful constituents, and design features of cigarettes and other combusted products (Article 10 of FCTC) on a regular basis.

Surveillance

Surveillance is a critical measure to determine the consequences and public health impact of implementing a nicotine standard. The purpose of surveillance would be to: 1) monitor illegal cigarette use; 2) determine the prevalence of smoking; and 3) monitor other unintended consequences. Cigarette prevalence can be monitored by the Global Adult and Youth Tobacco Surveys or ideally by more frequent and detailed country-specific surveys. Additional surveillance methods include tracking sales data for cigarettes and other nicotine products. Regarding unintended consequences, several areas could be assessed, including the uptake and extent of use of ANDS among youth and adults who are naïve to cigarette use; increases in the prevalence and use of other reinforcing drugs such as alcohol or other substances of abuse; adverse events or serious adverse events; tampering of cigarette or other combusted products; and impacts on the most vulnerable populations.

Research Gaps and Future Research

There are limitations associated with the existing studies. First, the majority of the studies on reduced nicotine content cigarettes have been conducted in the United States; therefore the generalizability of the study results to other countries, particularly in middle and low-income countries, are uncertain. Second, these studies were conducted on smokers who volunteered to participate. No study has been conducted in a community-wide setting to obtain a more accurate understanding of the impact of implementing a reduced nicotine content regulation on the society as a whole. Third, the population impact is extrapolated based on relatively short-term studies that provide free cigarettes and do not provide access to a complex marketplace that simulates the real-world environment. The possible pattern of dual or poly-tobacco use and the consequent health effects are unknown, although studies that expose smokers to reduced nicotine cigarettes and a complex marketplace are underway. Fourth, relatively little is known about the economic burden for industry, farmers, and governments associated with the implementation of this regulation, including considerations stated in Article 15 of the FCTC. Fifth, although studies with vulnerable populations are being conducted and to date show no major adverse effects, the longer-term impact of reducing levels of nicotine in cigarettes in these populations is relatively unknown. Finally, although modeling of the public health impact of a nicotine product standard has been conducted for the U.S.,[4,121] taking into account a modest illicit market, no modeling studies have been conducted for other countries.

Discussion

Reducing nicotine in cigarettes and preferably all combusted products can have a profound public health impact. The importance of nicotine in promoting and sustaining addiction is clearly described in a 1959 document from British American Tobacco[122] that stated: [Reducing nicotine in cigarettes] "might end in destroying the nicotine habit in a large number of consumers and prevent it ever being acquired by new smokers." Major tobacco companies have recently been court ordered to provide the truth behind their deceptions in misleading the public on the harms and addictiveness of cigarettes.[123] These corrective statements include admitting that tobacco companies intentionally designed cigarettes to make them more addictive, even when they knew that cigarettes caused many diseases.

We now have a growing body of evidence that will guide us in the implementation of reducing the addictiveness of combusted products (See Table 1). However, not all countries would have the necessary infrastructure and resources, as previously described,

Table 1. Recommendations for Implementing a Reduced Nicotine Product Standard

- Reduce nicotine levels in all combusted products to less than or equal to 0.4 mg nicotine/g of tobacco with the potential exception of premium cigars and waterpipes.
- Implement an immediate rather than a gradual nicotine reduction in combusted tobacco products.
- Provide affordable and easily accessible smoking cessation treatments to smokers, including medicinal products.
- Allow access to alternative nicotine delivery systems (ANDS) that are scientifically demonstrated to reduce harm to promote switching smokers unwilling or unable to quit smoking from a highly toxic combusted product to a less harmful product. This strategy would require regulation of all tobacco- and nicotine-containing products, and warning labels that would indicate that these products are not harmless and for some products, can be addictive. It is important to note that not all countries embrace a harm reduction approach and therefore the feasibility of reducing nicotine in combusted tobacco, if smoking prevalence is high, is uncertain.
- Implement a strong enforcement policy that tracks, penalizes, and monitors illicit cigarette and combusted tobacco manufacturing and sales.
- Imbed a nicotine reduction policy within a strong and comprehensive tobacco control program that includes the Articles of the Framework Convention on Tobacco Control.
- Before implementing a nicotine reduction policy, educate the public on the rationale for the policy, the continued harms of combusted tobacco even with reduced nicotine, and the reduced harms of nicotine replacement therapies and ANDS compared to cigarettes.
- Develop the infrastructure for testing combusted tobacco and surveillance of tobacco and nicotine product use and potential unintended consequences.

or the political will to implement a nicotine product standard. At this juncture, relatively few countries can implement a regulation of nicotine for practical reasons. Therefore, it is prudent for low capacity (infrastructure, resources, political will) countries to wait until capacity-rich countries (e.g., New Zealand, Canada, United States) adopt this regulatory approach to determine the effects on public health. The lessons learned from their experiences can provide more informed guidance to countries that might consider following this regulatory approach in the future. Lessons learned can include knowing how the tobacco industry might seek to subvert this product standard, including using nicotine analogs, finding loopholes that would allow for illegal trade, deceptive marketing or launching lawsuits. Because of U.S. law, the U.S. government cannot ban any class of tobacco products. For some countries, banning cigarettes and other combusted tobacco products might provide an easier route to regulation. Other countries may want to adopt other measures such as reducing the palatability of combusted products (e.g., banning menthol or other flavors,[124] banning ventilation in filters[92,125]). Regardless of the tobacco product regulatory path that is chosen, strong and comprehensive tobacco control policies are essential with one of the primary goals to reduce the use of cigarettes, the most prevalent, deadly, and addictive of tobacco products.

Supplementary Material

A Contributorship Form detailing each author's specific involvement with this content, as well as any supplementary data, are available online at https://academic.oup.com/ntr.

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Declaration of Interests

None for DKH, DQXu, and GFW.

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