ADVISORY NOTE

Global Nicotine Reduction Strategy

WHO Study Group on Tobacco Product Regulation (TobReg)

World Health Organization

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Contents

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Rio de Janeiro, Brazil, 4–6 December 2013

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We thank all the members of TobReg for their full, whole-hearted dedication, time and unfailing commitment to fulfilling their mandate to advise WHO on tobacco product regulation, a highly complex area of tobacco control. As independent experts, members of TobReg serve WHO without remuneration. In response to the requests to WHO made by the Conference of the Parties at its fifth session, TobReg members provided guidance in drafting the terms of reference for commissioning a series of reviews to serve as background documents and as a basis for discussions at TobReg's seventh meeting, held in Rio de Janeiro, Brazil, in December 2013. The TobReg recommendations on these issues were published as Technical Report Series 989 (WHO, 2015), which was presented by the Director-General of WHO to the 136th session of the Executive Board, held in Geneva, Switzerland, on 25 January to 3 February 2015.

The background paper on reducing the dependence potential of manufactured cigarettes by reducing their nicotine content to levels that cannot cause or sustain addiction, which served as the basis for this advisory note, was written by Mr Geoff Ferris Wayne. It was appended as Annex 3 to Technical Report Series 989. WHO thanks Mr Wayne for the time and effort invested in writing the background paper, which was presented to TobReg in December 2013, and for continuing to

work with TobReg in finalizing their conclusions and recommendations on this important topic. This advisory note was finalized by Dr Dorothy Hatsukami.

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Preface

The WHO Study Group on Tobacco Product Regulation (TobReg)[1] is mandated to provide the WHO Director-General with scientifically sound, evidence-based recommendations for Member States about tobacco product regulation. In line with the provisions of Articles 9 and 10 of the WHO Framework Convention on Tobacco Control (WHO FCTC), TobReg identifies approaches for regulating tobacco products that pose significant public health issues and raise questions for tobacco control policy.

Regulation of tobacco products is essential for tobacco control and is endorsed by the WHO FCTC in provisions of its Articles 9, 10 and 11. Regulation serves public health goals by ensuring meaningful surveillance of the manufacture, packaging, labelling and distribution of tobacco products. Scientifically based principles for implementing the provisions create synergy and mutual reinforcement of the regulatory practices described in each article.

Tobacco product regulation includes regulating their contents and emissions by testing, measuring and mandating disclosure of the results and regulating their packaging and labelling. Government supervision is required for manufacture and for enforcement of regulations on the design, contents and emissions of tobacco products, as well as their distribution, packaging and labelling, with the aim of protecting and promoting public health.

Chemical consumer products are usually regulated after a review of the scientific evidence on the hazards associated with them, probable exposure, patterns of use and the marketing messages of the manufacturer. Many jurisdictions require manufacturers to classify and label products according to their hazardous properties, to control the hazardous content or to limit the advertising, promotion and sponsorship of such products.

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[1] http://www.who.int/tobacco/industry/product_regulation/tobreg/en/, accessed 24 July 2015.

TobReg reviews the scientific evidence on topics related to tobacco product regulation and identifies the research necessary to fill regulatory gaps in tobacco control. It is composed of national and international scientific experts on product regulation, treatment of tobacco dependence and laboratory analysis of tobacco contents and emissions. As a formalized entity of WHO, TobReg reports to the WHO Executive Board through the Director-General to draw the attention of Member States to the Organization's work in tobacco product regulation, which is a complex area of tobacco control.

The seventh meeting of TobReg was held in Rio de Janeiro, Brazil, on 4–6 December 2013. The discussions mainly addressed the request of the Conference of the Parties of the WHO FCTC at its fifth session (Seoul, Republic of Korea, 12–17 November 2012) to WHO to:

- Monitor and follow closely the evolution of new tobacco products, including products with potentially "modified risks", and to report any relevant development to the Conference of the Parties.
- Direct some of its activities towards aspects of addictiveness (or dependence liability) of both smoked and smokeless tobacco products that remain to be studied.
- Monitor and research country experience and scientific developments with respect to reduced ignition propensity cigarettes.
- Identify measures likely to reduce the toxicity of both smoked and smokeless tobacco products, and describe the evidence supporting the effectiveness of such measures and the experience of Parties on the matter for consideration by the Conference of the Parties.
- Compile, make available to Parties and update a non-exhaustive list of the toxic contents and emissions of tobacco products, and provide advice on how such information could be best used by Parties.
- Prepare draft fact sheets on measures recommended in the partial guidelines for implementation of Articles 9 and 10 of the WHO FCTC.
- Continue and report on progress in validation of analytical chemical methods for testing and measuring cigarette contents and emissions.

Subsequent to this request, a number of background documents were commissioned. In addition, information on the availability and regulation of novel tobacco products, smokeless tobacco products and reduced ignition propensity cigarettes was collected in a WHO survey of tobacco products sent to all Member States. Ninety countries responded, representing approximately 77% of the world's population.

The WHO report to the sixth session of the WHO FCTC Conference of the Parties in October 2014 is now published (WHO, 2015). Because of the complexity of the topic of reducing the dependence potential of manufactured cigarettes by reducing their nicotine content to levels that cannot cause or sustain addiction, however, was further discussed by TobReg members for more than 18 months. The result of those discussions is encapsulated in this TobReg advisory note on a global nicotine reduction strategy.

Main recommendation

This advisory note introduces a policy of limiting the sale of cigarettes to brands with a nicotine content that is not sufficient to lead to the development and/or maintenance of addiction; they are referred to as "reduced-nicotine" cigarettes. Conventional cigarettes—even those brands that deliver low nicotine yields as measured by machine smoking under the conditions of the International Organization for Standardization (ISO)—contain addicting levels of nicotine, but the nicotine yields are reduced as a result of many design features, including ventilated filters. Users puff ISO low-nicotine-yield cigarettes more intensely (i.e. they draw larger puffs more frequently than the conditions prescribed by machines) to obtain addicting levels of nicotine. Unlike conventional cigarettes, reduced-nicotine cigarettes can limit the addictiveness of the product, as the low content in the tobacco filler[2] cannot deliver addicting levels of nicotine. Research shows that switching from conventional to cigarettes with a nicotine content of 0.4 mg/g of cigarette tobacco filler does not significantly increase craving or withdrawal symptoms and does not result in compensatory smoking (such as more intense smoking or smoking more cigarettes per day). No specific amount of nicotine has yet been identified as the absolute threshold for addiction; however, it is likely to be equal to or possibly less than 0.4 mg/g of dry cigarette tobacco filler. The ultimate health benefits of a nicotine reduction strategy for individual smokers will require complete cessation of intake of all combusted tobacco. Population benefits will result from decreased use of combusted tobacco by current cigarette smokers and from prevention of addiction of non-smokers to cigarettes, especially among young people. To achieve the public health goal, not only product modification but also the provision of treatment will be required, including behavioural support,

[2] Cigarette tobacco filler is defined as the tobacco-containing part of a cigarette, including a blend of different tobacco types, reconstituted tobacco sheets, stems, expanded tobacco and additives. (See WHO, 2014.)

nicotine replacement and other medications, for cigarette smokers who will no longer be able to obtain adequate levels of nicotine from cigarettes. For people who switch from cigarettes to non-combusted forms of tobacco to sustain their nicotine intake, the health benefits will depend, partly, on the level of tobacco-related toxicants delivered by the alternative products and the behaviour and duration of use of such products.

Significance for public health policies

A nicotine reduction strategy could decrease the acquisition of smoking and progression to addiction among experimenters, limit the number of cigarettes smoked by some proportion of addicted smokers and both increase the number of addicted smokers who stop smoking and reduce the number of those who relapse.

Implications for WHO programmes

Implementation of a nicotine-reduction policy should be supported by a comprehensive programme, involving:

- a strategy on health communication and public education;
- the absence of products with higher levels of nicotine in tobacco filler on the market;
- effective, affordable, available cessation treatment that includes behavioural support, alternative forms of nicotine in products that pose a significantly lower risk for tobacco-related disease and medicines approved for treating tobacco dependence and withdrawal;
- capacity to monitor the market and test tobacco products for nicotine and other constituents and emissions; and
- continued research to assess:
    - the likelihood of use and the effects of reduced-nicotine cigarettes in non-smoking adolescents;
    - the likelihood that users will switch back to high-nicotine products if they are available on the market;
    - additional use of other types of product (e.g. smokeless tobacco products, e-cigarettes);
    - long-term use of reduced-nicotine cigarettes;

– the long-term impact of reduced-nicotine cigarettes on smoking behaviour and
– comprehensive surveillance to ensure rapid detection of unintended consequences.

TobReg hopes that the conclusions and recommendations contained in this advisory note will be useful to countries implementing the product regulation provisions of the WHO FCTC.

Reducing the addictiveness of manufactured cigarettes by reducing their nicotine content: research needs and regulatory recommendations

1. Introduction

A policy to reduce the addictiveness of tobacco by reducing its nicotine content comprises setting a maximum allowable limit on the nicotine content of all cigarettes and potentially other forms of tobacco (both combusted and non-combusted) that are available for sale, with the intention of minimizing the development and/or maintenance of nicotine addiction. The report reflects increasing scientific understanding about the population effects of cigarettes containing reduced-nicotine tobacco; it includes recommendations for policy and regulations based on the current state of science and discusses issues raised by regulatory authorities and the Conference of the Parties to the WHO Framework Convention on Tobacco Control (WHO FCTC). It is based on a background report[3] commissioned by WHO (WHO, 2015), with input from the Study Group on Tobacco Product Regulation (TobReg) at its seventh meeting in Rio de Janeiro, Brazil, in December 2013.

[3] The background report, entitled "Reducing the dependence potential of manufactured cigarettes by reducing their nicotine content to levels that cannot cause or sustain addiction", appears as Annex 3 in WHO (2015), for further information for researchers and policy-makers.

2. Background

Addiction is a chronic, relapsing brain disease characterized by compulsive self-administration of a drug, often despite harmful consequences (WHO, 1992; National Institute on Drug Abuse, 2014). Since the 1980s, it has been generally recognized that nicotine is the primary addicting chemical in tobacco products; by the 1990s, it was increasingly accepted that tobacco products without nicotine would not sustain addiction (Benowitz & Henningfield, 1994; Henningfield et al., 1998). The tobacco industry recognized this many years earlier and designed cigarettes to ensure that they could deliver addicting levels of nicotine despite reduced machine-estimated deliveries as measured by the ISO and United States Federal Trade Commission test methods (National Cancer Institute, 2001; WHO, 2001; WHO, 2003a). Earlier reports from TobReg and its predecessor SACTob similarly concluded that nicotine was the primary addicting chemical common to combusted and non-combusted tobacco products and that it should be regulated, with other content and design features. To date, however, TobReg has not published a clear position on reducing the addiction potential of manufactured cigarettes (WHO, 2002; WHO, 2007; WHO, 2009; WHO, 2012a).

During the past decade, experimental research and modelling have been conducted to assess the potential public health impact of a policy to reduce the addictiveness of cigarettes, as discussed in this report. The results led to the current recommendation: that reducing the maximum allowable nicotine content in cigarettes to minimally addicting levels be considered a suitable strategy for reducing the demand for these products, which account for the vast majority of tobacco-attributable morbidity and mortality in most countries and regions. This report does not provide a detailed proposal of how such a policy might be enacted but rather focuses on the scientific basis for recommending this policy. It presents the conditions that might be necessary for viable enactment of such a policy and many of the challenges to be met, including unanswered research questions.

3. Cigarettes with a reduced nicotine content

In a policy to reduce the addictiveness of tobacco, the nicotine content of all cigarettes permitted for sale would be inadequate to cause or sustain addiction. Such cigarettes have been referred to as "reduced-nicotine cigarettes", "very low nicotine content cigarettes" and "de-nicotinized cigarettes". They are distinct from

reduced-*yield* cigarettes, which were developed in the 1970s in response to public health concern and marketed with descriptors such as "light", "low tar" and "mild". Those descriptions implied lower deliveries and less exposure to nicotine and other substances (commonly termed "tar"), but the products actually contained similar amounts of nicotine and delivered nicotine doses that were associated with risks for addiction and other diseases as high as those of their "full-flavoured" counterparts (National Cancer Institute, 2001; WHO, 2001; WHO, 2003a). Whereas cigarettes with a very low nicotine content cannot sustain addiction, cigarettes marketed as "reduced yield" on the basis of machine testing have been found to extend the prevalence of addiction in many populations because they are perceived as safer and are easier to inhale (Kozlowski & O'Connor, 2002).

4. Goals of a policy to reduce addiction to cigarettes

A policy to reduce the addictiveness of cigarettes has many goals: to reduce the risk that non-smokers will become addicted to cigarettes, to make it easier for smokers to quit smoking, to help prevent smokers who have quit from relapsing and, if needed, to encourage cigarette smokers to substitute a less harmful and, ideally, less addictive source of nicotine (Henningfield et al., 1998; Hatsukami et al., 2010a; Benowitz & Henningfield, 2013). Since nicotine reduction was first proposed by Benowitz and Henningfield in 1994, a number of health scientists have concluded that the approach could significantly impact public health (Gray et al., 2005; Zeller et al., 2009; Benowitz & Henningfield, 2013; Hatsukami et al., 2013a; Smith et al., 2013). The approach is consistent with Article 9 of the WHO FCTC, which calls for guidelines for regulating the contents and emissions of tobacco products (WHO, 2003b; WHO, 2012a).

5. Tobacco addictiveness factors

As discussed elsewhere and in earlier WHO reports (WHO, 2001; WHO, 2007; WHO, 2012a), nicotine is a highly addictive, potent drug, which can generate psychoactive rewarding effects even at very low doses,. Cigarettes are a particularly effective form of nicotine delivery: when smoke from a cigarette is inhaled, nicotine in the tobacco is rapidly absorbed into the lungs and carried to the brain.

Individual responses to nicotine, including sensitivity, are highly variable. Early exposure to nicotine (i.e. before or during adolescence) is associated with more severe dependence, greater reward and increased self-administration, suggesting that the developing brain may be more susceptible to permanent changes caused by nicotine that support addiction (Benowitz, 2008; Hatsukami et al., 2010a). Women are more strongly influenced than men by the sensory aspects of smoking and have more difficulty in quitting (Fant et al., 1996; Gritz et al., 1996; Eissenberg et al., 1999; Perkins et al., 1999; Wetter et al., 1999; Perkins et al., 2006; Perkins, 2009). Individuals with psychiatric and/or substance abuse disorders have much higher rates of nicotine dependence and have more difficulty in quitting (Ziedonis et al., 2008).

The sensory characteristics of smoking (taste, aroma, tracheobronchial sensations) facilitate delivery of nicotine and come to be associated with its pharmacological effects, further reinforcing addiction (WHO, 2007; Henningfield et al., 2011; WHO, 2012a). Because non-nicotine components of tobacco are critical to the sensory experience of smoking, de-nicotinized tobacco is more effective in reducing craving and producing greater pleasure in smokers than nicotine without tobacco (Rose, 2006). Nicotine also plays a central role in the sensory composition of cigarette smoke: nicotine-containing cigarettes are consistently rated as stronger than de-nicotinized cigarettes because of the greater sensory stimulus.

Some non-nicotine components of tobacco may interact chemically or have a synergistic effect (e.g. acetaldehyde) with nicotine, further potentiating its effects, or may have measurable pharmacological effects on their own. For example, various minor tobacco alkaloids reinforce self-administration by rats, and monoamine oxidase inhibitors present in tobacco smoke have been shown to increase response rates substantially when given to rats that are self-administering nicotine (Guillem et al., 2005). Thus, although drastically reducing nicotine should substantially decrease the addictiveness of tobacco for most people, a product with a very low nicotine content may still have some reinforcing effects for certain people.

Expectations about the effects of a drug play an important role in determining subjective and behavioural responses to tobacco products, particularly in women (Perkins et al., 2006). Expectancy may be due to sensory stimuli produced by the product, by packaging or by other information cues. Social context also determines smoking behaviour and dependence, such as where it is permissible to use tobacco products (both legally and in terms of social norms), the cost of tobacco use both individually and to one's family, and whether tobacco use is stigmatized in subpopulations such as by gender, religious affiliation or social status.

6. Establishing a performance standard for nicotine products

Various tests are available for identifying potentially addicting drugs and the dosages of the drugs that reinforce and sustain use, by producing either psychoactive effects or physical dependence and withdrawal. These tests are recommended by WHO (2006) and have been described in scientific reviews and by various regulatory agencies (Balster & Bigelow, 2003; Schuster & Henningfield, 2003; Carter et al., 2009). No single amount of nicotine can be identified as an absolute threshold for addiction in all individuals, under all circumstances and by all routes or means of administration; however, numerous studies conducted in both animals and humans confirm that there are doses above which nicotine is consistently self-administered and below which self-administration is not observed or, in humans, results in significantly reduced dependence (Hatsukami et al., 2010a; Donny et al., 2012). The doses of nicotine necessary to produce psychoactive or discriminative effects reliably in humans and animals have also been studied (Department of Health and Human Services, 1988; Carter et al., 2009). Taken together, these and other types of studies provide a basis for setting standards for the levels of nicotine above which addiction is likely and below which addiction is less likely (Carter et al., 2009; Sofuoglu & LeSage, 2012; Benowitz & Henningfield, 2013).

Smokers self-administer nicotine intravenously within a range of intake well below that from a typical cigarette, with a threshold somewhere between 0.1 and 0.4 mg of nicotine, assuming 70 kg body weight (Sofuoglu et al., 2008). Similarly, in dose–response studies, animals commonly self-administer doses of nicotine below 10 µg/kg and maintain self-administration with unit doses of as low as 3 µg/kg, equivalent to around 0.23 mg nicotine, although there is considerable individual variation in response rates at the lower end of this range (Donny et al., 2012; Smith et al., 2013).

As tobacco-delivered nicotine differs substantially from intravenous nicotine, it may not be sufficient to rely on studies of intravenous nicotine self-administration to predict the potential reinforcing effects of tobacco with reduced nicotine content. Administration parameters such as the timing of dose delivery play a role in determining the pharmacology and reinforcing effects of a given dose (Sorge & Clarke, 2009). Nonetheless, the limited evidence available suggests that the nicotine threshold for self-administration of cigarette-delivered nicotine is not substantially different from that identified above. Tobacco manufacturers have used brain imaging to determine effective ranges of cigarette nicotine delivery under controlled smoking conditions (Panzano et al., 2010); the results suggest

a threshold for a neurophysiological effect of 0.1–0.3 mg of machine-measured smoke nicotine. The findings are also consistent with research on nicotine discrimination, which indicates that the threshold levels for discrimination are in a comparable range and do not differ for smokers and non-smokers (Hatsukami et al., 2010a).

Whereas most studies in humans have been conducted among established smokers, studies in animals suggest that the threshold for acquisition of nicotine self-administration behaviour is equal to or higher than that for maintenance of such behaviour (Donny et al., 2014). In adult rats, self-administration of low doses of nicotine is more frequent after exposure to high doses of nicotine and subsequent dose reduction than during acquisition (Smith et al., 2014). Acquisition of nicotine self-administration behaviour and dependence among adolescents may, however, be different from that among adults. Both cross-sectional and longitudinal studies indicate that young people who smoke less than daily nonetheless report the onset of dependence symptoms. Reward expectancy plays a significant role in smoking behaviour and motivation to smoke among adolescents (Kassel et al., 2007).

De-nicotinized cigarettes suppress acute craving and delay the onset of ad-libitum smoking in the same way as nicotine-containing cigarettes (Rose et al., 2003; Barrett, 2010); in contrast, intravenous nicotine suppresses ad-libitum smoking to only a small extent (Rose et al., 2003). This suggests that the non-nicotine stimuli associated with smoking become conditioners, serving as cues to the smoker for anticipated nicotine delivery. The conditioning properties of tobacco smoking are acquired only after long-term prior use of nicotine-containing cigarettes. Studies in animals suggest that the conditional reinforcing properties acquired by a stimulus are a direct function of dose. This implies that stimulus control of tobacco-seeking behaviour will be most potent in people exposed to high levels of nicotine and are likely to be greatly reduced by exposure to very low nicotine, with a reduction in conditional stimuli (Palmatier et al., 2008).

Variations in sensitivity to the behavioural and potentially addictive effects of nicotine have important implications for setting product performance standards for nicotine. Thus, to minimize the risk for addiction of all individuals who sample cigarettes, the maximum allowable content should be well below that which might have behavioural and addictive effects. Comprehensive surveillance and epidemiological studies will be important to determine if the performance standards set initially are effective and to assess any unintended consequences rapidly. Corrections and risk management plans can be made accordingly.

7. Feasibility of reducing nicotine

Currently, most conventional cigarettes contain 10–15 mg of nicotine each, of which approximately 10% is delivered in smoke, resulting in a typical systemic intake of 1–2 mg of nicotine per cigarette. Higher levels can be delivered with more intense smoking behaviour. Thus, establishing a maximum allowable limit for nicotine would require an overall reduction in nicotine intake of the order of 90–95% or more.

The concentration of nicotine in tobacco is readily altered and controlled by manufacturers, for example by genetic modification, enzymatic processes or nicotine extraction, to levels approaching or exceeding this range of nicotine reduction (Wayne & Carpenter, 2009). Reduced-nicotine cigarettes are now available that contain < 1 mg nicotine per gram of tobacco and, when smoked on a standard smoking machine (ISO), have a nicotine yield of 0.03–0.1 mg, equivalent to 3–10% of the nicotine yield of standard commercial brands. Most behavioural research on nicotine reduction has been conducted with cigarettes that provide this range of nicotine in smoke.

Production of cigarettes with a very low nicotine content is technically feasible. The loss of sensory impact due to reduced nicotine has been discussed as a potential technical challenge; however, the fact that commercial cigarette brands such as Next and Quest with a nicotine content of < 1 mg have been produced and that these products can substitute for conventional cigarettes and at least temporarily reduce cigarette craving provides strong evidence that the production of cigarettes with a very low nicotine content is technically feasible (Butschky et al., 1995; Rose et al, 2003; Johnson et al., 2004; Rose, 2006; Hatsukami et al., 2013b). Spectrum cigarettes, currently produced for research purposes by 22nd Century Manufacturers, have a reported level of 0.4 mg nicotine per gram of tobacco.

Another concern raised with respect to nicotine reduction is that smokers will respond by altering their smoking behaviour. Evidence from clinical studies indicates, however, that smokers of products with a very low nicotine content (< 1 mg/g) do not significantly alter their behaviour from that with their usual brand, and their exposure to nicotine remains significantly reduced (Benowitz et al., 2006; Hatsukami et al., 2010b; Benowitz et al., 2012). Smokers do, however, compensate for less extreme reductions in delivered smoke nicotine (0.2–0.3 mg) (Hatsukami et al., 2010b). Moreover, for smokers not interested in quitting,

progressive reduction of the nicotine content of their cigarettes to 0.5 mg/g does not lead to extinction of their dependence upon follow up (Benowitz et al., 2015).

The behavioural research conducted to date has been with cigarettes with reduced-nicotine tobacco but otherwise conventional design. Other physical and chemical parameters of cigarette construction can be manipulated to alter the basic formulation, with unknown behavioural and health consequences. Therefore, attention must continue to be paid to other product factors, in addition to nicotine delivery. Standard measures of smoke nicotine delivery do not differentiate between forms of nicotine (e.g. free-base versus protonated nicotine); comparisons of free-base nicotine delivery may provide a more accurate measure of subjective response to reduced-nicotine content products (Wayne & Carpenter, 2009).

8. Potential behavioural and population outcomes

Reduced-nicotine cigarettes can give acute subjective satisfaction (Hatsukami et al., 2010a) and immediately reduce craving in smokers (Rose et al., 2003); however, with repeated use, reduced-nicotine cigarettes give less satisfaction than those with a higher dose of nicotine (Hatsukami et al., 2013c). Clinical data indicate that withdrawal is not a common adverse consequence of reduced nicotine intake in most smokers and that significant compensation in the form of more intense smoking or more cigarettes per day is not a probable outcome at very low nicotine levels (< 1 mg) (Hatsukami et al., 2010a; Hatsukami et al., 2010b; Benowitz et al., 2012).

Use of reduced-nicotine cigarettes over a long time weakens the reinforcing effects of smoking: smokers consistently report less dependence after prolonged use of such products (Donny et al., 2007; Benowitz et al., 2009; Hatsukami et al., 2010b; Benowitz et al., 2012). Reduced-nicotine cigarettes may represent a temporary coping mechanism and help smokers to achieve abstinence when they make an active attempt to quit. They may support quitting not only for smokers who seek treatment but also for smokers who have not previously expressed an interest in quitting (Benowitz et al., 2007; Benowitz et al., 2009).

The effects of reduced-nicotine cigarettes on quitting may be strengthened by the addition of nicotine-based treatment, particularly in men (Vogel et al., 2014). This suggests that other forms of treatment and behavioural support may be helpful as well and should be made accessible to support the transition

to reduced-nicotine cigarettes as well as to people attempting complete tobacco abstinence. The health benefits of switching from cigarettes to non-combusted forms of tobacco to sustain the nicotine intake will depend partly on the level of tobacco toxicants delivered by the alternative products and how long they are used. Some people may continue to smoke cigarettes after mandated nicotine reduction, either for a strong substitution effect or because the nicotine content of the cigarettes remains above their individual threshold for reinforcement. Few studies have been conducted, however, on the uptake of reduced-nicotine cigarettes by non-smoking populations and the long-term effects of reduced-nicotine cigarette use; there may be little, if any, health benefit if people continue to inhale high levels of combusted tobacco emissions. People should be encouraged and supported to discontinue use of any combusted tobacco product as quickly as possible. Surveillance and other research will be required to monitor effects—desired and undesired.

The literature provides no quantified estimates of the potential impact of a reduced-nicotine policy on smoking initiation among adolescents. It is theoretically possible that reduced-nicotine cigarettes could serve as "starter" products for products with a higher nicotine content, if such products were still available on the commercial market. Thus, product labelling and access restriction will remain important. Reduced-nicotine cigarettes should not be exempt from warnings about the risk for addiction, although the warnings may be somewhat different from those used on higher-nicotine products (Henningfield et al., 1994).

Various models have been created to estimate the probable effects of a nicotine reduction policy; all indicate a significant positive effect on public health outcomes. No published study has provided an estimate of the probable illicit sales of conventional cigarettes with a higher nicotine content in the context of a reduced-nicotine market. Both the appeal of reduced-nicotine cigarettes and the availability and appeal of alternative forms of nicotine are likely to affect the extent of illicit sales.

9. Policy approaches to nicotine reduction

The effects of a cigarette nicotine reduction policy will depend to a significant degree on the availability, toxicity and appeal of alternative nicotine delivery systems, including other forms of combusted or non-combusted tobacco,

medicinal nicotine and commercial non-tobacco nicotine products, as discussed elsewhere (Henningfield et al., 1998; Benowitz & Henningfield, 2013; Department of Health and Human Services, 2014). Substitution of alternative products could have adverse health effects or maintain addiction in a significant segment of the population. Therefore, a successful nicotine reduction policy must be supported by comprehensive regulation of all tobacco- and nicotine-containing products (Gray et al., 2005; Zeller et al., 2009; Le Houezec et al., 2011; McNeill et al., 2012; Hatsukami et al., 2013a; Benowitz et al., 2015). The goals of comprehensive regulation would be to minimize use of highly toxic nicotine-containing products, to encourage the development of less toxic nicotine delivery systems as alternatives to more toxic products and to continue to monitor and regulate the health effects of the less toxic products (Gray et al., 2005; Le Houezec et al., 2011; Benowitz & Henningfield, 2013).

Policy approaches could be considered to motivate smokers who are unable to quit to substitute less hazardous forms of tobacco and nicotine use, e.g. through restrictions on access, marketing and use, in order to encourage complete cessation of use of the more toxic products. The health benefits for people who switch from cigarettes to non-combusted forms of tobacco to sustain their nicotine intake will depend partly on the level of tobacco-related toxicants delivered by the alternative products, the extent to which they continue to smoke cigarettes and how long they continue to use the products.

The effects of reducing nicotine to very low levels either gradually or immediately have been evaluated in clinical studies; no adverse effect was found in either condition, indicating that neither approach poses a significant safety concern (Hatsukami et al., 2013a; Smith et al., 2013; Hatsukami et al., 2015). A gradual reduction would maintain smokers at nicotine doses more likely to support compensatory behaviour for an extended period and could theoretically enable them gradually to adapt effective compensatory behaviour to products with a low nicotine content. Therefore, an immediate reduction in nicotine, preceded by health communication strategies and public education, is the more promising approach.

Product performance standards are necessary to ensure successful implementation of nicotine reduction. While a number of approaches could be considered, reducing the total nicotine available in unburnt cigarettes is the most promising, as it is both easily measured and not subject to behavioural manipulation or individual variation. Although this report addresses cigarettes, a similar regulatory approach

would be appropriate for other combusted and non-combusted products. Product performance standards must remain responsive to the changing marketplace (Hatsukami et al., 2012; O'Connor, 2012; Hatsukami et al., 2013a), and new products and technologies must be evaluated carefully. Commercial introduction of new products should be permitted only when they have been shown sufficiently to be associated with reduced risk, addictiveness and appeal.

Whether a policy will result in a reduction in the addictiveness of cigarettes will depend partly on how effectively the risks are communicated. Mistaken beliefs about the greater safety of reduced-nicotine products could lower the likelihood of quitting and could encourage more experimentation. Implementation of smoke-free policies might provide a useful model, and public education can support compliance and ensure continued support for the law. Studies in the USA (Hatsukami et al., 2013a) have shown strong support for mandated nicotine reduction among both smokers and non-smokers, but no surveys have been reported from other parts of the world. Education of smokers and non-smokers about the health risks of tobacco without nicotine, the relative harm of different products and opportunities for treatment is critical. The marketing of tobacco and nicotine products will have to be strongly regulated (McNeill et al., 2012; Hatsukami et al., 2013a).

Although the evidence is inconclusive, various models have indicated that setting a maximum allowable nicotine content will sharply increase the number of smokers who want to quit (Tengs et al., 2005; Morrison, 2013). Many smokers are likely to seek nicotine replacement or behavioural therapy to aid cessation or to obtain relief from withdrawal symptoms. Effective, affordable treatment offered by health care professionals and coverage by insurance programmes will be invaluable in ensuring the success of the policy, as will individualized services to populations in whom the adverse effects may be more severe, such as those with psychiatric disorders. Wide availability of pharmacotherapy and treatment might not only reduce the discomfort associated with smoking reduced-nicotine cigarettes but might also lead to a substantial reduction in cigarette smoking and possibly to cessation of use of all tobacco and nicotine products by some or many current smokers (Zeller et al., 2009; O'Connor, 2012; Benowitz & Henningfield, 2013).

The appeal of alternative tobacco products, such as oral and smokeless tobacco, waterpipes, pipes and cigars, may increase, as they may substitute for conventional cigarettes more effectively than reduced-nicotine cigarettes; however, few data are available. This prospect must be included in any assessment of the health effects of

existing and new products that could serve such a purpose. Extending a nicotine reduction policy to other combusted products or possibly non-combusted tobacco products should be considered. Electronic nicotine delivery devices and other products designed expressly to replicate the act of smoking may present viable alternatives; in some countries, however, if they are marketed as cessation aids, they would first have to be proven safe and effective in clinical trials (Department of Health and Human Services, 2014; WHO, 2014b).

Reduced availability of conventional cigarettes as a consequence of adoption of a maximum allowable limit for the nicotine content of all cigarettes might increase the demand of addicted smokers for contraband conventional cigarettes. Minimizing sales of illicit cigarette will require effective surveillance of wide-scale organized smuggling and other types of illegal trade, such as in bootlegged and counterfeit products (Joossens & Raw, 2008). Unregulated combusted tobacco, such as roll-your-own, could be substituted for manufactured cigarettes. Other areas of potential concern include use of both reduced-nicotine cigarettes and nicotine delivery devices, use of pH modification or additives to increase the impact and pharmacological effect of manufactured products and unanticipated behavioural changes, such as deeper inhalation or increased or more frequent long-term use of reduced-nicotine cigarettes. The production of more appealing alternative nicotine products is likely to serve as a check on these unintended market outcomes (Benowitz & Henningfield, 2013; Hatsukami et al., 2013a).

An adequate surveillance system would allow regulators to monitor the impact of tobacco products on the prevalence, initiation and harm of smoking and to address unintended outcomes (Hatsukami et al., 2013a). Mandatory reporting of all nicotine and tobacco products, as described in the partial guidelines to implementing Articles 9 and 10 of the WHO FCTC (WHO, 2012b), are a necessary condition for adequate surveillance. Mandatory reporting should include the physical design (tobacco weight, nicotine concentration, filter ventilation), the tobacco and added constituents, the emissions of combusted products and measures of possible abuse (Carter et al., 2009; Hatsukami et al., 2012; McNeill et al., 2012). The complexity of tobacco products and the knowledge required to assess toxicological effects, the possibility of abuse and other outcomes may be barriers for some Parties. A global data repository would facilitate tobacco product regulation and surveillance worldwide, would ease the burden on regulators by providing access to analysed data and global comparisons, and would provide information to national regulators, with recommendations in an easily understandable form (McNeill et al., 2012).

10. Conclusions

There is clear evidence that reducing the nicotine content of cigarettes to a very low level can reduce their dependence potential. The maximum nicotine content of cigarettes that leads to dependence is likely to vary individually and is possibly lower for young people. Thus, the maximum nicotine content should be as low as is technically feasible. At present, that level would appear to be 0.4 mg nicotine per gram of cigarette tobacco filler.[4] Compensatory smoking has been observed with highly ventilated cigarettes but not with cigarettes with a nicotine content of 0.4 mg per gram of cigarette tobacco filler.

The evidence indicates that setting a maximum allowable nicotine content for all cigarettes could:

- reduce acquisition of smoking and progression to addiction;
- reduce the prevalence of smoking in a proportion of addicted smokers as a result of behavioural extinction;
- increase the rate of quitting and reduce the number of smokers who relapse; and
- increase the development, availability and use of alternative forms of nicotine, e.g. smokeless tobacco products, nicotine aerosol products and medicinal nicotine, which have potential adverse health effects, including maintenance of addiction, but less than those of combusted products or conventional cigarettes.

11. Research needs

Major research projects, including clinical trials, are under way and are providing relevant information for implementing an approach to reducing the addictiveness of cigarettes. The research priorities include:

- the probable use and effects of reduced-nicotine cigarettes in non-smoking adolescents, non-smoking adults[5] and non-dependent smokers (i.e. light

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[4] In the working group report FCTC/COP/5/9, dated 17 July 2012, reference is made to commercial cigarettes containing 0.03 mg nicotine. This measure refers to the smoke nicotine yield, which is only a fraction (in this case, approximately 10%) of the nicotine contained in unburnt cigarette tobacco. Spectrum cigarettes, produced for research by 22nd Century Manufacturers, have a reported content of 0.4 mg nicotine per gram of tobacco.

[5] As administering reduced nicotine cigarettes to tobacco-naive humans is unethical, studies on animals or indirect ways of assessing the impact on non-smokers will have to be considered.

or occasional smokers who experience minimal withdrawal symptoms yet continue to smoke);[6]
- potential use of reduced-nicotine products as "starters" or "gateway" products by adolescents, leading to use of other forms of nicotine or drugs;
- the effects of reduced-nicotine cigarettes in populations at risk, such as people with moderate or severe depression or other comorbid conditions;
- the comparative health risks of smoking reduced-nicotine cigarettes and conventional cigarettes, including in special sub-populations (e.g. women of reproductive age);
- long-term use of reduced-nicotine cigarettes and the long-term impact on smoking behaviour and health outcomes, including cancer;
- comparison of the long-term public health effects of reduced-nicotine cigarettes and of alternative non-combusted forms of nicotine (e.g. some smokeless tobacco products with reduced tobacco-specific nitrosamines or electronic nicotine and non-nicotine delivery systems); and
- surveillance and epidemiology to assess any unintended consequences, including on health, and to guide modification of the policy and supporting strategies.

12. Regulatory recommendations

- Mandated reductions in nicotine to minimally addictive levels should be supported by comprehensive regulation of all nicotine- and tobacco-containing products.

- Mandated reductions in nicotine to minimally addictive levels must be part of comprehensive tobacco control, including increased taxes on cigarettes, comprehensive smoking bans, anti-smoking educational campaigns and graphic warning labels or plain packaging.

- Mandated reductions in nicotine to minimally addictive levels might be considered for all combusted products because of the overwhelming

[6] A subset of light or occasional smokers consumes five or fewer cigarettes per day and appears to smoke primarily for the positive reinforcing effects of nicotine (Benowitz, 2008). These smokers use cigarettes mainly in association with specific activities, such as after meals or with alcohol, and less in response to negative affect; they may be more reactive to smoking cues (Watson et al., 2010). Although these occasional smokers experience minimal or no withdrawal symptoms, many have difficulty in quitting, suggesting a form of dependence that is distinct from that of everyday smokers.

toxicity associated with combustion and to minimize substitution of reduced-nicotine cigarettes for other combusted products.

- The original proposal for nicotine reduction (Benowitz & Henningfield, 1994) urged a gradual reduction over many years. More recent scientific evidence suggests that an immediate reduction in the intake of nicotine below the established product performance standard, preceded by health communication strategies and public education, is a better approach, for practical reasons. There is no scientific basis for concluding that a one-time reduction is more or less likely to be associated with unintended consequences than gradual reduction.

- Health professionals must be taught to communicate the risks, once they are known, and ensure compliance with and support for the law. The availability of effective, affordable cigarette cessation treatment, alternative forms of nicotine, optimal medicinal forms of nicotine and other approved treatments and medicines for tobacco dependence and withdrawal will help dependent smokers who experience adverse effects or withdrawal symptoms.

- The potential adverse health effects and increased use of alternative nicotine products must be weighed against the benefits of a reduction in cigarette consumption. The health benefits for people who switch from conventional cigarettes to non-combusted forms of tobacco to sustain their nicotine intake will partly depend, however, on the level of tobacco-related toxicants delivered by such alternative products, the extent to which people continue to smoke some cigarettes and how long they continue to use such products.

- A strategy to reduce the addictiveness of tobacco is not recommended in the absence of developed capacity for market surveillance and product testing. Countries without an adequate infrastructure to ensure a comprehensive approach to nicotine reduction should carefully consider increasing that capacity before implementing such a strategy.

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This advisory note presents the conclusions and recommendations of the members of the WHO Study Group on Tobacco Product Regulation (TobReg) on a policy for limiting the sale of cigarettes to brands with a nicotine content that is not sufficient to lead to the development and/or maintenance of addiction. Initial discussions began at the seventh meeting of TobReg, which was held in December 2013; discussions subsequently continued for more than 18 months because of the complexity and sensitivity of the topic.

One of the main conclusions was that no specific amount of nicotine has yet been identified as the absolute threshold for addiction; however, it is likely to be equal to or possibly less than 0.4 mg/g of dry cigarette tobacco filler. The following topics are also covered in the advisory note:

- Cigarettes with a reduced nicotine content
- Goals of a policy to reduce addiction to cigarettes
- Tobacco addictiveness factors
- Establishing a performance standard for nicotine products
- Feasibility of reducing nicotine
- Potential behavioural and population outcomes
- Policy approaches to nicotine reduction

The conclusions reached by TobReg and recommendations and research needs are discussed at the end of the advisory note.

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