Feasibility of Manufacturing Tobacco with Very Low Nicotine Levels

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Objective: In this paper, we evaluate the effectiveness of agricultural approaches and manufacturing techniques that can be applied to reduce nicotine content of tobacco to minimally addictive levels (< 0.4 mg/g). **Methods:** Using a semi-structured approach, we searched scientific and grey literature including patents and internal industry documents, using keywords like tobacco, nicotine, alkaloids, denic(otinized) tobacco, reduced nicotine content, very low nicotine tobacco. **Results:** Nicotine can be reduced via genetic modification or traditional breeding techniques. Contents and emissions are similar to regular cigarettes, but consumers rated them as less satisfactory. Extraction techniques yield less palatable tobacco too, due to co-extraction of flavor components in tobacco. Microbial and enzymatic degradation lead to other, mostly undesirable, changes to tobacco. Supercritical extraction resulted in a taste most similar to regular cigarettes, but still failed in the marketplace. **Conclusions:** Most of the available techniques are successful in reducing nicotine levels, sometimes to levels lower than 0.4 mg/g. However, in almost all cases, the resulting tobacco leads to a less satisfactory smoking experience. Although reduction of nicotine to a non-addictive level is feasible from a technical perspective, it is not clear whether such measures could be successfully implemented.

Key words: nicotine reduction; tobacco; addiction; plant technology; tobacco product manufacturing
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According to the 2014 Surgeon General's report, tobacco use remains the leading cause of preventable disease and death in the United States (US), with at least 480,000 deaths occurring each year.[1] Projecting on the future, almost 6 million youth currently below 17 years of age will die prematurely from smoking-related illnesses. To prevent this disaster, new regulatory strategies are needed. In 2018, the Food and Drug Administration (FDA) issued an advance notice of proposed rulemaking (ANPRM), stating that "making cigarettes minimally addictive or nonaddictive would limit the number of youth and young adults who progress from experimentation to regular use, and who, thereby, increase their risk for dangerous smoking-related diseases."[2]

Although nicotine asserts only a minor impact on tobacco related toxicity, it is the most important factor for addictiveness, and thus, is responsible for the high and sustained use of tobacco products. Because tobacco addictiveness depends mainly on nicotine, mandatory nicotine reduction strategies are the most obvious way to decrease dependence.[3-5] Policies to limit the nicotine content in cigarettes to minimally- or non-addictive levels have been proposed by the World Health Organization (WHO) Study Group on tobacco products (TobReg) and the FDA.[2,6] Although strong arguments also have been raised against such *de-facto* prohibition,[7,8] this concept is widely supported.

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To define the levels of nicotine that can be regarded as non-addictive is vital in the development of reduced nicotine cigarettes. This might be challenging, because there is considerable individual variability in dose sensitivity to drugs,[5] it is not likely that a single threshold will apply to all people. However, several studies show that there are doses of nicotine that would not produce self-administration in animals, or psychoactive or rewarding effects in humans.[9,10] Specifically, recent data suggest that nicotine should be reduced to a maximum of 2.4 mg/g and that there may be additional benefits to decreasing content to 0.4 mg/g.[11] One reason to consider the lower standard is that specific populations such as non-tolerant adolescents may be more sensitive to the effects of nicotine.[4] As smokers require a sufficient amount of nicotine to satisfy their addiction, reducing nicotine levels in cigarettes often leads to compensatory smoking. However, studies have shown that this is not the case for cigarettes with 2.4 mg or less nicotine per g of tobacco.[9,11-13] Because uncertainties remain where nonaddictive levels can be set, this term refers here to minimally addictive levels as well.

Because conventional commercial cigarettes contain up to 12 mg nicotine per gram of tobacco, an important question is whether nicotine in tobacco can be reduced to minimally addictive levels, and whether this is also feasible in mass industrial production. In this paper, we describe various manufacturing techniques by which nicotine content can be reduced, including traditional agricultural practice, genetic engineering and technical modifications, and evaluates their effectiveness and consequences for the consumer appeal of such products.

METHODS

This study comprises a semi-structured review, with the aim of synthesizing the state of knowledge about manufacturing tobacco with very low nicotine levels. To achieve this, relevant scientific literature was searched between March and June 2018, primarily using the PubMed database. We performed the search by using a combination of keywords for tobacco, nicotine, alkaloids, denic(otinized) tobacco, reduced nicotine content, and very low nicotine tobacco. We also included relevant articles cited in publications obtained through the database research. There were no restrictions on date, language, or geographical region. In addition, we searched tobacco manufacturers' websites and tobacco document repository research websites. Internal industry documents were accessed via https://www.industrydocumentslibrary.ucsf.edu/. Patent literature and internal research conducted by the industry can reveal research efforts and outcomes targeted at the reduction of nicotine in tobacco.

RESULTS

Strategies to Reduce the Nicotine Content of Tobacco

An overview of agricultural practices and manufacturing techniques that can be used to reduce the nicotine content of tobacco is presented in Table 1.

Agricultural practice and genetic manipulation of the tobacco plant. The nicotine content in the cultivated *Nicotiania tabacum* and *Nicotiania rusitica* can range from 0.5 to 8% in the tobacco leaf.[14] Properties of tobacco,[15] as well as nicotine content in the leaf, depend on multiple factors, such as soils, irrigation, plant density or nitrogen fertilization.[16] In fact, nitrogen fertilization is crucial to ensure optimal growth of high-quality tobacco.[17] Nicotine is also a major determinant of taste that is affected by the ratio of nicotine, nitrogen and acids within the leaf as a review by Mendell et al[18] describes. As a consequence, both low and excessive levels of nicotine can negatively affect the sensory characteristics, such as taste and smell, as well as the commercial value of tobacco products. However, low nicotine tobacco is not necessarily a less desirable product for tobacco users. For example, German tobacco contains comparatively low nicotine levels, but is in high demand for flavored shisha tobaccos.

In the late 1920s, initial reports on adverse health effects of smoking [19] were published, and at the same time anti-tobacco movements gained importance to take on the fight against tobacco dependence. Even before a comprehensive scientific framework was established, nicotine was already considered as harmful and a major incentive for smoking. Notably, this coincided with initial successful efforts to breed nicotine-free tobacco by selection.[20,21] It was realized that the generated nicotine-deficient strains acquired 2 different phenotypes. Plants either showed hardly any nicotine in the green leaf,

Table 1
Overview of Techniques to Lower Nicotine Levels in Tobacco Leaves, as Described in Scientific Literature and Internal Tobacco Industry Documents

Nicotine reduction strategy			Amount of nicotine reduced	Implications for other product aspects	Other remarks
Agricultural techniques	Traditional breeding	Nic1/nic2 mutation	Up to 95% of nicotine content	Negative effects on aroma-properties and sensation and perception of the smoke.	Lower plant yields.
	GMO	Antisense (NtQPT1)	Up to 97% of nicotine content	Flavor similar to regular cigarettes but still rated as less satisfactory by consumers.	Prior approval by regulatory authorities.
		RNA interference (NtBBL)	Up to 91% of nicotine content	Formation of a novel alkaloid Reduced cured leaf yield.	
Manufacturing techniques	Nicotine extraction	Water or solvent	Up to 100% of nicotine content	Poorer subjective characteristics and in many cases making the tobacco no longer suitable for smoking. May leave trace elements of toxic solvent.	Reintroduction of important flavor components was discussed by industry.
		Steam/ammonia treatment	Up to 90% of nicotine content	Poorer sensory quality tobacco. Increased ammonia content and pH of the tobacco	
		Supercritical extraction	Over 96% of nicotine content	Retained flavor character and little off-taste	
	Microbial degradation		Nicotine reduced up to 0.5% of tobacco	May cause tobacco to darken, have a higher pH, lose mass and undergo changes in nitrogen compounds. Product acceptability equal to that of untreated tobacco.	Does not work in mixtures containing 8 or more mg/ml of nicotine.
	Enzymatic degradation		10% to 27% of nicotine content	Physical appearance unchanged. Intensity of aroma and softness are increased, impact and irritation lowered.	Increased amounts of other toxicants such as formaldehyde and isoprene.
	Photocatalytic degradation				

or normal levels that were rapidly lost during drying.[22] These variants were later investigated in the Kentucky Agricultural Experimental Station during the 1940s and 1950s.[23] It was concluded that nicotine levels are controlled by 2 different sets of factors that regulate total alkaloid production and the conversion of nicotine to nor-nicotine in the leaf.[23] Notably, these early approaches later illustrated that nicotine reduction can lead to novel toxicological risks. Genetic variations that enhance demethylation lead to increased levels of nor-nicotine. However, this pathway is also a major source for carcinogenic tobacco specific nitrosamines (TSNA), as nitrosation of nor-nicotine can occur during tobacco processing. Notably, this leads to an enhanced formation of N-nitrosonornicotine (NNN). Consequently, current concepts of genetic modifications aim to prevent demethylation of nicotine.[24] As an alternative, tobacco strains can be selected that are deficient in nicotine synthesis.

From an agricultural perspective, it is feasible to generate nicotine free tobacco by traditional methods, due to a sufficient genetic diversity of the tobacco plant.[25] Starting in the 1970s, attempts to decrease alkaloids were extensively explored by industry, as part of an overall strategy to create a low nicotine product segment. The alkaloid reduced tobacco (ART) program by Philip Morris was dedicated to this objective for nearly 30 years.[26] However, besides the intended reduction of nicotine, it was noted that breeding projects did often result in tobaccos that do not meet typical criteria of commercialized products.[27] Furthermore, tobacco plants that lack nicotine can be more susceptible to pest infestation and might require an increased use of pesticides.[28]

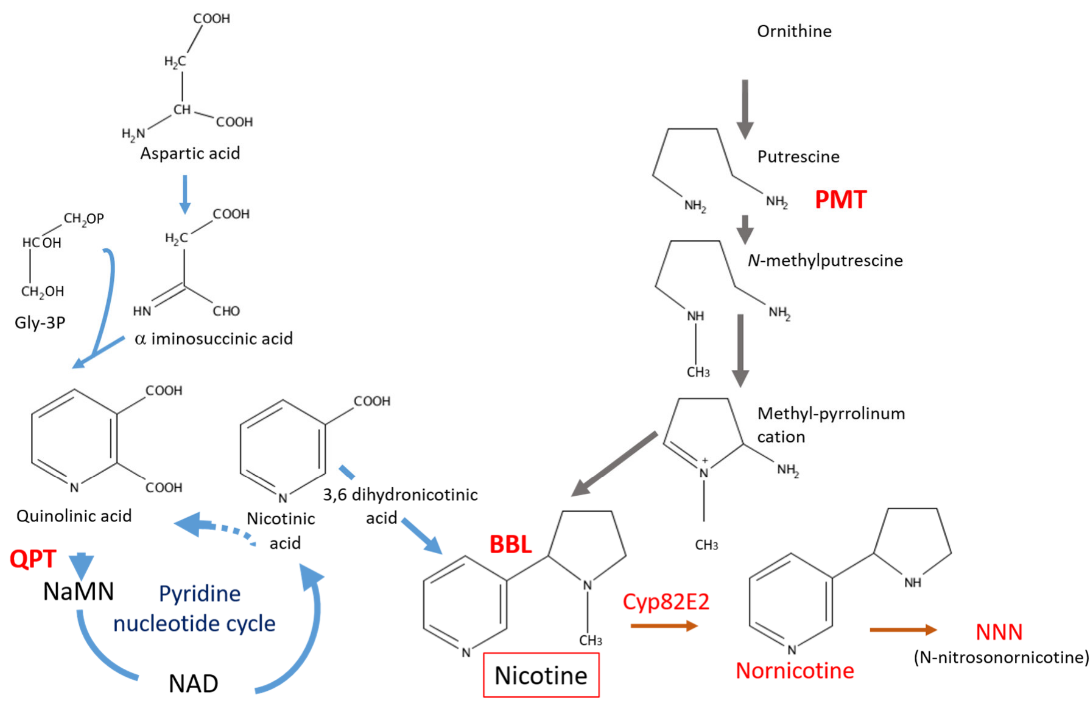
Loss of nicotine in tobacco has already profound effects on aroma-properties and sensation. In addition, there is evidence that nicotine synthesis is genetically linked to other traits desired by the industry for its products [26,27] that determine for example perception of the smoke. The focus to derive nicotine free tobacco did consequently shift to genetic engineering, aimed to introduce specific alterations with minimal effects on other properties of tobacco. Nicotine synthesis in the plant depends on 2 molecular pathways (Figure 1), leading to the pyrrolidine (right branch) and pyridine (left branch) ring systems Firstly, ornithine, an intermediate of the urea cycle is de-carboxylated into putrescine, followed by methylation *via* PMT (putrescine methyltransferase), leading finally to formation of methylpyrroline cation. In the parallel branch, quinolinic acid is converted by quinolinate phosphoribosyltransferase (QPT) leading further to nicotinic acid. Finally, the methylpyrrolinium cation reacts with a metabolite of nicotinic acid (NA) to form nicotine, although the mechanism is not yet fully understood.[29] PMT and QPT had already been linked by Saunders and Bush[30] to 2 previously identified distinct genetic loci.[29] These findings had confirmed essential roles for both genes, each controlling one molecular branch in the nicotine synthesis pathway.

Both PMT and QPT became early targets for genetic engineering approaches.[31,32] Downregulation of nicotine by inhibition of PMT via transgenic anti-sense RNA expression was patented in 1997 (US Patent 5684241). Although this did not generate nicotine free tobacco, a reduction by 80% was achieved.[26] Xie et al[33] used an antisense approach to downregulate *NtQPT1*, a tobacco specific QPT variant.[31] This modified tobacco was used in the "Quest" brand by Vector Tobacco Ltd, which included a version that contains only 0.05 mg nicotine yield per cigarette. According to Forbes, "Quest" was discontinued in 2010. The finding that consumer acceptance was low for "Very low yield cigarettes" was also confirmed in scientific studies.[34-36] Recent developments are driven by the 22nd Century Group, the company that had initially licensed the *NtQPT1* based nicotine reduction approach to Vector Tobacco Ltd. Internet releases indicate that current commercial approaches explore new targets for genetic engineering, including the berberine bridge enzyme-like (BBL) that is involved in the late step of nicotine synthesis[37] and was described as a promising target before.[31] Further, target assessments include tobacco specific transcription factors that are activated by jasmonic acid in response to insect induced damage.[38] Notably, there was considerable progress to reduce nicotine in tobacco towards non-addictive levels and to minimize the impact on taste and organoleptic properties.[32] However, this strategy is likely to depend on genetically modified tobacco variants at the current stage.

Tobacco product engineering techniques. In addition to plant technology and agricultural practices, many tobacco product-engineering techniques exist to lower nicotine levels in tobacco leaves. In the 20th century, the tobacco industry or researchers filed more than 100 patents to use solvents, steam, microbes, and gases to remove nicotine from tobacco.[26] Criteria for nicotine reduction are, on the one hand, an effective and efficient removal without leaving unwanted components, and on the other hand, being selective, especially with regards to unintended extraction of compounds important for flavor and palatability.

Nicotine extraction. Since the 1950s, many processes using water or organic solvents to extract nicotine from tobacco leaves have been developed and used by the tobacco industry.[26,39-43] For example, methyl ethyl ketone (MEK) extraction was reported to result in a 75% reduction in nicotine,[44] water or freon in 80%-85%,[40] water 92%,[45] MEK combined with water in 90%-100%,[46] and trichloroethylene up to 100%.[47] Solvents other than water may introduce trace amounts of new, often toxic compounds to the tobacco. For example, it was shown that removal of all MEK took several days.[46] Apart from nicotine, water and other solvents also may extract other tobacco constituents, resulting in

Figure 1
Nicotine Synthesis Pathways and Key Enzymes that are Targets for Genetic Modifications



Note.
Nicotine synthesis depends on 2 molecular pathways leading to nicotinic acid (blue arrows) and the Methyl-pyrollinium cation (grey arrows). The key enzymes QPT (quinolinate phosphor-ribosyltransferase), PMT (putrescine N-methyl-transferase) and BBL (berberine bridge enzyme-like) that have been used as targets to inactive the biosynthesis in Nicotiana tabacum are indicated red. Elevated activity of CYP82E2 in selected N. tabacum variants is associated with an efficient demethylation of nicotine during curing. However, nitrosylation of the resulting nornicotine leads to the formation of carcinogenic NNN.

Abbreviations: NaMN: Nicotine acid mononucleotide; NAD: nicotineamide adenine dinucleotide; Gly-3P: Glycerol 3-phosphate.

poorer subjective characteristics and in many cases making the tobacco no longer suitable for smoking.[40,46,48] Reintroduction of important flavor components was therefore discussed by industry.[42]

Steam treatment of tobacco, especially in the presence of a base such as ammonia or potassium hydroxide, can reduce nicotine levels up to 90%.[41,44,49] The heat treatment disassociates nicotine salts naturally present in tobacco into free nicotine, which is then driven from the tobacco.[42] Whereas the addition of ammonia helps to reduce nicotine effectively, it remains in tobacco after treatment. For example, one study reported reduced nicotine levels ranging from 0.06%-0.3%, but also significantly increased the ammonia content and the pH of the tobacco.[50]

Supercritical fluid extraction (SCFE) is fast and efficient.[39,51] For instance, one study from Altria shows that extraction with supercritical carbon dioxide removed 96% of nicotine content tobacco to levels of 0.1% per dry weight.[52] The PMI patent on which this technique is described, mentions a minimal loss of flavors[53] but sensory study results are not described. An earlier patent of the same PMI author also reported more than 96% nicotine reduction, but indicated "... the product was subjectively rated as average in smoking characteristics."[54] Brown and Williamson note that carbon dioxide is the best choice for SCFE since it is a good solvent with a low critical temperature that, therefore, does not cause thermal damage to tobacco. Furthermore, it is non-toxic, leaves no solvent residues, and is relatively inexpensive.[55] They also report that supercritical extraction is more effective than ammonia based steam extraction (90% versus 60% nicotine reduction), with retained flavor character and little off-taste, while steam extraction resulted in poorer sensory quality tobacco.[56]

In a process similar to decaffeinating coffee, nicotine levels are reduced by 95%-98% when tobacco leaf is treated with ammonium salt, and carbon dioxide/water vapor. Philip Morris's "denicotinized" cigarette brand called "Next"[57] launched in 1989 as a "low-nicotine" brand in the US,[26] was prepared by a technology based on General Food's process for decaffeinating coffee beans which used supercritical fluid extraction. The ammonium salt deprotonates nicotine to its free-base form, which makes extraction by carbon dioxide and water 2-3 times faster, resulting in 95%-98% reduction in nicotine. The product was marketed as "natural" like decaffeinated coffee but failed in the marketplace.

Microbial degradation. Nicotine-degrading microorganisms (NDMs) also could be applied to reduce the nicotine content in tobacco. These NDMs use nicotine as their single carbon and nitrogen source for growth and can break down nicotine in tobacco leaves without resulting in the loss of desirable flavor or smoking properties.[58] Many NDMs have been isolated and identified from tobacco plantation soil, leaves, and tobacco waste. Amongst them are bacteria such as Arthrobacter,[59] Pseudomonas,[60,61] Ochrobactrum,[62] Agrobacterium,[63] Shinella,[64] as well as several nicotine-degrading fungi, including Aspergillus.[65] The metabolic pathways of nicotine degradation have been characterized in several NDMs. Pyridine and pyrrolidine pathways are the 2 best-defined nicotine metabolic pathways, and most of the catalytic enzymes in these 2 pathways have been functionally characterized.[59,66]

Early industry documents reveal that microbial degradation can reduce nicotine in tobacco mixtures up to 0.5%.[67,68] Moreover, product acceptability, as assessed by a panel for the low nicotine tobacco derived from this process was equal to that of untreated tobacco.[69] However, several disadvantages of this approach have been identified, as the vigorous treatment of tobacco can cause it to darken, have a higher pH, lose mass, and undergo changes in nitrogen compounds. Moreover, the depletion of nicotine seems most effective in tobacco that already contains low amounts of nicotine, as degradation was slowed down or completely inhibited in mixtures containing 8 or more mg/ml of nicotine.[70]

Enzymatic degradation. Similar to the process of microbial degradation, enzymatic treatment of tobacco also results in reduced nicotine levels. For instance, a Philip Morris study showed that this process resulted in a 10% decrease in nicotine.[71] Other studies have also demonstrated lower yields of nicotine (16%-27%) in tobacco leaves and mainstream smoke but reported increased amounts of other toxicants such as formaldehyde and isoprene.[72,73] In contrast to microbial degradation, enzymatic degradation leaves the physical appearance of tobacco unchanged. However, it increases the perceived softness and intensity of aroma, whereas impact and irritation are lowered.[72] Currently, the enzymatic breakdown of nicotine is also pursued as a smoking cessation strategy.[74,75]

Photocatalytic degradation. Within 200 minutes of irradiation, nicotine in wastewater or landfill samples can be degraded using titanium dioxide as photocatalyst resulting in 9 degradants including cotinine.[76] Whether this also works in a tobacco matrix, and specifically for nicotine, is unknown.

Technical Feasibility of Manufacturing Tobacco/Cigarettes with Reduced Addictiveness Potential

From a technical perspective, it is feasible to reduce nicotine in tobacco products to minimally addictive levels. In fact, several cigarettes with a very low nicotine content[2] (compared to conventional commercial cigarettes) have been marketed or produced for research purposes. In spite of the technical feasibility, there are still several practical issues that need to be taken into account in producing viable reduced nicotine products. First, nicotine is known to have very noticeable perceptual characteristics.[26] Therefore, regardless of the technique applied, reducing nicotine levels may always result in a certain loss of flavor and sensation aspects of cigarette smoke. This could lead to a lower individual acceptance of reduced nicotine cigarettes (RNC). Notably, smokers do frequently rate RNC comparatively negative[34-36] and major brands like "Quest" have not been commercially successful. However, future developments may enable the reintroduction of flavor components or other technical improvements to compensate for the sensory effects of nicotine or flavors that had been lost due to breeding or processing. It is important to follow such developments, as they may provide alternate incentives to use RNC while they still pose the same toxicological risk as conventional cigarettes.

DISCUSSION

Our aim was to provide an updated and integrated perspective on the feasibility of manufacturing tobacco with reduced addictiveness potential. The most evident and impactful target for reducing the addictiveness potential is nicotine. Although a clear threshold has not been defined yet and individual differences in sensitivity to nicotine should be accounted for, various studies indicate that decreasing nicotine content below 0.4 mg/g would minimize and probably abolish the risk of dependence for cigarette smokers. This paper provides an overview of agricultural practices, including genetic manipulation, and tobacco product manufacturing techniques that have been developed and used by tobacco manufacturers to remove nicotine from tobacco leaves. Table 1 summarizes the available evidence. Most of the available techniques are successful in reducing nicotine levels, but differ in their effectiveness, and their possible unintended consequences such as flavor change. Although some techniques can reduce nicotine to levels lower than 0.4 mg/g, in almost all cases, the resulting tobacco leads to a less satisfactory smoking experience. This is partly due to the absence of the flavor and rewarding effects of nicotine, which is an inherent problem of nicotine removal. However, in cases of extraction techniques, the poorer sensory quality is also caused by the co-extraction of flavor components in tobacco. Analytical papers on flavors extracted from tobacco list many compounds including solanone, β-damascone, and furfuryl alcohol.[77,78] In principle, extracted flavor components could be replaced, or other combinations of additives with the appropriate flavor properties could be added to the extracted tobacco. Indeed, reintroduction of aromatic constituents after treatment was considered by industry.[42]

Nevertheless, supercritical extraction (which is similar to the process of manufacturing decaffeinated coffee) allows manufacture of cigarettes that were claimed to taste rather similar to regular cigarettes. PMI Next cigarettes were manufactured via this process, but still failed in the markets. Microbial and enzymatic degradation also lead to other, mostly undesirable, changes to tobacco such as an increased pH and even increased amounts of certain toxicants in mainstream smoke.

Other commercially ventured reduced nicotine cigarettes are made of genetically modified tobacco (ie, "Quest" and "Magic"). Genetic modifications that affect single and specific mechanisms are generally considered to have the fewest unintended consequences. Although nicotine affects the taste of tobacco, it is the intention to maintain a flavor similar to regular cigarettes. However, further studies revealed that "Quest" cigarettes containing 0.05 mg/cig in mainstream smoke (0.48 to 1.5 mg in tobacco) were rated as less satisfactory and with poorer taste as compared to participants' own brand, as well as compared to "Quest" cigarettes with higher nicotine content (0.3 and 0.6 mg/cig).[34,36] Genetic modification may also lead to issues in countries with strict GMO legislation. Thus, even though producing cigarettes with nicotine levels low enough to limit addiction is possible, there are many unanswered questions concerning product acceptability and legal issues.

Reducing the addictiveness of cigarettes may prove a valuable approach to significantly decreasing the use of combustible tobacco products. However, data are frequently derived from internal tobacco industry documents that often include short reports of work in progress. This means that the final outcomes are often not made public, and that the work has not been peer-reviewed and independently corroborated. Therefore, the validity of the information presented in publicly available industry documents is uncertain. Furthermore, little is known about the cost implications, possibilities for exploitation by manufacturers, and timing and feasibility of large-scale production of reduced nicotine tobacco by any of the techniques described. If reduced nicotine policies are considered as options for tobacco control, it is recommended that persons perform independent in-depth studies that cover agricultural aspects, especially with regard to genetically modified plants and to analyze modified tobacco for altered content of minor alkaloids, as well as other toxicological relevant constituents that might occur as consequence of genetic modification. Independent research is also needed on the effectiveness of nicotine reduction, its selectivity (eg, no co-extraction of flavor compounds), its effect on toxicity and the physical and chemical properties of the tobacco, and its consumer appeal – particularly for sensitive subgroups such as adolescents. The feasibility to establish reduced nicotine cigarettes in a regulated market is a complicated issue that also should be further studied. For example, post-marketing studies need to be carried out to check whether there is large-scale tampering with the reduced nicotine products, for example, to re-introduce nicotine, and whether the product is attractive to new users. It is known that positive expectancies about smoking reinforcement are associated with subsequent smoking initiation.[79] However, when it is known (eg, by public communication) that reduced nicotine cigarettes are less reinforcing, this would reduce expectations and possibly initiation of use. One trial showed no evidence of compensatory smoking or reduced intake of reduced nicotine cigarettes in a non-choice environment.[80] However, much is still unknown about the uptake of reduced nicotine cigarettes in the current evolving market of alternative nicotine sources.[81,82] Therefore more research is needed using real-world scenarios where alternative and 'illegal' nicotine containing products and options for tampering are available.

Moreover, additional data are needed on the content of nicotine that makes a tobacco product non- or minimally-addictive. Currently, there is no complete consensus on the nicotine level that will decrease the level and especially development of tobacco dependence. As adolescents are particularly vulnerable to developing addiction, research in this group is particularly relevant. Besides, other compounds and design characteristics are known to enhance addictiveness of cigarettes. To prevent new developments that maintain addictiveness by circumventing reduction of nicotine, it is important to identify as much as possible all additives, nicotine analogues and design features that can enhance addictiveness. Also, effective ways to reduce them should be investigated.

Conclusions

Manufacturing of cigarettes with reduced addictiveness potential is technically feasible. By means of GMO techniques and supercritical extraction, nicotine levels can be reduced to 0.4 mg/g tobacco, which will result in decreased dependency. Criteria for successful nicotine reduction are on the one hand an effective and efficient removal, without leaving unwanted components, and on the other hand, being selective, especially with regards to unintended extraction of compounds important for flavor and palatability. It needs to be noted that only little recent, independent, peer-reviewed research on manufacturing techniques to lower nicotine is available. Overall, removal efficiencies of up to 100% have been reported, and therefore, lowering nicotine is technologically feasible, but usually the resulting tobacco is less acceptable to consumers due to a deteriorated flavor. In addition, little is known about the cost implications, possibilities for exploitation by manufacturers, and timing and feasibility of large-scale production of reduced nicotine tobacco by any of the techniques described.

IMPLICATIONS FOR TOBACCO REGULATION

When considering nicotine reduction as a regulatory strategy, policymakers are advised to reflect on the following points in the context of their jurisdiction. First, genetically modified tobaccos might be the most promising strategy for manufacturers given it results in the lowest nicotine levels in tobacco currently reported, while unintended consequences such as flavor change are quite minimal. However, its feasibility in the actual marketplace will depend on both the legal issues posed by GMO legislative frameworks, as well as the consumer perception towards GMO. Extraction techniques, especially supercritical extraction, microbial and enzymatic degradation are alternative strategies. Second, there are many unanswered questions regarding product acceptance; therefore, it should be taken into account that although nicotine reduction is technologically feasible, the lower acceptance by consumers may result in an increase in demand towards illegal products. On the other hand, lower acceptance also may lead to reduced smoking prevalence, which is ultimately the aim of measures relating to cigarettes with reduced addictiveness potential.

Human Subjects Approval Statement

Not applicable.

Conflict of Interest Disclosure Statement

All authors of this article declare they have no conflicts of interest.

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