

Preliminary Analysis of a Nicotine Reduction Strategy Toward Non-Addictive Smoked Tobacco Products



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Under pending federal legislation, the U.S. Food and Drug Administration will soon have the legal authority to promulgate products standards for cigarettes including mandating the reduction of nicotine to non-addictive levels. This working paper reviews relevant research and identifies key policy issues that demand fuller exploration if such a product regulatory scheme can be successfully implemented. If it can, the tobacco control landscape would be transformed and the public health impact of tobacco use in the U.S. would be dramatically reduced.

I. INTRODUCTION

Smoking of conventional cigarettes is, far and away, the leading cause of preventable morbidity and mortality in the United States.¹ Current initiatives in tobacco product regulation focus on reducing tobacco use through a variety of interventions such as public education programs, taxation, and restricting the environments in which smoking is permitted. No current regulatory approach makes any attempt to eliminate cigarette smoking entirely.

The anticipated imminent passage of amendments to the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321) known as the "Family Smoking Prevention and Tobacco Control Act," (hereinafter "the Act" and referring to the provisions of H.R. 1256p.c.s. as passed by the U.S. House of Representatives on April 2, 2009 and placed on the U.S. Senate Calendar on April 20, 2009) provides an extraordinary opportunity for the U.S. Food and Drug Administration (hereafter "FDA"), through the Secretary of Health and Human Services (hereafter "Secretary"), to promulgate new standards that could profoundly reduce the morbidity and mortality associated with the use of tobacco products.

This concept is not new and proposals of this nature have been made previously. The best known of these proposals would seek to reduce the addictiveness of cigarettes. In 1998, researchers Henningfield and Benowitz described a strategy involving the reduction of nicotine in tobacco products to non-addictive levels.² They have since revised their previous proposal to address some outstanding issues and unanswered questions involved with such a strategy, but it is still the only nicotine reduction proposal to have attracted widespread attention. Cigarette companies themselves examined this idea closely as a potential new market segment beginning in the 1980s.³ The purpose of this paper is to explore the concept of nicotine reduction in smoked tobacco products and its implications: – Could it work? How could it best be implemented? What political challenges would it likely face?

IA. Context

The prevalence of smoking in the United States and across the world has been well-established. According to the World Health Organization, someone dies from tobacco use every eight seconds.⁴ Cigarettes are the cause of more than one in five American deaths.⁵ More than 4,000 toxic or carcinogenic chemicals have been found in tobacco smoke.⁶ Smoking-related diseases cost the United States alone in excess of \$150 billion each year.⁷ The vast majority of tobacco-related morbidity and mortality in the U.S. is attributable to cigarette smoking and secondhand smoke from cigarettes. Nicotine is the constituent in cigarettes primarily responsible for the formation and maintenance of nicotine dependency among cigarette smokers.⁸

The Center for Disease Control estimates that 20.8%, or 45.3 million people, of all United States adults smoke cigarettes.⁹ Among these adult smokers, 70% that they would like to quite completely, and in excess of 40% attempt to quit each year.¹⁰

If regulatory approach can lead to a non-addictive cigarette, the premature deaths of many millions of Americans will be avoided and the loss of productivity and healthcare costs to the nation associated with cigarette morbidity will be saved.

II. The Science

Various forms of tobacco contain different amounts of nicotine. The average cigarette contains roughly 8 mg of nicotine. This amount is similar across brands, including so-called “low yield” brands. The amount of nicotine delivered to the smoker, however, does vary considerably among brands, from 0.1 to 1.0 mg per cigarette. Protocols for accurate measurement of nicotine delivery to consumers have yet to be firmly established. The National Cancer Institute issued a monograph citing technical and, likely, deliberate underestimates for nicotine delivery in the measurement methods long utilized by manufactures.¹¹ Nicotine is the major alkaloid in tobacco, accounting for roughly 1.5% of the dry weight of tobacco. Other pharmacologically important alkaloids, such as nornicotine, anabasine, myosmine, ananatine, and cotinine, are present in smaller quantities, accounting for a total of roughly 8 to 12 % of the alkaloid content of tobacco.¹²

Since the early filtered cigarettes of the 1950s, cigarette manufacturers have introduced many additional features to the manufactured cigarettes including: reconstituted leaf, expanded leaf, more than six hundred additives, different blends, and different systems for the curing of tobacco (including the use of propane gas as a drying agent), variously porous and impregnated papers, ventilated filters, and others.¹³ These design changes have resulted in changes in how cigarettes affect smokers, both in terms of health effects and the likelihood smokers will develop nicotine dependence.

Smokers exhibit a persistent use of cigarettes to satisfy their nicotine dependence despite general knowledge that such use may result in serious bodily harm. In fact, most smokers who are hospitalized for a myocardial infarction will relapse back to smoking.¹⁴ No specific vulnerability factors have been consistently identified for nicotine dependence.¹⁵ Tobacco differs from other drugs of abuse because it has a higher percentage of samplers who become regular users, compared to samplers of other drugs of abuse.¹⁶ There are a variety of contributing factors to this phenomenon, including the greater social acceptance of tobacco than other drugs of abuse, the comparatively low

cost of cigarettes, and the ready availability of cigarettes. Additionally, tobacco use generally begins at an earlier age than use of other drugs of abuse.¹⁷

Biological Effects of Nicotine Use

The nicotine in cigarettes is distilled from the burning tobacco and is transported on tar droplets in the vapor phase.¹⁸ Deep inhalation of cigarette smoke is facilitated by ensuring these droplets are of optimal size, which results in exposure of the periphery of the lung to greater volumes of smoke and delivery of nicotine and tobacco-specific nitrosamines, the primary carcinogen in cigarettes, as efficiently as possible.¹⁹ Smokers are able to absorb roughly 90% of the nicotine present in the smoke from mainstream cigarettes.²⁰ Sugars are frequently among the additives found in cigarettes because when burned they yield acetaldehyde, which is synergistic with nicotine and facilitates its absorption. Unfortunately, acetaldehyde is also a carcinogen.²¹

The pH of tobacco and cigarette smoke significantly affects the impact of nicotine on smokers. Once carried into the lung, the pH of the smoke rises to 7.4 and nicotine is rapidly absorbed by the lung's large surface area.²² Chemical techniques that change the pH of cigarette smoke make nicotine more addictive because these techniques increase the so-called unprotonated or "free" component of cigarette smoke.²³ For example, ammonia technology employed frequently by the tobacco industry increases the pH of the smoke and, with it, frees nicotine levels. This increases the speed of nicotine absorption in the body and gives the smoker a "better kick" by increasing the impact of the existing nicotine.²⁴ This ammonia technology, which increases pH by increasing the amount of unprotonated or "free" nicotine in smoke, has been used by Philip Morris in its Marlboro brand since 1965, and by Philip Morris' competitors shortly after they became aware of it.²⁵

Nicotine is metabolized in the body extensively before it is excreted. The typical range for unchanged nicotine in urine is between 5 and 10%. Between 85 and 90% of the metabolism of nicotine occurs in the liver, which rapidly changes nicotine into its primary metabolites, cotinine and nicotine oxide.²⁶

The half-life of nicotine in the blood is roughly 120 minutes. Upon waking, the level of nicotine in smokers' blood averages 5ng/ml. These levels rise with the day's smoking, usually reaching a plateau of 30-40 ng/ml over three to four half-lives, or six to eight hours. The blood levels of nicotine then slowly decline after the day's smoking has ceased. There is considerable accumulation of nicotine over the day, and levels of nicotine acceptable for the maintenance of dependence persist in the blood plasma during the night.²⁷

The physiological effects of nicotine depend upon the dose, rate of administration, tolerance level of the individual smoker, and the rate of elimination. Nicotine readily crosses biological membranes and acts upon specific receptors in the brain. Certain effects of nicotine are mediated by the peripheral nervous system, as well as the modulation of the endocrine system.

Nicotine causes the adrenal gland and peripheral nervous tissue to release epinephrine and norepinephrine, which cause the increased heart rate observed after nicotine administration. Nicotine also releases norepinephrine and dopamine from brain neurons.²⁸

Nicotine affects cardiovascular, neural, endocrine, and skeletal muscle functions. Increased heart rate and blood pressure are among the most prominent effects of nicotine administration. Another prominent effect is decreased skin temperature resulting from vasoconstriction in the extremities. This is caused by nicotine's stimulation of the sympathetic autonomic ganglia, the release of catecholamine from the adrenal medulla, and the discharge of catecholamines from sympathetic nerve endings. Nicotine also stimulates the chemoreceptors in the carotid artery and the aortic arch with causes reflex tachycardia, increased blood pressure, and vasoconstriction.²⁹

Nicotine Dependence

Nicotine dependence meets the criteria for drug addiction as set forth by the DSM- IV. The definition of nicotine dependence is based on the assumption that "prolonged heavy use" of nicotine is required before to the onset of physiological dependence.³⁰ Nicotine dependence symptoms include "tolerance, cravings, feeling a need to use tobacco, withdrawal symptoms during periods of abstinence, and loss of control over the amount or duration of use."³¹ Withdrawal symptoms include "cravings, depressed mood, irritability, frustration, anger, anxiety, difficulty concentrating, and restlessness."³² It is clinically unclear which symptoms related to nicotine use represent traditionally understood neurochemical dependence and which represent the affect of nicotine on other structures or physiological functions.³³ As an example, weight gain and reduction in heart rate after tobacco use cessation are considered by the American Psychiatric to be symptoms of nicotine withdrawal, and therefore, manifestations of dependence.³⁴

Drug dependence is synonymous with drug addiction, although the World Health Organization and other public health organizations prefer the term 'dependence.'³⁵ Drug dependence is defined as substance-seeking behavior involving a psychoactive drug that acts in the central nervous system, even without tolerance and physiologic withdrawal.³⁶ It is viewed as a subset of habitual or compulsive behaviors in which the role of a specific, exogenously administered, centrally active chemical is critical.³⁷ Tobacco dependence involves self-administration of a specific psychoactive substance that shares critical common features with prototypic dependence-producing substances, like morphine, cocaine, and alcohol.³⁸

A series of studies on nicotine demonstrated that in doses comparable to those found in conventional cigarettes, nicotine is an abusable drug.³⁹ That nicotine is psychoactive was evidenced by reliable distinction from a placebo: self-reported

effects peaked within one minute after administration and dissipated within a few minutes.⁴⁰ Nicotine was shown to be a potent euphoriant by dose-related increases in the drug liking scale. In fact, intravenously-administered nicotine was five to ten times more potent than intravenously-administered cocaine in terms of elevated liking scale scores.⁴¹ As with opiates and sedatives, one of the prominent characteristics of nicotine dependence is an increased tendency to want to use the drug, which is usually referred to as a “craving.”⁴²

Nicotine affects the neurotransmitters and receptors in key areas of the brain responsible for the initiation and sustenance of addictive behavior. Regular ingestion of nicotine produces dependence in the same way that regular ingestion of heroin, cocaine, and alcohol produces dependence.⁴³ Nicotine is as addictive, but not more than, heroin and cocaine.⁴⁴ The rate of nicotine dependence among alcoholics and other drug abusers is significantly higher than the rate among the general population. For example, in 1991 over 85% of alcoholics were also addicted to nicotine, while 29% of the general population of Americans was addicted to nicotine.⁴⁵ Nicotine has been shown to be the first drug used by alcoholics prior to their initiation into the use of other drugs.⁴⁶ There is evidence to suggest that the active use of cocaine and marijuana reduces cigarette consumption during the period of active use, although smokers tend to return to a higher nicotine use when not actively using these other substances.⁴⁷ Like morphine, nicotine can cause vomiting and a reduction in skeletal muscle tone. Like cocaine, nicotine can cause increased heart rate and vasoconstriction. Like alcohol and barbiturates, nicotine can induce significant intoxication, especially during early use; however, none of these adverse effects appear to have a sufficiently deterring influence on tobacco use.⁴⁸

Compensatory Smoking

When deprived of tobacco, smokers have an increased desire to smoke cigarettes and a decreased latency to smoke when the opportunity arises. Nicotine’s effect on smokers’ behavior during tobacco deprivation has been conclusively established.⁴⁹ This effect has been shown to be inversely related to the magnitude of nicotine preloading when nicotine is administered either in tobacco smoke or through other delivery devices, including transdermally.⁵⁰ Smoking perpetuates itself by reducing displeasure, rather than by inducing the pleasure that initially led to nicotine dependence.⁵¹ “When the number of cigarettes available to an individual smoker is reduced from an average of 38 to 5 per day, the intake of nicotine per cigarette increases an average of threefold, a figure consistent with the maximal absolute bioavailability cited, 40%.”⁵² Cigarette brands that have been rated as lower tar according to machine-smoking yields are smoked more intensely than regular cigarettes.⁵³

“It is well established that smokers tend to take larger puffs or otherwise increase smoke intake when they switch to a lower yield cigarette, and that these shifts in behavior compensate for nicotine exposure.”⁵⁴ The prevalence of

compensatory smoking has been one of the primary criticisms of “light” and “ultra-light” cigarettes.

Filter Blocking

Filter blocking is one of the most prevalent means of achieving desired nicotine levels through compensatory behaviors. Cigarette filters are usually ventilated by creating a number of small holes in the filter itself, which then allow air to mix with the smoke before inhalation by the smoker. This essentially dilutes the smoke, in theory giving the smoker less nicotine and tar.⁵⁵ It also results in lower measures of nicotine using the testing protocols relied upon by cigarette makers (called the “FTC” or “Cambridge” method).⁵⁶ These ventilation holes are frequently blocked by the lips and fingers of smokers. Tobacco companies are well aware of this phenomenon, and fully exploit it to obtain desired measurements of tar and nicotine in their light and ultra light cigarettes, which comprise the majority of the cigarette marked in the United States.

Some cigarette manufacturers are taking steps to change filters to minimize the harm of inhaled smoke to the smoker. For example, a BF cigarette brand launched a cigarette with a three-part filter in Greece that captured six percent of the market share within its first month.⁵⁷ This three-part filter, called the Biofilter, has a middle section containing carbon impregnated with hemoglobin.⁵⁸ The theory behind the inclusion of hemoglobin is that chemical reactions would occur in the filter that otherwise would happen inside the body.⁵⁹ The company that produced these filters claimed that the iron content in the hemoglobin creates “ion reactions” that neutralize harmful chemicals in the smoke, including “oxides, free radicals, trace elements, aldehydes, nitroso-compounds, quinines, [and] benzene derivatives.”⁶⁰ Not surprisingly, the reaction to this filter was mixed. An unnamed “industry scientist” criticized the filter, saying, “Once hemoglobin is outside an animal, it becomes inactive by oxidizing . . . in the atmosphere.”⁶¹ Aside from the debate as to the efficacy of this particular filter, this development illustrates that manipulating cigarette filters in a variety of ways significantly affects the delivery of smoke to the smoker.

Youth Smoking

There is a considerable amount of smoking that occurs in American youth. In order for a nicotine reduction strategy to be meaningful, it must address this phenomenon by creating a cigarette with such a low dose of nicotine that youths who take up smoking cannot and do not become nicotine dependent. As it now stands, each day almost 6,000 children eighteen and under begin to smoke and a third of these minors will become regular smokers, resulting in nearly 800,000 new smokers annually.⁶² Approximately ninety per cent of smokers begin smoking before the age of twenty one.⁶³ If these trends continue, an estimated 6.4 million children will die prematurely as a result of a disease related to smoking.⁶⁴

One of the primary issues for concern when constructing a nicotine reduction strategy is how the strategy will affect not only current smokers, but also future smokers. Nicotine does not have the same effects on children that it has on adults. As a consequence, a successful nicotine strategy must also take adolescents into account when determining a nicotine threshold and when creating associated policies. Some of the responses to first exposure to nicotine that are thought to deter young people from continuing to smoke are actually predictors of continued smoking; these responses include nausea, dizziness, and feeling relaxation upon first inhalation.⁶⁵ Young people can experience nicotine dependence before having prolonged exposure to nicotine: it has been reported that eight per cent of youth smokers who had smoked twenty or fewer cigarettes in their lifetime had difficulty quitting.⁶⁶ Young smokers can inhale and absorb the same amount of nicotine and carbon monoxide as can adults, and tolerance can begin with the very first dose of nicotine.⁶⁷ Once tolerance has been achieved, other symptoms of dependence can quickly follow.⁶⁸ With studies showing that the mean age for first tobacco use is 11.7 years and for first monthly use is 12.8 years,⁶⁹ it is not hard to see how adolescent smokers could potentially be more sensitive to nicotine than adults. Adolescents also have a harder time quitting than do adults: one month into withdrawal, midbrain nicotine receptors are still significantly up-regulated in adolescents, but not in adults.⁷⁰

One of the most significant studies concerning youth smoking is the Development and Assessment of Nicotine Dependence in Youth (“DANDY”) study. This study included six hundred and eighty-one subjects for a longitudinal study, beginning when the subjects were seventh grade students between the ages of twelve and thirteen.⁷¹ The study used questionnaires and interviews to record smoking attitudes and behaviors, and the study was specifically designed to minimize false positives to crucial questions.⁷² The results of this study should be emphasized in developing a nicotine reduction strategy.

The most common initial symptom among the subjects was feeling addicted, while strong urges, irritability, nervousness, restlessness or anxiety when unable to smoke were the most commonly reported symptoms.⁷³ The third interview conducted revealed that ninety-five subjects were monthly smokers. Of these subjects, there were sixty symptomatic subjects; of these subjects, thirty-seven, or sixty-two percent, had experienced their first nicotine dependence symptom before they began smoking daily or began smoking as a result of experiencing dependence symptoms.⁷⁴ Of the forty-two subjects who reported smoking daily, six (fourteen per cent) denied experiencing any symptoms of dependence, twelve (twenty-nine percent) reported experiencing one or more symptom of dependence before daily smoking, and twenty four (fifty-seven per cent) reported experiencing symptoms some time after they commenced smoking daily.⁷⁵

Some of the subjects reported experiencing symptoms within days of starting to smoke, which is possible because nicotine causes an increase in the number of

high affinity nicotinic cholinergic receptors in the brain structures associated with reward pathways.⁷⁶ The number of these receptors increases as soon as after the second dose of nicotine.⁷⁷ Therefore, it is unlikely that daily smoking is a prerequisite for nicotine dependence.⁷⁸ Compare these adolescent results with results demonstrating that adult smokers “experience physiologic withdrawal symptoms when daily intake [of nicotine] falls below 8-12 cigarettes and have considerable difficulty maintaining intake below this level.”⁷⁹

The increased sensitivity of adolescents to nicotine, compared to that of adults, has been demonstrated in laboratory studies using rats.⁸⁰ It appears the same may be true of human adolescents, as those who initiate tobacco use during adolescence are “more likely to become dependent, have a greater difficulty quitting, smoke for a greater number of years, and smoke more heavily” than those who begin smoking later in life.⁸¹

A follow up to the DANDY study revealed that forty per cent of subjects reported dependence symptoms, with a mean of 2.3 symptoms per subject.⁸² Strong cravings and needing a cigarette were the most commonly reported symptoms.⁸³ Of subjects who reported symptoms, eighteen percent reported symptoms soon after their first use.⁸⁴ Ninety five per cent of symptomatic subjects reported experiencing symptoms prior to smoking a half pack of cigarettes per day.⁸⁵ The data from this study “suggest that about half of the symptomatic youths had experienced symptoms by the time they were smoking two cigarettes in one day each week, and that about two thirds had symptoms by the time they were smoking one cigarette per day.”⁸⁶ Girls reported a much faster onset of symptoms than did boys, as well as a greater number of dependence symptoms.

The Machine Smoking Process

Protocols for the machine smoking process are established by a handful of different organizations. These protocols are all essentially the same. The International Organization for Standardization (“ISO”), which is a non-governmental organization with members from one hundred and thirty countries dedicated to developing standardization, have created a set of protocols frequently used in this process.⁸⁷ The smoking machines are used to measure the levels of cigarette components and then rank cigarettes according to these measurements, although the machine smoking system does not measure delivery to human smokers.⁸⁸ “It has been known for decades that the standard ISO measurement to determine tar and nicotine yield. . . does not reflect the amount of tar and nicotine delivered to the smoker, a fact that is acknowledged. . . by the tobacco industry.”⁸⁹ Cigarette design has been manipulated to “cheat” these smoking machines into measuring component levels at far lower numbers than what is actually delivered to smokers.⁹⁰

Establishing a Threshold for Dependence

In order for a nicotine phase-out strategy to be viable, reductions in nicotine must continue until a specific non-addictive level of nicotine is achieved. This non-addictive level is often referred to as a threshold for dependence: above this level, smokers can and will become addicted to nicotine. Determining this level is vitally important to creating a successful strategy, but it has proved difficult to ascertain a non-addictive level of nicotine.

In a 1994 article published in the *New England Journal of Medicine*, Benowitz and Henningfield proposed a threshold level for nicotine in cigarettes of 0.4 to 0.5 mg of nicotine per cigarette.⁹¹ To arrive at this threshold level, smokers' blood levels of cotinine, the primary metabolite of nicotine, were examined. As part of this examination, the researchers measured cotinine levels of smokers who did not experience nicotine dependence. Benowitz and Henningfield postulated that a level of 5 mg of nicotine per day would readily establish and maintain nicotine dependence.⁹²

According to this study, American cigarettes contain, on average, 8 to 9 mg of nicotine; the concentration of nicotine ranges from 1.5 to 2.5 percent.⁹³ Cigarettes normally deliver about 1 mg of nicotine to the smoker, which indicates an absolute bioavailability of around twelve per cent.⁹⁴ However, the manner in which a cigarette is smoked has a significant impact on nicotine intake: intake ranges from 0.3 to 3.2 mg per cigarette, which corresponds to a range of bioavailability of 3 to 40%.⁹⁵ Benowitz and Henningfield reached the conclusion that "[a]ssuming that the estimated target daily dose of nicotine should be 5 mg or less to avert addiction and that a young person may smoke up to 30 cigarettes per day, one can conclude that a maximal available (i.e., systemic) dose of 0.17 mg of nicotine per cigarette is the threshold level for a less-addictive cigarette. Assuming a maximal bioavailability of 40 percent with intensive smoking, an absolute limit of 0.4 to 0.5 mg of nicotine per cigarette should be adequate to prevent or limit the development of nicotine in most young people. At the same time, it may provide enough nicotine for taste and sensory stimulation."⁹⁶

This nicotine threshold was proposed in tandem with other recommendations for reducing cigarette consumption. In response to a letter to the editor of *Tobacco Control* criticizing their study, Jack Henningfield and John Slade, another author of the original study wrote: "[A] nicotine reduction strategy must be done as part of an overall strategy that considered issues ranging from education, treatment, legislation, and meaningful tobacco labeling, to the need for supportive research and surveillance to guide the process as well as the importance of alternative products being available."⁹⁷

However, Benowitz and Henningfield published a subsequent article in *Tobacco Control* in 2004 withdrawing their previously proposed nicotine threshold level. In the later article, they stated that ". . . conclusions by the FDA and advisory committees to WHO and subsequent discussions by Henningfield, Benowitz, and colleagues, suggest that progress is needed in several areas in order to

implement such a proposal—for example, verification of the threshold nicotine dose per cigarette and per day to sustain nicotine addiction; and education, regulation, and surveillance to reduce unintended effects such as increased toxicity caused by compensatory smoking.”⁹⁸ Even this more conservative statement by these researchers drew criticism. “[I]sn’t there a danger that reducing the addictiveness (ie, the pharmacological impact) will mean smokers seeking more nicotine for the same satisfaction?”⁹⁹

It is no secret that the tobacco industry can manipulate the nicotine levels in cigarettes. Indeed, nicotine levels have risen in cigarettes in recent years. A study published in the *Tobacco Control* journal in 2007 found a cumulative increase of eight and a half per cent in the amount of nicotine in cigarettes between 1997 and 2005.¹⁰⁰ This study also found an increase of ten percent in the number of puffs per cigarette over this time period,¹⁰¹ which demonstrates that manufacturers are seeking a slower burn time to increase the nicotine actually delivered to the smoker. The tobacco industry has also been capable of reducing the amount of nicotine in cigarettes for decades.

Conclusions

An effective nicotine reduction strategy requires a scientifically sound understanding of the threshold for nicotine dependence. An understanding of the role of cigarette additives is also required because these chemicals affect the amount of nicotine smokers are able to absorb from cigarettes.

Cigarettes can be made with sufficiently low nicotine availability levels as not to either maintain dependence in current smokers or create dependence in those at-risk for initiation. While some existing smokers might continue to smoke, it is likely that their numbers will dwindle and few new smokers will have the motivation to continue long enough to develop illness without nicotine dependence. The issue of compensatory smoking were per-cigarette nicotine levels are gradually reduced is, however, troubling. The population shifts first to filtered cigarettes and then to “low tar” cigarettes were each accompanied by increases in per capita cigarette consumption. For this reason, it may be a better public health strategy to plan for a one-time reduction in nicotine rather than a gradual phase-out. At the least, any nicotine reduction strategy must include other policy considerations and interventions to ensure that smokers receive support as they titrate down and hopefully become no longer nicotine dependent.

III. Policy Analysis

The cigarette has been described as the “dirty needle” of nicotine delivery systems.¹⁰² While determining best practices to implement tobacco harm reduction continues to be a source of controversy within the scientific and tobacco control communities, there is consensus for a goal of elimination of combustible tobacco products.¹⁰³ The vast majority of tobacco-related morbidity

and mortality in the U.S. is attributable to cigarette smoking and secondhand smoke from cigarettes. Nicotine is the constituent in cigarettes primarily responsible for the formation and maintenance of nicotine dependency among cigarette smokers.¹⁰⁴

The FDA, under Sec. 907(a)(4)(A)(i) of the "Family Smoking Prevention and Tobacco Control Act," (hereinafter "the Act" and referring to the provisions of H.R. 1256p.c.s. as passed by the U.S. House of Representatives on April 2, 2009 and placed on the U.S. Senate Calendar on April 20, 2009), may soon be able to promulgate product standards for nicotine yields of cigarettes, including the reduction, short of elimination, of nicotine. Were levels of nicotine in cigarettes reduced to levels insufficient to create or sustain dependence, it is likely that morbidity and mortality attributable to tobacco products would be drastically reduced.

To accomplish this, the development of a legal and policy framework is needed to provide near term guidance to the FDA should it utilize its regulatory authority under the Act to transform the conventional cigarette into a non-addictive and consequently far less lethal product. Such a framework should consider: 1) the public health and policy implications of different approaches to possible rulemaking; 2) the experiences of prior legislative or regulatory harm reduction efforts and how they might inform nicotine reduction rulemaking; 3) tobacco industry strategies to avoid or evade nicotine and other product regulations including potential legal responses as well as possible product modifications; and 4) other potential legal and policy issues around enforcement of a possible regulations to reduce nicotine yields.

If such a regulatory approach can lead to a non-addictive cigarette, the premature deaths of many millions of Americans will be avoided and the loss of productivity and healthcare costs to the nation associated with cigarette morbidity will be saved.

III a AVOIDING ISSUES INVOLVED WITH THE WAR ON DRUGS AND ALCOHOL PROHIBITION

A. A Major Critique of Nicotine Elimination

A 2006 survey conducted by public opinion polling organization Zogby International showed that 45% of Americans would support a federal law making cigarettes illegal in the next five to ten years. Among 18-19 year olds, 57% were in favor. These statistics seem to support a nicotine reduction policy, even one that reduces the level to zero or nearly zero. However, the very organization that commissioned the survey, the Drug Policy Alliance,¹⁰⁵ has taken aim at this public perception. Although acknowledging that cigarette "prohibition" (as the Alliance calls it) – would have the obvious benefit of reducing smoking-related

death and disease, the organization's Executive Director, Ethan Nadelmann, strongly criticizes such as measure.¹⁰⁶

On a social level, Nadelmann feels that prohibition would demonize and dehumanize smokers, and, citing the history of opium and cocaine bans, he also points out that prohibition has historically been tied to racism and classism. Nadelmann also notes that several public health advocates do not see prohibition as a viable solution to the problem of tobacco-related death and disease.

Nadelmann's chief argument, however, is that if cigarettes were made illegal, millions of Americans would keep smoking and the tobacco industry would go underground into the hands of those "skilled in violence and intimidation."¹⁰⁷ Nadelmann notes that prohibition would thus cause an increase in criminal behaviors similar to those involved with the "War on Drugs"¹⁰⁸: some tobacco farmers would continue to grow overtly and thus become outlaws; Mexican and Columbian drug traffickers would enjoy new markets and profits; fights over turf and markets would increase "tobacco-related murders"; and crimes would skyrocket as "tobacco junkies" try to feed their increasingly costly additions. Additionally, Nadelmann argues, some would start to experiment with more dangerous forms of tobacco – resulting in "[f]ewer people [dying] in their sixties of cancer and emphysema, but more [dying] from the harms and life style associated with illicit tobacco addiction."¹⁰⁹

B. Responding to the Concerns

To learn how best to avoid the pitfalls involved in all-out prohibition, it is wise to evaluate how the experiences of prior legislative or regulatory harm reduction efforts may inform nicotine reduction rulemaking.

This should include, first, The Harrison Narcotics Tax Act of 1914 and its successor legislation, the Controlled Substances Act of 1970 - The Harrison Act is a prime example of a federal harm reduction strategy involving substances such as heroin, morphine, and cocaine that create potent physiological addiction. Dependent users of these substances found their way to hospitals and sanitariums where physicians were prohibited from treating these patients' dependence with the prohibited substances. A legal challenge led the U.S. Supreme Court to overturn this provision of the Act (*Linder v. United States*, 268 U.S. 5 (1925)). A federal effort to seek state support for the goals of the Harrison Narcotics Tax Act was initiated in 1932 as the Uniform State Narcotics Act, which provided an option to include marijuana. Concerns over criminal activity and black market sales were raised at the time of the Harrison Act's passage and persist today, as do concerns that criminalizing use has harmed the very people the statute was designed to protect. These concerns raised by Nadleman deserve serious consideration. When do harm reduction efforts lead to unintended consequences that may be just as or more harmful than the harms purportedly being addressed? Any approach to nicotine undertaken by the FDA

or other legal authorities must fully consider such unintended consequences while also bearing in mind the extraordinary morbidity and mortality associated with the cigarette.

The Eighteenth Amendment to the U.S. Constitution and Volstead Act establishing alcohol prohibition from 1919 until its repeal in 1933 is widely believed to have been a failure and, historically, the word "prohibition" has been one that tobacco control advocates have sought to avoid and, likely, why Nadleman uses the term. Prohibition was the culmination of a long and coordinated temperance movement.

Some view alcohol prohibition as an important public health measure that reduced consumption and, in turn, alcohol-related death and disease, and created a "cultural and legal climate . . . increasingly inhospitable to drink."¹¹⁰ One commentator attributes the repeal of the Eighteenth Amendment (by the Twenty-First Amendment in 1933) not to the failure of the program but to a "contextual shift" at the time – namely, the onset of the Great Depression, which created a need for the jobs and tax revenue that repeal would create. Another commentator notes that repeal did not signal a rejection of temperance goals but rather a recognition that centralized regulation of alcohol did not work; post-repeal, many states expressed the desire to remain dry, and the Twenty-First Amendment was crafted to ensure that states would have this right.¹¹¹ However, prohibition still has been referred to as a "failed experiment" or a "strange aberration."¹¹²

There are many parallels between alcohol prohibition and nicotine reduction. First, prohibition was preceded by a century-long history of temperance, with liquor control being a stage on which Americans confronted public health issues.¹¹³ Similarly, the United States has a long history of interest in reducing smoking-related death and disease, dating back as far as the Advisory Committee to the Surgeon General's first report on smoking and health in 1964, which concluded that smoking causes cancer.¹¹⁴ As with alcohol control, tobacco control is now a major arena for debate over public health issues. Additionally, prohibition came to pass only when other methods of alcohol control failed, such as self-help and medical treatment,¹¹⁵ just as other methods of tobacco control have not eliminated smoking-related death and disease.¹¹⁶ Unlike the temperance movement, tobacco control is not concerned with moral issues but, rather, is concerned with health issues alone.

An important consequence of national prohibition was the virtual destruction of the liquor industry.¹¹⁷ This "industrial and economic devastation" was unexpected to brewers, who had anticipated being able to produce beer of moderate strength but were banned from doing so pursuant to the Volstead Act. That act, which followed adoption of the Eighteenth Amendment, prohibited beverages containing 0.5% or more alcohol by volume and thus illegalized virtually all alcoholic drinks.¹¹⁸ Although public health advocates may see the dissolution of the major United States tobacco companies in a positive light, the

lesson learned from alcohol prohibition is that care must be taken to prepare to change the business climate gradually rather than all at once in order to gain popular and political support for nicotine reduction. An approach that takes up to a decade to implement may be required.

One of the biggest lessons of the prohibition era has to do with its effect on public perception of drinking. Instead of paving the way for a generation of abstemious individuals, prohibition instead was “transformed from progressive reform to an emblem of a suffocating status quo.”¹¹⁹ Cultural media at the time helped to encourage the breakdown of cultural proscriptions against liquor, referred to as the “normalization of drinking.”¹²⁰ This lends further support to gradual nicotine reduction rather than an all-at-once ban.

Another of Nadleman's concerns is that a nicotine reduction law may result in an increase in a cigarette black market similar to the black market for illegal drugs, with a corresponding upsurge in crime to meet the demand for nicotine-containing cigarettes. One source of such products may be the smuggling of products across national borders. To help curb this effect, tough anti-smuggling laws would need to be established that would severely penalize entities involved in the importation or transport of illegal cigarettes, such as tobacco companies, distributors, and common carriers. Cigarettes are, dose for dose, much bulkier than currently illegal drugs, so the failure of the “war on drugs” to significantly reduce drug supplies does not mean that counteracting cigarette smuggling would be equally futile. They are not, however, bulkier than alcohol, which was smuggled during Prohibition; though law enforcement in that instance cut overall supplies to a small fraction of prior consumption levels. Additionally, the availability of alternative nicotine products can help reduce the black market by allowing those addicted to nicotine to obtain the drug legally – while at the same time eliminating its delivery in conjunction with the toxins contained in conventional cigarettes. Finally, surveys consistently show that the majority of smokers (unlike alcohol users) would like to quit, and indeed have tried unsuccessfully to quit.

Drug policy, sometimes referred to as the “war on drugs,” has generated much controversy particularly in regards to cannabis/marijuana. A number of states have either decriminalized marijuana use or provided exemptions to criminal approaches for medicinal users of marijuana who obtain documentation similar to a prescription from a treating physician. Additional state legislation following this trend is expected subsequent to statements from the current federal administration indicating that application of federal law to these situations will be deemphasized.¹²¹ The approach to marijuana appears to be heading on a path separate from other illegal drugs and organic substances. The legal and policy differences between approaches to marijuana and, for example cocaine, heroin, and methamphetamine in a harm reduction and public health context and their relevant to nicotine reduction rulemaking should be explored, beginning with the passage of The Marihuana Tax Act of 1937 and subsequent federal approaches.

III b. The public health and policy implications of different approaches to possible rulemaking to reduce nicotine levels in cigarettes.

Legal and policy analysis of possible approaches to a time frame for nicotine yield reductions in cigarettes is needed. A reduction to a nicotine yield level insufficient to create or sustain dependence could be achieved by a series of small reductions over time or could be achieved by setting a specific date for a one-time reduction to a level insufficient to create or sustain dependence.

Policy and legal research should consider the possible construction of key provisions of the "Family Smoking Prevention and Tobacco Control Act" that specify the public health factors that the FDA, through the Secretary under Sec. 907(a)(3)(B) of the Act, must consider. These provisions describe how the public health impact of product standards should be construed as well as the rights of objecting parties to provide scientific evidence in opposition to the rule. The impact on rulemaking from objecting parties' potential evidence submissions addressing concerns over the health impact of smoker compensation behavior were a phased reduction pursued or direct or indirect health consequences of nicotine withdrawal were a single reduction approach adopted should be analyzed.

The Act expressly encourages consideration by the Secretary of involving the expertise, consultation, and support of other federal agencies as well as other competent persons and organizations in the development of product standards under Sec. 907(a)(6). Coordination of rulemaking involving reduction of nicotine yields with these entities should be explored in terms of evaluating the potential legal and policy impact of, for example, a) use of price controls such as taxation and discounting restrictions; b) promotion of and access to evidence-based smoking cessation resources including nicotine replacement therapies; and c) public communication and education strategies to facilitate achievement of the public health goals of the rulemaking.

The scope of the challenge to the FDA and to society as a whole that a regulated reduction in cigarette nicotine yields to non-addictive levels cannot be overstated. Researching and analyzing the legal and policy implications of what approach to the reductions can be pursued, the likely objections of parties, and the importance of developing innovative ways to coordinate with federal and state agencies as well as non-governmental entities under this provision of the Act, is needed and would provide vital information to the FDA to implement such a rulemaking process.

IV. OTHER PROPOSALS

There are a number of other proposals afoot that, like nicotine reduction, aim to reduce product use through regulation of the tobacco industry rather than through other, more commonly proposed methods such as public education, counter-marketing campaigns or cessation programs. Although many of these other proposals differ from nicotine reduction in certain key area, lessons can also be learned from them in building an effective nicotine reduction proposal.

A. *Cigarette Phase-Out*

This proposal is similar to nicotine reduction, but instead of requiring that the nicotine in cigarettes be phased out it proposes that the nicotine delivery device itself – i.e., the cigarette – be eliminated over time. This proposal has been put forth most prominently by the organization SmokeLess New Zealand.¹²² SmokeLess proposes a “Smokers Choices Bill” stating: “[n]o person shall import for sale, sell, pack, supply, or distribute any tobacco product labeled or otherwise described as suitable for smoking, one year after this law is enacted.”¹²³

A cornerstone of this proposal is the long-term availability of “alternative nicotine products,” thus allowing smokers to “buy a nicotine fix without smoking.”¹²⁴ Such products would be made available for some years before and many years after cigarette sales are phased out and would include nasal snuff as well as oral snuff (the sale of which is currently banned in New Zealand).¹²⁵ SmokeLess contends that the use of such alternative nicotine products will keep any black market small because “[s]mokers are not going to pay exorbitant prices for an uncertain supply of black market cigarettes if they can get a regular legal nicotine hit from smokeless tobacco or fast acting addictive nicotine products 10 or 20 times a day for a few dollars a day from the corner dairy.”¹²⁶

Although this proposal differs in its approach from nicotine reduction (by targeting the cigarette as a whole rather than the nicotine in the cigarette), it bears many similarities. First, like nicotine reduction, the cigarette phase-out law would not ban possession, smoking, or growing of tobacco for personal use. Thus, smokers will not face criminal liability even if they are smoking a product that cannot be lawfully sold. Next, like nicotine reduction, cigarette phase-out would allow for the sale of nicotine in forms other than smokable tobacco. Thus, under either proposal, smokers can obtain their nicotine fix without the need for conventional cigarettes. A major advantage of this, as mentioned above, is a small or non-existent black market for conventional cigarettes.

B. *Toxic-Tobacco Law*

Very similar to cigarette phase-out is a proposal that would ban U.S. companies from making, marketing or importing cigarettes, cigars, chew, snuff, pipe tobacco and cigarette tobacco. Its proponent, Terence Gerace,¹²⁷ claims that the law

would end youth access, cease all advertising and promotional marketing, take tobacco from the hands of retailers, and stop the normalization of tobacco consumption. According to Gerace, “the advertising and retail milieu, devoid of tobacco products, will become an environment more conducive to quitting tobacco than the current one.”¹²⁸ The result, he says, will be significant reductions in youth smoking, cancer and other smoking-related diseases, and home and commercial fires.

Like both nicotine reduction and cigarette phase-out, this proposal would not criminalize an individual’s purchase, possession or use of nicotine-containing products. Unlike those proposals, however, this law would allow the importation of tobacco products from abroad and contemplates the possibility of allowing adults to buy tobacco products at federal stores.

C. Two-Cigarette Society

One commentator, David G. Adams,¹²⁹ feels that a gradual approach to nicotine reduction would still permit the addiction of the next generation of smokers.¹³⁰ He thus proposes that only non-addictive cigarettes¹³¹ be sold to those under the age of twenty-one – or that sales of addictive cigarettes be restricted to those born nineteen or more years before this strategy takes effect (thus prohibiting those aged eighteen and under from ever buying addictive cigarettes). The theory behind this is that teens begin to smoke to copy peers, but continue to smoke as adults because they are addicted to nicotine. Thus, in the absence of addictive levels of nicotine in their cigarettes, most young smokers would ultimately quit.

The most important criticism of this plan, however, lies in its own theory – that teens begin to smoke to copy other smokers. Because of this, teens may not want to smoke “junior” (i.e., non-addictive) cigarettes and instead may seek out the “adult” (i.e., addictive) version. Additionally, such a measure, even if successful, would only reduce the amount of new smokers (Adams himself notes this shortcoming). It would do nothing to change the smoking behaviors of those currently addicted Americans smokers over the age of twenty-one – 400,000 of whom die every year from smoking-related illnesses.¹³²

D. Cap-and-Trade

In July 2007, Senator Mike Enzi (R-WY) proposed a legislative response to the Act.¹³³ Enzi’s bill would consist of a “cap and trade” arrangement similar to those with a proven track record in the environmental arena, particularly Clean the Air Act Amendments of 1990.¹³⁴ The proposal would shrink the size of the tobacco market over the next twenty years by requiring cigarette manufacturers to meet specific user level limits by specific deadlines. A market share allocation and transfer system would be established in which allowances could be used, banked, traded or sold freely on the open market. The number of allowances

would decrease every year, ultimately resulting in a 90% reduction in tobacco use from today's level. Enzi's bill, however, failed to garner support and is no longer under consideration in 2009.

In addition to setting usage caps, the bill also would increase the tobacco excise tax based on a product's relative risk. The revenue from the tax would be distributed to Medicare, Medicaid, and tobacco control and prevention (including a counter-advertising campaign), thus maintaining a tight nexus between tobacco taxation and tobacco health policy. Additionally, unlike the Act (which explicitly states that the FDA will not be allowed to ban nicotine or tobacco outright), the Enzi bill would have given the FDA explicit authority to ban nicotine. However it is not clear whether it is technically feasible to completely eliminate nicotine from burley tobacco used for cigarettes. If this is indeed the case, then the nicotine ban would, in effect, amount to a ban on burley tobacco products altogether.

E. Placing Nicotine under the Controlled Substances Act

Another, and perhaps the most radical, proposal would place nicotine under Schedule II of the Controlled Substances Act.¹³⁵ This would group it with other drugs with a high potential for abuse and dependence but with continued medical usefulness, such as cocaine and various opioids, stimulants and hypnotics. Unlike the other proposals, this proposal seemingly carries the possibility of sanctions for possessors and users as well as manufacturers. Although it does allow for tobacco to be locally grown for personal use, presumably any further possession or use would be considered illegal and would subject the offender to jail time.

A major criticism of such a proposal, of course, is that it has the possibility of creating the same problems that surround other illegal drugs such as heroin and cocaine – the same issues that have been noted by critics (such as Ethan Nadelmann) of the War on Drugs.

V. Conclusion

While the notion of eliminating the vast majority of the public health harm caused by smoked tobacco products may have seemed relegated to the realm of fantasy not long ago, the imminent passage of the "Family Smoking Prevention and Tobacco Control Act" and with it, the FDA's authority to reduce nicotine levels in cigarettes means that public health and tobacco control policymakers need to engage in immediate scientific and policy research and analysis in order to maximize and accelerate the potential of this opportunity.

Such research would result in a nicotine reduction rulemaking process to maximize the public health potential of the Act and transform the tobacco control landscape. If such a regulatory approach can lead to a non-addictive cigarette, the premature deaths of many millions of Americans will be avoided and the loss

of productivity and healthcare costs to the nation associated with cigarette morbidity will be saved.

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